Incidence of mild cognitive impairment in the Pittsburgh Cardiovascular Health Study–Cognition Study

Oscar L. Lopez, MD
James T. Becker, PhD
Yue-Fang Chang, PhD
Robert A. Sweet, MD
Steven T. DeKosky, MD
Michael H. Gach, PhD
Owen T. Carmichael, PhD
Eric McDade, DO
Lewis H. Kuller, MD

Correspondence & reprint requests to Dr. Lopez: lopezol@upmc.edu

ABSTRACT

Objectives and Methods: The purpose of this study was to examine the incidence of mild cognitive impairment (MCI) and patterns of progression from incident MCI to dementia in 285 cognitively normal subjects (mean age, 78.9 years) in the Cardiovascular Health Study–Cognition Study from 1998–1999 to 2010–2011.

Results: Two hundred (70%) of the participants progressed to MCI; the age-adjusted incidence of MCI was 111.09 (95% confidence interval, 88.13–142.95) per 1,000 person-years. A total of 107 (53.5%) of the incident MCI subjects progressed to dementia. The mean time from MCI to dementia was 2.8 ± 1.8 years. Forty (20%) of the incident MCI cases had an “unstable” course: 19 (9.5%) converted to MCI and later returned to normal; 10 (5%) converted to MCI, to normal, and later back to MCI; 7 (3.5%) converted to MCI, to normal, to MCI, and later to dementia; and 4 (2%) converted to MCI, to normal, and later to dementia. There was an increased mortality rate among the cognitively normal group (110.10 per 1,000 person-years) compared to those with incident MCI who converted to dementia (41.32 per 1,000 person-years).

Conclusions: The majority of the subjects aged >80 years developed an MCI syndrome, and half of them progressed to dementia. Once the MCI syndrome was present, the symptoms of dementia appeared within 2 to 3 years. Progression from normal to MCI or from normal to MCI to dementia is not always linear; subjects who developed MCI and later returned to normal can subsequently progress to dementia. Competing mortality and morbidity influence the study of incident MCI and dementia in population cohorts. *Neurology*® 2012;79:1599–1606

GLOSSARY

3MSE = Modified Mini-Mental State Examination; **AD** = Alzheimer disease; **BVRT** = Benton Visual Retention Test; **CES-D** = Center for Epidemiology Studies Depression Scale; **CHS-CS** = Cardiovascular Health Study–Cognition Study; **CN** = cognitively normal; **DQ** = Dementia Questionnaire; **DSST** = Digit Symbol Substitution Test; **IADLs** = instrumental activities of daily living; **IQ CODE** = Informant Questionnaire for Cognitive Decline in the Elderly; **MCI** = mild cognitive impairment; **py** = person-years.

Older persons with mild cognitive impairment (MCI) have an increased risk of developing dementia, especially Alzheimer disease (AD).^{1–4} The prevalence rates of MCI range from 3% to more than 20%, depending on the classification methods (e.g., amnesic vs multiple cognitive domain),^{5,6} and although there are extensive data on the incidence of dementia in subjects with MCI, there are few data on the incidence of MCI in cognitively normal subjects.^{3,7–16} The existing data show an incidence in the range of 37 to 77 per 1,000 person-years (py).⁷

Individuals with MCI progress to dementia at a rate of 5% to 15% per year,^{1,4} although as many as 40% to 50% of the subjects can return to cognitive normality (normal)^{3,9}; thus, the natural history of MCI could be very unstable. If so, this makes the determination of its incidence a challenge, because individuals who have normal cognition at one point in time may

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Supplemental Data

From the Departments of Neurology (O.L.L., J.T.B., E.M.), Psychiatry (O.L.L., J.T.B., R.A.S.), Psychology (J.T.B.), Epidemiology (Y.-F.C., L.H.K.), Radiology (M.H.G.), Neurosurgery (Y.-F.C.), and Neurobiology (R.A.S.), University of Pittsburgh School of Medicine, Pittsburgh, PA; University of Virginia School of Medicine (S.T.D.), Charlottesville; and Department of Neurology (O.T.C.), University of California Davis, Davis. **Study funding:** Supported by grants AG20098 and AG15928 from the National Institute on Aging (NIA) and by contracts N01-HC-85239, N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, and grant HL080295 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through AG-023629, AG-027058, and AG-027224 (to R.A.S.) from the NIA. A full list of principal CHS investigators and institutions can be found at <http://www.chs-nhlbi.org/pi.htm>.

