Outcomes of Mild Cognitive Impairment by Definition

A Population Study

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**Background:** Mild cognitive impairment (MCI) has been defined in several ways.

**Objective:** To determine the 1-year outcomes of MCI by different definitions at the population level.

**Design:** Inception cohort with 1-year follow-up. Participants were classified as having MCI using the following definitions operationalized for this study: amnestic MCI by Mayo criteria, expanded MCI by International Working Group criteria, Clinical Dementia Rating (CDR) = 0.5, and a purely cognitive classification into amnestic and nonamnestic MCI.

**Setting:** General community.

**Participants:** Stratified random population-based sample of 1982 individuals 65 years and older.

**Main Outcome Measures:** For each MCI definition, there were 3 possible outcomes: worsening (progression to dementia [CDR $\geq 1$] or severe cognitive impairment), improvement (reversion to CDR = 0 or normal cognition), and stability (unchanged CDR or cognitive status).

**Results:** Regardless of MCI definition, over 1 year, a small proportion of participants progressed to CDR $> 1$ (range, 0%-3%) or severe cognitive impairment (0%-20%) at rates higher than their cognitively normal peers. Somewhat larger proportions of participants improved or reverted to normal (6%-53%). Most participants remained stable (29%-92%). Where definitions focused on memory impairment and on multiple cognitive domains, higher proportions progressed and lower proportions reverted on the CDR.

**Conclusions:** As ascertained by several operational definitions, MCI is a heterogeneous entity at the population level but progresses to dementia at rates higher than in normal elderly individuals. Proportions of participants progressing to dementia are lower and proportions reverting to normal are higher than in clinical populations. Memory impairments and impairments in multiple domains lead to greater progression and lesser improvement. Research criteria may benefit from validation at the community level before incorporation into clinical practice.

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nition used, we now report 1-year outcomes of MCI according to these multiple definitions.

**METHODS**

**STUDY AREA, SAMPLING, AND RECRUITMENT**

The Monongahela-Youghiogheny Healthy Aging Team study cohort was an age-stratified random sample of the population aged 65 years and older drawn from the publicly available voter registration list for a small-town region of Pennsylvania. Community outreach, recruitment, and assessment protocols were approved by the University of Pittsburgh institutional review board for the protection of human subjects. The recruitment criteria were (1) age 65 years or older, (2) living in the selected towns, and (3) not already in long-term care institutions. Individuals were ineligible if they (1) were too ill to participate, (2) had severe vision or hearing impairments, or (3) were decisionally incapacitated. In a 2-year period, 2036 individuals were recruited.

**ASSESSMENT AND CLASSIFICATION (OVERVIEW)**

Trained interviewers obtained written informed consent and administered the Mini-Mental State Examination (MMSE) and scored it immediately, applying a standard correction for age and education. We classified 54 individuals (2.7%) scoring less than 21 of 30 (age and education corrected) as moderately or severely impaired and, thus, unsuited to a study of mild impairment; we did not assess them further. Having designated the remaining 1982 participants as cognitively normal or only mildly impaired, we immediately performed detailed assessments; a year later, we invited the participants to undergo repeated assessments. At each assessment, we classified participants according to several criteria for MCI: the CDR, a purely cognitive classification, and the standard Mayo and IWG criteria. All the results reported herein refer to our operational definitions of these criteria.

**NEUROPSYCHOLOGICAL ASSESSMENT**

We assessed cognitive functioning using a comprehensive test battery on which we have reported population-based norms also available on the study Web site (http://www.wpic.pitt.edu/research/dementia_epidemiology/MYHAT/MYHATHomePage.htm). We categorized these tests according to the principal cognitive domains that they tap (attention/processing speed, executive function, language, memory, and visuospatial function) and created a composite score for each domain.

**CLINICAL DEMENTIA RATING**

Appropriately certified interviewers rated participants on the CDR scale using an assessment protocol composed of standardized questions and observations regarding everyday functioning in the 6 areas of memory, orientation, judgment, home and hobbies, community affairs, and personal care. Most of these normal or only mildly impaired older adults provided their own self-report information and did not have surrogate informants; thus, this CDR may be considered a field adaptation for population settings. The CDR for each participant was finalized by consensus among 2 or more interviewers, ignoring the neuropsychological data but determining that the reported or observed functional impairments were attributable to cognitive rather than, for example, sensory or motor difficulties.

