Higher risk of progression to dementia in mild cognitive impairment cases who revert to normal

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ABSTRACT

Objective: To estimate rates of progression from mild cognitive impairment (MCI) to dementia and of reversion from MCI to being cognitively normal (CN) in a population-based cohort.

Methods: Participants ($n = 534$, aged 70 years and older) enrolled in the prospective Mayo Clinic Study of Aging were evaluated at baseline and every 15 months to identify incident MCI or dementia.

Results: Over a median follow-up of 5.1 years, 153 of 534 participants (28.7%) with prevalent or incident MCI progressed to dementia (71.3 per 1,000 person-years). The cumulative incidence of dementia was 5.4% at 1 year, 16.1% at 2, 23.4% at 3, 31.1% at 4, and 42.5% at 5 years. The risk of dementia was elevated in MCI cases (hazard ratio [HR] 23.2, $p < 0.001$) compared with CN subjects. Thirty-eight percent ($n = 201$) of MCI participants reverted to CN (175.0/1,000 person-years), but 65% subsequently developed MCI or dementia; the HR was 6.6 ($p < 0.001$) compared with CN subjects. The risk of reversion was reduced in subjects with an APOE $\epsilon 4$ allele (HR 0.53, $p < 0.001$), higher Clinical Dementia Rating–Sum of Boxes (HR 0.56, $p < 0.001$), and poorer cognitive function (HR 0.56, $p < 0.001$). The risk was also reduced in subjects with amnesic MCI (HR 0.70, $p = 0.02$) and multidomain MCI (HR 0.61, $p = 0.003$).

Conclusions: MCI cases, including those who revert to CN, have a high risk of progressing to dementia. This suggests that diagnosis of MCI at any time has prognostic value. *Neurology*® 2014;82:317–325

GLOSSARY

AD = Alzheimer disease; **aMCI** = amnesic mild cognitive impairment; **CDR** = Clinical Dementia Rating; **CI** = confidence interval; **CN** = cognitively normal; **HR** = hazard ratio; **MCI** = mild cognitive impairment; **MCSA** = Mayo Clinic Study of Aging; **MD** = multiple-domain; **naMCI** = nonamnesic mild cognitive impairment; **SD** = single-domain.

The risk of dementia is higher in persons with mild cognitive impairment (MCI) compared with cognitively normal (CN) subjects.^{1–5} Although some subjects with MCI revert back to CN status, this reversion has not been fully characterized. In particular, the rates of reversion to CN may vary across studies because of differences in the sources of study participants.^{4,6} For example, higher estimates of MCI incidence and prevalence in clinic-based studies than in population-based studies^{4,6} suggest that the rates of reversion to CN may be lower in the clinic setting than in population-based studies.^{7,8}

The Mayo Clinic Study of Aging (MCSA) is a population-based, prospective study that was designed to evaluate the prevalence, incidence, and natural history of cognitive decline. The objective of the present study was to determine the evolution of MCI by estimating rates of progression to dementia and rates of reversion to CN, and to study outcomes after reversion to CN and predictors of these transitions. The MCSA is unique because the Rochester Epidemiology Project medical records-linkage system allowed us to obtain information about subjects with incomplete follow-up and to more completely describe the evolution of cognitive impairment in a population.^{9,10}

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METHODS Study population. The study procedures have been published elsewhere and are only briefly described here.^{9,10} We used the records-linkage system of the Rochester Epidemiology Project to construct a sampling frame of Olmsted County residents who were aged 70 to 89 years on October 1, 2004 (total population = 9,953).¹¹ We selected an age- and sex-stratified random sample of 5,233 subjects, and excluded persons with prevalent dementia, in hospice, or terminally ill. Of the remaining 4,398 eligible subjects, 2,719 (61.8%) participated in person (n = 2,050, full participants) or by telephone (n = 669). Our present analyses include only the full participants because incident MCI cannot be reliably assessed by telephone.

Baseline evaluation. A direct interview of participants by a nurse assessed demographic information and included questions about memory. The Clinical Dementia Rating (CDR)¹² scale and Functional Activities Questionnaire¹³ were administered to an informant. An evaluation performed by a physician included the Short Test of Mental Status,¹⁴ and a neurologic examination (e.g., Unified Parkinson's Disease Rating Scale). A neuropsychological assessment performed by a psychometrist included 9 tests to measure 4 cognitive domains: memory (3 tests), executive function (2 tests), language (2 tests), and visuospatial skills (2 tests).¹⁵ For each test, the raw scores were first age-adjusted, then *z* scores were computed using data from the Mayo's Older American Normative Studies.^{9,10,15} Scores within a domain were then summed and scaled to allow comparisons across domains. A decision about cognitive impairment was based on a consensus agreement among the examining nurse, physician, and neuropsychologist.^{9,10,16} The clinical evaluations were performed without using information from imaging or other biomarkers acquired during the study.

