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Classification and Epidemiology of MCI

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Abstract

Mild cognitive impairment (MCI) is an intermediate stage in the trajectory from normal cognition to dementia. Despite controversies about the classification of MCI, recent published criteria for MCI allow better comparison of the prevalence, incidence, and outcomes of MCI. Subjects with MCI have a high rate of progression to dementia over a relatively short period. Even among subjects who revert to normal cognition at one point in time, the rate of subsequent MCI or dementia is higher than among those who never develop MCI. Subjects with MCI also experience a greater mortality than cognitively normal subjects. Better characterization of MCI and understanding of the condition, may contribute to development of better diagnostic mechanisms including imaging and fluid biomarkers, and the development of therapeutic, and non-therapeutic interventions for MCI. In this review, we present an overview of the classification of MCI, estimates of the incidence and prevalence of MCI, risk factors for MCI, and the outcomes following an MCI diagnosis.

Keywords

Classification; Epidemiology; Incidence; Mild cognitive impairment; Prevalence; Risk factors

Introduction

Mild cognitive impairment (MCI) is the widely used term that describes an intermediate stage from normal cognitive function to dementia. The concept of MCI is highly significant and important to the field of aging and dementia for several reasons. Subjects with MCI have a high rate of progression to dementia over a relatively short period. Even among subjects who revert to normal cognition, the rate of subsequent MCI or dementia is higher than among those who never develop MCI. Research related to MCI provides insights into disease mechanisms in the pre-dementia stage of disease. The increasing use of imaging modalities to detect abnormalities in brain structure using magnetic resonance imaging, *in vivo* imaging of amyloid accumulation using 11C-Pittsburgh Compound-B positron emission tomography (PiB-PET, plaque density using Florbetapir F18, and the ability to

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Conflict of Interest:
None

detect brain hypometabolism using fluorodeoxyglucose (FDG), has shed light on our understanding of the predictors and prognostic markers for MCI and MCI progression to dementia. Furthermore, studies on cerebrospinal and other fluid biomarkers will have long-term implications for early detection and treatment of MCI and dementia. Finally, studies on MCI may contribute to development of biomarkers for early detection of MCI, strategies for prevention, and development of therapeutic, and non-therapeutic interventions for MCI and dementia. In this review, we present an overview of the classification of MCI, estimates of MCI incidence and prevalence, risk factors for MCI, and the outcomes following an MCI diagnosis.

CLASSIFICATION

Overview

The definition of MCI identifies a symptomatic pre-dementia stage. The earliest reference to MCI described a stage in the severity of dementia;[1] several alternate criteria mostly related to typical cognitive aging, will not be addressed here, but have been described elsewhere.[2, 3] In addition to MCI, two other classifications that will be briefly noted, are cognitive impairment not demented (CIND) which captures a broader spectrum of cognitive impairment, and MCI due to Alzheimer's disease (AD) that primarily identifies persons with an underlying AD pathology.

Mild cognitive impairment

MCI identifies a spectrum of disease that includes impairment in both memory and non-memory cognitive domains.[4–6] This is in contrast to the earlier criteria for MCI where memory impairment was a requirement for the diagnosis.[7] The criteria for MCI are: Cognitive complaint, decline or impairment; objective evidence of impairment in cognitive domains; essentially normal functional activities; not demented (Table 1).[4, 6] The wide spectrum of cognitive and functional impairment that is captured by the MCI designation has an impact on the heterogeneity of outcomes in MCI.

MCI subtypes

A clinical presentation with memory impairment is characterized as amnestic MCI (aMCI), whereas the absence of memory impairment with presence of impairment in one or more non-memory cognitive domains including executive function/attention, language, and visouspatial skills domains, is characterized as non-amnestic MCI (naMCI). This classification by subtype relates to the underlying etiology and pathology, the clinical presentation, and outcomes (Table 2). In addition, MCI may consist of impairment in a single cognitive domain or multiple cognitive domains. The number of affected domains has important implications for understanding the extent of the underlying brain disease or pathology, disease severity, and likelihood of progression to dementia. Multiple-domain MCI denotes a greater extent of disease than single domain MCI, which in turn has implications for a higher rate of progression from MCI to dementia. Information from both the MCI phenotype (aMCI vs. naMCI) and the number of cognitive domains affected (single vs. multiple) is hypothesized to determine future outcomes. Single or multiple domain aMCI is hypothesized to progress to AD if there is an underlying degenerative etiology.[6] In contrast, naMCI may progress to non-AD dementias such as frontotemporal dementia if a single domain is affected with a degenerative etiology or Dementia with Lewy Bodies if multiple domains are affected with a degenerative etiology.[6] Although there is inadequate research in this area, it is likely that any MCI subtype could precede vascular dementia.

