International Psychogeriatrics (2014), 26:3, 353–359 © International Psychogeriatric Association 2013
doi:10.1017/S1041610213002275

GUEST EDITORIAL

The unbearable lightness of MCI

The title of this Editorial, with apologies to Milan Kundera (Kundera, 1985) implies no lack of *gravitas* in the concept of Mild Cognitive Impairment (MCI). Rather, it refers to the current definitions of MCI being somewhat free-floating, loosely anchored to diagnostic frameworks, and more conceptual than operational. In their defense, we cannot completely obliterate the flexibility clinicians need in order to exercise expert judgment and take individual patients' circumstances into account when making clinical diagnoses. Further, it would be imprudent to prematurely codify diagnostic criteria for MCI; after all, we are still gathering basic information about the wide range of mildly impaired states that we encounter in different clinical settings and in the population at large.

However, the field is also undertaking important and expensive trials of tests and interventions for specific diseases detected at the MCI stage, with potentially far-reaching implications. These trials can be undermined if diagnostic criteria are excessively flexible and of indeterminate validity and utility. As outlined by Kendell and Jablensky (Kendell and Jablensky, 2003), validity is present if a diagnostic category defines *either* a syndrome separated from normality and from neighboring syndromes by a zone of rarity, *or* an entity with biological underpinnings that are distinct from other conditions with similar syndromes. MCI clearly cannot meet this standard of validity, since it is a common state reached by multiple pathways reflecting different biological entities or processes. In contrast, utility is present if a diagnostic grouping represents sufficient etiologic and prognostic homogeneity that assigning a patient this diagnosis has real clinical implications (e.g. treatment outcomes and/or testable hypotheses about biological and social correlates). Unlike validity, utility is dependent on context. In practical terms, utility represents predictive value, and is potentially achievable even in our current state of incomplete knowledge about MCI.

The hallmark of MCI is cognitive functioning that is worse than expected for age but not bad enough to be called dementia. Dementia itself is acquired cognitive impairment sufficient to interfere with social and occupational functioning (American Psychiatric Association, 1987). A related concept, Cognitive Impairment, No Dementia (CIND) (Graham, 1997) requires only absence of dementia and presence of cognitive impairment. Thus, the key distinction between dementia and MCI (or CIND) is the severity of the cognitive impairment itself, as reflected in its functional consequences. Although the original usage of the term MCI referred to an early stage of Alzheimer's disease on the Global Deterioration Scale (Flicker *et al.*, 1991) and to an entity blending DSM-III-R and ICD-10 diagnostic criteria (Zaudig *et al.*, 1992) its most cited version is the Mayo Criteria or Petersen Criteria (Petersen *et al.*, 1999) describing what we now call Amnestic MCI. An expanded definition of MCI, proposed a few years later by an international working group (IWG or Winblad Criteria) (Winblad *et al.*, 2004), also included non-amnestic impairments. The IWG criterion set is the current prevailing standard for the MCI syndrome, and is echoed in the NIA-AA Work Group guidelines for the diagnosis of MCI due to Alzheimer's disease (AD) (Albert *et al.*, 2011). It includes the following elements: (i) the person is neither normal nor with dementia; (ii) there is evidence of cognitive deterioration shown by *either* objectively measured decline over time *and/or* subjective report of decline by self and/or informant, in conjunction *with* objective cognitive deficits; and (iii) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired.

In this exponentially growing area of the literature, even a cursory review reveals wide variation in how different studies operationally implement the same criteria, usually depending on the data that are available in a given setting or study. The greatest inherent challenge in diagnosing MCI is the inter-individual variability among older adults, both in intellectual function at a given age and in rates of decline over time. In different studies, objective neuropsychological measures have included multiple global and domain-specific tests (Jorm *et al.*, 2005; Wadley *et al.*, 2007; Allegri *et al.*, 2008; Albert *et al.*, 2011). Subjective cognitive concerns are sometimes assumed from the very fact of the patient's seeking services, or reflect spontaneous complaints by patients or families; at other times, they are elicited by a single question or a standardized questionnaire, and/or represent the clinician's impression (St. John *et al.*, 2002; Arnaiz *et al.*, 2004; Di Carlo *et al.*, 2007). The MCI diagnosis itself has been based on expert clinical judgment, often by a consensus group (Di Carlo *et al.*, 2007), sometimes using a rating scale (Dickerson *et al.*, 2007), or by psychometric

