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Center for International Rehabilitation Research Information and Exchange (CIRRIE)
515 Kimball Tower
University at Buffalo, The State University of New York
Buffalo, NY 14214
E-mail: ub-cirrie@buffalo.edu
Web: http://cirrie.buffalo.edu

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Mild Cognitive Impairment: Case Definitions, Age, and Other Risk Factors

Lesley J. Ritchie, M.Sc.
University of Victoria
Victoria, BC, Canada

Holly Tuokko, Ph.D. (Corresponding author)
University of Victoria
PO Box 1700 STN CSC
Victoria, BC
Canada V8W 2Y2
Telephone: 250 721-6576
Fax: 250 721-6499
Email: htuokko@uvic.ca

The term Mild Cognitive Impairment (MCI) has emerged in the context of the study of aging and implies a descriptive, quantified, behavioral classification. Identifying people with MCI involves specifying those cognitive and behavioral functions to be considered, and the procedure for their quantification. Inherent in the definition is the notion of decline or change in function. MCI typically implies an underlying pathology and poor eventual outcome (e.g., dementia, institutionalization, death). Such a classification is highly important to researchers and clinicians faced with an increasing proportion of older adults in the population, many of whom will be expected to exhibit some form of cognitive impairment that may interfere with their abilities to function independently in society.

According to the World Health Organization (2009), the number of persons aged 60 years and older will increase two-fold to 1.2 billion people by 2025. This finding has important healthcare and caregiver implications as the prevalence of cognitive impairment is positively related to advancing age. In Canada, persons aged 65 years and older represent the fastest growing population, with an 11.5% increase in prevalence between 2001 and 2006 (Statistics Canada 2009) and dementia and cognitive impairment not meeting the criteria for dementia are estimated to affect 8% and 16.8% of Canadians aged 65 years and older, respectively (Graham et al. 1997).

Historically, there have two approaches to defining cognitive decline with age: 1) that which is considered part of the normal aging process, and 2) that which is associated with underlying pathology and considered an atypical or abnormal aging process. From the first perspective, cognitive decline has been described as a natural and normal process experienced by the aged (Table 1). Kral (1962, 1966) introduced benign senescent forgetfulness (BSF) as an age-related process involving general forgetfulness and difficulty recalling factual information (i.e., names, dates), with preserved global knowledge and intact awareness of deficits. He coined the term malignant senescent

forgetfulness (MSF) to describe the rapidly progressing age-related process of memory impairment (both recent and remote memories) and loss of awareness of deficits.

Over time, descriptions of cognitive decline associated with aging have progressed to include detailed diagnostic criteria. For example, the National Institute of Mental Health (NIMH) work group proposed a set of criteria for the diagnosis of "age-associated memory impairment" (AAMI; Crook et al. 1986; Table 1). The NIMH AAMI criteria have been criticized for failing to reflect a decline in cognitive performance and an age- or disease-related process (Davis and Rockwood 2004). For example, persons with low premorbid functioning or limited education may qualify for a diagnosis of AAMI (Davis and Rockwood 2004). Moreover, using the proposed AAMI criteria, the majority of persons aged 65+ years qualify for a diagnosis (Bamford and Caine 1988). To improve the diagnostic criteria, Blackford and LaRue (1989) restricted the age range to apply to persons aged 50-79 years and altered the NIMH criteria for AAMI to reflect impaired performance (at least one standard deviation below the mean) on at least one memory test, as compared to young adults. They also created the classifications of age-consistent memory impairment (ACMI) and late-life forgetfulness (LLF).

From the second perspective, cognitive decline is viewed as a pathological process. The aforementioned conceptualizations of cognitive impairment are based on a model of normal aging, rather than a disease-related process, and they fail to address impairment in other cognitive and functional abilities necessary for a diagnosis of dementia (Smith et al., 1996). The American Psychiatric Association (APA 2000) criteria for dementia are listed in Table 2. More recently, definitions with specific diagnostic criteria for MCI as a precursor to dementia have been proposed (Table 3). It is hypothesized that the American, diseased-based, definitions of MCI create more attractive conceptualizations of MCI as a precursor to dementia and introduce the opportunity for intervention (Ritchie, Artero and Touchon 2001).