Diagnostic criteria. A diagnosis of MCI was based on published criteria: cognitive concern by subject, informant, examining nurse, or physician; impairment in ≥ 1 of the 4 cognitive domains; essentially normal functional activities; and absence of dementia.^{4,9,10,16} MCI was categorized as amnesic MCI (aMCI) if the memory domain was impaired and nonamnesic MCI (naMCI) if the memory domain was not impaired, and as single-domain (SD) MCI if only one domain was impaired, and multiple-domain (MD) MCI if 2 or more domains were impaired. The diagnoses of dementia¹⁷ and Alzheimer disease (AD) were based on published criteria.¹⁸ Participants who performed within the normal range and did not meet criteria for MCI or dementia were considered to be CN.^{4,9,10} The final diagnosis was made at a consensus conference by the nurse and physician who examined the participant, and by the neuropsychologist who interpreted the psychometric data.

Longitudinal follow-up. Participants were evaluated at 15-month intervals to detect incident MCI or dementia using the same protocol used at the baseline examination. Cognitive diagnoses from previous evaluations were not considered in making diagnoses during follow-up. Full participants at baseline who declined further in-person evaluations were invited to participate in a telephone interview that included the Telephone Interview of Cognitive Status–modified,¹⁹ the CDR scale,¹² and the Neuropsychiatric Inventory Questionnaire.²⁰ We also reviewed the medical records of subjects lost to the in-person follow-up to determine physician diagnoses of incident dementia.

Statistical analyses. The onset of dementia was assigned at the midpoint between the last assessment as MCI and the first-ever assessment as dementia. Subjects who refused participation, could not be contacted, or died during follow-up were censored

at their last evaluation. We computed the person-years of follow-up as the time from the diagnosis of MCI to onset of dementia, censoring, or date of last follow-up. We estimated the rates of progression from MCI to dementia by age and sex using incidence density methods (cases per 1,000 person-years). The incidence rates were directly standardized by age and sex to the Olmsted County population on October 1, 2004. In separate analyses, we included medical record information about incident dementia for subjects who were lost to the in-person follow-up. We also estimated rates of first reversion from MCI to CN, and the incidence of dementia in CN subjects.

We used Cox proportional hazards models to evaluate the roles of demographic factors, *APOE* $\epsilon 4$, MCI subtype, cognitive performance, and functional status as predictors of progression from MCI to dementia and of reversion from MCI to CN. For analytic purposes, we computed domain *z* scores after scaling the raw cognitive test scores (mean = 0, SD = 1) using data for subjects without dementia at baseline. Domain *z* scores were summed and scaled to obtain global *z* scores. Considering MCI/CN status as a time-dependent covariate, we categorized subjects according to their diagnosis at each cycle (CN, normal with previous MCI, MCI without reversion) and computed the follow-up time in that category.²¹ We then computed the risk of dementia in MCI cases with and without reversion compared with CN. All models used age as the time variable and were adjusted for sex and years of education. The proportionality assumptions for proportional hazards models were met for age, sex, and education.

In addition, to obtain a graphic display of Kaplan-Meier curves that accounted for age and sex differences, we started from 172 subjects who developed MCI but experienced a reversion and matched them by age and sex to 172 subjects who developed MCI and did not revert, and to 172 subjects who were CN at baseline.

All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC). The *p* values were considered significant at an $\alpha < 0.05$ (2-tailed tests).

Standard protocol approvals, registrations, and patient consents. The study was approved by the Institutional Review Boards of the Mayo Clinic and the Olmsted Medical Center. Written informed consent was obtained from all participants.

RESULTS The study flowchart is presented in figure 1. Among the 724 participants with incident or prevalent MCI, 534 had at least one follow-up after the diagnosis: 195 had one follow-up evaluation, 147 had 2, 84 had 3, 72 had 4, and 36 had 5. Table 1 presents the characteristics of prevalent cases of MCI at baseline and incident cases at the time of the initial MCI diagnosis. Over a median of 5.1 years (interquartile range 2.9, 6.3) of follow-up of all MCI cases, 194 (36.3%) stayed as MCI, 139 (26.0%) progressed to dementia without reversion to CN (107 AD and 32 non-AD dementia), and 201 (37.6%) had at least one reversion to CN.