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have had MCI in the past. In addition, some subjects progress from normal cognition to dementia within a short period of time, apparently without transitioning through an MCI stage.^{1,4,17}

The Cardiovascular Health Study–Cognition Study (CHS-CS) is an ideal setting to examine the natural history of MCI because it has a well-characterized sample of normal participants with a long follow-up period (i.e., as many as 12 years). The present analysis has 2 objectives: 1) to determine the incidence of MCI in the CHS-CS cohort between 1998–1999 and 2010–2011 in those subjects who were cognitively normal from the study inception and 2) to identify different patterns of progression from normal to dementia through MCI.

METHODS CHS-CS. The CHS was initiated in 1989, and extensive clinical, radiologic, and laboratory data were obtained from participants in 4 US communities (Winston-Salem, NC; Hagerstown, MD; Pittsburgh, PA; and Sacramento, CA). All participants in the CHS completed the Modified Mini-Mental State Examination (3MSE)¹⁸ and the Digit Symbol Substitution Test (DSST)¹⁹ annually, and from 1994 through 1999, the Benton Visual Retention Test (BVRT) annually.²⁰ Information on cognition was obtained from proxies using the Informant Questionnaire for Cognitive Decline in the Elderly (IQ CODE)²¹ and the Dementia Questionnaire (DQ).²² Symptoms of depression were measured annually with the modified version of the Center for Epidemiology Studies Depression Scale (CES-D).²³ The subjects' evaluations and proxy interviews relevant for this study have been reported on previously.²⁴ This study was approved by the University of Pittsburgh Institutional Review Board, and informed consent was obtained from all participants in the study.

In 1998–1999, the CHS conducted the CHS Memory Study with 3,608 participants, who had a structural MRI scan of the brain in 1992–1994 and repeat MRI in 1998–1999.^{4,24} Of these subjects, 924 were examined at the Pittsburgh site, and 532 of these participants did not have dementia in 1998–1999; the CHS-CS sample comprised them (figure e-1 on the *Neurology*[®] Web site at www.neurology.org). Table e-1 shows the demographic, clinical, and genetic characteristics of the CHS-CS participants, compared to 1,732 from the CHS parent grant who were alive and did not have dementia in 1998–1999. The CHS-CS cohort had higher 3MSE scores, more education, and less hypertension and included more African Americans than the other sites. The characteristics of the CHS and the Pittsburgh CHS-CS cohorts have been described previously,^{4,24,25} as have the clinical evaluations.²⁶ Cognitive and neurologic examinations were conducted at the CHS clinic or at home, if the participant could not come in for an evaluation.

For the purpose of this study, we included the 285 participants who were alive and cognitively normal in 1998–1999. We excluded those who had MCI in 1998–1999 and 2002–2003 (MCI at both visits) or dementia in 2002–2003, as well as those MCI cases in 1998–1999 who returned to normal in 2002–2003. We also excluded subjects who went from normal to dementia without an identifiable MCI stage (figure e-1). This

specific sampling was done to maximize the likelihood that we included cognitively normal subjects in the longitudinal study. Twenty-three normal participants died between 1999 and 2002; 19 were retrospectively classified as cognitively normal (CN) and 4 as having MCI. In these cases, the diagnoses were made with information from the parent CHS study and postmortem DQ,²² as well as a Neuropsychiatric Inventory (NPI).²⁷ The status of the study sample in 2002–2003 is shown in table e-2.