**COGNITIVE CLASSIFICATION**

To complement the purely functionally based CDR, we developed a solely neuropsychologically based cognitive classification. Based on normative reference points, we classified participants as follows: (1) cognitively normal: composite scores in all domains within 1.0 SD of the mean for the individual’s age/sex/education group; (2) severe cognitive impairment: composite scores in at least 2 domains 2.0 SDs below the mean for the appropriate reference group; (3) MCI single domain: composite score in 1 domain greater than 1.0 SD below the mean, with all other domains in the normal range; and (4) MCI multidomain: composite scores in 2 or more domains 1.0 to 2.0 SDs below the appropriate mean or no more than 1 domain composite greater than 2.0 SDs below the mean with other domains 1.0 to 2.0 SDs below the mean. We also explored a “narrow” variation of these definitions, using a more stringent MCI threshold of 1.5 SDs rather than 1.0 SD below the mean, eliminating those with scores between 1.0 and 1.5 SDs.

**STANDARD MCI CRITERIA**

For the Mayo criteria for amnestic MCI1 and the expanded IWG criteria, we operationalized the objective cognitive deficit criteria as in the cognitive classification described previously herein (the memory domain alone for Mayo MCI and any domain for IWG MCI). For subjective reports and concerns, we operationalized the Mayo criteria as at least 2 items (median score) endorsed from a list of 16 “remembering” questions; for the IWG criteria, we included an additional 5 questions on “non-remembering” functions. We defined absence of dementia as CDR < 1, essentially normal daily functioning as no impaired instrumental activities of daily living on the Older Americans Resources and Services scale, and essentially normal mental status as an MMSE score of at least 21. Details have been reported previously.

Because the original Mayo criteria did not specify that domains other than memory could be impaired, we operationalized them as requiring isolated (single-domain) memory deficit. Subsequently, we also explored a multidomain definition, having been advised by a coauthor (R.C.P.) that the Mayo group included individuals with impairments in additional domains. We also examined the effects of (1) raising the MMSE score threshold from at least 21 at the 5th percentile of the original cohort to greater than 23 at its 10th percentile, thus eliminating those with scores of 21 to 23, and (2) lowering the cognitive composite threshold from 1.0 to 1.5 SDs below the appropriate mean. Because both of these changes reduce the number of people classified as having MCI, we refer to them as “narrow versions.”

**STATISTICAL ANALYSIS**

For each baseline MCI group, we identified 2 outcome variables at follow-up: CDR and the cognitive classification. For each outcome, we examined 3 possibilities:

1. Worsening: progression to CDR = 1 (dementia) in individuals with baseline CDR < 1 or severe cognitive impairment (defined previously herein) in persons with baseline cognitive classification of normal or MCI.
2. Improvement: reversion to CDR = 0 (no dementia) in those with baseline CDR = 0.5 or normal cognition (defined previously herein) in those with baseline cognitive classification of MCI.
3. Stability: no change in CDR or cognitive classification.

We compared proportions of participants experiencing these 6 outcomes using the 1-sample proportion z test at P < .05. This
At baseline, all 1982 cohort members with normal or mildly impaired cognition (MMSE score ≥21) were rated on the CDR; 1941 participants had sufficient neuropsychological data to be classified by the cognitive definitions; 1950 and 1937 participants provided sufficient cognitive, functional (instrumental activities of daily living), and subjective report data to be classified by the Mayo1 and IWG2 criteria, respectively. Proportions of participants meeting these criteria, corresponding to the published prevalence estimates,3,5 and their demographic characteristics were identified (Table 1). Note that the MCI definitions overlap: the Mayo criteria are a subset of the IWG criteria, and both overlap with the CDR; the 4 cognitive classification subgroups are mutually exclusive with one another but overlap with the CDR and the Mayo and IWG criteria. Of 697 individuals with MCI by the cognitive classification, 433 (62.1%) had CDR=0; most of these participants (n=316) had nonamnestic single-domain impairment. Of 45 participants meeting the Mayo criteria, 13 (28.9%) had CDR=0; of 350 participants meeting the IWG criteria, 143 (40.9%) had CDR=0. As expected, the narrow versions reduced baseline prevalence for the standard and cognitive criteria. Some individuals were classified as having MCI under the original versions and as normal under the narrow versions; others originally classified as having multidomain MCI were reclassified as having single-domain MCI.

Participants who met the operationalized Mayo criteria were significantly younger than were those with CDR=0.5, were more likely to be men, and had more education than did those classified by the IWG criteria, by CDR=0.5, and by the cognitive classification. Those fulfilling the IWG criteria were significantly younger and better educated than were those with CDR=0.5. The narrow versions of the criteria had minimal effects on the demographics of MCI (Table 1).