Progression from MCI to dementia (incidence rates). The incidence rates of dementia in prevalent and incident cases of MCI (per 1,000 person-years) are reported separately in table e-1 on the *Neurology*[®] Web site at www.neurology.org. In prevalent and incident cases combined, the rates were 66.4 in

Figure 1 Study flowchart

MCI = mild cognitive impairment.

men, 75.0 in women, and 71.3 in both sexes. Rates were higher, 72.4 in men, 80.2 in women, and 76.8 in both sexes, when we included information on incident dementia from the medical records for subjects who died or were lost to follow-up (table e-1, footnote b). Incidence rates were similar in men and women at age 70 to 79 years, but were higher in women than men at age 80 to 89 years (table e-1). The rate of progression from CN directly to dementia was 1.9 per 1,000 person-years (20 of 1,450 subjects; 2.1 in men vs 1.8 in women). The risk of dementia was increased in subjects who ever had MCI vs never (hazard ratio [HR] 23.2; 95% confidence interval [CI] 14.4, 37.2; $p < 0.001$).

Reversion from MCI to CN status. The rates of reversion from MCI to CN (per 1,000 person-years) for prevalent and incident cases are summarized in table e-2. The overall rates for prevalent and incident cases combined were 177.9 in men, 172.9 in women, and 175.0 in both sexes. The age-specific reversion rates varied with sex (table e-2). Among subjects aged 70 to 79 years at enrollment, the reversion rate was lower in men than in women (171.7 vs 236.3, $p = 0.13$); however, among subjects aged 80 to 89 years, the rate was higher in men than in women (191.9 vs 108.4, $p = 0.005$; test for interaction, $p = 0.003$).

Table 1 Demographic and clinical characteristics of participants with prevalent MCI or incident MCI

Characteristic	Prevalent MCI ^a (n = 282)	Incident MCI ^b (n = 252)	p
Age, c, y, n (%)			0.006
70–74	43 (15.2)	20 (7.9)	
75–79	53 (18.8)	47 (18.7)	
80–84	110 (39.0)	87 (34.5)	
85–89	76 (27.0)	98 (38.9)	
Sex, n (%)			0.32
Men	162 (57.4)	134 (53.2)	
Women	120 (42.6)	118 (46.8)	
Education, y, n (%)			0.33
≤12	163 (57.8)	135 (53.6)	
>12	119 (42.2)	117 (46.4)	
Marital status, n (%)			0.01
Married	174 (61.7)	129 (51.2)	
Not married	108 (38.3)	123 (48.8)	
APOE ε3ε4/ε4ε4, n (%) ^d	85 (30.9)	68 (28.6)	0.56
Cognitive domain z scores, median (IQR)			
Memory	−1.28 (−1.72, −0.69)	−0.78 (−1.26, −0.19)	<0.001
Executive function	−1.02 (−1.81, −0.20)	−0.61 (−1.43, 0.14)	<0.001
Language	−0.77 (−1.51, −0.25)	−0.55 (−1.13, −0.01)	0.001
Visuospatial	−0.78 (−1.35, −0.15)	−0.38 (−1.13, 0.21)	<0.001
Global	−1.18 (−1.74, −0.69)	−0.76 (−1.34, −0.21)	<0.001
FAQ, median (IQR)	1.00 (0.00, 3.00)	1.00 (0.00, 4.00)	0.51
CDR-Sum of Boxes, median (IQR)	0.5 (0, 1)	0.5 (0.5, 1.5)	0.72
Duration of follow-up, y, median (IQR)	3.85 (2.53, 5.43)	5.54 (4.34, 6.49)	<0.001
MCI to dementia, y, median (IQR)	2.65 (1.44, 4.59)	2.29 (1.97, 3.50)	0.93
Incident dementia, n (%)	105 (37.2)	48 (19.0)	<0.001
Alzheimer dementia, n (%)	75 (26.6)	41 (16.3)	0.004
Non-Alzheimer dementia, n (%)	30 (10.6)	7 (2.8)	<0.001

Abbreviations: CDR = Clinical Dementia Rating; FAQ = Functional Activities Questionnaire; IQR = interquartile range; MCI = mild cognitive impairment.

^a Prevalent MCI: from among 329 prevalent cases at baseline, 282 had ≥1 follow-up.

