

# Mild Cognitive Impairment

## Ten Years Later

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In the past 10 years, there has been a virtual explosion in the literature concerning the construct of mild cognitive impairment. The interest in this topic demonstrates the increasing emphasis on the identification of the earliest features of cognitive disorders such as Alzheimer disease and other dementias. Mild cognitive impairment represents the earliest clinical features of these conditions and, hence, has become a focus of clinical, epidemiologic, neuroimaging, biomarker, neuropathological, disease mechanism, and clinical trials research. This review summarizes the progress that has been made while also recognizing the challenges that remain.

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During the past decade, a major transition in the clinical characterization of cognitive disorders has taken place.<sup>1</sup> Many of the prodromal stages of conditions such as frontotemporal dementia and dementia with Lewy bodies have been recognized, and we can now make the clinical diagnosis at an earlier stage in the disease process.<sup>2</sup> At the same time, there has been a growing interest in the predementia phase of these conditions because of suggestions that we may be able to identify the earliest clinical features of these illnesses before functional impairment is evident. Toward this end, the construct of mild cognitive impairment (MCI) has evolved to capture this predementia phase of cognitive dysfunction.<sup>3,4</sup>

Most investigators believe that if we wait for functional impairment and perhaps even mild cognitive symptoms to emerge, it may be too late to treat the underlying disease process.<sup>5</sup> Ideally, we would like to be able to prevent or postpone the disease process by intervening early. If a disease-modifying therapy or effective lifestyle intervention were available, we would want to intervene as soon as possible, but these treatments are not on the immediate hori-

zon. As such, the construct of MCI serves a useful purpose as a clinical stage in which meaningful interventions can take place. Mild cognitive impairment may be an intermediate step on the way to primary prevention, but it remains important for formulating research hypotheses.

### HISTORY

Mild cognitive impairment as a term was introduced into the literature in 1988 by Reisberg and colleagues,<sup>6</sup> but at that time, it was intended to refer to stage 3 of the Global Deterioration Scale (GDS). In a similar vein, the Clinical Dementia Rating (CDR) scale has gained popularity as an instrument for characterizing either mild impairment or very early dementia, and both instruments have been catalysts for stimulating research on early impairment.<sup>7</sup> As the field has advanced, however, we have realized that these severity scales do not adequately characterize the subtle differences between MCI and early dementia. Participants with MCI, as currently diagnosed, can be classified as GDS stage 2 or 3 and as having a CDR of 0 or 0.5.<sup>3</sup> Therefore, a finer grain of diagnostic acumen was necessary to distinguish these prodromal conditions from the dementia stage beyond the granularity of the GDS and CDR instruments.

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In a 1999 article published in the *Archives of Neurology*,<sup>3</sup> a group of investigators from the Mayo Clinic described their experience with participants with MCI in a community cohort and put forth diagnostic criteria outlined in **Table 1**. These criteria have been the subject of a great deal of study, validation, and criticism,<sup>8</sup> and there has been an explosion of interest in the literature, as characterized in **Figure 1**.

### CRITERIA

The 1999 *Archives* article focused on MCI as a prodromal condition for Alzheimer disease (AD) and emphasized the importance of memory impairment for incipient AD. Subsequently, other investigators appropriately noted that not all forms of MCI may evolve into AD, and a broader conceptualization was necessary. In 2003, Winblad et al<sup>9</sup> convened a conference of international experts on MCI to revise criteria.<sup>10</sup> From that conference, new, more expansive criteria for MCI were proposed, and these criteria now form the foundation for the National Institute on Aging–sponsored Alzheimer Disease Centers Program Uniform Data Set and the public-private neuroimaging/biomarker consortium, the Alzheimer Dis-

ease Neuroimaging Initiative (ADNI).<sup>11</sup> These criteria depict the clinical phenotypes of amnesic MCI (aMCI) and nonamnesic MCI (naMCI) with the subtypes of single and multiple domain classifications (**Figure 2**). These clinical phenotypes are then combined with the presumed cause (**Figure 3**) as the next step in the diagnostic process. This is analogous to a physician diagnosing a particular syndrome and then searching for an etiologic explanation for the syndrome. This combination leads to the diagnostic impression of a possible outcome of the clinical entity of MCI. With this theoretical framework, many studies have been conducted to investigate the utility and prognostic outcome of the diagnoses.<sup>5</sup>

### EPIDEMIOLOGY

Numerous investigations worldwide have used these criteria as an infrastructure for estimating the frequency of MCI and its subtypes.<sup>12-15</sup> Some studies have retrospectively applied MCI criteria to previously acquired data sets and have provided important insights.<sup>13,16</sup> However, the most informative studies have been conducted prospectively to incorporate MCI criteria at the outset.<sup>12,17</sup> These studies have captured the subtleties of the diagnosis in a prospective fashion and are consequently better able to address the clinical characterization and mild features of the construct.