MCI and dementia diagnostic criteria. MCI was classified according to the CHS-CS diagnostic criteria.²⁴ The MCI amnesic type included subjects with impairments (defined as performance >1.5 SD below age/education appropriate means) in delayed recall of verbal or nonverbal material (or both) and with cognitive deficits that represented a decline from a previous level of functioning. Cognitive functions otherwise fell within normal limits. The diagnosis did not exclude individuals with mild alterations on instrumental activities of daily living (IADLs). Diagnosis of the second type, MCI–multiple cognitive deficits, required impairments in at least 1 cognitive domain other than memory (i.e., results of 2 or more tests were abnormal), or else 1 abnormal test result (which could be a memory test result) in at least 2 separate domains, without sufficient severity or loss of IADLs to constitute dementia. These cognitive deficits may or may not affect IADLs but must represent a decline from a previous level of functioning, in order to fulfill the diagnostic criteria. Participants were classified with possible MCI when there were psychiatric, neurologic, or systemic conditions that could themselves cause cognitive deficits. Subjects were classified as having probable MCI when no comorbid factors were identified. A diagnosis of dementia was based on a deficit in performance in 2 or more cognitive domains that was of sufficient severity to affect IADLs, with a history of normal intellectual function before the onset of cognitive abnormalities; a memory deficit was not required for the diagnosis of dementia.^{25,28}

Diagnostic procedure. Participants were classified by an Adjudication Committee comprising experts in dementia, who first classified participants as having dementia, MCI, or normal and then adjudicated the specific type of dementia or MCI. The Adjudication Committee had access to the historical CHS cognitive test scores from 1989 to 2011, primarily data from the 3MSE (and subscales), DSST, and BVRT, and detailed neuropsychological assessments from 1998 to 2011, as well as the CES-D scores. It also had data from vision and hearing testing; history of alcohol intake; DQ findings²²; vital status; date of death; history of hospitalizations; medications to treat dementia; findings of MRI scans (1992–1994, 1997–1998, and 2002–2009); the annual neurologic examination and the NPI from 1998 to 2011; and hospital records.

Statistical analysis. Incidence rates were calculated per 1,000 person-years (py), and were analyzed on the basis of age, gender, education level ($\pm$ high school), and presence of the *APOE4* allele. Analysis of variance, *t* test, and χ^2 were used to compare demographic and clinical characteristics among normal and MCI participants with and without conversion to dementia. Outcomes were the first visit with an MCI classification (dated at that visit) or the first dementia diagnosis (dated at that visit). Participants who died were censored at the date of death. Unadjusted Kaplan-Meier plots were used to describe the mortality rate among normal subjects, MCI subjects, and MCI subjects who converted to dementia, as well as the difference between the rate of conversion to dementia between probable and possible MCI.

Table 1 Demographic and clinical characteristics of the cohort as a function of progression to MCI and dementia (%)

Variable	All cases	Normal vs MCI			MCI by progression to dementia (compared to normal)		
		Normal	All MCI	χ^2/t test	Remained MCI	Progressed to dementia	χ^2/F
No. of subjects	285	85	200		93	107	
Age, y, mean $\pm$ SD (range)							
In 1998–1999	79.0 $\pm$ 3.8 (71–90)	79.5 $\pm$ 4.3 (71–90)	79.0 $\pm$ 3.5 (72–90)	0.95	78.4 $\pm$ 3.5 (72–89)	79.5 $\pm$ 3.6 (72–90)	2.35
At MCI diagnosis ^h	84.2 $\pm$ 3.8 (72–94.9)	83.1 $\pm$ 3.9 (72–94.9)	84.6 $\pm$ 3.7 (72–94)	–3.05 ^a	84.5 $\pm$ 4.1 (72–96)	84.7 $\pm$ 3.4 (77–94)	4.74 ^b
Gender, no. male/female	108/177	43/42	65/135	8.29 ^c	32/61	33/74	8.16 ^d
Education level > high school, n (%)	177 (62)	55 (65)	122 (61)	0.34	56 (60)	66 (62)	0.39
Race, white, n (%)	234 (82)	71 (83.5)	163 (81.5)	0.16	78 (84)	85 (79)	0.83
APOE4 allele (n = 258), n (%)	51 (20)	16 (20)	35 (19)	0.017	14 (17)	21 (22)	0.72
3MSE							
In 1998–1999	95.5 $\pm$ 3.7	96.7 $\pm$ 3.7	96.4 $\pm$ 3.7	0.70	96.7 $\pm$ 3.4	96.0 $\pm$ 3.9	1.32
At MCI diagnosis (n = 245) ^h	94.1 $\pm$ 6.1	95.8 $\pm$ 3.7	93.5 $\pm$ 6.5	2.41 ^e	94.6 $\pm$ 4.7	92.5 $\pm$ 7.5	5.83 ^f
Clinical features present in 1998–1999, n (%)							
Hypertension	142 (50)	45 (53)	97 (49)	0.42	42 (46)	55 (51)	1.07
Diabetes mellitus	34 (12)	7 (8)	27 (13)	1.24	8 (9)	19 (18)	5.31 ^g
Heart disease	69 (24)	19 (22)	50 (25)	0.22	21 (23)	29 (27)	0.78