^b Incident MCI: from among 395 incident MCI cases, 252 had ≥1 follow-up after the MCI diagnosis. Cognitive scores, CDR, and FAQ for these subjects were based on measurements at the time of the MCI diagnosis.

^c Age was determined at baseline for prevalent MCI and at the time of diagnosis for incident MCI.

^d We excluded 21 MCI cases (4 prevalent, 14 incident) with ε2ε4 and 3 prevalent MCI cases with missing data.

Percentages reported are among subjects who were included in the analyses.

Outcomes in subjects who reverted to CN status. The cumulative incidence of a first reversion from MCI to CN was 13.1% after 1 year of follow-up, 32.9% at 2 years, 41.3% at 3 years, and 50.5% after 4 years of follow-up. Of the 201 MCI cases who reverted to CN, 19 died and 54 did not return. Of the 128 with at least one follow-up, 45 (35.2%) remained CN, whereas 83 (64.8%) had MCI (n = 71) or dementia (n = 12) at the last follow-up. Compared with subjects who were CN at baseline, the HR for dementia was 28.82 (95% CI 17.91, 46.37; $p < 0.001$) for MCI without reversion and 6.56 (95%

CI 3.18, 13.56; $p < 0.001$) for MCI with reversion (figure 2).

Predictors of progression and reversion. Table 2 describes predictors of MCI progression to dementia. The risk of dementia was increased for older subjects and in persons with an APOE ε4 allele. The risk of progression was higher for MD MCI vs SD MCI, increased with worse functioning (CDR, Functional Activities Questionnaire), and decreased with better cognitive performance in the 4 cognitive domains and in global scores. The risk of dementia due to AD was elevated

Figure 2 Cumulative incidence of dementia in subjects who developed MCI and did not revert to CN, subjects who developed MCI and reverted to CN, and subjects who were CN at baseline

For graphic representation and to avoid confounding by age and sex, we identified 172 subjects who developed mild cognitive impairment (MCI) but experienced a reversion and matched them by age and sex to 172 subjects who developed MCI and did not revert, and to 172 subjects who were cognitively normal (CN) at baseline. When multiple subjects were available for matching, we chose one randomly.

for subjects with MD MCI vs SD MCI, MD aMCI vs SD aMCI, and MD aMCI vs MD naMCI (table 2, footnote a). The risk of non-AD dementia was elevated for MD MCI vs SD MCI, MD aMCI vs SD aMCI, and SD naMCI vs SD aMCI (table 2, footnote a). In sex-stratified analyses, women who were not married were less likely to progress to dementia compared with married women (HR 0.54 [95% CI 0.33, 0.88], $p = 0.01$), but there was no difference for unmarried vs married men (HR 1.13 [95% CI 0.69, 1.85], $p = 0.62$; p for interaction = 0.05). Women with a history of stroke were more likely to progress to dementia (HR 2.38 [95% CI 1.40, 4.06], $p = 0.001$), but there was no difference for men with a history of stroke vs without (HR 1.22 [95% CI 0.70, 2.14], $p = 0.49$; p for interaction = 0.10).

Table 3 describes the predictors of reversion from MCI to CN. In prevalent and incident cases combined, women had a reduced risk of reversion to CN. The risk of reversion to CN was reduced in subjects who were not married, had an *APOE* $\epsilon 4$ allele, worse functioning (CDR, Functional Activities Questionnaire), and poorer cognitive function. The risk of reversion was also reduced in aMCI vs naMCI and in MD MCI vs SD MCI (table 3). There were no sex differences.

DISCUSSION In this prospective, population-based, longitudinal study, we demonstrate the dynamic nature of MCI diagnoses over time: 1) progression to dementia increased with age, was higher in older women than in older men, and in MCI than in CN participants; 2) progression to dementia was higher

for MD MCI than SD MCI; 3) MD aMCI was associated with an increased risk of both AD and non-AD dementia; 4) worse functional status was a marker for progression; 5) subjects who reverted to CN had an increased risk of dementia compared with CN subjects; and 6) the risk of reversion to CN was lower for aMCI, MD MCI, and *APOE* $\epsilon 4$ allele carriers.

Important strengths of this study include the population-based design, in-depth characterization of all participants including neuropsychological testing, information from an informant, a physician examination, and diagnoses made by a consensus process. In addition, we included dementia outcomes for the majority of participants lost to in-person follow-up. Importantly, the evaluators were blinded to diagnoses from prior evaluations. Although this allowed for unbiased judgments at each visit, it may have contributed to higher reversion rates compared with clinical practice or clinical trials in which clinicians are aware of a prior diagnosis of MCI.