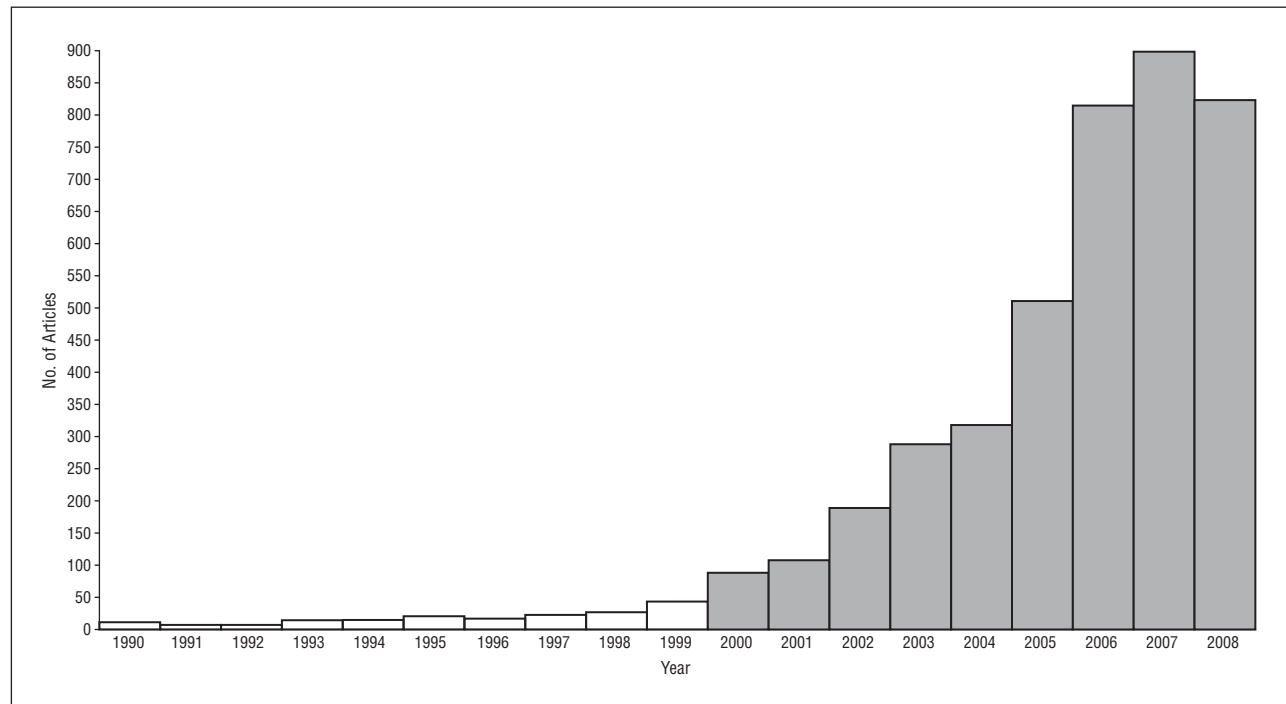
The Mayo Clinic Study of Aging was designed as a population-based study in Olmsted County, Minnesota, involving a random sample of nearly 3000 participants, aged 70 through 89 years, who were nondemented and cognitively normal or who had MCI at entry.<sup>18</sup> The prevalence of MCI from this study is estimated at approximately 15% of the nondemented population, with a 2:1 ratio of aMCI to naMCI. The most common putative cause

**Table 1. Original 1999 Mild Cognitive Impairment Criteria<sup>a</sup>**

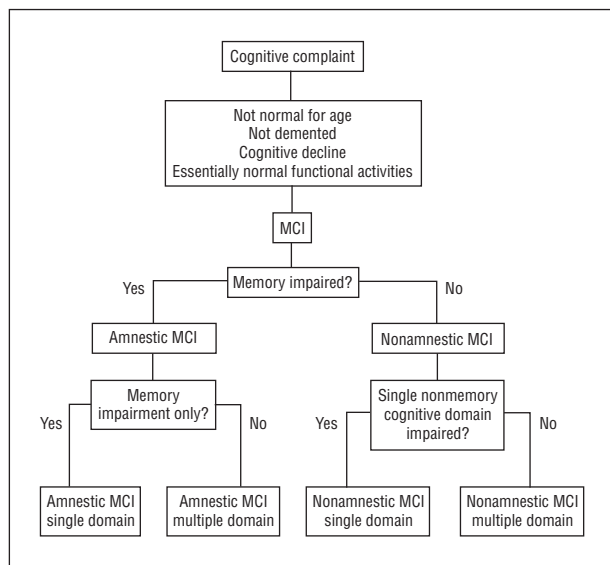
#### Criterion

Memory complaint, preferably corroborated by an informant  
 Memory impairment documented according to appropriate reference values  
 Essentially normal performance in nonmemory cognitive domains  
 Generally preserved activities of daily living  
 Not demented

<sup>a</sup>Based on information from Petersen et al.<sup>3</sup>



**Figure 1.** The number of publications with “mild cognitive impairment” in the title or abstract from 1990 through 2008.



**Figure 2.** Current flowchart for the diagnosis of mild cognitive impairment (MCI) and its subtypes.<sup>10</sup> Reprinted with permission from Blackwell Publishing.

is degenerative, and this cause predominates to a greater extent for aMCI than for naMCI.

Other studies<sup>12,13,17,19-27</sup> have also addressed this issue and are summarized in **Table 2**. Although these studies incorporate a variety of tools to fulfill the diagnostic criteria for MCI, yielding some variability, there is a coalescence of prevalence rates from around the world.<sup>12,17</sup> In general, the rates appear to converge in the 14% to 18% range for individuals aged 70 years and older.