Abbreviations: 3MSE = Modified Mini-Mental State Examination; MCI = mild cognitive impairment.

Normal subjects different from MCI: ^a p = 0.002; ^c p = 0.007; ^e p = 0.01.

Remained MCI and MCI that progressed to dementia different from normal subjects: ^b p = 0.009; ^d p = 0.01.

MCI that progressed to dementia different from those who remained MCI and normal subjects: ^f p = 0.009; ^g p = 0.04.

^h Age or 3MSE scores in normal subjects in 2002–2003 vs those at the MCI diagnosis between 2002 and 2011.

RESULTS A total of 200/285 (70%) of these cognitively normal participants developed MCI, and 107 (53.5%) of these subsequently developed dementia. Table 1 shows the demographic characteristics of the normal and incident MCI subjects at the beginning of the observation period. There were no statistical differences in terms of age, education level, race, proportion of subjects carrying the *APOE4* allele, and 3MSE scores. However, the proportion of women was higher in the incident MCI group than in the normal group (relative risk [RR] = 2.09; 95% confidence interval [CI] = 1.24–3.51). Table 1 also shows the characteristics of the incident MCI cases that progressed to dementia, in comparison with those that did not. The 3MSE scores were lower in the group who progressed to dementia than for those who did not (at the time of the MCI diagnosis). The incidence of MCI was 111.23 (88.8–140.19) per 1,000 py. Table 2 shows the incident rates of MCI by age, gender, education level, and *APOE4* status (available for 258 participants).

Table 3 shows the pattern of progression of the normal participants from 1998–1999 to 2010–2011. The mean follow-up time of the cohort was 9.7 $\pm$ 3.6 years (range, 0.60–13.0 years). Of the 200 incident MCI cases, 93 (46.5%) remained as

MCI, and 107 (53.5%) converted to dementia. The mean time to development of MCI was 5.9 $\pm$ 2.7 years, and that to development of dementia from MCI was 2.8 $\pm$ 1.8 years. Forty incident MCI cases (20%) were considered “unstable,” that is, their diagnoses changed 1 or more times during follow-up (table 3). Nineteen (9.5%) converted to MCI and later returned to normal; 10 (5%) converted to MCI, to normal, and later to MCI; 7 (3.5%) converted to MCI, to normal, to MCI, and later to dementia; and (2%) converted to MCI, to normal, and later to dementia (table 3).

When we compared the overall follow-up time from 1998–1999 to last contact or death among CN and MCI subjects, there was a statistical difference among CN (7.1 $\pm$ 4.2 years), the MCI participants who remained as MCI (10.4 $\pm$ 3.3 years), and those who converted to dementia (11.1 $\pm$ 2.1 years) (F = 35.9; df = 283; p < 0.001) (table 3). There were more deaths in the normal group (n = 62 [73%]) than in the incident MCI group (n = 88 [44%]) (χ^2 = 20.7; df = 1; p < 0.001). The age-adjusted mortality rate was 110.10 per 1,000 py (CI, 82.97–146.09) in the CN, 26.95 per 1,000 py (CI, 17.39–51.54) in the MCI group who remained MCI, and 41.32 per 1,000 py (CI, 24.31–

Table 2 Incidence rates of MCI according to age, gender, education level, and APOE4 status