algorithm (Jorm *et al.*, 2005). For the purpose of exclusion, dementia has been diagnosed by standard measures such as the Clinical Dementia Rating scale (Morris *et al.*, 1993) or the application of standard diagnostic criteria such as ICD-10 (World Health Organization, 1994) and DSM-III-R (American Psychiatric Association, 1987).

Neither CIND nor the Mayo or IWG definitions of the MCI syndrome specify the etiology of the mild impairment; identifying the cause of the syndrome is intended as the next step in diagnosis. Yet, the term MCI is often used to represent sub-threshold AD and a substantial proportion of the MCI literature focuses on older adults whose mild impairment is assumed to be due to AD. In 2011, the NIA-AA work group helped reduce the etiological ambiguity by providing guidelines for the diagnosis of "MCI due to AD." (Albert *et al.*, 2011) Similarly, in 2012, the Movement Disorders Society published guidelines for the diagnosis of "MCI due to Parkinson's disease (PD)" (Litvan *et al.*, 2012).

Another widespread implicit assumption is that MCI is not only an intermediate state between normal cognition and dementia, but also a transitional state between the two; i.e. that MCI is by definition a prodromal state of a dementing disorder. This assumption has been strongly challenged by the data; many cases of MCI, particularly outside the specialty settings, are static or transient states that do not progress to dementia (Mitchell and Shiri-Feski, 2009) and may represent a variety of etiological entities. Nevertheless, as a group, individuals with mild impairment have an indisputably higher likelihood of developing severe impairment or dementia than those with normal cognition (Petersen *et al.*, 2009). This has led some to refer to MCI as a risk state or even a risk factor for dementia, and to MCI "converting" to dementia (Lehrner *et al.*, 2005; Ewers *et al.*, 2012). Others have argued that, where MCI is an early stage of the same disease that eventually causes dementia, MCI is merely a very mild dementia (Morris, 2006) or a step along the continuum from normalcy to mild dementia.

Inconsistencies in concept and terminology are mutually aggravating and jointly undermine the rigorous definition of MCI. In clinical settings, most practitioners employ some eclectic and idiosyncratic interpretation of the published criteria. In research settings, the literature reveals a wide range of MCI prevalence and incidence estimates and progression rates, which depend on the MCI definitions used (Mitchell and Shiri-Feski, 2009; Stephan *et al.*, 2010; Ganguli *et al.*, 2011). Thus, there are increasing calls for the field to unite behind a single definition of MCI with adequate validity and utility,that encompasses the relevant components, and that can be used consistently across studies and settings (Allegri *et al.*, 2008; Matthews *et al.*, 2008; Stephan *et al.*, 2013). Rather than propose yet another new set of criteria for MCI, a potential approach might be to reframe the current criteria to (i) enhance their reliability, validity, and utility and (ii) allow them to be readily updated as new knowledge accrues.

In the newly released fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013), the American Psychiatric Association has introduced the term Neurocognitive Disorder (NCD). It encompasses two syndromes, Major NCD and Mild NCD, distinguished by the severity of the cognitive impairment and its effect on functional independence. Nomenclature aside, these entities parallel the existing concepts of dementia and MCI. The rest of this paper examines not the DSM-5 criteria for NCD but rather the overall structure of the DSM-5 diagnostic framework as a potential model for reframing the MCI criteria (Ganguli, 2013). The DSM-5 structure for all mental disorders includes (1) core diagnostic criteria, (2) subtypes of the disorder, and (3) specifiers for the disorder. Criteria are distinct from (i) associated or supportive features, (ii) risk and prognostic factors, (iii) diagnostic markers, and (iv) functional consequences of the disorder.