At 1-year follow-up, 1697 of the original 1982 cohort members (85.6%) underwent repeated assessment. The total attrition of 14.4% represented 3% from mortality and 11.4% from other causes, including relocation, illness, and elective dropout. The 285 attrited individuals were significantly older (78.7 vs 77.5 years, P<.02) and were less likely to be women (55.1% vs 62.1%, P<.03) than were those who were seen at follow-up, with no significant difference in educational level (16.8% and 13.3% with less than a high school
Compared with participants who were reassessed, those lost to follow-up had slightly but significantly lower mean (SD) baseline MMSE scores (26.4 [2.7] vs 27.0 [2.4]), had a lower proportion with baseline CDR=0 (60.0% vs 73.2%), and were significantly more likely to be classified at baseline by the CDR and all the cognitive definitions except multidomain amnestic MCI (P<.001 for all).

1-YEAR CDR OUTCOMES

Progression to CDR=1 ranged from 0% for purely cognitive nonamnestic multidomain MCI to 2.8% for the Mayo criteria, noting that the latter represents only 1 participant. Reversion to CDR=0 ranged from 10.8% in those with baseline amnestic multidomain MCI (and CDR=0.5) to 26.5% in those with nonamnestic single-domain MCI (and CDR=0.5). The stability of the CDR was uniformly high across groups, ranging from 72% for CDR=0.5 and the Mayo criteria and 78% for the purely cognitive amnestic single-domain MCI to 80% to 88% for all other definitions (Table 2).

1-YEAR COGNITIVE OUTCOMES

Progression to severe cognitive impairment ranged from 1.1% for purely cognitive nonamnestic single-domain MCI to 19.8% for amnestic multidomain MCI. Reversion to cognitively normal ranged from 6.3% for purely cognitive amnestic multidomain MCI to 53.4% for nonamnestic single-domain MCI. Cognitive classification stability ranged from 28.6% for the nonamnestic single-domain category to 54.3% for CDR=0.5 (Table 3).

VARYING THE DEFINITIONS

Expanding the Mayo MCI criteria by allowing impairment in additional domains besides memory increased baseline prevalence from 2.27% to 6.21%, that is, 123 individuals (of whom 96 completed follow-up). Seventy of these participants had baseline CDR=0.5, of whom 1 (1.4%) progressed to CDR=1 at follow-up, 8 (11.4%) reverted to CDR=0, and 61 (87.1%) remained at CDR=0.5. Of 26 participants with baseline CDR=0, 7 (26.9%) progressed to CDR=0.5 and none to CDR=1, whereas 19 (73.1%) were stable at CDR=0. Overall, progression from a lower to a higher CDR level was seen in 8 individuals (8.3%).

Narrowing the definitions by raising the MMSE score threshold to 24 (Mayo and IWG criteria) and by lowering the cognitive threshold to 1.5 SDs below the appropriate mean (Mayo, IWG, and cognitive classification) in reducing prevalence also reduced the denominator for calculating proportions with the different outcomes (eTable 1 and eTable 2; http://www.archneurol.com). Although the actual numbers were mostly too small to be compared for statistical significance, the overall pattern was that the narrow definitions very slightly increased the proportions that worsened, reduced the proportions that improved on CDR, reduced sensitivity, and increased specificity.

ATTRITION EFFECTS: SENSITIVITY ANALYSES

The actual outcomes of those lost to follow-up are not knowable. In the worst case, if all attrited participants with baseline MCI had remained in the study and worsened, expanding the Mayo MCI criteria by allowing impairment in additional domains besides memory increased baseline prevalence in the worst case, if all attrited participants with baseline MCI had remained in the study and worsened, the proportion that progressed to CDR=1 would be 10% (72 individuals). Reversion to CDR=0 would be 49% (43 individuals). The proportion that remained stable would be 41% (36 individuals).