Cognitively impaired, not demented (CIND)

The concept of CIND is a broader definition of impairment that encompasses subjects who meet criteria for MCI as well as others who are cognitively impaired but do not meet all the criteria for MCI.[8–10] The criteria for CIND include participant or informant-reported significant decline in cognition or function; physician-detected significant impairment in cognition; cognitive test score (s) at least 1.5 SD below the mean compared to normative data; no clinically important impairment in activities of daily living assessed by physician/informant; absence of dementia (Table 1).

Subtypes of CIND

Subtypes of CIND are based on presumed etiology; they typically include: circumscribed (or medically unexplained) memory impairment, delirium, chronic alcohol and drug use, depression, psychiatric illness, and mental retardation, and other cognitive impairment. Others medical illness, stroke or cerebrovascular disease,[9] as many as 12 categories have been noted.[10] To our knowledge, diagnostic criteria using CIND that link the syndrome to biomarkers have not been developed.

MCI due to AD

The classification of MCI due to AD was developed by the National Institute on Aging (NIA) and the Alzheimer's Association (AA) primarily for research purposes.[11] The motivation was to link the MCI syndrome to a specific etiology by the use of biomarkers for AD. It is based on a clinical criteria for MCI described above, in combination with additional information from structural magnetic resonance imaging, PIB-PET, FDG-PET, and cerebrospinal fluid biomarkers, and determines the certainty with which a person with MCI has underlying AD pathology. This level of certainty is determined from; 1) evidence of amyloid β accumulation in the brain assessed by positron emission tomography (PET), decreased cerebrospinal fluid (CSF) levels of amyloid β (Aβ42), and 2) evidence of neuronal injury assessed as increased CSF tau (total and phosphorylated), brain hypometabolism assessed from ^{18}fluorodeoxyglucose PET, and hippocampal atrophy from structural magnetic resonance imaging. The utility of this classification is the potential prognostic value for future dementia outcomes. Subjects with a high likelihood of MCI due to AD have a greater certainty of progression to AD. The clinical utility of this classification system remains to be established.

RISK AND PROTECTIVE FACTORS FOR MCI

Several risk factors have been identified for MCI. These include non-modifiable risk factors such as age, sex, genetic factors, and modifiable risk factors such as level of education, vascular risk factors, cardiovascular outcomes, neuropsychiatric conditions, and imaging biomarkers (Table 3). There is a large body of literature on associations of these risk factors with MCI that cannot be thoroughly vetted in this review. In some reports cognitive and functional severity ratings are considered to be risk- or protective-factors for progression to dementia, but because the features underlying these ratings are actually metrics for the severity of cerebral dysfunction, these features should be considered in a separate category from demographic, genetic, and medical risk factors.

PREVALANCE AND INCIDENCE OF MCI

MCI prevalence

Several different criteria have been described for MCI. Therefore, we have limited our review of prevalence studies to those that used the more recently published criteria for MCI,[4, 5, 12] studies with an adequate sample size (≥ 300 participants); population-based

studies, studies that provided a clear description of participant recruitment, clear description of MCI criteria and how the criteria were operationalized; and studies that recruited participants at 60 years and older. These inclusion criteria allow us to compare estimates across studies of similar design. We also include a few representative studies that used the earlier criteria for aMCI, published criteria for CIND, purely algorithmic criteria for MCI, and a clinic-based study of MCI. However, we excluded studies that were restricted to a narrow age range or to the oldest old ≥ 90 years[13, 14] since these studies have limited generalizability, and earlier studies that used definitions of cognitive impairment that are not consistent with the current MCI definition such as benign senescent forgetfulness,[15] age associated memory impairment,[16] and age-associated cognitive decline.[17]

Prevalence estimates of MCI ranged from 16% to 20% for the majority of the reviewed studies (Table 4). A few studies had very high estimates that could be due to issues with non-participation or elements peculiar to the study.[18] Estimates from studies conducted in urban sites, multiethnic cohorts, and in clinic-based studies were also at the higher end of the spectrum.