Perhaps the most prominent classification of MCI is Petersen et al.'s (1999) original definition requiring a subjective memory complaint, impaired performance on objective memory tests, intact cognitive function, intact functional abilities, and a non-demented status. Despite the proposed clinical criteria, the diagnosis of MCI is described as being the result of clinical judgment (Petersen 2003). Petersen further contends that, for persons "*destined to develop dementia*" (2003, p.2; italics in original text), MCI represents an intermediary stage on a gradual clinical and pathological continuum from normal aging to dementia (Petersen 2006). In 1999, Petersen and colleagues reported a conversion rate of 12% from MCI (as defined by their clinical criteria) to AD, in a clinical population. An evidence-based review of the literature revealed a rate of progression ranging from 6% to 25% (Petersen et al. 2001). Larrieu et al. (2002) subsequently reported a conversion rate of 8.3% in a longitudinal population-based sample.

The contention that MCI is indicative of incipient dementia has received much criticism. It has been suggested that Petersen et al.'s (1999) conceptualization of MCI is too stringent and hinders the accurate and early detection of persons exhibiting MCI who

subsequently progress to a dementia other than AD (Low et al. 2004). For example, in a longitudinal, population-based study, the MCI classification was found to be a poor predictor of senile dementia, identifying only 11% of persons who went on to dement (Ritchie, Artero and Touchon 2001). Moreover, the MCI classification is reported to be unstable, as many (~ 40%) MCI subjects fail to meet MCI criteria the following year and revert to a diagnosis of no cognitive impairment (Ritchie et al. 2001; Larrieu et al. 2002).

Researchers also attribute the instability of the MCI classification to its reliance on impaired memory as the primary symptom (Ritchie et al., 2001). Evidence suggests that the cognitive impairment in MCI often includes deficits in multiple cognitive domains (Loewenstein, Acevedo, Agron, and Duara 2007; Morris et al. 2001). Even persons classified with MCI have been found to demonstrate poor performance on measures of executive function, category fluency, and design fluency (Kramer et al. 2006). Moreover, persons exhibiting multiple cognitive impairments have a higher rate of conversion to dementia. Bozoki and colleagues (2001) report two-year conversion rates of 6% for persons with memory impairment only, compared to 48% for those with memory impairment plus deficit in at least one of language, attention, visuospatial function, and executive functioning. Additionally, most individuals diagnosed with MCI exhibit deficits beyond just memory impairment (Busse, Hensel, Gühen, Angermeyer, and Riedel-Heller 2006).

Over the years, Petersen's MCI criteria have undergone several revisions – the most recent version (Table 3) was published by both Petersen (2004) and the International Working Group on Mild Cognitive Impairment (Winblad et al., 2004). With a view to empirically validate the four clinical classifications of MCI (see Table 3 for definitions), Busse et al. (2006) examined a sample of community-dwelling and institutionalized persons aged 75 years and older. Diagnostic classifications based on original criteria (i.e., 1.0 *SD* below age- and education-matched norms) revealed prevalence rates of 4.5%, 5.5%, 2.1%, and 7.1% for aMCIsd, aMCImd, naMCImd, and naMCIsd, respectively. Significantly higher prevalence rates were observed when modified criteria (i.e., omission of the subjective memory complaint requirement) were used (9.3%, 10.9%, 3.9%, and 17.4% for aMCIsd, aMCImd, naMCImd, and naMCIsd, respectively). Increasing the cut-off to 1.5 *SD* below age- and education-matched norms significantly decreased the prevalence rates, under both conditions. Three of the four clinical subtypes preferentially progressed to AD. Persons diagnosed with naMCImd were more likely to progress to a non-AD type of dementia. The highest conversion rate was associated with the amnestic forms of MCI. Similarly, in a study comparing the course of original (i.e., amnestic MCI) and revised (i.e., allowance for non-amnestic forms of MCI and proxy reports) criteria, Storandt, Grant, Miller, and Morris (2006) found that 100% and 90% of MCI subjects meeting original and revised criteria, respectively, progressed to AD. As in the Busse et al. (2006) study, impairment was defined as performance falling 1.5 *SD* below expected values. These results suggest that the prevalence, course, and outcome of the four clinical subtypes of MCI are the result of the operationalizations of the MCI definition.

The stability of the four clinical subtypes of MCI remains controversial. Busse et al. (2006) report a 20% reversion rate (i.e., participants with a diagnosis of MCI at baseline failed to meet the criteria for MCI at follow-up). Improved cognitive performance was most frequently associated with the non-amnestic MCI subclassifications. Moreover, 4% to 13% of participants had unstable diagnoses and qualified for a different diagnosis at each follow-up. Some researchers suggest that the instability of the MCI diagnosis is attributable to practice effects and intra-individual fluctuation in cognitive performance. In a one-year follow-up study, Loewenstein et al. (2007) observed stable neuropsychological performance among participants diagnosed with MCI at baseline. However, persons in this MCI groups may represent a more cognitively impaired sample given that impairment was defined as performance at least 1.5 *SD* below the norm and the majority of MCI participants demonstrated impairment in multiple cognitive domains.