Core criteria

Each criterion for a specific disorder should be unambiguous; taken together, the core criteria should be both necessary and sufficient for that mental disorder to be diagnosed. To go a step further than DSM-5, the core criteria for MCI could be further divided into inclusion criteria (which must be present) and exclusion criteria (which must be absent).

Translating the contents of the IWG criteria (Winblad *et al.*, 2004) into this framework, the *Inclusion Criteria* for MCI could be stated as *either* (1) and (2), *or* (3) below:

(1) *Subjective impression of decline in cognitive functioning*. Impressions are not restricted to the individual's own concerns and can include impressions by a family member or observer, or the clinician. These observations are clearly context-dependent and reflect the expectations of the observer. Users can operationalize this criterion further for a given clinical or research purpose, e.g. by relying on spontaneous reports or by asking standardized questions.

(2) *Measurable objective cognitive deficit in one or more domains of cognition*. This criterion refers to formal

https://doi.org/10.1017/S1041610213002275 Published online by Cambridge University Press

neuropsychological testing or "bedside" cognitive screening. The individual's test performance should fall somewhere in between the expected ranges for normal cognition and for dementia. Typically, normal-range performance is one standard deviation on either side of the mean, and dementia-range performance is two or more standard deviations below the mean. Thus, the MCI-range performance would be between one and two standard deviations below the mean for the individual's peer group, on any standard test for which appropriate norms are available. To standardize MCI criteria across studies and settings, it would be helpful to designate and describe the cognitive domains of interest, and provide guidelines on how to assess them, as has been done in DSM-5.

(3) *Evidence of decline over time on objective cognitive tasks*. More decline than would be expected for age, without falling into the "dementia" range of impairment. This criterion can only be implemented with serial cognitive assessments, and with established expectations for normal aging. Thus, interpreting the observed decline requires availability of norms for rate of decline, further complicated by individual fluctuations and learning (practice) effects. Note that this third criterion of objectively measured decline is a part of the IWG definition but not a separate criterion in DSM-5.

The *Exclusion Criteria* of the IWG definition might be framed as follows.

(1) *Significant impairment/loss of independence in everyday functioning*. Excluding significant functional impairment and loss of functional independence, as in the IWG Criteria, is equivalent to including marginal functional impairment and preserved functional independence, as in DSM-5. In DSM-5, an inclusion criterion for Mild NCD is that everyday functioning may have become more effortful and require the use of compensatory strategies, but that the individual remains independent of others for these functions. (See "Functional Consequences" below.)

(2) *Substantial impairment in general mental status*. As measured by some threshold on a global screening measure; this exclusion criterion was part of the Mayo Criteria but not of the IWG criteria.

(3) In DSM-5, an exclusionary criterion is the *presence of another mental condition* (e.g. depression, delirium, intoxication, psychosis) that could account for the observed impairment. However, an alternative approach could be considered, assuming the inclusion criteria are met. Rather than exclude these individuals, the practitioner could classify them as having MCI, and then designate the other mental disorder as the etiologic subtype (Graham *et al.*,1997; Rabins and Lyketsos, 2011).

"Dementia" with a clearly defined threshold is an additional exclusion criterion in the IWG criteria. However, the criteria already listed specify that the cognitive deficits must be mild, and that independence in everyday functioning must be essentially preserved. Thus, dementia has effectively been excluded already, and the additional criterion of "absence of dementia" or "neither normal nor demented" could be considered redundant. DSM-5 addresses this issue by making Mild and Major NCD mutually exclusive.