MCI incidence

In contrast to prevalence studies, there are fewer studies on MCI incidence rates.[19] There is a wide range of incidence rates (1000 person years) from 5.1 to 168 (Table 5). A few studies reported estimates of incident aMCI only and these ranged from 10 to 14. The key risk factors for MCI described from these incident studies included older age, low education, and APOE ε4 allele. In addition, cardiovascular disease (type 2 diabetes), Black and Hispanic ethnicity, subjective memory complaints, and stroke have also been associated with incident MCI.

MCI OUTCOMES

Progression to dementia

An important MCI outcome is the increased risk of progression to dementia.[20] In fact, the designation of MCI, in addition to characterizing a particular level of cognitive and functional impairment, also carries with it a prognosis that is decidedly less favorable than persons with normal cognition. The majority of studies reported rates of progression from MCI to dementia from 20–40% (10–15% per year) with a few outliers at the lower and higher ends of the spectrum (Table 6). Several of the studies also demonstrate that subjects with MCI progress to dementia at a higher rate than cognitively normal subjects. These studies indicate that a higher frequency of subjects with MCI remain in the MCI stage or progress to dementia, than revert to normal cognition.

Risk factors for progression to dementia

Interestingly, risk factors for progression have not been consistently found to be the same as the risk factors for incident MCI (Table 6). For example, some studies have observed an association of vascular risk factors with progression to dementia,[21, 22] but others have not.[23] However, markers for the severity of the underlying pathology and cerebral dysfunction have more consistently been associated with progression to dementia. These include the degree of functional impairment, severity of neuropsychological test scores,[24] and presence of neuropsychiatric behaviors[25] at the time of MCI diagnosis. In addition, abnormalities in structural magnetic resonance imaging (e.g. hippocampal atrophy, volumetric brain changes) and magnetic resonance spectroscopy of the brain are associated with increased risk of progression.[26, 27]

MCI reversion to normal

An interesting outcome of MCI is that of reversion to normal cognitive function at a subsequent evaluation (Table 6). Rather than representing a flaw in the concept, the observations of reversion to normal among individuals points out an inherent clinical feature of the syndrome, namely that its severity exhibits slow oscillations over time. On average, about 20% of subjects with MCI will improve over time. Despite this, subjects who revert to normal cognition may not be altogether cognitively normal. These subjects have a greater likelihood of progression to MCI or dementia at a subsequent evaluation than do subjects who never developed MCI[28, 29] (Roberts, RO-unpublished data). This suggests that subjects who revert to normal may already have some degree of underlying brain pathology.

Risk factors for reversion

Risk factors for reversion to normal appear, in general, to be the opposite of those that predict progression to dementia (Table 6). Factors that have been associated with increased risk of reversion to normal include demographic factors: younger age, male sex; markers of MCI severity at the diagnosis: single domain MCI, higher Mini-Mental State Examination (MMSE), lower CDR sum of boxes, MCI type (naMCI), lower Functional Activities Questionnaire score; absence of medical conditions, and alcohol abuse (reversible condition). One study suggested that reversion to normal was less likely with higher than lower levels of education.[30] This may be consistent with studies that suggest that higher levels of education provide greater cognitive reserve that may reduce the clinical expression of symptoms; however, they may have greater underlying disease pathology at the time of presentation of MCI or dementia.[31–33]

MCI mortality

There are relatively few studies on mortality in persons with MCI. These studies suggest an increased mortality among subjects with MCI compared to cognitively normal subjects.[10, 34, 35] In one study, however, the rate (per 1,000 person years) was higher in cognitively normal subjects than in MCI cases (27.0) who progressed to dementia (41.3).[29] This may have occurred because the period of follow-up was assessed from the time when participants were cognitively normal rather than when they had MCI or dementia, thus attributing a longer follow-up including times when subjects did not actually have MCI or dementia.

DISCUSSION

MCI is an important public health concern due to the increased risk of progression to dementia and increased mortality. However, certain issues hinder the clinical utility of the diagnosis. In particular, cognitive and functional severity within the MCI definition varies over a wide range, so that the syndrome of MCI is not homogeneous. The variability in prevalence rates, incidence rates, and rates of progression to dementia underscores the need to recognize that heterogeneity, and to develop standardized criteria for diagnosis of MCI that are easy to operationalize, have high reliability and validity in the clinical setting, and yield consistent estimates across studies. The clinical utility of imaging and cerebrospinal fluid biomarkers in the diagnosis of MCI is yet to be established. However, there are strong suggestions from the research literature that including these biomarkers in the MCI criteria may result in a greater sensitivity and specificity of the MCI diagnosis, greater predictive value positive and negative, and may have greater prognostic implications than the current MCI definition. There is considerable research yet to be done before the biomarkers can be used for diagnosis in routine clinical care. Factors that would limit their inclusion in routine care, however, include the cost of the imaging procedures and the invasiveness of the lumbar puncture to acquire CSF.