## OUTCOMES

The next issue regarding MCI pertains to the participants' outcomes following a diagnosis. A major factor in determining outcome depends on the source of participants being studied. In general, it appears that participants from referral sources, such as memory disorders clinics or AD centers, likely have a progression rate to dementia, particularly AD, of 10% to 15% per year.<sup>28</sup> This is likely also true for some of the clinical trials on MCI, such as those designed to incorporate the protocols used by the Alzheimer's Disease Cooperative Study and the ADNI.<sup>29</sup> However, if we address a population from an epidemiologic perspective in which participants are prospectively approached about participation, the progression rates are likely lower (in the 6%-10% per year range)<sup>12,24,30-32</sup> (R.C.P.; R.O.R.; Y.E.G.; D.S.K.; Ruth H. Cha, MS; Shane Pankratz, PhD; B.F.B; R.J.I.; Eric G. Tangalos, MD; Walter A. Rocca, MD; unpublished data, 2009) (**Table 3**). This outcome reflects several factors: One factor concerns the prior probability of having an underlying disorder such as MCI when a participant seeks treatment at a referral clinic. In the referral clinic setting, this probability is reasonably high and hence the higher annual rate of progression to dementia in this setting (10%-15%). However, in epidemiologic studies, there is a broader spectrum of MCI severity, more heterogeneity as to the underlying condition, and likely lower annual rates of progression (6%-10%). It is noteworthy that

		Pathogenesis			
		Degenerative	Vascular	Psychiatric	Medical Conditions
Clinical Classification	Amnesic MCI	Single domain AD		Depr	
	Multiple domain	AD	VaD	Depr	
Nonamnesic MCI	Single domain	FTD			
	Multiple domain	DLB	VaD		

**Figure 3.** Presumed outcome of the subtypes of mild cognitive impairment (MCI) when combined with the presumed pathogenesis. Adapted from Petersen.<sup>4</sup> Reprinted with permission from Oxford University Press, Inc. AD indicates Alzheimer disease; Depr, depression; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; and VaD, vascular dementia.

in both the referral clinic and the epidemiologic settings, the rates are greatly elevated over the base incidence rates of dementia and AD of 1% to 2% per year.<sup>3</sup>

## PREDICTORS

Among those individuals who exhibit an elevated rate of progression from MCI to AD, can we predict who will progress more rapidly? A great deal of research on this issue has been generated in the past decade. **Table 4** lists the most common factors related to rate of progression.

## SEVERITY OF COGNITIVE IMPAIRMENT

As would be expected, those who are more impaired in the clinical spectrum, by virtue of degree of memory impairment or other cognitive deficits, are more likely to progress to dementia more rapidly.<sup>8</sup> This factor has been demonstrated in several clinical studies and likely reflects the underlying extent of pathological involvement.

## GENETIC CONSIDERATIONS

In 1995, the initial report of the effect of apolipoprotein E  $\epsilon 4$  carriers progressing more rapidly from MCI to dementia was published in *JAMA*; since that time, there have been numerous replications.<sup>33,34</sup> This finding is particularly relevant for AD because apolipoprotein E  $\epsilon 4$  carrier status is a major genetic risk predictor of late-onset AD.<sup>35</sup>

## MAGNETIC RESONANCE IMAGING

Quantitative magnetic resonance imaging (MRI) has perhaps been the most intensively studied imaging and biomarker entity in the context of MCI.<sup>36</sup> Jack and colleagues at the Mayo Clinic<sup>37</sup> have published the initial and many of the subsequent studies in this area. Following this lead, the National Institute on Aging-sponsored ADNI was designed to assess the utility of neuroimaging and chemical biomarkers in predicting prodromal AD and characterizing features that likely predict progression.<sup>11</sup>

In general, structural MRI has been shown to predict progression from MCI to AD such that volumetric mea-

**Table 2. Prevalence Studies**

Source	Study Location	No. of Participants	Participant Age, y	Prevalence of MCI, %
Unverzagt et al, <sup>19</sup> 2001	Indianapolis, IN	2212	≥65	23.4
Hänninen et al, <sup>20</sup> 2002	Finland	806	60-76	5.3
Lopez et al, <sup>17</sup> 2003	CHS	1690	≥75	22
Ganguli et al, <sup>13</sup> 2004	MoVIES	1248	≥65	3.2
Busse et al, <sup>12</sup> 2006	Leipzig, Germany	980	75-79	19.3
Das et al, <sup>22</sup> 2007	India	745	≥50	14.9
Di Carlo et al, <sup>23</sup> 2007	Italy	2830	65-84	16.1
Fischer et al, <sup>24</sup> 2007	Vienna, Austria	581	75	24.3
Manly et al, <sup>25</sup> 2008	Manhattan, NY	2364	≥65	21.8
Palmer et al, <sup>21</sup> 2008	Kungsholmen, Stockholm, Sweden	379	75-95	11.1
Plassman et al, <sup>26</sup> 2008	ADAMS	856	≥71	22.2
Roberts et al, <sup>27</sup> 2008	Rochester, MN	1969	70-89	14.8

Abbreviations: ADAMS, Aging, Demographics and Memory Study; CHS, Cardiovascular Health Study; MCI, mild cognitive impairment; MoVIES, Monongahela Valley Independent Elders Survey.

**Table 3. Rates of Progression**

Source	Study Location	No. of Participants	Participant Age, y	Reported Rate of Progression	Annual Crude Progression Rate, % <sup>a</sup>
Solfrizzi et al, <sup>30</sup> 2004	Italy	1524	≥65	3.8/100 person-years	3.8
Busse et al, <sup>12</sup> 2006	Leipzig, Germany	863	≥75	44% per 4.3 y	10.2
Tschanz et al, <sup>31</sup> 2006	Cache County, Utah	3266	≥65	46% per 3 y	15.3
Fischer et al, <sup>24</sup> 2007	Vienna, Austria	476	75-76	33.9% per 30 mo	13.6
Ravaglia et al, <sup>32</sup> 2008	Italy	937	≥65	14% per 1 yr	14.0
Farias et al, <sup>28</sup> 2009	California	111	>60	3% per 1 y <sup>b</sup>	3.0 <sup>b</sup>
Petersen et al, unpublished data, 2009	Rochester, MN	1969	70-89	7.5% per 1 y	7.5

<sup>a</sup>Reported or crude rate estimated from data.