Subtypes

If subtypes are listed for a mental disorder, they must be mutually exclusive and jointly exhaustive, i.e. all individuals with that disorder should be classifiable under one or other subtype. The principal subtypes of MCI are etiological, e.g. MCI due to Alzheimer's disease, vascular disease, traumatic brain injury, HIV Infection, or other medical conditions. Since the individual has already been diagnosed as MCI, the subtype criteria are essentially the diagnostic criteria for the underlying disease. For example, for MCI due to AD, the criteria could mirror the guidelines published by the NIA-AA work group for Probable and Possible AD (Albert *et al.*, 2013). Criteria for the MCI subtype due to (for example) traumatic brain injury could be harmonized with the corresponding expert consensus position (Institute of Medicine, 2004). Differential diagnosis is made easier when criteria for multiple etiological subtypes of MCI are laid out in parallel fashion, as has been done in DSM-5.

Particularly for research diagnosis, exclusion criteria for one subtype might include strong evidence of other etiologic subtypes if sufficient to explain the presence of MCI. Depending on its objectives, a given study might include or exclude cases with mixed etiology. Some research settings may require greater specificity (sacrificing some sensitivity) than the clinical setting; e.g. the Research Criteria for AD (Dubois *et al.*, 2007) require a minimum symptom duration of six months, and specify an episodic memory deficit that does not improve or normalize with cueing or recognition testing. The clinician does not have the luxury of "excluding" patients whose characteristics do not neatly map to research criteria, and may not always have access to the type of data required for research. However, clinical criteria should be able to accommodate additional background or ancillary information unique to a given patient and available to the clinician. Further, comorbidity is the norm in older adults; for example, MCI in a given individual often represents both degenerative and vascular brain disease (Schneider *et al.*, 2009). For clinical

https://doi.org/10.1017/S1041610213002275 Published online by Cambridge University Press

purposes, it should be possible to diagnose both as present, as provided for in DSM-5.

MCI is also frequently subtyped according to its cognitive profile, e.g. the number of affected domains (e.g. single domain vs. multi-domain), and/or the cognitive domains that are affected (e.g. amnestic vs. non-amnestic) or even more specifically a "hippocampal memory profile." (Allegri *et al.*, 2008; Hughes *et al.*, 2011) Much of this work has been conducted in relation to AD, to identify MCI characteristics that increase the likelihood of progression to AD dementia. Descriptive subtypes with established prognostic significance would enhance utility in both clinical and research settings.

Specifiers

These are additional features that may or may not be present in the disorder and may not be mutually exclusive. However, their presence has some form of clinical significance for the disorder, e.g. with regard to prognosis. For many disorders, including dementia, it is common to specify severity (e.g. as mild, moderate, and severe) and thus, enhance utility. However, it can be difficult to specify further severity levels within the MCI syndrome, which by definition is already characterized as "mild." For a given etiological subtype of MCI, such as AD, severity or stage can be specified e.g. early or late MCI (ADNI-GO 2013), pre-MCI and MCI (Duara *et al.*, 2011), with appropriate anchors in cognitive test performance, everyday functional ability, or both. In the foreseeable future, we may use biomarkers to specify MCI stages in a given etiologic subtype, based on the underlying pathological process in that disease.

For both levels of NCD, DSM-5 lists as a specifier the presence of concomitant behavioral and psychological features (such as depression or psychosis). These features are not present in every case, and are not specific to neurocognitive disorders; they are thus neither necessary nor sufficient for diagnosis of the neurocognitive disorder itself. However, they are often the focus of treatment and research, and have clearly demonstrated prognostic value (Peters *et al.*, 2012).

Earlier editions of DSM specified the age of onset (early vs. late) in the diagnosis of dementia due to AD (American Psychiatric Association, 1987, 1994). DSM-5 removed this distinction because the age 60 threshold between early and late onset was arbitrary, and because age at onset does not seem to define a specific pathologic entity. However, clinicians can still distinguish between earlier and later onset cases, e.g. with respect to the social consequence of AD at different life stages, and researchers might choose to select study participants or stratify certain analyses by age at onset. Thus, formal specifiers can be updated as knowledge advances, and do not limit clinicians and researchers from addressing other characteristics of interest.