	No. of subjects	No. of MCI subjects (%)	Incidence rate per 1,000 person-years (95% CI)
Age, y, in 1998-1999			
≤75	33	20 (60.6)	85.48 (55.14-132.48)
76-81	170	128 (75.2)	114.57 (96.27-133.33)
≥81	52	33 (61.11)	117.14 (86.91-151.30)
Total	285	200 (70.18)	111.23 (88.8-140.19)
Gender^a			
Male	111	68 (61.26)	103.31 (74.66-143.74)
Female	174	132 (75.86)	128.99 (84.67-200.25)
APOE4^a			
Present	50	34 (68)	108.25 (61.96-199.44)
Absent	208	145 (69.71)	105.45 (76.59-146.78)
Education level^a			
>High school	177	122 (68.93)	108.72 (80.81-146.37)
≤High school	108	78 (72.22)	123.11 (81.03-188.09)

Abbreviations: CI = confidence interval; MCI = mild cognitive impairment.

^a Age-adjusted rates.

68.64) in the MCI group who converted to dementia. We completed a Kaplan-Meier analysis of time to death (in years) comparing the normal subjects (who remained normal) with all incident MCI participants (figure 1A); the time to death differed significantly between the 2 groups (log rank [Mantel-Cox] $\chi^2 = 41.8$; $df = 1$; $p < 0.001$). We then compared the survival of the normal subjects to that of the MCI subjects who remained MCI and the MCI subjects who developed dementia (figure 1B); again, there was a significant difference between the survival

functions ($\chi^2 = 42.0$; $df = 2$; $p < 0.001$). However, the effect was due to the difference between the CN and all MCI subjects; there was no significant difference in survival between the 2 groups of MCI subjects ($\chi^2 = 0.10$; $df = 1$; $p > 0.05$).

The incident rates and the characteristics of the subjects by cognitive type, certainty of the presence of neurodegenerative disorder, and stability in their clinical progression are shown in table 4. There were 19 subjects (9%) with MCI amnesic type (MCI-AT) and 184 (91%) with MCI multi-cognitive domain (MCI-MCD). The proportion of women was higher in the MCI-MCD group than in the MCI-AT and control groups. Twelve MCI-AT subjects (63%) and 98 MCI-MCD subjects (53%) progressed to dementia; the time to dementia was similar between groups.

There were 111 probable (55%) and 89 possible (45%) MCI cases. The proportion of women in both the probable and possible MCI groups was higher than in the normal group. The 3MSE scores in 2002-2003 were lower in the possible MCI group than in the normal group. The time to dementia in the possible MCI group was faster than in the probable MCI group (figure e-2) (log rank [Mantel-Cox] $\chi^2 = 9.16$; $df = 1$; $p < 0.002$).

There were 40 (20%) "unstable" MCI and 160 (80%) "stable" MCI participants. The 3MSE in 2002-2003 was lower in the stable MCI group than in the unstable MCI and normal groups. Only 1 subject with unstable MCI carried the APOE4 allele. The types of dementia by MCI groups are shown in table e-3. Of the 107 incident dementia cases, 102 (95%) converted to AD.

Table 3 Time of follow-up by pattern of progression and clinical diagnosis from 1998-1999 to 2010-2011

Pattern of progression	No. of subjects	Deceased during follow-up, n (%)	Follow-up time		Time to MCI		Time to dementia from MCI	
			Years ^a (range)	Person-years	Years ^b (range)	Person-years	Years ^c (range)	Person-years
Normal	85	62 (73)	7.1 ± 4.2 (0.60-12.9)	609.9				
Normal to MCI	64	34 (53)	9.8 ± 3.5 (1.5-12.9)	610.6	6.4 ± 3.0 (2.7-12.4)	400.1		
Normal to MCI to normal	19	1 (5)	12.0 ± 0.32 (12.0-13.0)	239.1	8.3 ± 2.4 (4.8-12.0)	158.2		
Normal to MCI to normal to MCI	10	2 (20)	12.0 ± 0.82 (10.3-12.6)	121.8	5.0 ± 1.6 (3.6-8.9)	51.1		
Normal to MCI to dementia	96	48 (50)	10.9 ± 2.3 (3.6-12.9)	1070.8	5.2 ± 1.7 (3.0-10.8)	511.1	2.6 ± 1.7 (0.98-8.2)	267.8
Normal to MCI to normal to MCI to dementia	7	0 (0)	12.6 ± 0.27 (12.2-12.9)	88.1	5.2 ± 1.8 (3.6-7.8)	34.7	5.0 ± 1.8 (3.0-8.4)	40.5
Normal to MCI to normal to dementia	4	3 (75)	9.3 ± 3.7 (4.0-12.9)	37.6	4.5 ± 1.2 (3.5-6.4)	18.3	4.3 ± 2.5 (2.0-7.8)	17.3

Abbreviation: MCI = mild cognitive impairment.