<sup>b</sup>Progression rate for clinic cohort reported as 13% per 1 year.

**Table 4. Factors Influencing Rates of Progression****Predictor of Progression**

Clinical severity  
*ApoE* ε4 carrier status  
 Atrophy on MRI  
<sup>18</sup>FDG PET pattern of Alzheimer disease  
 CSF markers compatible with Alzheimer disease  
 Positive amyloid imaging scan

Abbreviations: *ApoE*, apolipoprotein E; CSF, cerebrospinal fluid; <sup>18</sup>FDG PET, fludeoxyglucose F 18–positron emission tomography; MRI, magnetic resonance imaging.

surements of the hippocampal formation, entorhinal cortex, whole brain, and ventricular volumes are commonly used in clinical studies.<sup>38</sup> This precision has been translated into a proposed design of clinical trials to reduce the sample size of the treatment groups for proposed therapies.<sup>39</sup> The sample size for therapeutic interventions can be greatly reduced using volumetric indices gained from MRI as a stratifying variable.

In addition to structural MRI, other measures such as magnetic resonance spectroscopy, diffusion tensor imaging, and arterial spin labeling have been useful in differentiating among those participants with MCI and AD and those who are cognitively normal, and these measures may also be useful in predicting progression to dementia and AD.<sup>40</sup> The breadth of useful measures involv-

ing MRI is impressive and clearly represents an advance in the field during the past decade.

### FLUDEOXYGLUCOSE F 18–POSITRON EMISSION TOMOGRAPHY

A functional imaging modality that has been studied to a lesser extent than MRI includes the use of <sup>18</sup>FDG PET (fludeoxyglucose F 18–positron emission tomography) scans. The available data suggest that many participants with the clinical syndrome of MCI exhibit the “AD pattern” of hypometabolism in the temporoparietal regions, which predicts progression to clinical AD.<sup>41</sup> This imaging modality likely detects an aspect of neurodegeneration that perhaps reflects the loss of synaptic integrity and provides dynamic information on progression.

### CEREBROSPINAL FLUID

One of the more active areas of biomarker prediction of progression has arisen in the area of cerebrospinal fluid (CSF) biomarkers,<sup>42</sup> such as amyloid β 1 to 42 peptide (Aβ<sub>1-42</sub>), total tau, and tau phosphorylated at threonine 181. An influential article in 2006 by Hansson and colleagues<sup>43</sup> highlighted the finding that among those participants with MCI who possess the profile of AD, low Aβ<sub>1-42</sub> and elevated total tau or phosphorylated tau or the ratio of Aβ<sub>1-42</sub> to tau is predictive of progression from MCI to AD. A recent report of a group of 12 research centers from Europe involv-

ing a large group of participants with MCI essentially replicated the findings from Hansson et al.<sup>44</sup> A similar study from the ADNI recently reported the utility of CSF biomarkers in predicting progression, so there is a wealth of data now converging that CSF may provide useful information in predicting progression from MCI to AD.<sup>45</sup> Because most of the participants in these studies have MCI of moderate severity, the real utility of these indices will reside in their ability to be accurate predictors in participants with less severe manifestations of disease.

## MOLECULAR IMAGING

A recent advancement in imaging involves the use of molecular imaging of amyloid.<sup>46</sup> The initial agent to address this issue was the carbon 11 compound known as Pittsburgh Compound B; this tracer has been the most widely studied in the world. However, since its introduction, several <sup>18</sup>F compounds have been introduced, and some of these agents are likely to become commercial products; as such, new data are emerging. Early data from the University of Pittsburgh indicate that amyloid imaging may be important in selecting a subset of participants who are more likely to progress rapidly and perhaps in differentiating among those participants with aMCI and nMCI who might be appropriate for anti-amyloid therapies.<sup>47</sup>

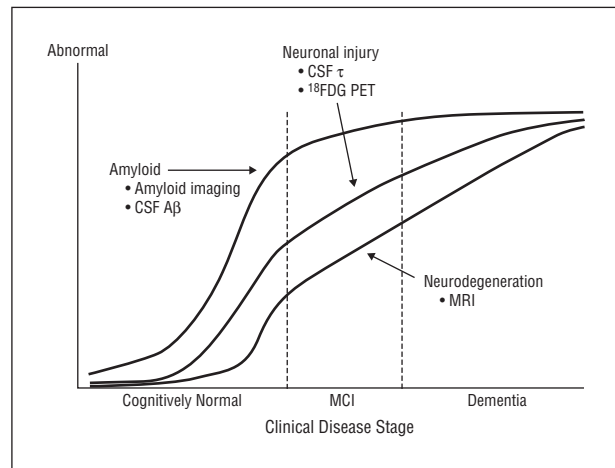
## COMBINATION OF MARKERS

In the final analysis, it is likely that the best prediction model will involve a combination of neuroimaging and chemical biomarker measures. Several recent studies have suggested that, depending on the stage in the clinical spectrum, certain neuroimaging and biomarker measures or their combinations may be quite informative.<sup>48</sup> As shown in **Figure 4**, it is possible that a deposition of amyloid is the initial event, characterized by a low CSF A $\beta_{1-42}$  level or a positive amyloid imaging scan, followed by measures of degeneration, such as seen on <sup>18</sup>FDG PET or by CSF levels of total tau or phosphorylated tau, or, as the preponderance of evidence suggests, as characterized by structural changes on MRIs.<sup>49</sup>

Then, as Figure 4 indicates, clinical changes become manifest typically as a change in memory function for early AD followed by other cognitive changes and eventually functional impairment. Certain neuroimaging and biomarker measures may be differentially sensitive and informative at different stages in the underlying progression of the diseases. No single measure will be uniformly predictive throughout the entire disease process. Toward that end, Jack and colleagues<sup>50</sup> have proposed that amyloid deposition as depicted on amyloid imaging may set the stage for subsequent cognitive decline.