The high rate of progression to dementia among subjects who reverted to CN suggests that any diagnosis of MCI may have prognostic implications. The relatively long follow-up of these subjects allowed for a more thorough assessment of the stability of the diagnosis. Although 37.6% of subjects diagnosed with MCI were labeled as CN at a follow-up evaluation, 65% of those who reverted to CN subsequently progressed to MCI or dementia, a 6.6-fold higher risk of dementia than in subjects who were CN at enrollment and did not receive a diagnosis of MCI.

The differences in rates of progression to dementia by MCI subtype support the hypothesis that the MCI subtype is a meaningful diagnostic category. It underscores the utility of the amnesic vs nonamnesic distinction. In particular, the higher rate of progression to dementia for MD MCI than for SD MCI is consistent with the presence of multiple deficits and is indicative of more severe pathophysiologic changes compared with the presence of a single deficit. There is compelling evidence that aMCI frequently represents the earliest symptomatic manifestation of AD pathophysiology. Consistent with this, the risk of dementia due to AD was higher in subjects with MD aMCI compared with MD naMCI. By contrast, there are uncertainties about pathologic processes that underlie progression among subjects with naMCI. However, the association of MD MCI and MD aMCI with non-AD dementia suggests that concurrent vascular and degenerative etiologies may contribute to non-AD dementias.^{22,23} The current analysis did not include information from imaging or other biomarkers obtained through the MCSA.

The rate of progression to dementia was higher in women than men, particularly at older ages. This

Table 2 Predictors of progression from MCI to dementia

Characteristic	Prevalent MCI				Incident MCI				Prevalent and incident MCI ^a			
	At risk, n	Events, n	HR (95% CI)	p	At risk, n	Events, n	HR (95% CI)	p	At risk, n	Events, n	HR (95% CI)	p
Age, y												
70–79	96	23	1.00 (ref.)		67	8	1.00 (ref.)		163	31	1.00 (ref.)	
80–89	186	82	1.85 (0.70, 4.92)	0.22	185	40	1.46 (0.26, 8.31)	0.67	371	122	1.60 (0.68, 3.79)	0.29
Sex												
Men	162	59	1.00 (ref.)		134	24	1.00 (ref.)		296	83	1.00 (ref.)	
Women	120	46	1.20 (0.81, 1.77)	0.36	118	24	0.90 (0.48, 1.70)	0.76	238	70	1.06 (0.77, 1.47)	0.73
Education, y												
>12	119	44	1.00 (ref.)		117	27	1.00 (ref.)		236	71	1.00 (ref.)	
≤12	163	61	1.11 (0.75, 1.64)	0.60	135	21	0.67 (0.37, 1.21)	0.19	298	82	0.98 (0.71, 1.35)	0.89
Marital status												
Married	174	66	1.00 (ref.)		129	21	1.00 (ref.)		303	87	1.00 (ref.)	
Not married	108	39	0.71 (0.45, 1.10)	0.13	123	27	1.31 (0.67, 2.57)	0.43	231	66	0.79 (0.55, 1.14)	0.21
APOE ε4												
ε2ε2/ε2ε3/ε3ε3	190	64	1.00 (ref.)		170	33	1.00 (ref.)		360	97	1.00 (ref.)	
ε3ε4/ε4ε4	85	37	1.43 (0.95, 2.15)	0.09	68	13	1.03 (0.53, 1.99)	0.94	153	50	1.30 (0.92, 1.84)	0.14
MCI subtype												
naMCI	79	24	1.00 (ref.)		65	13	1.00 (ref.)		144	37	1.00 (ref.)	
aMCI	203	81	1.45 (0.91, 2.32)	0.12	174	33	0.89 (0.46, 1.70)	0.72	377	114	1.22 (0.83, 1.77)	0.31
SD MCI	185	57	1.00 (ref.)		167	33	1.00 (ref.)		352	90	1.00 (ref.)	
MD MCI	97	48	2.18 (1.47, 3.21)	<0.001	72	13	0.90 (0.47, 1.73)	0.75	169	61	1.70 (1.22, 2.35)	0.002
Functional measures (continuous variables)^b												
FAQ	275	102	1.09 (1.05, 1.14)	<0.001	247	48	1.11 (1.04, 1.19)	0.002	522	150	1.10 (1.06, 1.13)	<0.001
CDR-SOB	282	105	1.64 (1.37, 1.95)	<0.001	251	48	1.47 (1.12, 1.94)	0.006	533	153	1.58 (1.36, 1.83)	<0.001
Cognitive z scores (continuous variables)^c												
Memory	279	105	0.61 (0.45, 0.83)	0.002	234	46	0.50 (0.33, 0.76)	0.001	513	151	0.54 (0.43, 0.69)	<0.001
Executive function	260	93	0.65 (0.51, 0.83)	<0.001	213	36	0.84 (0.61, 1.16)	0.29	473	129	0.68 (0.57, 0.82)	<0.001
Language	267	98	0.58 (0.48, 0.71)	<0.001	222	40	0.76 (0.54, 1.07)	0.12	489	138	0.61 (0.52, 0.72)	<0.001
Visuospatial	260	96	0.69 (0.55, 0.87)	0.002	212	39	0.94 (0.68, 1.30)	0.71	472	135	0.73 (0.61, 0.88)	<0.001
Global score	251	92	0.34 (0.25, 0.47)	<0.001	202	33	0.63 (0.39, 1.00)	0.052	453	125	0.39 (0.30, 0.50)	<0.001