^a Normal subjects different from the other 6 groups: $F = 15.7$, $df = 6$, $p < 0.001$.

^b Normal-MCI-normal-dementia different from normal-MCI-normal: $F = 4.59$, $df = 5$, $p < 0.001$.

^c Normal-MCI-normal-MCI-dementia different from normal-MCI-normal-dementia: $F = 9.75$, $df = 2$, $p < 0.001$.

Figure 1 Time to death in normal subjects who progressed to mild cognitive impairment (MCI) and dementia

(A) Time to death in normal subjects is compared for those who remained normal during the observation period vs those who converted to MCI ($p < 0.001$). (B) The time to death in normal subjects who remained normal during the observation period was statistically different from those who converted to MCI and remained as MCI ($p < 0.001$), and the latter group was not different from those with MCI who converted to dementia ($p > 0.05$).

DISCUSSION This longitudinal study shows that the majority of the elderly subjects after age 80 developed an MCI syndrome and that more than half of them progressed to dementia. This is consistent with the increased prevalence and incidence of dementia in individuals age 85 or older.^{29,30} Progression from normal cognition to MCI, or from normal to MCI to dementia, was not linear in 20% of the subjects, which has important implications for the study and diagnosis of MCI and dementia. First, only 1 of the unstable individuals was an *APOE4* allele carrier,

suggesting that the absence of the *APOE4* allele may attenuate the rate of progression and decrease mortality.³¹ Second, the fact that subjects with MCI can revert to normal and later return to MCI will influence the estimates of prevalence and incidence of MCI, especially if the follow-up period is short (i.e., < 5 years). Indeed, without having a period of normal cognition before developing MCI, it is possible to include subjects with recent history of MCI (e.g., 2 years previously) in a “cognitively normal” group.

The proportion of subjects who developed MCI-AT was smaller than that of MCI-MCD^{3,24}; the proportion of subjects with probable or possible MCI who converted to dementia was similar. However, there was a faster conversion rate in the possible MCI group, suggesting that cerebral and systemic comorbidities accelerate the development of clinical dementia. It is important to point out that some subjects with possible MCI converted to probable AD, and subjects with probable MCI converted to possible AD. This occurred when comorbid factors surrounding the initial MCI diagnosis subsided during follow-up, or when subjects developed new complications around the time they developed dementia.

The incident rates of MCI in previous studies ranged from 37 to 77 per 1,000 py.^{7,10} There are multiple methodologic differences that may explain the different rates among studies, including, for example, the definition of MCI,⁷ the use of 2-stage screening protocols,¹¹ and the age of the subjects; the incidence is lower in younger cohorts.^{9,12} Our incidence rates were similar to those described in population studies that included subjects predominantly aged 85+, and we also found increasing incidence with age. The Leipzig Longitudinal Study found that the incidence of MCI was 76.5/1,000 py among subjects aged 75 or older and 157.6/1,000 py in those 85 years or older,¹⁴ and a recent report from the Mayo Clinic Study of Aging showed an incidence of 90.2/1,000 py among subjects aged 80–84 and 125.2/1,000 py among those aged 85–89.¹⁶

Our findings regarding mortality raise a critically important point in the interpretation of these and similar longitudinal data. We found increased mortality among the participants who remained cognitively normal throughout follow-up and decreased mortality among the subjects who developed MCI or dementia. Although this might be viewed as paradoxical, it is in fact a demonstration of the effects of competing mortality and morbidity. Other medical factors, the competing risks, resulted in the death of individuals who were cognitively normal before they had the opportunity to develop MCI or dementia. Those individuals who lived longer (because they did not succumb to a competing risk) went on to develop

