

- 1 Petersen, R. C., Aisen, P., Boeve, B. F., Geda, Y. E., Ivnik, R. J., Knopman, D. S. et al. (2013). Criteria for mild cognitive impairment due to Alzheimer's disease in the community. *Annals of Neurology*.
Notes: OBJECTIVE: The newly proposed National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for mild cognitive impairment (MCI) due to Alzheimer's disease (AD) suggest a combination of clinical features and biomarker measures, but their performance in the community is not known. METHODS: The Mayo Clinic Study of Aging (MCSA) is a population-based longitudinal study of non-demented subjects in Olmsted County, Minnesota. A sample of 154 MCI subjects from the MCSA was compared to a sample of 58 amnesic MCI subjects from the Alzheimer's Disease Neuroimaging Initiative 1 (ADNI 1) to assess the applicability of the criteria in both settings and to assess their outcomes. RESULTS: In the MCSA, 14% and in ADNI 1 16% of subjects were biomarker negative. In addition, 14% of the MCSA and 12% of ADNI 1 subjects had evidence for amyloid deposition only, while 43% of MCSA and 55% of ADNI 1 subjects had evidence for amyloid deposition plus neurodegeneration (MRI atrophy, FDG PET hypometabolism or both). However, a considerable number of subjects had biomarkers inconsistent with the proposed AD model, e.g., 29% of MCSA subjects and 17% of the ADNI 1 subjects had evidence for neurodegeneration without amyloid deposition. These subjects may not be on an AD pathway. Neurodegeneration appears to be a key factor in predicting progression relative to amyloid deposition alone. INTERPRETATION: The NIA-AA criteria apply to most MCI subjects in both the community and clinical trials settings however, a sizeable proportion of subjects had conflicting biomarkers which may be very important and need to be explored.
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- 3 Petersen, R. C., Aisen, P. S., Beckett, L. A., Donohue, M. C., Gamst, A. C., Harvey, D. J. et al. (2010). Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. *Neurology*, 74, 201-209.
Notes: BACKGROUND: Neuroimaging measures and chemical biomarkers may be important indices of clinical progression in normal aging and mild cognitive impairment (MCI) and need to be evaluated longitudinally. OBJECTIVE: To characterize cross-sectionally and longitudinally clinical measures in normal controls, subjects with MCI, and subjects with mild Alzheimer disease (AD) to enable the assessment of the utility of neuroimaging and chemical biomarker measures. METHODS: A total of 819 subjects (229 cognitively normal, 398 with MCI, and 192 with AD) were enrolled at baseline and followed for 12 months using standard cognitive and functional measures typical of clinical trials. RESULTS: The subjects with MCI were more memory impaired than the cognitively normal subjects but not as impaired as the subjects with AD. Nonmemory cognitive measures were only minimally impaired in the subjects with MCI. The subjects with MCI progressed to dementia in 12 months at a rate of 16.5% per year. Approximately 50% of the subjects with MCI were on antedementia therapies. There was minimal movement on the Alzheimer's Disease Assessment Scale-Cognitive Subscale for the normal control subjects, slight movement for the subjects with MCI of 1.1, and a modest change for the subjects with AD of 4.3. Baseline CSF measures of Abeta-42 separated the 3 groups as expected and successfully predicted the 12-month change in cognitive measures. CONCLUSION: The Alzheimer's Disease Neuroimaging Initiative has successfully recruited cohorts of cognitively normal subjects, subjects with mild cognitive impairment (MCI), and subjects with Alzheimer disease with anticipated baseline characteristics. The 12-month progression rate of MCI was as predicted, and the CSF measures heralded progression of clinical measures over 12 months
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- 4 Petersen, R. C., Roberts, R. O., Knopman, D. S., Geda, Y. E., Cha, R. H., Pankratz, V. S. et al. (2010). Prevalence of mild cognitive impairment is higher in men. The Mayo Clinic Study of Aging. *Neurology*, 75, 889-897.