Abbreviations: aMCI = amnesic mild cognitive impairment; CDR-SOB = Clinical Dementia Rating-Sum of Boxes; CI = confidence interval; FAQ = Functional Activities Questionnaire; HR = hazard ratio; MCI = mild cognitive impairment; MD MCI = multiple-domain MCI; naMCI = nonamnesic MCI; ref. = reference; SD MCI = single-domain MCI.

^a Additional estimates for prevalent and incident cases combined were as follows: risk of Alzheimer disease (AD) (HR [95% CI]): MD MCI vs SD MCI, 1.53 (1.04, 2.24), $p = 0.03$; MD aMCI vs MD naMCI, 1.80 (0.79, 4.09), $p = 0.16$; MD aMCI vs SD aMCI, 1.55 (1.01, 2.37), $p = 0.05$; aMCI vs naMCI, 1.41 (0.90, 2.21), $p = 0.14$; risk of non-AD dementia: MD MCI vs SD MCI, 2.31 (1.19, 4.47), $p = 0.01$; MD aMCI vs SD aMCI, 3.96 (1.69, 9.27), $p = 0.002$; SD naMCI vs SD aMCI, 2.25 (0.86, 5.91), $p = 0.10$. Subjects with non-AD dementias were included in the non-AD group in assessing predictors of AD.

^b Higher FAQ and CDR scores indicate greater impairment. The HR represents a 1-unit change (1-point increase) in score.

^c Higher cognitive z scores indicate better performance. HRs <1 indicate a reduced risk of progression with better cognitive function. The HR represents a 1-unit change (1 SD) in the z score. Tests included in the 4 domains were memory, Logical Memory-II and Visual Reproduction-II from the Wechsler Memory Scale-Revised, and the Auditory Verbal Learning Test; executive function, Trail-Making Test B and Digit Symbol Substitution from the Wechsler Adult Intelligence Scale-Revised (WAIS-R); language, Boston Naming Test and category fluency; and visuospatial skills, Picture Completion and Block Design from the WAIS-R. For analytic purposes, the cognitive scores were z-transformed but not adjusted by age. The domain z scores were calculated by scaling the raw scores to have a mean = 0 and SD = 1, based on the mean and SD of the subjects without dementia at baseline. Domain scores were summed and scaled to compute the global score.