Variability in estimates of MCI prevalence and incidence

Several methodological reasons have been proposed for varying estimates of MCI prevalence and incidence across studies. These include the source of subjects (population-based vs. clinic based), the criteria used for MCI, how these MCI criteria were operationalized, domain scores vs. single global tests, cut-points for abnormality for neuropsychological test scores (≥ 1SD vs ≥ 1.5 SD), number of tests used to assess abnormality; and the use of clinical vs. algorithmic approaches (not informant based) to assign an MCI diagnosis. Although there were relatively few outliers in the selected studies for prevalence, there were some differences. Studies in Europe, specifically Finland and Germany reported lower estimates of prevalence,[36, 37] than the more comparable estimates reported across the US studies.[38] In the US, estimates were higher for studies in larger cities[39, 40] and studies including ethnic groups other than whites.[9] Differences in how MCI criteria were applied may have resulted in higher estimates of prevalence in the Sydney and Aging Study in Australia.[18] than in the Mayo Clinic Study of Aging in the US[41] even though the study designs were similar. The original description of the MCI criteria were intended to guide clinicians rather than to be used as absolute cut-points for assigning abnormality.[42] Even when an algorithmic classification was used in two studies, retrospective application of MCI criteria to previously collected data yielded low estimates of prevalence[43] compared to concurrent application of MCI criteria.[44] As expected, the estimate from a clinic-based design was on the higher end of the spectrum.[45] Finally, estimates across studies may vary when a single test was used to assess cognition, and whether or not cognitive test scores were compared to normative data.

The variability in incidence rates across studies was even greater than for prevalence estimates. This could be due to the same issues as for prevalence: differences in sample size, MCI criteria and they were operationalized, cut-points for cognitive scores, but also to differences in duration of follow-up for endpoints.[38] It is not sufficient to compare summary rates only; comparison of age-specific rates are important since MCI is an age-related condition. However, not all studies provide age specific rates, and when they do, age ranges for estimates are not consistent across studies.[38] While the majority reported rates per 1,000 person years, some studies only reported the percent of people who had progressed from MCI to normal, making it even more difficult to compare rates across studies.

Clinical implications of MCI progression, reversion, and mortality

The high rate of progression to dementia among subjects with MCI emphasizes the need to identify methods to prevent MCI, reduce the burden of MCI, and identify those at increased risk of MCI who may benefit from early interventions. Furthermore, considering that a high proportion of risk factors are preventable, it is essential that physicians and health care personnel 1) educate their patients on how to reduce their risk of MCI through dietary measures, exercise, engagement in cognitively stimulating activities, stroke prevention; 2) detect and reduce risk factors and achieve adequate control of cardiovascular risk factors and outcomes; and 3) initiate non-therapeutic and therapeutic interventions when they become available. These measures have the potential to reduce the risk of MCI, with direct beneficial implications for progression from MCI to dementia, and reduced mortality from MCI.

Several studies have now established that subjects with MCI may improve to a cognitively normal state at a subsequent follow-up. This phenomenon has been observed not only in population-based studies with a milder disease spectrum of MCI cases, but also among subjects seen at memory clinics where a narrower and more severe disease spectrum of MCI would be expected.[28] This suggests that the phenomenon is real and not simply a function of diagnostic characterization, but may actually be due to oscillations or variations in

manifestation of symptoms from one evaluation to the next, until the all-absorbing state of dementia occurs. Subjects who revert to normal after MCI may differ from subjects who never develop MCI. The higher risk of progression to MCI or dementia in persons who revert, suggests the control and risk factors and presence of an underlying brain pathology. These subjects require active follow-up and timely intervention to prevent decline to dementia.

SUMMARY

MCI is a stage that is potentially amenable to interventions that may prevent further decline to dementia the stage of cognitive impairment that has more substantial impact on daily function. The classification of MCI is improving over time, and inclusion of imaging and other biomarkers may further enhance the detection of subjects with MCI. This would facilitate comparisons across studies, contribute to better selection of subjects for clinical trials, enhance the detection of clinical trials outcomes, provide a better understanding of MCI outcomes, and contribute to early detection of subjects with MCI. Subjects with MCI may benefit from interventions that will reduce their risk of progression to dementia, and may be eligible for treatment with disease modifying drugs that reverse previous damage or prevent further decline, when such treatments become available.