## NEUROPATHOLOGICAL ANALYSIS

Relatively few neuropathology studies have been completed on participants during the MCI stage of AD. Some investigators contend that this stage of MCI is, in fact, AD but also indicate that these participants may be more clinically advanced than others in the literature.<sup>51,52</sup> The



**Figure 4.** Hypothetical temporal ordering of neuropathological processes in the course of Alzheimer disease and corresponding imaging and biomarker measures. A $\beta$  indicates amyloid  $\beta$ ; CSF, cerebrospinal fluid; <sup>18</sup>FDG PET, fludeoxyglucose F 18–positron emission tomography; MCI, mild cognitive impairment; and MRI, magnetic resonance imaging.

Religious Orders Study has followed up a group of nuns and priests for many years and has an excellent autopsy rate. In general, they found that approximately 60% of the participants with MCI have neuropathological evidence of AD, but they indicate that vascular disease also accounts for a significant degree of the neuropathological features.<sup>53</sup> Other studies have highlighted the importance of neurofibrillary tangle density when accounting for the symptoms of MCI.<sup>54</sup>

Two studies from the Mayo Clinic published in the *Archives of Neurology* shed additional light on these participants.<sup>55,56</sup> One study evaluated participants who died while their clinical classification was MCI and found that most had a low probability of having the neuropathological features of AD at that point in time.<sup>55</sup> However, it appeared as if the participants were in transition to greater degrees of pathological involvement. A second study observed participants who had been previously diagnosed with MCI and had progressed to dementia and characterized these participants as having the ultimate pathological characteristics.<sup>56</sup> This study indicated that, while most of the participants with aMCI developed AD, a considerable proportion (20%-30%) developed another type of dementing disorder, indicating that, while the clinical criteria for aMCI likely predict AD, they are not absolutely specific.

## CLINICAL TRIALS

In the past 10 years, there have been numerous clinical trials on aMCI that tested most of the current therapies available for AD.<sup>29,57,58</sup> All of the acetylcholinesterase inhibitors have been evaluated, and, with one partial exception, results of all these analyses were negative<sup>29,57-60</sup> (**Table 5**). Cumulatively, these trials have involved between 4000 and 5000 participants. One trial with rivastigmine, two with galantamine, and one with rofecoxib failed to achieve the anticipated rates of progression from MCI to AD and consequently had to be extended, resulting in a lack of power.<sup>57-59</sup> The rivastigmine trial was

**Table 5. Clinical Trials<sup>a</sup>**

Source	Study Sponsor	Duration	End Point	Medication
Petersen et al, <sup>29</sup> 2005	Alzheimer's Disease Cooperative Study	3 y	AD	Vitamin E, donepezil
Thal et al, <sup>58</sup> 2005	Merck	3-4 y	AD	Rofecoxib
Feldman et al, <sup>57</sup> 2007	Novartis	4 y	AD	Rivastigmine
Winblad et al, <sup>59</sup> 2008	Johnson & Johnson	2 y	CDR 1	Galantamine
Doody et al, <sup>60</sup> 2009	Pfizer	48 wk	AD	Donepezil

Abbreviations: AD, Alzheimer disease; CDR 1, Clinical Dementia Rating of 1.

<sup>a</sup>All trials used the clinical diagnosis of AD as an end point.

**Table 6. Sources of Variability in MCI Studies**

Source of Variability
Sources of participants
Clinical heterogeneity
Variability in clinical outcomes
Vagueness of criteria related to cognitive function
Proactive vs retroactive application of criteria
Neuropsychological normative data
Blinded nature of evaluators on each visit
Is MCI a clinical entity, a pathological entity, or both?

Abbreviation: MCI, mild cognitive impairment.

conducted in multiple countries with multiple languages and likely recruited a heterogeneous group of participants with very mild disease.<sup>57</sup> Hence, the rate of progression was lower.

Two trials involving galantamine used mild entry criteria and required a more advanced degree of "conversion" of CDR 1 rather than the clinical diagnosis of AD as an end point.<sup>59</sup> Therefore, this criterion may have inadvertently required participants to remain in the MCI stage for a longer period, resulting in a lower rate of progression than anticipated. However, this trial almost achieved its anticipated rate and had a suggestion of a therapeutic response.<sup>59</sup>

The rofecoxib trial initially required a more stringent degree of memory impairment and had to loosen the inclusion criteria to recruit enough participants. This may have contributed to its low rate of progression, necessitating an extension of the trial.<sup>58</sup> Consequently, for a variety of reasons, all of these trials did not meet their anticipated therapeutic goals.