Associated features supporting diagnosis

These features are frequently present and consistent with the presence of the disorder, but neither necessary nor sufficient for the mental disorder to be diagnosed. Some but not all associated features may have utility as specifiers. Behavioral and psychological symptoms e.g. apathy, anxiety, depression, psychosis, are frequently present in MCI and dementia and are often the primary reason that individuals seek health services. In psychiatry, their presence has sufficient clinical utility to be listed in DSM-5 as specifiers of the diagnosis at both NCD levels, but this may vary across settings. A positive family history of dementia is also often present in MCI but (except in autosomal dominant familial cases) does not enhance diagnostic utility at our present state of knowledge. Family history is therefore an associated feature, consistent with diagnosis but not useful as a specifier, although it may be clinically relevant in working with a given patient or family.

Diagnostic measures and markers

These features reflect the underlying pathology of the disease causing the mental disorder, and should have adequate sensitivity and specificity for the disorder, a characterization consistent with the standard definition of biomarkers (Biomarkers Working Group, 2001). In MCI, markers will likely reflect the underlying biology of a given etiological subtype and possibly of disease stages, varying accordingly in sensitivity and specificity. For MCI due to AD, some have characterized specific neuropsychological tests as diagnostic measures or markers (Jedynak *et al.*, 2012). Relevant autosomal dominant genes would be diagnostic in some early onset familial cases; other biomarkers could include medial temporal atrophy, CSF levels of beta amyloid and tau proteins, temporoparietal glucose metabolism, and amyloid imaging on PET scans, if and when these and/or other markers are validated for clinical use (Jack *et al.*, 2011). In contrast, the *APOE*4* genotype would not be a diagnostic marker (see Risk Factors, below) although some have suggested it is a "biomarker" for MCI (Brainerd *et al.*, 2011). Positive serology would be a diagnostic marker for MCI due to HIV

https://doi.org/10.1017/S1041610213002275 Published online by Cambridge University Press

infection; positive genetic testing for CAG repeats on chromosome 4 would be a diagnostic marker for MCI due to Huntington's disease (American Psychiatric Association, 2013).

Risk factors

These are factors that are independent of the disorder and underlying disease pathology, and promote or contribute to the development of the disorder. For MCI due to AD, the best examples of independent risk factors are greater age and the *APOE*4* gene. Neither factor is necessary or sufficient for the diagnosis of AD and therefore neither can be considered a diagnostic criterion or a biomarker. The risk of AD increases with advancing age, and the likelihood of MCI being caused by AD is relatively high in the ninth and tenth decades of life, but everyone does not develop AD simply by living long enough. The *APOE*4* gene increases the risk of developing AD up to around age 80, but individuals can have this gene but not develop the disease, and can develop the disease without having the gene; carrying the gene hastens the onset of disease (Khachathurian *et al.*, 2004).

Functional consequences

The primary functional consequence of MCI is loss of independence in everyday activity (Jorm *et al.*, 2005). The logical trap is self-evident when we define MCI as cognitive impairment in the face of preserved functional independence, and when the emergence of functional dependence by definition moves the diagnosis across the threshold from MCI to dementia. The International Classification of Function (World Health Organization, 2001) argues that the consequences of a disorder cannot be treated as diagnostic criteria for that disorder, and can only be used to measure its severity. While logical, the ICF position is at odds with the prevailing clinical approach to distinguishing between MCI and dementia based on functional consequences. Further, whether or not a given level of cognitive impairment results in functional impairment depends in large part on the cognitive demands or challenges of a given individual's everyday activities, and on societal expectations. Perhaps as the MCI criteria continue to evolve, a way will be found around this potential circularity.