In addition to being clinically heterogeneous, Petersen (2003) acknowledged that MCI is etiologically heterogeneous. Apart from a degenerative dementing process, cognitive impairments of insufficient severity to warrant a diagnosis of dementia may be the result of head trauma, depression, cerebrovascular disease, anoxia, stroke, Parkinson's disease (PD), medications, and substance abuse, to name a few. Unlike typical research applications of Petersen's (1999, 2003, 2004) criteria for MCI, the classification of Cognitive Impairment, No Dementia (CIND) does not exclude persons based on the etiology of their cognitive impairments (Ebly, Hogan and Parhad 1995).

Given its less restrictive criteria, the classification of CIND is reported to have a higher population prevalence rate than all the dementias combined (Graham et al. 1997; Di Carlo et al. 2000). In the CSHA, the overall population prevalence of CIND was 16.8% (Graham et al. 1997). A prevalence rate of 10.7% for CIND was identified in the Italian population (DiCarlo et al. 2000). Using the MMSE, approximately 15% of persons aged 75 years and older were identified as CIND in the Kungsholmen Project (Palmer, Bäckman, Small and Fratiglioni 2006). The highest population prevalence rate for CIND (33.3%) was observed among Australian community-dwelling elderly aged 70-79 years (Low et al. 2004). The observed variability in the population prevalence rates for CIND is hypothesized to reflect differences in the age groups sampled and different inclusion criteria (Low et al. 2004).

Predicting Conversion to Dementia

Age & Other Demographic Risk Factors

Variability in the prevalence and conversion rates associated with different diagnostic criteria of MCI limits the identification of persons who will go on to dement. The most prominent risk factor associated with cognitive decline is age. Advancing age is significantly related to the prevalence of CIND in the older Italian (Di Carlo et al. 2000), Australian (Low et al. 2004), and Canadian (Graham et al. 1997) populations. The prevalence of dementia has been shown to increase from 2.4% in persons aged 65-74, to 11.1% in persons age 75-84, to 34.5% in persons aged 85+ years, respectively, in the Canadian population (CSHA 1994; Figure 1).

Gender is also related to the development of dementia, with women being at greater risk for AD. In contrast, men have a heightened risk of vascular dementia (VaD; Yamada et al. 1999). A third demographic variable identified as a risk factor for dementia is education. Low education is associated with an increased risk of developing dementia (Mortimer, Snowdon and Markesbery 2003), whereas higher educational attainment is reported to delay the onset of dementia by increasing one's cognitive reserve (Cummings, Vinters, Cole and Khachaturian 1998).

Neuropsychology

Neuropsychological assessment has a high sensitivity for identifying persons with cognitive impairment and dementia (Larrea, Fisk, Graham and Stadnyk 2000). However, MCI definitions do not specify which neuropsychological measures should be administered when assessing for MCI. Some suggest that the cross-comparison of cognitive research findings would be greatly improved if MCI research were based on a standardized neuropsychological battery (Ritchie, Artero and Touchon 2001). Others recommend that neuropsychological batteries with an emphasis on memory assessment be administered to persons at risk for conversion to dementia (i.e., those exhibiting memory deficits) (Petersen et al. 2001). Verbal memory measures are recommended for the identification of memory impairment (Petersen et al. 1999; 2001). However, an estimated 20% of cognitively impaired individuals may be incorrectly excluded from the amnestic MCI classification when only verbal measures are used to determine semantic memory impairment. Moreover, multiple-domain MCI is more prevalent among persons with both verbal and visual memory deficits (Alladi, Arnold, Mitchell, Nestor and Hodges 2006). Additionally, conversion to dementia is reported to be more prominent among nondemented persons who demonstrate mild impairment in memory *and* other cognitive domains (Bozoki et al. 2001).

The operationalization of cognitive decline is related to the topic of utilizing neuropsychological testing as a means of identifying cognitively impaired individuals. Some suggest that a single evaluation of memory functioning provides insufficient evidence of memory impairment, as test performance may be influenced by psychiatric and neurological conditions, or normal fluctuations in individual performance. Examination of memory performance over two-years revealed the possibility of identifying memory decline in healthy elderly individuals, prior to a classification of MCI or dementia. As such, longitudinal monitoring of cognitive function by means of repeated neuropsychological assessment is recommended (Collie et al. 2001). However, Morris and Storandt (2006) argue that repeated neuropsychological assessment is unfeasible for research given the recommended one-year interval between repeated neuropsychological evaluations. Instead, these researchers recommend referring to reports from collateral informants (e.g., spouse, child, close friend) for evidence of cognitive decline. The focus on intra-individual change in cognitive performance as an indicator of cognitive decline has recently been included in the revised criteria for MCI (Petersen 2004; Winblad et al. 2004).