The Alzheimer's Disease Cooperative Study conducted a therapeutic trial on participants with aMCI to test high-dose vitamin E and donepezil and achieved its anticipated progression rate of 16% per year.<sup>29</sup> It is interesting to note that virtually the same recruitment techniques were used in the ADNI, and this study has achieved a virtually identical progression rate of 16% per year.<sup>11</sup> The Alzheimer's Disease Cooperative Study suggested a therapeutic effect of donepezil for the first 12 months in all participants with MCI and up to 24 months for the apolipoprotein E  $\epsilon$ 4 carriers. However, because the study was designed to assess effects over 36 months, the ultimate outcome was negative.<sup>29</sup> A subsequent 48-week trial of donepezil alone failed to replicate the Alzheimer's Disease Cooperative Study results, and hence no treatments have been approved for MCI.<sup>60</sup>

## IMPLICATIONS

From a clinical trials perspective, if we were designing a disease-modifying therapeutic trial involving participants at the MCI stage, we could consider aMCI criteria of a degenerative pathogenesis and require positive imaging and biomarker data to enrich the clinical population to enhance the likelihood of progression to clinical AD. This could very well be consistent with the presumed therapeutic target of the agent. That is, if we were testing an amyloid-specific agent, we could use aMCI clinical criteria and stratify participants according to their apolipoprotein E  $\epsilon$ 4 carrier status, amyloid imaging, or markers of CSF involving amyloid to create a subset of participants who are more likely to progress rapidly and harbor the underlying amyloid pathological substrate.

## CHALLENGES

While the construct of MCI has engendered a great deal of attention (Figure 1), it has also raised a great deal of controversy. Much of the concern about the construct pertains to its heterogeneity, lack of specific ability to predict outcome, and vagueness of the criteria, eg, the degree of cognitive impairment in nonmemory cognitive domains and the degree of functional impairment. **Table 6** depicts many of the sources of variability in studies on MCI, and a few deserve mention.

The source of participants is a prominent aspect of variability in many of these studies. As mentioned earlier, participants from a referral clinic, memory disorders clinic, or AD center likely have a prior probability of having AD at the outset. On the contrary, participants who are recruited proactively through an epidemiologic procedure are likely more heterogeneous, have multiple medical comorbidities, and are "less pure" from an AD substrate perspective. These participants would cause more "noise" in the system if used in clinical trials but likely represent the reality of MCI in the population.

Several early studies retrospectively applied MCI criteria to previously collected data sets.<sup>16</sup> This approach necessitates the use of an algorithmic model to retrofit previously acquired neuropsychological data.

An issue inherent in the discussion of neuropsychological test scores pertains to the use of normative data on neuropsychological instruments and cutoff scores. It is important to emphasize that MCI is not just a neuropsychological entity. Although findings from neuropsy-

chological testing constitute a cornerstone of the objective assessment, the ultimate diagnosis involves more than just a set of cognitive test scores.

Two other sources of variability merit discussion. In longitudinal studies, the blinding of the investigators to the previous clinical diagnoses is important. If the investigators know that the participants were previously classified as having MCI, they would be less likely to label them as being cognitively normal on a subsequent visit. This approach is not necessarily inappropriate because it may reflect the natural variability of the clinical course of these participants and may actually consider this in the diagnostic process. However, in a research setting, previous knowledge can confound the interpretation of the data. Hence, investigators in many studies are blinded to previous clinical classifications. These types of studies lead to higher degrees of "reversion" to normal.

Finally, we need to address the issues of MCI as a clinical or pathological entity along with constructs of sensitivity and specificity. That is, when we make the diagnosis of MCI, does this diagnosis refer to the clinical state of the patient or to the underlying pathophysiological features leading to the symptoms, or both? It might be most productive to keep these entities separate.

#### CLINICAL IMPLICATIONS

These studies, coupled with the neuropathological findings, suggest that the clinical criteria for aMCI may designate a mildly impaired set of participants, many of whom, but not all, have the underlying neuropathological features of AD. These findings have implications for the labeling of the clinical condition of MCI and the design of future trials. It may be inappropriate to label participants at the aMCI stages as having AD, or even incipient or prodromal AD, because many will not eventually evolve to AD. Hence, we cannot afford to mislabel all participants with MCI as having AD features because this is the only label that they will perceive. In other words, participants and families will only "hear" the AD part of the label, yet we will be incorrectly labeling some of them because not all will progress to AD. Therefore, it might be preferable to use an etiologically neutral term such as "MCI," coupled with a suspected pathogenesis evidenced through history and ancillary testing, and explain to the participants the possibility that this term may imply development of AD in the future or might imply stability or, even less commonly, improvement in their clinical symptoms. This approach may be more consistent with the longitudinal data.

In 2001, the American Academy of Neurology published an evidence-based medicine practice parameter on MCI and recommended that physicians should identify and monitor patients with MCI because these persons had an increased risk of developing dementia.<sup>61</sup> At that time, this recommendation was based on relatively few longitudinal studies. Now, the literature has expanded greatly, and numerous prospectively designed longitudinal studies are available from which to draw conclusions. The American Academy of Neurology is repeating the evidence-based medicine exercise at present reassessing the clinical utility of MCI. In addition, to assess the clinical

acceptance of the construct, a recent survey by the American Academy of Neurology indicated that 80% of neurologists use the term "MCI" and find it relevant when describing this type of patient, implying that the construct of MCI is becoming clinically useful and is gaining more widespread acceptance.<sup>62</sup>

#### SUMMARY

The construct of MCI has influenced the field of aging and dementia in several significant spheres. It has focused the attention of investigators on the earlier prodromal states of many cognitive disorders. Research programs ranging from epidemiologic studies to explorations of the mechanisms of disease have been influenced by the construct of MCI, and these investigations will hopefully lead to more effective therapies. This work has stimulated discussions regarding new clinical criteria for conditions such as AD and will likely have an effect on the development of international classification systems for cognitive disorders.<sup>63</sup>

Ultimately, we hope that this work will lead to the development of imaging measures and biomarkers for assessing the asymptomatic stages of neurodegenerative diseases. By augmenting our knowledge of the role of imaging and biomarker measures in the MCI stage, we will be able to validate their utility when predicting the progression to more advanced stages of cognitive disorders and to suggest their further utility by being applied to the asymptomatic stages of these conditions. As such, MCI will have served an important role in advancing our understanding of disease mechanisms with the ultimate goal of finding preventive therapies.