The wide range of prevalence, incidence, and outcome reported in MCI reflects in large part the wide range of operational definitions and criterion sets in use. Not surprisingly, demand is growing for a unified set of MCI diagnostic criteria. Progress is being made towards updating diagnostic criteria for etiologic subtypes of MCI, such as those due to AD and PD (Albert *et al.*, 2011; Litvan *et al.*, 2012). However, the criteria for the broad MCI syndrome itself, without altering their substantive content, might be reframed to better disentangle cause from consequence, maximize internal consistency, and minimize redundancy. Diagnosis would become more conceptually rigorous if we clearly distinguished among core diagnostic features (inclusion as well as exclusion criteria), subtypes, specifiers, associated features, and risk factors. Clinical judgment will remain essential for the validity of clinical diagnosis, which would become more reliable if the diagnostic criteria could be rendered less ambiguous. We could enhance reliability by providing suitable anchor points, if not precise thresholds or cutpoints. We could avoid conflating criteria for the broad or generic MCI syndrome with criteria for its etiologic subtypes. Each level of classification, subtyping, and specification, should delineate an increasingly homogeneous subgroup with a stronger likelihood of having common underpinnings and prognosis – a hypothesis we could test if our information was appropriately organized. (Ganguli, 2013)

The suggested reframing of the MCI criteria may have additional implications in the broader global context. The most rapid aging of the world's population is taking place in the emerging economies, where the fewest studies have been conducted in aging, cognition, and dementia (Prince *et al.*, 2013). Where each generation is living to be older than the previous one, societal expectations of independent and productive aging will vary over time. Rather than assume a one-size-fits-all approach, we should explore systematically the extent to which standard clinical and research definitions, measurements, and thresholds are applicable across regions. If we can gather normative data on appropriate measures of cognition, subjective concern, and everyday functioning in a broad array of settings, we can more accurately anchor our definitions of normal aging, mild impairment, and dementia. This goal can be accomplished without excessive recourse to technology. Efforts at etiological subtyping will vary according to available resources. They should be pursued, however, because they will provide needed information about the worldwide distribution of the underlying causes of MCI. These may include a larger proportion of treatable conditions in some under-resourced populations. Improving the utility of our diagnoses should improve the quality of clinical information, and in turn, the quality of clinical and public health services to older adults.

The "lightness" referred to in the title of this Editorial invokes, of course, the novel *"The*

https://doi.org/10.1017/S1041610213002275 Published online by Cambridge University Press

Unbearable Lightness of Being" (Kundera, 1985). Its author Milan Kundera challenges Nietzsche's concept of eternal recurrence (i.e. that the universe and its events have already occurred and will continue to re-occur), which imposes a heavy burden on our lives. Kundera proposes the opposite; that each person lives only once and each experience occurs only once – hence, the "lightness" of being. Viewing MCI as a theme that has recurred constantly over the past 20 years, this Editorial could have been entitled "The Unbearable Heaviness of MCI." Perhaps improving its diagnostic utility will help to lighten the load.

Conflict of interest

The author was a member of the Work Group on Neurocognitive Disorders for DSM-5 (*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition) of the American Psychiatric Association.

MARY GANGULI

Departments of Psychiatry and Neurology, School of Medicine, University of Pittsburgh and Department of Epidemiology, Graduate School of Public Health, Pittsburgh, Pennsylvania, USA
Email: GanguliM@upmc.edu

Acknowledgments

The work reported here was supported in part by grant # K24 AG022035 from the National Institute on Aging, NIH, U.S. DHHS.

References

Albert, M. S. *et al.* (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's and Dementia*, 7, 270–279.

Allegri, R. F., Glaser, F. B., Taragano, F. E. and Buschke, H. (2008). Mild cognitive impairment: believe it or not? *International Review of Psychiatry*, 20, 357–363.

Alzheimer's Disease Neuroimaging Initiative (2010). *Grand Opportunity (ADNI-GO) Protocol Synopsis*. http://www.adni-info.org/Scientists/Pdfs/ADNI_GO_Protocol.pdf; last accessed 25 May 2013.

American Psychiatric Association (1987). *DSM-III-R. Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn, revised. Washington, DC: American Psychiatric Association.

American Psychiatric Association (2000). *DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders*, 4th edn, Text Revision. Washington, DC: American Psychiatric Association.