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Key Points

1. The prevalence and incidence of MCI is high among elderly persons.
2. Persons with MCI have a high risk of progression to dementia.
3. Several risk factors for MCI are potentially modifiable and amenable to interventions to reduce risk.
4. Persons with MCI have a higher mortality than cognitively normal persons.
5. Persons with MCI who revert to normal have a higher risk of developing MCI or dementia at a later date.

Table 1

Criteria for MCI and CIND

MCI
Cognitive complaint, cognitive decline or impairment
Objective evidence of impairment in cognitive domains: memory, executive function/attention, language, or visuospatial skills
Essentially normal functional activities
Absence of dementia
CIND
Participant or informant-reported significant decline in cognition or function;
Physician-detected significant impairment in cognition
Cognitive test score (s) at least 1.5 SD below the mean of published norms
No clinically important impairment in activities of daily living assessed by physician/informant
Absence of dementia

MCI, mild cognitive impairment; CIND, cognitive impairment, no dementia

Table 2

MCI subtypes by etiology, pathology, presentation and outcomes

Variable	Amnestic	Non-amnestic
Etiology	Neurodegenerative disease	Vascular damage
	APOE ε4	Cerebrovascular disease
Pathology	Neurodegenerative	Cerebrovascular
	Amyloid β plaques	Cortical infarctions
	Neurofibrillary tangles	Subcortical infarctions
	Hippocampal atrophy	White matter hyperintensities
	Reduced brain volume	
Presentation	Memory impairment present	Impairment in non-memory domains
Long term outcomes	Alzheimer's dementia (AD)	Non-Alzheimer dementias: Vascular dementia
		Lewy body, Frontotemporal

MCI, mild cognitive impairment; APOE, apolipoprotein E.

Table 3

Risk factors for MCI

Older age
Apoplipoprotein ε4 allele
Sex: Higher in men,[10, 36, 41, 43, 46, 47] higher in women,[45] and no sex difference.[48]
Low number of years of education
Vascular risk factors: Type 2 diabetes, hypertension, obesity, dyslipidemia, smoking
Cardiovascular disease outcomes: coronary artery disease, atrial fibrillation, congestive heart failure, cerebrovascular disease
Systemic inflammation: C-reactive protein.
Neuropsychiatric conditions: depression, anxiety, apathy.
Protective factors
Higher education
Cognitively stimulating activities
Physical exercise/activities
Dietary factors: mono and polyunsaturated fatty acids
Mediterranean diet