Notes: OBJECTIVE: We investigated the prevalence of mild cognitive impairment (MCI) in Olmsted County, MN, using in-person evaluations and published criteria. METHODS: We evaluated an age- and sex-stratified random sample of Olmsted County residents who were 70-89 years old on October 1, 2004, using the Clinical Dementia Rating Scale, a neurologic evaluation, and neuropsychological testing to assess 4 cognitive domains: memory, executive function, language, and visuospatial skills. Information for each participant was reviewed by an adjudication panel and a diagnosis of normal cognition, MCI, or dementia was made using published criteria. RESULTS: Among 1,969 subjects without dementia, 329 subjects had MCI, with a prevalence of 16.0% (95% confidence interval [CI] 14.4-17.5) for any MCI, 11.1% (95% CI 9.8-12.3) for amnesic MCI, and 4.9% (95% CI 4.0-5.8) for nonamnesic MCI. The prevalence of MCI increased with age and was higher in men. The prevalence odds ratio (OR) in men was 1.54 (95% CI 1.21-1.96; adjusted for age, education, and nonparticipation). The prevalence was also higher in subjects who never married and in subjects with an APOE epsilon3epsilon4 or epsilon4epsilon4 genotype. MCI prevalence decreased with increasing number of years of education (p for linear trend <0.0001). CONCLUSIONS: Our study suggests that approximately 16% of elderly subjects free of dementia are affected by MCI, and amnesic MCI is the most common type. The higher prevalence of MCI in men may suggest that women transition from normal cognition directly to dementia at a later age but more abruptly
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- 5 Petersen, R. C., Roberts, R. O., Knopman, D. S., Boeve, B. F., Geda, Y. E., Ivnik, R. J. et al. (2009). Mild cognitive impairment: ten years later. *Archives of Neurology*, 66, 1447-1455.
Notes: 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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- 6 Petersen, R. C. & Negash, S. (2008). Mild cognitive impairment: an overview. *CNS Spectrum*, 13, 45-53.
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Mild cognitive impairment (MCI) refers to the transitional state between the cognitive changes of normal aging and very early dementia. MCI has generated a great deal of research from both clinical and research perspectives. Several population- and community-based studies have documented an accelerated rate of progression to dementia and Alzheimer's disease in individuals diagnosed with MCI. Clinical subtypes of MCI have been proposed to broaden the concept and include prodromal forms of a variety of dementias. An algorithm is presented to assist the clinician in identifying subjects and subclassifying them into the various types of MCI. Progression factors, including genetic, neuroimaging, biomarker, and clinical characteristics, are discussed. Neuropathological studies indicating an intermediate state between normal aging and early dementia in subjects with MCI are presented. The recently completed clinical trials as well as neuropsychological and nutritional interventions are discussed. Finally, the clinical utility of MCI, and directions for future research are proposed

- 7 Petersen, R. C. (2007). Mild cognitive impairment: current research and clinical implications. *Seminars in Neurology*, 27, 22-31.
Notes: Mild cognitive impairment refers to the transitional state between the cognitive changes of normal aging and the fully developed clinical features of dementia. This topic has received a great deal of attention in the literature in recent years and is being proposed for clinical applications as well. Clinical guidelines, including the original memory-focused criteria and the more recent broadly defined set of criteria, will be presented. The clinical outcome of individuals with mild cognitive impairment will be discussed and several explanations for variability in the literature will be considered. Predictors of progression, including genetic, neuroimaging, biomarker, and clinical characteristics, will be presented, as will the controversies regarding the underlying neuropathology of mild cognitive impairment. The recently completed mild cognitive impairment clinical trials will be discussed and the lessons learned from them translated into recommendations for future investigations. Finally, the clinical utility of mild cognitive impairment, its incorporation into clinical practice, and directions for future research will be proposed
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- 9 Petersen, R. C., Parisi, J. E., Dickson, D. W., Johnson, K. A., Knopman, D. S., Boeve, B. F. et al. (2006). Neuropathologic features of amnesic mild cognitive impairment. *Archives of Neurology*, 63, 665-672.
Notes: Alzheimer's Disease Research Center and Department of Neurology, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA. peter8@mayo.edu
BACKGROUND: The neuropathologic substrate of amnesic mild cognitive impairment (aMCI) is not known. OBJECTIVE: To determine the neuropathologic features of patients who died while their clinical classification was aMCI. DESIGN: Cohort study. SETTING: Community based. PARTICIPANTS: Sixty-six individuals, including 15 who had memory impairment beyond that allowed for aging but who were not demented, were studied along with 28 clinically healthy individuals and 23 patients with probable Alzheimer disease (AD) for comparison. MAIN OUTCOME MEASURES: Standard neuropathologic techniques and classification according to Khachaturian, Consortium to Establish a Registry for Alzheimer Disease, and National Institute on Aging-Reagan criteria were used to analyze autopsy tissue from 15 individuals who died while their clinical diagnosis was aMCI. For comparison, autopsy data on age-matched groups of clinically healthy individuals and patients with probable AD were analyzed. RESULTS: Most patients with aMCI did not meet the neuropathologic criteria for AD, but their pathologic findings suggest a transitional state of evolving AD. All the patients with aMCI had pathologic findings involving medial temporal lobe structures, likely accounting for their memory impairment. In addition, there were many concomitant pathologic abnormalities, including argyrophilic grain disease, hippocampal sclerosis, and vascular lesions. CONCLUSIONS: The neuropathologic features of aMCI matched the clinical features and seemed to be intermediate between the neurofibrillary changes of aging and the pathologic features of very early AD
- 10 Petersen, R. C. (2006). Alzheimer disease and mild cognitive impairment. In J.H.Noseworthy (Ed.), *Neurological therapeutics: Principles and practice*, Vol.3 (2 ed., pp. 3137-3155). Abingdon, UK: Informa Healthcare.