Biological Risk Factors

Biological and familial characteristics are also identified as markers of incipient dementia. Vascular risk factors for dementia include diabetes (Hassing et al. 2002; Xu, Qiu, Wahlin, Winblad and Fratiglioni 2004; Hayden et al. 2006), hypertention and obesity (Hayden et al., 2006), and hypotention (Verghese, Lipton, Hall, Kullansky and Katz, 2003). A family history of dementia increases the risk two-fold for AD and VaD (Boston, Dennis and Jagger 1999). Neurodegenerative risk factors typically include genetic mutations or an increased presence of the apolipoprotein E (ApoE) ε4 allele, which is significantly more prevalent among persons with dementia (Frikke-Schmidt, Nordestgaardm, Thudium, Moes Grøholdt and Tybjærg-Hansen, 2001; Hsiung, Sadonick and Feldman, 2004; Baum et al. 2006) and among individuals who progress from CIND to dementia (Hsiung et al., 2004). Cognitive decline has also been associated with decreased cortical glucose metabolism (Fellgiebel et al. 2007), heightened protein levels (phosphorylated tau) in the cerebral spinal fluid (Buerger et al. 2005; Fellgiebel, et al. 2007), and medial temporal lobe atrophy (DeCarli et al. 2007; Bouwman, Schoonenboom and van der Flier, 2007).

Neuropsychiatric Risk Factors

Depression is the most prominent neuropsychiatric condition associated with cognitive impairment. In a study using data from the Canadian Study of Health and Aging (CSHA), higher rates of proxy-reported depression, loss of interest, and changes in personality and mood were noted among cognitively impaired (CI), compared to not cognitively impaired (NCI), persons. The presence of depression or loss of interest at baseline significantly predicted cognitive impairment (i.e., MCI, dementia, and AD) five years later (Stepaniuk, Ritchie and Tuokko 2008). Impaired neuropsychological performance is common among individuals with depression (Lockwood, Alexopoulos and van Gorp 2002). Despite frequent comorbidity, the sequence of onset of presenting symptoms has yet to be identified (Barberger-Gateau, Fabrigoule, Amieva, Helmer, & Dartigues, 2002).

Protective Factors

Despite the abundance of risk factors, research has identified factors that appear to protect against cognitive decline. For example, maintaining an active lifestyle in old age is reported to postpone the development of cognitive deficits (Weuve et al. 2004). Additionally, cognitive stimulation, through education, social interaction, or occupational achievements, serves to promote neural synaptogenesis (Churchill et al. 2002). These risk and protective factors do not necessarily occur in isolation. For example, vascular risk factors are reported to vary according to gender (Hayden et al. 2006) and the protective effects of education are limited by age (McDowell, Xi, Lindsay and Tuokko 2004).

Interventions

To date, no cognitive or pharmaceutical intervention has effectively prevented the progression of pathological decline from MCI to dementia. Practice guidelines from the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia

(Chertkow et al., 2008) recommend against the implementation of formal cognitive interventions, citing an absence of supportive evidence, in favor of promoting a "healthy lifestyle" (p.1275), including endorsing physical, social, and cognitive activities and managing vascular risk factors. The authors also recommend treating physical (i.e., sleep) and psychological (i.e., depression) conditions, which may increase cognitive difficulties. Additionally, Chertkow et al. do not recommend treating MCI with cholinesterase inhibitors as they are not associated with an improvement in MCI or the prevention of conversion to dementia. Moreover, the practice guidelines recommend against the use of estrogen, antioxidant (i.e., vitamin E, ginkgo biloba), and non-steroidal anti-inflammatory treatment, due to their adverse effects in patients with MCI.