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## REFERENCES

- Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. *Arch Neurol*. 2001;58(12):1985-1992.
- Molano J, Boeve B, Ferman T, et al. Mild cognitive impairment associated with limbic and neocortical Lewy body disease: a clinicopathological study. *Brain*. In press.
- Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999;56(3):303-308.
- Petersen RC. Conceptual overview. In: Petersen RC, ed. *Mild Cognitive Impairment: Aging to Alzheimer's Disease*. New York, NY: Oxford University Press; 2003:1-14.
- Gauthier S, Reisberg B, Zaudig M, et al; International Psychogeriatric Association Expert Conference on mild cognitive impairment. Mild cognitive impairment. *Lancet*. 2006;367(9518):1262-1270.
- Reisberg B, Ferris S, de Leon MJ, et al. Stage-specific behavioral, cognitive, and in vivo changes in community residing subjects with age-associated memory impairment and primary degenerative dementia of the Alzheimer type. *Drug Dev Res*. 1988;15(2-3):101-114.
- Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43(11):2412-2414.
- Visser PJ, Scheltens P, Verhey FR, et al. Medial temporal lobe atrophy and memory dysfunction as predictors for dementia in subjects with mild cognitive impairment. *J Neurol*. 1999;246(6):477-485.
- Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med*. 2004;256(3):240-246.
- Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2004;256(3):183-194.
- Petersen RC, Aisen PS, Beckett LA, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. *Neurology*. In press.
- Busse A, Hensel A, Guhne U, Angermeyer MC, Riedel-Heller SG. Mild cognitive impairment: long-term course of four clinical subtypes. *Neurology*. 2006;67(12):2176-2185.
- Ganguli M, Dodge HH, Shen C, DeKosky ST. Mild cognitive impairment, amnesic type: an epidemiologic study. *Neurology*. 2004;63(1):115-121.
- Larrieu S, Letenneur L, Orgogozo JM, et al. Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. *Neurology*. 2002;59(10):1594-1599.
- DeCarli C. Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. *Lancet Neurol*. 2003;2(1):15-21.
- Ritchie K, Artero S, Touchon J. Classification criteria for mild cognitive impairment: a population-based validation study. *Neurology*. 2001;56(1):37-42.
- Lopez OL, Jagust WJ, DeKosky ST, et al. Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 1. *Arch Neurol*. 2003;60(10):1385-1389.
- Roberts RO, Geda YE, Knopman D, et al. The Mayo Clinic Study of Aging: design and sampling, participation, baseline measures and sample characteristics. *Neuroepidemiology*. 2008;30(1):58-69.
- Unverzagt FW, Gao S, Baiyewu O, et al. Prevalence of cognitive impairment: data from the Indianapolis Study of Health and Aging. *Neurology*. 2001;57(9):1655-1662.
- Hänninen T, Hallikainen M, Tuomainen S, Vanhanen M, Soininen H. Prevalence of mild cognitive impairment: a population-based study in elderly subjects. *Acta Neurol Scand*. 2002;106(3):148-154.
- Palmer K, Bäckman L, Winglad B, Fratiglioni L. Mild cognitive impairment in the general population: occurrence and progression to Alzheimer disease. *Am J Geriatr Psychiatry*. 2008;16(7):603-611.
- Das SK, Bose P, Biswas A, et al. An epidemiologic study of mild cognitive impairment in Kolkata, India. *Neurology*. 2007;68(23):2019-2026.
- Di Carlo A, Lamassa M, Baldereschi M, et al. CIND and MCI in the Italian elderly: frequency, vascular risk factors, progression to dementia. *Neurology*. 2007;68(22):1909-1916.
- Fischer P, Jungwirth S, Zehetmayer S, et al. Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. *Neurology*. 2007;68(4):288-291.
- Manly JJ, Tang MX, Schupf N, Stern Y, Vonsattel JP, Mayeux R. Frequency and course of mild cognitive impairment in a multiethnic community. *Ann Neurol*. 2008;63(4):494-506.
- Plassman BL, Langa KM, Fisher GG, et al. Prevalence of cognitive impairment without dementia in the United States. *Ann Intern Med*. 2008;148(6):427-434.
- Roberts RO, Geda YE, Knopman DS, et al. Men are more likely to have mild cognitive impairment than women: the Mayo Clinic Study of Aging [abstract]. *Neurology*. 2008;70(11)(suppl 1):A225.
- Farias ST, Mungas D, Reed BR, Harvey D, DeCarli C. Progression of mild cognitive impairment to dementia in clinic- vs community-based cohorts. *Arch Neurol*. 2009;66(9):1151-1157.
- Petersen RC, Thomas RG, Grundman M, et al; Alzheimer's Disease Cooperative Study Group. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med*. 2005;352(23):2379-2388.
- Solfrizzi V, Panza F, Colacicco AM, et al; Italian Longitudinal Study on Aging Working Group. Vascular risk factors, incidence of MCI, and rates of progression to dementia. *Neurology*. 2004;63(10):1882-1891.
- Tschanz JT, Welsh-Bohmer KA, Lyketsos CG, et al; Cache County Investigators. Conversion to dementia from mild cognitive disorder: the Cache County Study. *Neurology*. 2006;67(2):229-234.
- Ravaglia G, Forti P, Montesi F, et al. Mild cognitive impairment: epidemiology and dementia risk in an elderly Italian population [published online ahead of print November 20, 2007]. *J Am Geriatr Soc*. 2008;56(11):51-58.
- Petersen RC, Smith GE, Ivnik RJ, et al. Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals. *JAMA*. 1995;273(16):1274-1278.
- Aggarwal NT, Wilson RS, Beck TL, Bienias JL, Berry-Kravis E, Bennett DA. The apolipoprotein E ε4 allele and incident Alzheimer's disease in persons with mild cognitive impairment. *Neurocase*. 2005;11(1):3-7.
- Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993;261(5123):921-923.
- Killiany RJ, Gomez-Isla T, Moss M, et al. Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. *Ann Neurol*. 2000;47(4):430-439.
- Jack CR Jr, Petersen RC, Xu YC, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology*. 1999;52(7):1397-1403.
- Fox NC, Scahill RI, Crum WR, Rossor MN. Correlation between rates of brain atrophy and cognitive decline in AD. *Neurology*. 1999;52(8):1687-1689.
- Jack CR Jr, Slomkowski M, Gracon S, et al. MRI as a biomarker of disease progression in a therapeutic trial of milameline for AD. *Neurology*. 2003;60(2):253-260.
- Kantarci K, Weigand SD, Petersen RC, et al. Longitudinal <sup>1</sup>H MRS changes in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging*. 2007;28(9):1330-1339.
- Jagust WJ, Landau SM, Shaw LM, et al. Relationships between biomarkers in aging and dementia. *Neurology*. 2009;73(15):1193-1199.
- Shaw LM, Korecka M, Clark CM, Lee VM, Trojanowski JQ. Biomarkers of neurodegeneration for diagnosis and monitoring therapeutics. *Nat Rev Drug Discov*. 2007;6(4):295-303.
- Hansson O, Zetterberg H, Buchhave P, Londo E, Blennow K, Minthon L. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. *Lancet Neurol*. 2006;5(3):228-234.
- Mattsson N, Zetterberg H, Hansson O, et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. *JAMA*. 2009;302(4):385-393.
- Shaw LM, Vanderstichele H, Knopik-Czajka M, et al; Alzheimer's Disease Neuroimaging Initiative. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Ann Neurol*. 2009;65(4):403-413.
- Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol*. 2004;55(3):306-319.
- Wolk DA, Price JC, Saxton JA, et al. Amyloid imaging in mild cognitive impairment subtypes [published correction appears in *Ann Neurol*. 2009;66(1):123]. *Ann Neurol*. 2009;65(5):557-568.
- Jack CR Jr, Lowe VJ, Senjem ML, et al. <sup>11</sup>C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnesic mild cognitive impairment. *Brain*. 2008;131(pt 3):665-680.
- Ewers M, Bokde A, Walsh C, Hampel H. Multidimensional biomarker-based diagnosis of early Alzheimer's disease. *Alzheimers Dement*. 2009;5(4):P136-P137.
- Jack CR Jr, Lowe VJ, Weigand SD, et al; Alzheimer's Disease Neuroimaging Initiative. Serial PiB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. *Brain*. 2009;132(pt 5):1355-1365.