Table 2. One-Year Outcomes of MCI Defined by CDR3,a

<table>
<thead>
<tr>
<th>MCI Definition at Baseline</th>
<th>With Baseline CDR &lt; 1 Also Assessed at Follow-up</th>
<th>Worsened to CDR ≥ 1</th>
<th>Unchanged</th>
<th>With Baseline CDR=0.5</th>
<th>Improved From CDR=0.5 to CDR=0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Mayo criteria (operational definitions)1,2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mayo criteria1</td>
<td>36</td>
<td>1 (2.8)</td>
<td>26 (72.2)</td>
<td>23</td>
<td>4 (17.4)</td>
</tr>
<tr>
<td>IWG criteria2</td>
<td>290</td>
<td>2 (0.7)b</td>
<td>232 (80.0)c</td>
<td>164</td>
<td>30 (18.3)</td>
</tr>
<tr>
<td>Cognitive classification15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amnestic single-domain MCI</td>
<td>72</td>
<td>1 (1.4)</td>
<td>56 (77.8)</td>
<td>26</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td>Amnestic multidomain MCI</td>
<td>114</td>
<td>2 (1.8)</td>
<td>100 (87.7)c,d</td>
<td>65</td>
<td>7 (10.8)</td>
</tr>
<tr>
<td>Any amnestic MCI</td>
<td>186</td>
<td>3 (1.6)</td>
<td>156 (83.9)b</td>
<td>91</td>
<td>11 (12.1)</td>
</tr>
<tr>
<td>Nonamnestic single-domain MCI</td>
<td>267</td>
<td>2 (0.8)b</td>
<td>230 (86.1)c,d</td>
<td>68</td>
<td>18 (26.5)c</td>
</tr>
<tr>
<td>Nonamnestic multidomain MCI</td>
<td>119</td>
<td>0 (0.0)</td>
<td>101 (84.9)c,e</td>
<td>48</td>
<td>7 (14.6)</td>
</tr>
<tr>
<td>Any nonamnestic MCI</td>
<td>386</td>
<td>2 (0.5)b</td>
<td>331 (85.6)c,d</td>
<td>116</td>
<td>25 (21.6)</td>
</tr>
<tr>
<td>Any cognitively defined MCI</td>
<td>572</td>
<td>5 (0.9)b</td>
<td>487 (85.1)c,d</td>
<td>207</td>
<td>36 (17.4)</td>
</tr>
<tr>
<td>Normal cognition (for comparison)</td>
<td>1054</td>
<td>1 (0.1)b,e</td>
<td>925 (87.8)c,d</td>
<td>200</td>
<td>75 (37.5)c,d</td>
</tr>
<tr>
<td>CDR (field-adapted version)3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDR = 0.5</td>
<td>440</td>
<td>8 (1.8)d</td>
<td>318 (72.3)e</td>
<td>440</td>
<td>114 (25.9)c,d</td>
</tr>
<tr>
<td>CDR = 0 (for comparison)</td>
<td>1242</td>
<td>1 (0.8)b,e</td>
<td>1137 (91.5)c,d</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: CDR, Clinical Dementia Rating; IWG, International Working Group; MCI, mild cognitive impairment; NA, not applicable.

a Proportions were compared for significant differences using the 1-sample z test (P<.05).
b Significantly lower than the Mayo criteria.
c Significantly higher than the Mayo criteria.
d Significantly higher than the IWG criteria.
e Significantly lower than the IWG criteria.
In a randomly sampled population-based cohort, the baseline prevalence of MCI varied by definition, as would be expected with any syndromic entity. During 1-year follow-up, the same MCI definitions led to different proportions of progression (worsening), reversion (improvement), and stability. Because the various criterion sets overlap only partially, individuals can be classified as impaired by one definition and as normal by another. For example, with the Mayo criteria defined as including CDR=1, individuals with MCI could be either CDR=0 or CDR=0.5; among these, only those at CDR=0.5 can revert to CDR=0. Similarly, by designating worsening as progression to CDR=1, we could be underestimating progression by not including worsening from CDR=0 to CDR=0.5.

With the previous caveats, across MCI definitions, relatively small proportions of participants (0%-3%) progressed to dementia defined as CDR=1 but at significantly higher rates than did those with normal cognition. Progression was most likely to be seen in the definitions that emphasized memory. Larger proportions of participants (up to 20%) were found to worsen when the outcome was defined as severe cognitive impairment; again, MCI definitions with amnestic components showed the highest progression. In the purely cognitive classification, multidomain amnestic impairment showed more progression than did single-domain amnestic impairment, whereas nonamnestic impairments had the lowest progression.

Greater proportions of individuals with baseline MCI showed improvement compared with worsening at 1-year follow-up. With CDR=0 as the outcome, the range of reversion was approximately a quarter of those with baseline CDR=0.5 alone. When reversion was characterized as normal cognition, the lowest proportion reverted from amnestic multidomain MCI (which also had the highest proportion progressing to severe cognitive impairment). Although reversion in the purely cognitive definition could be attributed to instability of measurement or intraindividual variability, the same phenomenon was also observed for the functional (CDR) and combined cognitive-functional (Mayo and IWG) definitions.

However, the most frequent outcome was stability, that is, no change in MCI status. These proportions ranged from 72% to 88% for stable CDR and from 29% to 55% for stable MCI by broad cognitive classification. The single-domain MCIs, whether amnestic or nonamnestic, were the least likely to remain cognitively unchanged, whereas the CDR=0.5 group was the most likely to remain cognitively unchanged.