Notes: From Section XIV: Neurobehavioral disorders: Cognitive rehabilitation, behavioral management and pharmacologic therapies. Section editor: Kenneth M. Heilman
- 11 Petersen, R. C., Thomas, R. G., Grundman, M., Bennett, D., Doody, R., Ferris, S. et al. (2005). Vitamin E and donepezil for the treatment of mild cognitive impairment. *New England Journal of Medicine*, 352, 2379-2388.
BACKGROUND: Mild cognitive impairment is a transitional state between the cognitive changes of normal aging and early Alzheimer's disease. METHODS: In a double-blind study, we evaluated subjects with the amnesic subtype of mild cognitive impairment. Subjects were

randomly assigned to receive 2000 IU of vitamin E daily, 10 mg of donepezil daily, or placebo for three years. The primary outcome was clinically possible or probable Alzheimer's disease; secondary outcomes were cognition and function. RESULTS: A total of 769 subjects were enrolled, and possible or probable Alzheimer's disease developed in 212. The overall rate of progression from mild cognitive impairment to Alzheimer's disease was 16 percent per year. As compared with the placebo group, there were no significant differences in the probability of progression to Alzheimer's disease in the vitamin E group (hazard ratio, 1.02; 95 percent confidence interval, 0.74 to 1.41; P=0.91) or the donepezil group (hazard ratio, 0.80; 95 percent confidence interval, 0.57 to 1.13; P=0.42) during the three years of treatment. Prespecified analyses of the treatment effects at 6-month intervals showed that as compared with the placebo group, the donepezil group had a reduced likelihood of progression to Alzheimer's disease during the first 12 months of the study (P=0.04), a finding supported by the secondary outcome measures. Among carriers of one or more apolipoprotein E epsilon4 alleles, the benefit of donepezil was evident throughout the three-year follow-up. There were no significant differences in the rate of progression to Alzheimer's disease between the vitamin E and placebo groups at any point, either among all patients or among apolipoprotein E epsilon4 carriers. CONCLUSIONS: Vitamin E had no benefit in patients with mild cognitive impairment. Although donepezil therapy was associated with a lower rate of progression to Alzheimer's disease during the first 12 months of treatment, the rate of progression to Alzheimer's disease after three years was not lower among patients treated with donepezil than among those given placebo.

- 12 Petersen, R. C. (2003). Conceptual overview. In R.C.Petersen (Ed.), *Mild cognitive impairment. Aging to Alzheimer's disease* (pp. 1-14). New York: Oxford University Press.
- 13 Petersen, R. C. & et al. (2003). Mild cognitive impairment update 2002. In K.Iqbal & B. Winblad (Eds.), *Alzheimer's disease and related disorders: Research advances* (pp. 111-119). Bucharest: Ana Aslan International Academy of Aging.
- 14 Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V. et al. (2001). Current concepts in mild cognitive impairment. *Archives of Neurology*, 58, 1985-1992. The field of aging and dementia is focusing on the characterization of the earliest stages of cognitive impairment. Recent research has identified a transitional state between the cognitive changes of normal aging and Alzheimer's disease (AD), known as mild cognitive impairment (MCI). Mild cognitive impairment refers to the clinical condition between normal aging and AD in which persons experience memory loss to a greater extent than one would expect for age, yet they do not meet currently accepted criteria for clinically probable AD. When these persons are observed longitudinally, they progress to clinically probable AD at a considerably accelerated rate compared with healthy age-matched individuals. Consequently, this condition has been recognized as suitable for possible therapeutic intervention, and several multicenter international treatment trials are under way. Because this is a topic of intense interest, a group of experts on aging and MCI from around the world in the fields of neurology, psychiatry, geriatrics, neuropsychology, neuroimaging, neuropathology, clinical trials, and ethics was convened to summarize the current state of the field of MCI. Participants reviewed the world scientific literature on aging and MCI and summarized the various topics with respect to available evidence on MCI. Diagnostic criteria and clinical outcomes of these subjects are available in the literature. Mild cognitive impairment is believed to be a high-risk condition for the development of clinically probable AD. Heterogeneity in the use of the term was recognized, and subclassifications were suggested. While no treatments are recommended for MCI currently, clinical trials regarding potential therapies are under way. Recommendations concerning ethical issues in the diagnosis and the management of subjects with MCI were made
- 15 Petersen, R. C. (2000). Mild cognitive impairment or questionable dementia? [editorial; comment]. *Archives of Neurology*, 57, 643-644.