Table 4

Prevalence rates for MCI

Publication	Country	Design & criteria for MCI	N	Age, yrs	Prevalence (%)
Hanninen, 2002[36]	Kuopio, Finland	Population-based sample.	806	60–76	Overall, 6.5%. aMCI, 5.3%; Age 60–64 years, 2.4%; 65–69, 4.8%, 70–76, 8.4% Men, 7.1%); women (4.1%
Busse, 2003[37]	Leipzig Longitudinal Study of the Aged, Germany	Population-based, prospective, community dwelling cohort.	929	≥ 75	Overall, 5.1%; Age 75–59, 4.7%; 75–79, 5.6%; ≥ 85, 5.2%.
Fisk, 2003[49]	Canadian Study of Health and Aging, Canada	Population-based, aMCI criteria. Urban and rural cohort	1,790	≥ 65	aMCI, 2.4%. No sex or age-specific estimates provided
Lopez, 2003[48]	Cardiovascular health Study, US	Representative prospective, multiethnic, cohort. Predominantly urban setting.	2,470	≥ 75	Overall, 18.8%. <70, 75–79, 14.7%, 80–84: 22.6, 19%; ≥ 85, 28.9%. Men, 19%; women, 18.7%
Manly, 2005[39]	North Manhattan study, US	Prospective, population-based, multi-ethnic cohort. MCI criteria. Urban setting.	1,315	≥ 65	Overall, 28.3% Age 65–75 years, 24.0%; > 75, 32.6%. No sex difference
Busse, 2006[50]	Leipzig Longitudinal Study of the Aged, Germany	Population based, prospective study. Community dwelling cohort.	980	≥ 75	Overall, 19.4% (9.3% if subjective memory complaint criterion excluded); No age- and sex-specific rates reported.
Das, 2007[51]	Kolkata, India	Cross-sectional design. Systematic random sampling within city blocks, random sampling within households. Urban setting. aMCI criteria and multiple domain *.	745	≥ 50	aMCI, 14.9% Age 65–69: 11.7%, 70–74, 12.3%, 75–79: 17.9%, ≥ 80, 10.6%. Men: 7.6%; women, 4.5%; Multiple domain: Men 6.3%, women: 11.4%.
Artero, 2008[40]	3 City Study, France	Population-based, community dwelling: Revised published MCI consensus criteria	6,892	≥ 65	Overall, 42% (frequency)
Petersen, 2010[46]	Mayo Clinic Study of Aging	Population-based, Published MCI criteria	1969	70–89	Overall, 16.0%; Age 70–79, 12.1%; 80–89, 22.2% Men:19.0%; Women: 14.1%
Sachdev, 2012[18]	Sydney Memory and Aging Study, Australia	Population based. Published MCI criteria	757	70–90	Overall: 39.1%. Age 70–79, 36.7%; 80–89: 43.3%. Men: 70–79, 41.9%, ≥ 80: 43.6%. Women: 70–79, 32.2% ≥ 80, 43.0%.
Unverzagt, 2001[9]	Indianapolis Study of Health and Aging, Indianapolis, US	Representative sample of community-dwelling, African American, CIND	2212	≥ 65	Overall, 23.4% Age 65–74, 19.2%; 75–84: 27.6%, ≥ 85, 38%.
Plassman, 2008[10]	Aging, Demographics, and Memory Study, USA	Population-based, nationally representative Criteria: exclusion of dementia & other impairments, cognitive testing battery, CIND	856	≥ 71	Overall: 22.2% Age 71–79:16.0%; 80–89, 29.2% ≥ 90, 39.0% Men vs. women: OR, 1.62 (95%CI, 1.09, 2.41)
Luck, 2007[45]	Ageing, Cognition, Dementia in Primary Care Patients, Germany	General practice; clinic-based. Published MCI criteria.	3,242	≥ 5	Overall, 25.2% Age 75–79, 24.6; 80–84. 24.2; 85–98, 32.8 Women vs. men; OR, 1.36, (95%CI, 1.14–1.63)

Publication	Country	Design & criteria for MCI	N	Age, yrs	Prevalence (%)
Ganguli, 2004[43]	Monongahela Valley Independent Elders Survey, US	Representative community-based, prospective cohort, aMCI criteria applied to previously collected data. Algorithmic criteria *	1248	≥ 75	Overall, 6.3%. No age-specific rates. Men vs. women: OR 1.9 (95% CI, 1.3, 2.8; p = .001).
Ganguli, 2010[44]	Monongahela-Youghiogheny Healthy Aging Team Project, USA	Population-based. Purely cognitively defined MCI, modified expanded MCI criteria; algorithmic classification *.	1982	≥ 65	17.7%

MCI, mild cognitive impairment; CIND< cognitive impairment, no dementia; CIND cognitive impairment, not demented.

* Based on neuropsychological testing

Table 5

Incidence rates and risk factors for MCI

Incidence Studies	Study, country	Design, follow-up	N	Age, yrs	Incidence (per 1,000 pyrs) or frequency (%)	Risk factors
Larrieu, 2002[52]	Personnes Agees QUID study, France	Population-based, 5 years.	1,265	≥ 65	9.9/1,000 (aMCI)	Female sex Higher education
Busse, 2003[37]	Leipzig Longitudinal Study of the Aged, Germany	Population-based, 1,756 person-years	684	≥ 75	8.5/1,000 (aMCI)	Not reported
Tervo, 2004[53]	Kuopio, Finland	Population-based, 3.3 years (aMCI criteria).	550	60–76	25.9/1,000 pyrs (aMCI)	Older age, low education, APOE ε4, treated hypertension cardiovascular disease.
Solfrizzi, 2004[54]	Italian Longitudinal Study on Aging, Italy	Population-based, 3.5 yrs follow-up (retroactively applied MCI criteria).	2,963	65–84	21.5/1,000 pyrs	Older age, low education.
Palmer, 2008[55]	Kungsholmen Project, Sweden	Population-based; 3.4 years	379	≥ 75	168/1,000; single domain aMCI, 34/1000, single domain naMCI, 82/1000, multiple domain MCI: 52/1000 person-yrs	Not reported
Carraciolo, 2008[56]	Kungsholmen Project, Sweden	Population-based; 9 years (4,292 person years)	1,070	≥ 75	aMCI: 13.7/1,000; other cognitive impairment: 42.1/1000.	Older age, higher risk in men
Manly, 2008[57]	North Manhattan study, US	Multi-racial cohort; mean 4.7 yrs (7504.9 person years of follow-up	1800	≥ 65	Overall, Incidence 5.1% aMCI, 2.3%; naMCI, 2.8/%	Older age Ethnicity Black, Hispanic greater than white ethnicity. Hypertension
Ravaglia, 2008[58]	Conselice Study of Brain Ageing, Italy	Population–based, mean, 3.8 years	685	≥ 65	76.8/1000	Not reported
Luck, 2010[59]	Leipzig Longitudinal Study of Aging Germany,	Population-based, 8 years of follow-up.	732	≥ 75 yrs	Overall: 76.5/1,000 pyrs aMCI: 27.9/1000 pys naMCI: 48.6/1000 pyrs	Older age, Subjective memory complaints:
Roberts, 2012[41]	Mayo Clinic Study of Aging, USA	Population-based; 3.4 years follow-up	1,450	≥ 70	63.6 per 1,000 pyrs aMCI;37.7; naMCI:14.7	Older age Male sex
Luck, 2010[60]	German Study on Ageing, Cognition and dementia in Primary Care Patients, Germany	Community-dwelling patients of general practitioners; 3 years (6,198 person years)	2331	≥ 75	56.5/1000 pyrs aMCI: 12.3/1000, naMCI: 49.8/1000 Age: 75–79; 52.7; 80–84; 55.4, ≥ 85, 94.0. Men, 60.4, women, 54.4.	Older age, stroke, APOE ε4 allele, subjective memory complaints.