American Psychiatric Association (2013). *DSM-5. Diagnostic and Statistical Manual of Mental Disorders*, 5th edn. Washington, DC: American Psychiatric Association.

Arnaiz, E. *et al.* (2004). Mild cognitive impairment: a cross-national comparison. *Journal of Neurology, Neurosurgery, and Psychiatry*, 75, 1275–1280.

Biomarkers Definition Working Group, NIH Director's Initiative (2001). Biomarkers and surrogate endpoints. Preferred definitions and conceptual endpoints. *Clinical Pharmacology and Therapeutics*, 69, 89–95.

Brainerd, C. J. *et al.* (2011). Is the Apolipoprotein E genotype a biomarker for mild cognitive impairment? Findings from a nationally representative study. *Neuropsychology*, 25, 679–689.

Crowe, M. *et al.* (2006). Subjective cognitive function and decline among older adults with psychometrically defined amnestic MCI. *International Journal of Geriatric Psychiatry*, 21, 1187–1192.

Di Carlo, A. *et al.* (2007) CIND and MCI in the Italian elderly: frequency, vascular risk factors, and progression to dementia. *Neurology*, 68, 1909–1916.

Dickerson, B. C., Sperling, R. A., Hyman, B. T., Albert, M. A. and Blacker, D. (2007). Clinical prediction of Alzheimer disease dementia across the spectrum of mild cognitive impairment. *Archives of General Psychiatry*, 64, 1443–1450.

Duara, R. *et al.* (2011) Pre-MCI and MCI: neuropsychological, clinical, and imaging features and progression rates. *American Journal of Geriatric Psychiatry*, 19, 951–960.

Dubois, B. *et al.* (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurology*, 6, 734–746.

Ewers, M., Walsk, C. and Trojanowski, J. Q. (2012). Prediction of conversion from mild cognitive impairment to Alzheimer's disease dementia based upon biomarkers and neuropsychological test performance. *Neurobiology of Aging*, 33, 1203–1214.

Flicker, C., Ferris, S. H. and Reisberg, B. (1991). Mild cognitive impairment in the elderly: predictors of dementia. *Neurology*, 41, 1006–1009.

Ganguli, M. (2013). Can the DSM-5 framework enhance the diagnosis of MCI? *Neurology*, e-Pub, doi 10.1212/01.wnl.0000436944.01023.e5.

Ganguli, M. *et al.* (2011). Outcomes of mild cognitive impairment by definition. A population study. *Archives of Neurology*, 68, 761–767.

Graham, J. E. *et al.* (1997). Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet*, 349, 1793–1796.

Hughes, T. F., Snitz, B. E. and Ganguli, M. (2011). Should mild cognitive impairment be subtyped? *Current Opinion in Psychiatry*, 24, 237–242.

Institute of Medicine of the National Academies Board on Population Health and Public Health Practice (2008). Neurocognitive outcomes. In *Gulf War and Health: Volume 7: Long-Term Consequences of Traumatic Brain Injury* (pp. 173–196). Washington, DC: The National Academies Press.

Jack, C. R. *et al.* (2011). Introduction to revised criteria for the diagnosis of Alzheimer's disease: National Institute on

Aging and the Alzheimer Association workgroups. *Alzheimer's and Dementia*, 7, 257–262.

Jedynak, B. M. *et al.* (2012). A computational neurodegenerative disease progression score: method and results with the Alzheimer's Disease Neuroimaging Initiative Cohort. *Neuroimage*, 63, 1478–1486.

Jorm, A. F. *et al.* (2005). Cognitive deficits 3 to 6 years before dementia onset in a population sample: the Honolulu-Asia Aging Study. *Journal of the American Geriatrics Society*, 53, 452–455.

Kendell, R. and Jablensky, A. (2003). Distinguishing between the validity and utility of psychiatric diagnoses. *American Journal of Psychiatry*, 160, 4–12.

Khachaturian, A. S. *et al.* (2004). Apolipoprotein E epsion4 count affects age at onset of Alzheimer disease, but not lifetime susceptibility: the Cache County Study. *Archives of General Psychiatry*, 61, 518–524.