- 16 Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Archives of Neurology*, 56, 303-308.
Notes: Department of Neurology, Mayo Clinic, Rochester, Minn 55905, USA ; ABSTRACT: BACKGROUND: Subjects with a mild cognitive impairment (MCI) have a memory impairment beyond that expected for age and education yet are not demented. These subjects are becoming the focus of many prediction studies and early intervention trials. OBJECTIVE: To characterize clinically subjects with MCI cross- sectionally and longitudinally. DESIGN: A prospective, longitudinal inception cohort. SETTING: General community clinic. PARTICIPANTS: A sample of 76 consecutively evaluated subjects with MCI were compared with 234 healthy control subjects and 106 patients with mild Alzheimer disease (AD), all from a community setting as part of the Mayo Clinic Alzheimer's Disease Center/Alzheimer's Disease Patient Registry, Rochester, Minn. MAIN OUTCOME MEASURES: The 3 groups of individuals were compared on demographic factors and measures of cognitive function including the Mini-Mental State Examination, Wechsler Adult Intelligence Scale-Revised, Wechsler Memory Scale- Revised, Dementia Rating Scale, Free and Cued Selective Reminding Test, and Auditory Verbal Learning Test. Clinical classifications of dementia and AD were determined according to the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria, respectively. RESULTS: The primary distinction between control subjects and subjects with MCI was in the area of memory, while other cognitive functions were comparable. However, when the subjects with MCI were compared with the patients with very mild AD, memory performance was similar, but patients with AD were more impaired in other cognitive domains as well. Longitudinal performance demonstrated that the subjects with MCI declined at a rate greater than that of the controls but less rapidly than the patients with mild AD. CONCLUSIONS: Patients who meet the criteria for MCI can be differentiated from healthy control subjects and those with very mild AD. They appear to constitute a clinical entity that can be characterized for treatment interventions
- 17 Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Kokmen, E., & Tangelos, E. G. (1997). Aging, memory, and mild cognitive impairment. *International Psychogeriatrics*, 9 Suppl 1, 65-69.
Notes: Department of Neurology, Mayo Clinic, Rochester, MN 55905, USA ; ABSTRACT: In recent years, patients who are at high risk for developing Alzheimer's disease (AD) have become a focus of study. Several research groups have identified these patients, developed diagnostic criteria, and followed the patients longitudinally. These patients therefore constitute a clinical entity that is suitable for therapeutic interventions. In this article, we report our 5-year experience at the Mayo Clinic in characterizing a group of patients with mild cognitive impairment. These subjects were recruited from community-dwelling individuals who were receiving general medical care in the Department of Internal Medicine. They received the diagnosis of mild cognitive impairment if they met the following criteria: (a) complaint of defective memory, (b) normal activities of daily living, (c) normal general cognitive function, (d) abnormal memory function for age, and (e) absence of dementia. In following more than 75 of these patients, some of whom have been studied for as long as 5 years, it appears that approximately 10% to 15% of the subjects evolve to AD each year. We therefore evaluated the cognitive profiles of these patients at the time of their initial diagnosis in an attempt to predict who would remain stable and who would evolve to AD. Certain features of learning and memory performance indicated patients who were more likely to progress, but the strongest predictor was their apolipoprotein E status. The patients who possessed an epsilon 4 allele were more likely to convert to AD at a more rapid rate than those who were not carriers. Our results and similar data from other study groups indicate that diagnostic criteria can be defined for patients who are likely to convert to AD; the natural history of these patients is becoming apparent, and variables that predict ultimate conversion can be defined. Consequently, patients with mild cognitive impairment constitute an important group for study, particularly from the aspect of therapeutic interventions.

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- 19 Petersen, R. C. & Weingartner, H. (1991). Memory nomenclature. In T. Yanagihara & R. C. Petersen (Eds.), *Memory disorders. Research and clinical practice* (pp. 9-20). New York: Marcel Dekker.
(short concise descriptions of terms)