The present cohort study indicates, as have previous studies, that the MCI syndrome is a heterogeneous entity at the population level regardless of definition.
A small proportion progresses to dementia or severe cognitive impairment, a somewhat larger proportion reverts to normal, and most remain unchanged. Most individuals with mild impairment remain at least mildly impaired. Some individuals who meet MCI criteria may have always functioned at a mildly impaired level, invoking the concept of "accidental MCI." The heterogeneity in outcome observed herein is greater than that reported from clinical settings, where individuals seek care for cognitive impairment and where progression occurs at a rate of 12% to 15% annually.13

Heterogeneity in outcome suggests heterogeneity in the underlying pathology. Definitions of MCI that reflect impairment in memory predicted more progression and less reversion than did impairment in other domains, regardless of whether the definition was neuropsychological, functional, or both. Because memory deficits are the hallmark of dementing disorders, such as Alzheimer disease, MCI definitions centered on memory may be identifying individuals in the early stages of these disorders, which may be in the minority at the population level.

Finally, the present data indicate that mild impairment in 1 domain, memory or otherwise, is more likely to predict reversion to normal than is mild impairment in 2 or more domains, as was also observed in another population study.25 This source of variation could represent heterogeneity in etiology or in stage along the course of a given disease. For example, an individual with a nonprogressive condition, such as depression, medication adverse effects, or hypoxia, might experience transient or reversible cognitive impairment that reflects resolution of the underlying condition. Alternatively, a person at a very early stage of Alzheimer disease might not manifest cognitive deficits unless a second condition is also present; if the second condition resolves, improvement might be noted temporarily. Furthermore, a person with any progressive dementia may experience lability or "wobble" in function and performance early in the disease course, before the deficits become more pervasive and sustained, and this intrindividual variability itself may reflect underlying brain disease.26 Compared with single-domain impairments, impairment in 2 domains suggests a greater likelihood of underlying disease, which has reached a later stage, closer to the dementia threshold. Even in the normal range of cognition, poorer neuropsychological test scores predict subsequent decline in CDR.20 In the present cohort, as in clinical practice, a minority of individuals did not return for follow-up assessment at 1 year because of death, relocation, illness, or elective dropout. At study entry, these individuals were older, less educated, and more cognitively impaired than were those who were followed up. Had they remained in the study and experienced worsening in large enough proportions, they may have increased the progression rates for most but not all MCI definitions.

Although 1 year is a relatively short period in which to observe MCI outcomes, it mirrors clinical practice wherein the first annual follow-up is often essential to validate the original diagnosis. Although longer prospective studies usually report annual progression rates averaged over multiple years,3,8,12,14 the annual rate changes over time.12 Repeated assessments of this cohort over a longer follow-up period will clarify these patterns and identify the profiles of individuals whose mild impairments are likely to develop into dementia eventually. The incorporation of biomarker and risk factor assessments may further improve the characterization of MCI at the population level.

Population-based cohorts experience less selection bias and are more representative of the community than are specialty clinic samples. Being large, they are powered to detect relatively small effects. However, participants recruited randomly from the community are not necessarily concerned about their cognition; their subjective reports ("complaints") are not spontaneously offered but rather are elicited by standardized questions and may vary in clinical and prognostic significance. Normal or mildly impaired individuals in the community who are not seeking care for cognitive difficulties may not have surrogate informants more knowledgeable than themselves about their own everyday functioning. Dementia ratings based on participants' self-reports plus raters' observations may differ from ratings based on family reports typically obtained in specialty clinics. In most population studies, participants are assessed using standardized protocols implemented by research personnel who, although highly trained, are not expert clinicians exercising judgment regarding help-seeking patients in the clinic. Classification is based on statistical or actuarial criteria, which in clinical settings could be overridden by expert clinical judgment. Thus, heterogeneity in the participant pool and methodological factors can account for variance in proportions with progression and reversion in MCI between clinical and community studies, with results fairly consistent in these groups of studies.27 Population-based data illustrate the importance of validating research criteria at the community level before they are recommended for clinical practice.

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Drafting of the manuscript: Ganguli. Critical revision of the manuscript for important intellectual content: Ganguli, Snitz, Saxton, Chang, Lee, Vander Bilt, Hughes, Loewenstein, Unverzagt, and Petersen.

Statistical analysis: Chang and Lee. Obtained funding: Ganguli and Saxton. Administrative, technical, and material support: Ganguli, Saxton, and Vander Bilt.

Study supervision: Ganguli, Snitz, and Saxton.

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