Table 4 Characteristics of the subjects with MCI vs normal subjects by cognitive type, certainty of neurodegenerative disorder, and stability of the diagnosis over time (%)

	MCI cognitive types			MCI by certainty of diagnosis			MCI by stability of diagnosis		
	Normal subjects	MCI-AT	MCI-MCD	χ^2/F	Probable MCI	Possible MCI	χ^2/F	Stable	Unstable
No. of cases	85	17	183		111	89		160	40
Incident rates per 1,000 person-years (95% CI), within each MCI group		208.0 (129.3–334.5)	167.7 (145.1–193.8)		161.0 (133.6–193.9)	184.1 (149.5–226.6)		175.7 (150.4–205.1)	152.5 (111.9–208.0)
Age, y, mean $\pm$ SD (range)									
In 1998–1999	79.0 $\pm$ 4.3 (71–90)	78.7 $\pm$ 3.1 (72–86)	79.0 $\pm$ 3.6 (72–90)	0.50	79.1 $\pm$ 3.2 (72–88)	78.9 $\pm$ 4.0 (72–90)	0.51	79.2 $\pm$ 3.8 (72–90)	78.0 $\pm$ 2.4 (72–86)
At MCI diagnosis	83.1 $\pm$ 3.9 (74–94.9)	83.8 $\pm$ 3.4 (76–90.5)	85.0 $\pm$ 3.7 (72–96)	3.98 ^a	83.2 $\pm$ 3.1 (77–96)	83.1 $\pm$ 3.6 (72–93.8)	4.54 ^b	83.4 $\pm$ 3.5 (72–94)	82.2 $\pm$ 2.4 (79.8–96)
Gender, M/F	42/43	8/11	59/124	8.35 ^d	37/74	28/61	8.36 ^e	51/109	14/26
Education level (>high school)	55 (65)	12 (71)	110 (60)	1.07	74 (63)	50 (56)	1.93	99 (62)	23 (57.5)
Race, white	71 (83.5)	15 (88)	148 (81)	0.74	93 (84)	70 (79)	1.05	129 (81)	34 (85)
APOE4 allele (n = 258)	16 (20)	4 (25)	31 (19)	0.38	14 (14)	21 (26)	4.06	34 (23)	1 (3)
3MSE									
In 1998–1999	96.7 $\pm$ 3.7	96.8 $\pm$ 2.5	96.4 $\pm$ 3.8	0.34	96.9 $\pm$ 3.5	95.8 $\pm$ 3.8	2.44	96.3 $\pm$ 3.8	96.8 $\pm$ 3.6
At MCI diagnosis ^h (n = 245)	95.8 $\pm$ 3.7	94.8 $\pm$ 4.5	92.6 $\pm$ 7.4	3.2 ⁱ	93.8 $\pm$ 5.5	93.0 $\pm$ 7.1	3.32 ^j	93.0 $\pm$ 6.8	95.4 $\pm$ 3.5
Clinical features present in 1998–1999									
Hypertension	45 (53)	9 (53)	88 (58)	0.55	55 (49.5)	42 (48)	0.58	76 (49)	21 (52.5)
Diabetes mellitus	7 (8)	1 (6)	25 (14)	2.17	16 (14)	10 (11)	1.74	20 (12.5)	6 (15)
Heart disease	19 (22)	3 (18)	47 (26)	0.77	28 (25)	22 (25)	0.23	40 (25)	10 (25)

Abbreviations: 3MSE = Modified Mini-Mental State Examination; AT = amnesic type; CI = confidence interval; MCD = multi-cognitive domain; MCI = mild cognitive impairment.

MCI-MCD different from MCI-AT and normal subjects: ^a $p = 0.02$; MCI-AT and MCI-MCD different from normal subjects: ^d $p = 0.01$; MCI-MCD different from normal subjects: ⁱ $p = 0.04$.Probable and possible MCI different from normal subjects: ^b $p = 0.01$, ^e $p = 0.01$, ^j $p = 0.03$.Unstable MCI different from normal subjects and stable MCI: ^c $p = 0.03$, ^f $p = 0.01$, ^g $p = 0.02$; stable and unstable MCI different from normal subjects: ^f $p = 0.01$; stable MCI different from normal subjects: ^k $p = 0.007$.^h Age or 3MSE scores in normal subjects in 2002–2003 vs those at the MCI diagnosis between 2002 and 2011.

either MCI or dementia, resulting in the apparent dementia-associated increase in longevity.