Kundera, M. *The Unbearable Lightness of Being*. (original publication in Czech, 68 Publishers, Toronto, Ont, Canada, 1985.) English translation, 1999, New York City: Harper Perennial Classics.

Lehrner, J. *et al.* (2005). Annual conversion to Alzheimer disease among patients with memory complaints attending an outpatient memory clinic: the influence of amnestic mild cognitive impairment and the predictive value of neuropsychological testing. *The Middle European Journal of Medicine (Wiener Klinische Wochenschrift)*, 117/18, 629–635.

Litvan, I. *et al.* (2012). Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Movement Disorders*, 27, 349–356.

Matthews, F. E. *et al.* (2008). Two-year progression from mild cognitive impairment to dementia: to what extent do different definitions agree? *Journal of the American Geriatric Society*, 56, 1424–1433.

Mitchell, A. J. and Shiri-Feshki, M. (2009). Rate of progression of mild cognitive impairment to dementia: meta-analysis of 41 robust inception cohort studies. *Acta Psychiatrica Scandinavica*, 119, 252–265.

Morris, J. C. (1993). The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*, 43, 2412–2414.

Morris, J. C. (2006). Mild cognitive impairment is early-stage Alzheimer disease: time to revise diagnostic criteria. *Archives of Neurology*, 63, 15–16.

Peters, M. E. *et al.* (2013). Neuropsychiatric symptoms as risk factors for progression from CIND to dementia: the Cache County Study. *American Journal of Geriatric Psychiatry*, 21, 1116–1124.

Petersen, R. C. *et al.* (1999). Mild cognitive impairment: clinical characterization and outcome. *Archives of Neurology*, 56, 303–308.

Petersen, R. C., Roberts, R. O. and Knopman, D. S. (2009). Mild cognitive impairment: ten years later. *Archives of Neurology*, 66, 1447–1455.

Prince, M. *et al.* (2013). The global prevalence of dementia: a systematic review and meta-analysis. *Alzheimer's and Dementia*, 9, 63–75.

Rabins, P. V. and Lyketos, C. G. (2011). A commentary on the proposed DSM revision regarding the classification of cognitive disorders. *American Journal of Geriatric Psychiatry*, 19, 201–204.

Schneieder, J. A., Arvanitakis, Z., Leurgans, S. E. and Bennett, D. A. (2009). The neuropathology of probable Alzheimer's disease and mild cognitive impairment. *Annals of Neurology*, 66, 200–208.

St. John, P. and Montgomery, P. (2002). Are cognitively intact seniors with subjective memory loss more likely to develop dementia? *International Journal of Geriatric Psychiatry*, 17, 814–820.

Stephan, B. C. *et al.* (2010). Optimizing mild cognitive impairment for discriminating dementia risk in the general older population. *American Journal of Geriatric Psychiatry*, 18, 662–673.

Stephan, B. C. M. *et al.* (2013). Diagnosing mild cognitive impairment (MCI) in clinical trials: a systematic review. *British Medical Journal Open Access*, 3, Pii: e001909.

Wadley, V. G. *et al.* (2007). Changes in everyday function in individuals with psychometrically defined Mild Cognitive Impairment in the Advanced Cognitive Training for Independent and Vital Elderly study. *Journal of American Geriatrics Society*, 55, 1192–1198.

Winblad, B. *et al.* (2004). Mild cognitive impairment: beyond controversies, towards a consensus – report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine*, 256, 240–246.

World Health Organization (WHO) (2001). *International Classification of Functioning, Disability, and Health (ICF)*. Available at: http://www.who.int/classifications/icf/en/; last accessed 24 June 2010.

Zaudig, M. (1992). A new systematic method of measurement and diagnosis of "mild cognitive impairment" and dementia according to ICD-10 and DSM-III-R criteria. *Internal Psychogeriatrics*, 4 (suppl. 2), 203–219.