Table 3 Predictors of reversion from MCI to cognitively normal

Characteristic	Prevalent MCI				Incident MCI				Prevalent and incident MCI			
	At risk, n	Events, n	HR (95% CI)	p	At risk, n	Events, n	HR (95% CI)	p	At risk, n	Events, n	HR (95% CI)	p
Age, y												
70-79	96	42	1.00 (ref.)		67	31	1.00 (ref.)		163	73	1.00 (ref.)	
80-89	186	61	1.46 (0.67, 3.19)	0.34	185	67	0.37 (0.11, 1.18)	0.09	371	128	0.98 (0.52, 1.83)	0.94
Sex												
Men	162	67	1.00 (ref.)		134	58	1.00 (ref.)		296	125	1.00 (ref.)	
Women	120	36	0.79 (0.52, 1.19)	0.26	118	40	0.79 (0.51, 1.21)	0.27	238	76	0.80 (0.60, 1.08)	0.15
Education, y												
>12	119	41	1.00 (ref.)		117	47	1.00 (ref.)		236	88	1.00 (ref.)	
≤12	163	62	1.28 (0.86, 1.91)	0.23	135	51	0.91 (0.61, 1.36)	0.64	298	113	1.11 (0.84, 1.48)	0.45
Marital status												
Married	174	72	1.00 (ref.)		129	61	1.00 (ref.)		303	133	1.00 (ref.)	
Not married	108	31	0.79 (0.49, 1.27)	0.33	123	37	0.54 (0.34, 0.87)	0.01	231	68	0.64 (0.46, 0.90)	0.009
APOE ε4												
ε22/ε23/ε33	190	80	1.00 (ref.)		170	71	1.00 (ref.)		360	151	1.00 (ref.)	
ε34/ε44	85	21	0.47 (0.29, 0.76)	0.002	68	19	0.62 (0.36, 1.04)	0.07	153	40	0.53 (0.37, 0.75)	<0.001
MCI subtype												
naMCI	79	32	1.00 (ref.)		65	31	1.00 (ref.)		144	63	1.00 (ref.)	
aMCI	203	71	0.72 (0.47, 1.11)	0.14	174	64	0.68 (0.44, 1.07)	0.09	377	135	0.70 (0.52, 0.95)	0.02
SD MCI	185	82	1.00 (ref.)		167	68	1.00 (ref.)		352	150	1.00 (ref.)	
MD MCI	97	21	0.47 (0.29, 0.77)	0.003	72	27	0.74 (0.47, 1.18)	0.21	169	48	0.61 (0.44, 0.85)	0.003
Functional measures (continuous variables)^a												
FAQ	275	102	0.83 (0.75, 0.92)	<0.001	247	95	0.88 (0.80, 0.96)	0.006	522	197	0.85 (0.80, 0.91)	<0.001
CDR-SOB	282	103	0.43 (0.30, 0.61)	<0.001	251	98	0.69 (0.52, 0.91)	0.009	533	201	0.56 (0.45, 0.70)	<0.001
Cognitive z scores (continuous variables)^b												
Memory	279	101	1.64 (1.25, 2.14)	<0.001	234	92	1.84 (1.46, 2.32)	<0.001	513	193	1.61 (1.38, 1.88)	<0.001
Executive function	260	95	1.29 (1.03, 1.62)	0.028	213	86	1.29 (1.03, 1.61)	0.026	473	181	1.28 (1.10, 1.49)	0.002
Language	267	97	1.46 (1.16, 1.84)	0.001	222	89	1.53 (1.17, 2.01)	0.002	489	186	1.51 (1.27, 1.80)	<0.001
Visuospatial	260	96	1.01 (0.81, 1.26)	0.91	212	84	1.35 (1.05, 1.74)	0.018	472	180	1.14 (0.97, 1.33)	0.12
Global z score	251	91	1.82 (1.31, 2.53)	<0.001	202	83	1.97 (1.46, 2.68)	<0.001	453	174	1.80 (1.47, 2.21)	<0.001

Abbreviations: aMCI = amnesic mild cognitive impairment; CDR-SOB = Clinical Dementia Rating-Sum of Boxes; CI = confidence interval; FAQ = Functional Activities Questionnaire; HR = hazard ratio; MCI = mild cognitive impairment; MD MCI = multiple-domain MCI; naMCI = nonamnesic MCI; ref. = reference; SD MCI = single-domain MCI.

^a Higher FAQ and CDR scores indicate greater impairment. HR represents a 1-unit change (1-point increase) in score.

^b Higher cognitive z scores indicate better performance on cognitive testing and an increased risk of reversion to cognitively normal (CN). By contrast, a lower z score reflects lower risk of reversion to CN. For example, for global z score, an HR of 1.80 (prevalent and incident cases combined) indicates an increased risk of reversion to CN and is consistent with an HR of 0.56 indicating a reduced risk of reversion to CN with poorer cognitive function. The HR represents a 1-unit change (1 SD) increase in the z score. Tests included in the 4 domains were memory, Logical Memory-II and Visual Reproduction-II from the Wechsler Memory Scale-Revised, and the Auditory Verbal Learning Test; executive function, Trail-Making Test B and Digit Symbol Substitution from the Wechsler Adult Intelligence Scale-Revised (WAIS-R); language, Boston Naming Test and category fluency; and visuospatial skills, Picture Completion and Block Design from the WAIS-R. For analytic purposes, the cognitive z scores were z-transformed but not adjusted by age. The domain z scores were calculated by scaling the raw scores to have a mean = 0 and SD = 1, based on the mean and SD of the subjects without dementia at baseline. Domain scores were summed and scaled to compute the global score.