51. Morris JC. Mild cognitive impairment is early-stage Alzheimer disease: time to revise diagnostic criteria. *Arch Neurol*. 2006;63(1):15-16.
52. Markesbery WR, Schmitt FA, Kryscio RJ, Davis DG, Smith CD, Wekstein DR. Neuropathologic substrate of mild cognitive impairment. *Arch Neurol*. 2006; 63(1):38-46.
53. Bennett DA, Schneider JA, Bienias JL, Evans DA, Wilson RS. Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions. *Neurology*. 2005;64(5):834-841.
54. Guillozet AL, Weintraub S, Mash DC, Mesulam MM. Neurofibrillary tangles, amyloid, and memory in aging and mild cognitive impairment. *Arch Neurol*. 2003; 60(5):729-736.
55. Petersen RC, Parisi JE, Dickson DW, et al. Neuropathologic features of amnesic mild cognitive impairment. *Arch Neurol*. 2006;63(5):665-672.
56. Jicha GA, Parisi JE, Dickson DW, et al. Neuropathological outcome of mild cognitive impairment following progression to clinical dementia. *Arch Neurol*. 2006; 63(5):674-681.
57. Feldman HH, Ferris S, Winblad B, et al. Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEX study [published correction appears in *Lancet Neurol*. 2007;6(10):849]. *Lancet Neurol*. 2007;6(6):501-512.
58. Thal LJ, Ferris SH, Kirby L, et al; Rofecoxib Protocol 078 study group. A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. *Neuropsychopharmacology*. 2005;30(6):1204-1215.
59. Winblad B, Gauthier S, Scinto L, et al; GAL-INT-11/18 Study Group. Safety and efficacy of galantamine in subjects with mild cognitive impairment. *Neurology*. 2008;70(22):2024-2035.
60. Doody RS, Ferris SH, Salloway S, et al. Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. *Neurology*. 2009;72(18):1555-1561.
61. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST; Report of the Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2001;56(9):1133-1142.
62. Roberts JS. Clinical practices regarding mild cognitive impairment (MCI) among neurology service providers. Paper presented at: International Conference on Alzheimer's Disease; July 2009; Vienna, Austria. [http://www.alz.org/icad/documents/abstracts/abstracts\\_phaseIII\\_ICAD09.pdf](http://www.alz.org/icad/documents/abstracts/abstracts_phaseIII_ICAD09.pdf).
63. Petersen RC, O'Brien J. Mild cognitive impairment should be considered for DSM-V. *J Geriatr Psychiatry Neurol*. 2006;19(3):147-154.

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