Summary

There is substantial variability in the conceptualization of MCI. A primary difficulty with research in this area is the lack of a "gold-standard" or consensus definition. Additional variability in the data comes from the type of research sample (i.e., clinical versus population) and inclusion and exclusion criteria. Some argue that MCI research has been limited by small, highly specified clinical samples (e.g., participants selected from tertiary memory clinics), wherein the measures employed to group participants into MCI or dementia categories are also used to examine the relationship between MCI and dementia (Ritchie et al., 2001). However, clinical- and population-based studies each contribute important information to the study of MCI (Tuokko & McDowell, 2006). For example, clinic samples enable the evaluation of research hypotheses (including monitoring intra-individual change) under controlled conditions and are more economically feasible, while population samples enable the determination of the prevalence, incidence, and progression rates in a representative sample. Additionally, findings (e.g., risk factors) derived in clinical studies can then be evaluated in population studies, and vice versa (Tuokko & McDowell, 2006). Overall, the absence of a "gold standard" conceptualization of MCI creates a substantial obstacle for the development of cognitive and/or pharmaceutical interventions for delaying or, preferably, preventing the progression of MCI to dementia. In the interim, MCI is best viewed as a descriptive classification for the purposes of implementing cognitive strategies, making recommendations to caregivers, and evaluating associated behavioral, psychiatric, medical, social, functional, and demographic correlates of MCI.

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Table 1. Normal Model of Aging

Terminology	Case Definition
Benign Senescent Forgetfulness (Kral 1962, 1966)	General forgetfulness; difficulty recalling factual information; preserved global knowledge; intact awareness of deficits
Malignant Senescent Forgetfulness (Kral 1962, 1966)	Rapidly progressing age-related recent and remote memory impairment; lack of insight regarding memory deficits
Age-Associated Memory Impairment (Crook et al, 1986)	For persons aged 50+ years; subjective memory complaint; objective evidence of recent memory impairment (i.e., ≥ 1 standard deviation below the mean performance of young adults); etiological exclusion criteria
Age-Associated Memory Impairment (Blackford & LaRue 1989)	For persons aged 50-79 years; impaired performance (≥ 1 standard deviation below the mean), on 1+ memory test, as compared to young adults; etiological exclusion criteria
Late Life Forgetfulness (Blackford & LaRue 1989)	Impaired memory performance (1-2 standard deviations below the mean of similarly aged peers) on at least 50% of the memory tests; etiological exclusion criteria
Age-Consistent Memory Impairment (Blackford & LaRue 1989)	Memory performance within 1 standard deviation of the mean of similarly aged peers on ≥ 75% of memory tests
Age-Associated Cognitive Decline (Levy 1994)	Decline of at least one standard deviation, compared to age-matched norms, in any area of cognitive functioning

Table 2. DSM-IV-TR Criteria for Dementia (American Psychiatric Association, 2000)

Memory Impairment
Impairment in at least one of:
- Aphasia
- Apraxia
- Agnosia
- Executive Functioning

Decline from previous cognitive levels
Cognitive impairment interferes with
- Social and/or
- Occupational functioning

Decline in functional ability
- Activities of daily living

Table 3. Cognitive Decline as a Disease Process

Terminology	Case Definition
Amnestic MCI (Petersen, et al., 1999)	Subjective memory complaint; objective memory impairment; intact cognitive function; intact functional ability; not demented; etiological exclusion criteria
Amnestic MCI Single Domain – aMCIsd (Winblad et al. 2004)	Subjective or proxy cognitive complaint; objective memory impairment (decline from premorbid levels); intact cognitive function; relatively intact functional ability; not demented
Amnestic MCI Multiple Domain – aMCImd (Winblad et al. 2004)	Subjective or proxy cognitive complaint; objective impairment in memory *and* at least one other cognitive domain (decline from premorbid levels); intact cognitive function; relatively intact functional ability; not demented
Nonamnestic MCI Single Domain – naMCIsd (Winblad et al. 2004)	Subjective or proxy cognitive complaint; objective impairment in one non-memory domain (decline from premorbid levels); intact cognitive function; relatively intact functional ability; not demented
Nonamnestic MCI Multiple Domain – naMCImd (Winblad et al. 2004)	Subjective or proxy cognitive complaint; objective impairment in two or more non-memory domains (decline from premorbid levels); intact cognitive function; relatively intact functional ability; not demented
Cognitive Impairment No Dementia – CIND (Ebly et al. 1995; Tuokko et al. 2001)	Impaired cognitive function in one or more domains; not demented
MCI Type 1 (Zaudig 1992)	Short-term *and* long-term memory impairment; etiological exclusion criteria
MCI Type 2 (Zaudig 1992)	Short-term *and* long-term memory impairment *and* impairment in 1 or more of: abstract thinking, judgment, higher cortical functioning (i.e., aphasia, apraxia, agnosia), changes in personality; etiological exclusion criteria

Figure 1. Age as a Risk Factor in the Canadian Study of Health and Aging (CSHA Working Group, 1994).