Pyrs, person years; MCI, mild cognitive impairment; aMCI, amnestic MCI; naMCI, non-amnestic MCI;

Table 6

Rates of progression from MCI to dementia, predictors of progression and reversion from MCI to normal cognition

Citation	Study	MCI cases, years of follow-up	Progression to dementia (1,000 pyrs) or frequency MCI (% who progressed)	Predictors of progression	Reversion rate (% who reverted to normal), predictors
Unverzagt, 2001[9]	Indianapolis Study of Health and Aging, Indianapolis, US	Prevalent cases, 66. Follow-up, 18 months.	26% progressed to dementia; 50% had stable CIND	Stroke or cerebrovascular disease, medically unexplained memory loss.	24% reversion. Highest rates: other/indeterminate, with alcohol abuse.
Larrieu, 2002[52]	Personnes Agées Quid, France	Prevalent or incident MCI, 409 cases. Follow-up, 5 years	8.3% per year Progression to AD: aMCI: 83/1,000 pyrs, OCIND, 71/1,000 pyrs. Non-AD dementia: aMCI, 7.5/1,000 pyrs OCIND, 17/1,000 pyrs	aMCI predicted AD OCIND predicted non-AD dementia	41% reversion in prevalent MCI cases at 2-year follow-up
Solfrizzi, 2004[54]	Italian Longitudinal Study on Aging, Italy	Prevalent MCI, 72 cases with follow-up. Follow-up, 3.5 years.	Progression, 38/1000 pyrs (20.8% progressed). 41.7% remained MCI or declined further.	Stroke. No age or sex association.	37.5% improved
Artero, 2008[40]	3 Cities Study, France	Prevalent MCI, 2882 cases. Follow-up, 4 years	6.6% (n = 189) incident dementia, 56.5% stable MCI.	APOE ε4 allele, stroke, low education, impaired IADL, older age, hypertension, diabetes, stroke, subclinical depression, anticholinergic drugs, poor health status.	37% reversion. Men (39%) more likely to revert to normal vs. women (36%, p = .02)
Manly, 2008[57]	North Manhattan study, US	Prevalent or incident MCI, 564 cases. Follow-up, 4.7 yrs	21.8% MCI progressed to AD (5.4% per year) vs. 10.3% progression in cognitively normal. Stable MCI: 46.5%.	Older age, lower education, ethnicity (black, hispanic), APOE ε4 allele, type 2 diabetes, stroke, multi-domain MCI	30.2% reversion. Highest reversion rate for single domain MCI, lowest rate for multiple domain MCI.
Plassman, 2008[10]	Aging, Demographics, and Memory Study, US	Prevalent MCI, n = 180. Mean follow-up, 17 months.	16.7% progression to dementia (11.7% per year); stable 63.8% stable MCI.	Older age, lower education, trend for women. No association with race or APOE ε4 allele.	19.6% reversion.
Ravaglia, 2008[58]	Conselice Study of Brain Ageing, Italy	Prevalent MCI: n = 60 cases. Follow-up, 3.8 years	41.7% progressed to dementia (14% per year vs. 4% in cognitively normal). 65% (13/20 with without dementia) had stable MCI.	Older age, APOE ε4 allele, women, low level of education, lower MMSE scores, aMCI, multi-domain MCI.	35% reversion (7/20 of those without dementia).
Tervo, 2004[53]	Kuopio, Finland		60–76		
Palmer, 2008[55]	Kungsholmen Project, Sweden	Prevalent MCI n = 350; 3.4 years (11,961. follow-up	20.3% of 350 had incident dementia (77.5% had AD)	Progression higher with multi-domain MCI (HR, 23.6) and aMCI (HR, 17.9).	Not reported
Farias, 2009[24]	University of California Alzheimer's disease Center, US	Clinic and community based participants, 111 cases. Follow-up 2.4 years.	Total sample: 10% per year conversion to dementia; 13% for clinic sample: 3% per year for community sample.	Clinic recruitment, CDR at baseline (i.e. functional impairment), white matter hyperintensity volume.	Not reported