Unlike other studies, we measured mortality among individuals who were cognitively normal at the time that we began our observations, rather than starting the observation when the study participants met criteria for MCI or dementia, i.e., at the time that the “risk state” began.^{32,33,34} For example, among the individuals who developed MCI, the time to death (after the MCI diagnosis) was 2.2 years, but they spent an average of 4.3 years transitioning to MCI (i.e., a total of ~6.5 years). Individuals who developed dementia died within 2.0 years of diagnosis, after an average of 5.4 years developing dementia (i.e., a total of 7.4 years). When we recalculated the mortality rate from the time of diagnosis of MCI (including the unstable cases) or dementia, the death rate was 87.3 per 1,000 py for the MCI subjects and 195.9 per 1,000 py for the dementia group. Thus, measured this way, mortality is consistently higher in individuals with dementia. It is important to note that the length of follow-up is critical; those studies that follow MCI cases for relatively short periods of time find an association between MCI and mortality,^{32,33} whereas those with longer follow-up periods do not.³⁵

One of the limitations of our study was that the participants did not have extensive annual cognitive evaluations between 1999 and 2002, and consequently, we may be underestimating the incidence rate of MCI. However, as noted here, there is a group of subjects who progressed from normal to dementia within a year and subjects who also progressed from normal to dementia, but they could not be evaluated because of medical issues (e.g., hospitalizations) or family-related issues (e.g., death of a spouse). Therefore, it is difficult to determine whether the subjects who developed dementia during the lag period of the study had an MCI stage or had a true rapid progression.

The missed observation is a methodologic problem usually encountered in studies that do not examine the participants on an annual basis. Had we included the subjects who progressed from normal (i.e., no observed MCI) to dementia in the analysis, the incident estimates would have changed. For example, if we had censored those participants at their date of dementia, then our estimates of incident MCI would have been lower. By contrast, if we used the midpoint between the last normal visit and the first dementia visit as the date of MCI onset, then our estimates would have been higher. Finally, we may have missed incident MCI cases in those subjects who died between 1999 and 2002, although we made every effort to determine the level of cognitive functions in those participants prior to death.

In any longitudinal study of elderly subjects, there is a progressive loss of subjects over time, and consequently, the number of subjects reaching age 80 or older tends to be small. We found that once the MCI syndrome was present, the symptoms of dementia appeared within 2 to 3 years. This suggests that the window to detect symptomatic predementia cases is narrow, which has important implications for the development of preventive therapies. Furthermore, our results showed that a long observation time, probably a decade or more, is needed to examine the nature of the biological process that leads to MCI and later to dementia in normal populations. The causes that make subjects fluctuate or remain as MCI for a long period of time need further study.

AUTHOR CONTRIBUTIONS

Dr. Lopez participated in the conceptualization of the study, analysis and interpretation of the data, and drafting and revising the manuscript. Dr. Becker participated in the conceptualization of the study, analysis and interpretation of the data, and drafting and revising the manuscript. Dr. Chang participated in the analysis and interpretation of the data, conducted the statistical analysis, and revised the manuscript. Drs. Sweet, DeKosky, Gach, Carmichael, and McDade participated in the interpretation of the data and drafted and revised the manuscript. Dr. Kuller participated in the conceptualization of the study, analysis and interpretation of the data, and drafting and revising the manuscript.

DISCLOSURE

O. Lopez served as consultant for Johnson & Johnson and Lundbeck. J. Becker, Y.-F. Chang, and R. Sweet report no disclosures. S.T. DeKosky has served as consultant for Merck, Elan/Wyeth, Lilly, Novartis, Janssen, Helicon Therapeutics, and Genzyme. M. Gach, O. Carmichael, E. McDade, and L. Kuller report no disclosures. **Go to Neurology.org for full disclosures.**

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