pattern may partly explain the higher prevalence and incidence of MCI in men in our previous studies^{10,16}; it is consistent with the higher risk of progression in women but not men with a history of stroke in the

present study, and with studies that have reported higher incidence rates for dementia in women.^{2,8,24-26} Our failure to demonstrate a significant sex difference in risk of MCI progression after adjusting for age and

education may be attributable to the age- by sex-related differences in progression rates, limited power to detect a significant interaction, or to a stronger effect of education on risk of MCI in men observed in our previous studies.^{10,16} In unmarried women, the lower risk of progression to dementia (HR 0.54, $p = 0.01$) and lower risk of reversion to CN (HR 0.64, $p = 0.07$) suggests that they may remain as stable MCI; this remains to be validated.

Our rate of progression to dementia (71.3 per 1,000 person-years) is higher or comparable to rates from population-based studies using similar criteria for MCI. The published rates (per 1,000 person-years) are as follows: 38, Italian Longitudinal Study of Aging, Italy²⁷; 74 (aMCI) and 41 (naMCI) (progression to AD), North Manhattan Study, United States¹; 117, Aging Demographics and Memory Study, United States²⁵; 140, Conselice Study of Brain Ageing, Italy²; approximately 100, Kungsholmen Project, Sweden²⁸; 86, Korean Longitudinal Study on Health and Aging, Korea²⁹; 120, Cache County Study of Memory and Aging³⁰; and 83 (aMCI) and 71 (other cognitive impairment not dementia), Personnes Agées QUID, France.³¹ Possible reasons for the variability across studies may be differences in study design, criteria for MCI diagnosis, and frequency of evaluation and assessment of dementia.

Our estimates of reversion to CN are also consistent with estimates from 2 recent studies.^{7,8} In the Cardiovascular Health Study, 20% of incident MCI cases reverted to CN, and 53% of these subsequently progressed to MCI or dementia.⁸ In a study of patients at Alzheimer's Disease Centers, the rate of reversion to CN was 16% over 1-year follow-up. This lower rate may partly be attributable to the clinic-based design or to a higher frequency of later-stage MCI.⁷ However, more than 50% of those who reverted to CN subsequently developed MCI or dementia, at a 5-fold increased risk. The predictors of increased reversion reported in the 2 studies were consistent with our findings and included better functional status, lower CDR-Sum of Boxes, no *APOE* ε4 allele, better cognitive performance at MCI diagnosis, and having naMCI or SD MCI.⁷

Our findings suggest that a high proportion of subjects with MCI remain stable or progress to dementia. These findings corroborate the growing evidence that MCI is an important clinical entity.³² Although reversion to CN does occur, many subjects subsequently progress back to MCI or dementia. Therefore, subjects who revert may have pathology that leads to cognitive impairment. These subjects may be candidates for clinical trials or timely interventions to reduce their risk of future progression. Reversion to CN may also occur because, as MCI is a clinical diagnosis, it is inherently subject to variability in the subject's performance, the

caregiver's appraisal, interactions between subject and clinician, a learning effect, or to possible diagnostic error. There may, however, be a subset of subjects with mild disease who may not relapse.

A potential limitation to our study is that 99% of participants had Northern European ancestry. Although our rates are applicable to the US white population,³³ they remain to be confirmed in other ethnic groups.

AUTHOR CONTRIBUTIONS

Dr. Roberts: acquisition of data, study concept or design, analysis or interpretation of data, drafting/revising the manuscript, statistical analysis, study supervision, obtaining funding, administrative, technical, or material support. Dr. Knopman: acquisition of data, study concept or design, revising the manuscript, analysis or interpretation of data. Dr. Mielke: drafting/revising the manuscript. Ms. Cha: statistical analysis of data. Dr. Pankratz: statistical analysis and interpretation of data, revising of manuscript. Ms. Christianson: acquisition of data. Dr. Geda: study concept or design, revising the manuscript, acquisition of data. Dr. Boeve: acquisition of data. Dr. Ivnik: study concept or design, acquisition of data. Dr. Tangalos: acquisition of data. Dr. Rocca: study concept or design, analysis and interpretation of data, drafting/revising the manuscript, obtaining funding. Dr. Petersen: acquisition of data, study concept or design, revising the manuscript, administrative, technical, or material support, obtaining funding.

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