Citation	Study	MCI cases, years of follow-up	Progression to dementia (1,000 pyrs) or frequency MCI (% who progressed)	Predictors of progression	Reversion rate (% who reverted to normal), predictors
Luck, 2012[61]	German study on Aging, Cognition, and Dementia in Primary Care patients, Germany	Prevalent MCI, 483 cases. Follow-up, 4.5 years.	Progression, 73/1,000 pyrs (24.2%) in MCI cases vs. 21.6/1,000 pyrs (8.2%) in cognitively normal.	Impairment in IADL, older age, stroke, depressive symptoms, APOE ε4 allele	Not reported.
Mauri, 2012[62]	Laboratory of Neuropsychology & Alzheimer's Assessment Unit, Italy	Clinic-based 208 patients with aMCI, Follow-up, 6 years. Case-control design.	68% progression	Neuropsychiatric symptoms (Neuropsychiatric Inventory score ≥ 4); apathy.	Not reported.
Han, 2012[30]	Korean Longitudinal Study on Health and Aging, Korea	Prevalent MCI, 140 cases. Mean follow-up, 1.57 years.	13.6% progressed to dementia (8.64% per year conversion); 57.9% stable MCI.	Multi-domain MCI, low MMSE score.	28.6% reversion, (18.2% per year). Lower rate of reversion: multi-domain MCI, higher education, higher MMSE score.
Peters, 2012[63]	Cache County Study of Memory Health and Aging, US	Prevalent CIND, 230 cases. Follow-up, 3.3 years.	37% progressed to dementia (12.2% per yr); stable MCI 63%.	Older age, APOE ε4 allele low MMSE, high CDR Sum of boxes neuropsychiatric symptoms, nighttime behaviors.	
Lopez, 2012[29]	Pittsburgh Cardiovascular Health Study, US	Incident MCI, 200 cases. Follow-up, mean, 2.8 years.	53.5% progressed to dementia; 46.5% had stable MCI.	Older age, women, lower MMSE score,	20% reversion.
Koepsell, 2012[28]	Participants recruited from 33 Alzheimer's Disease Centers, US	Prevalent and incident MCI: n = 3020. Follow-up: 3 years (reversion to normal, 1 year)	20% progressed to dementia; 64% stable MCI.	Not reported.	16% reversion, Higher risk for: younger age, no APOE ε4; higher MMSE, lower CDR sum of boxes, aMCI, multi-domain MCI, low FAQ score.
Roberts RO; Neurology 2012 (unpublished data)	Mayo Clinic Study of Aging, USA	MCI cases: 478 (282 prevalent, 196 incident). Follow-up, median 2.5 years	Incidence: 82.1 per 1,000 pyrs. 27.6% progressed to dementia (2% (11) had 1 reversion to normal); 39.5% had stable MCI.	Higher progression rates for women (but non-significantly elevated risk), aMCI, and multi-domain MCI.	35.2% (15.7 per 100 pyrs). Lower risk for: aMCI, multi-domain MCI, APOE ε4 allele, high FAQ score, not married.

Abbreviations: pyrs, person-years; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating Scale; MCI, mild cognitive impairment, FAQ, Functional Activities Questionnaire; APOE, apolipoprotein E, OCIND, other cognitive impairment, not demented; aMCI, amnestic MCI, naMCI, non-amnestic MCI; IADL, Instrumental Activities of Daily Living.