DEMENTIA

The rising global tide of cognitive impairment

Harald Hampel and Simone Lista

A new study suggests that the application of uniform diagnostic criteria for mild cognitive impairment (MCI) substantially reduces variation in MCI prevalence estimates. Refinement and harmonization of clinical and research criteria are essential milestones towards improved testing of therapeutic interventions aimed at curbing the epidemic of MCI and dementia.

Refers to Sachdev, P. S. *et al.* The prevalence of mild cognitive impairment in diverse geographical and ethnocultural regions: the COSMIC collaboration. *PLoS ONE* **10**, e0142388 (2015)

Mild cognitive impairment (MCI) is an intermediate prodromal stage of memory impairment that often, but not invariably, precedes dementia[1]. The definition of MCI now incorporates the heterogeneity and aetiology of the syndrome[1], and includes the following criteria: absence of dementia, no or minimal functional impairment, subjective cognitive complaints, and objective cognitive impairment. In a new study[2], Perminder Sachdev and colleagues applied uniform diagnostic criteria for MCI to harmonized data from 11 longitudinal, population-based, cross-sectional studies of cognitive ageing from the Cohort Studies of Memory in an International Consortium (COSMIC), conducted in the USA, Europe, Asia and Australia[3]. Use of these criteria resulted in global MCI prevalence estimates ranging from 6–12%[2]. This variation is substantially smaller than those reported in the previous estimates.

Accurate estimates of MCI prevalence and identification of individuals with MCI who will convert to dementia are of paramount clinical importance to reliably test disease-modifying interventions that could delay progression of MCI to dementia[4]. The variability of dementia prevalence in individuals aged >60 years is relatively small, ranging from 5–7%[4]; however, the variation in reported prevalence of MCI is much larger. For example, as Sachdev *et al.* highlight[2], the individual studies by the COSMIC collaboration[3] reported MCI prevalences ranging from 5–37%. This variability is attributable partly to different prevalences of MCI in different populations, and partly to inconsistent definitions of MCI.

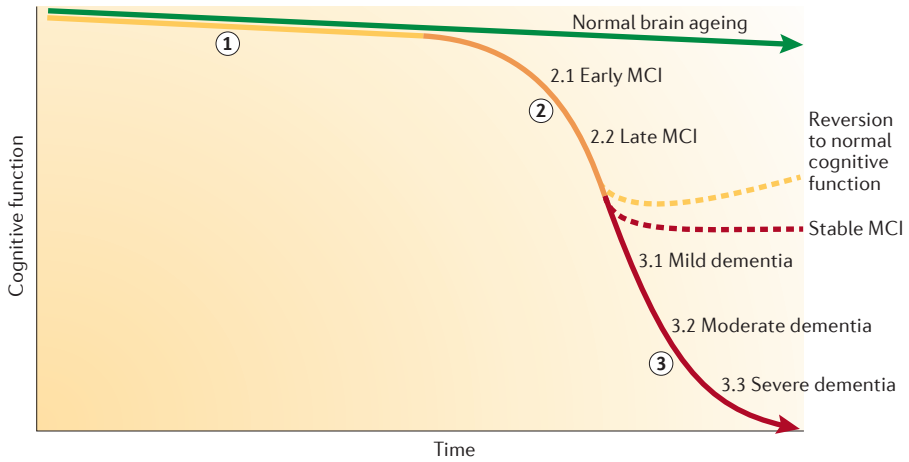
To date, two different sets of criteria have been proposed for diagnosing Alzheimer disease (AD) in individuals with MCI: the International Working Group (IWG) criteria IWG-1 and IWG-2 (REF. 5), and the National Institute of Ageing–Alzheimer Association (NIA–AA) criteria[6]. These criteria all represent an enriched, targeted diagnostic approach that integrates topographical and pathophysiological biomarkers to increase the likelihood of detecting the possibly underlying AD aetiology. The topographical markers include medial temporal lobe atrophy on MRI and reduced glucose metabolism in temporoparietal regions on ^{18}F-FDG–PET, and the pathophysiological biomarkers include amyloid-tracer PET, and cerebrospinal fluid levels of amyloid-β_{1-42}, total tau and hyperphosphorylated tau.

In the recently proposed IWG-2 criteria[5], the implementation of a validated multimodal biomarker framework[5,6] (FIG. 1) represents a major innovation in estimating the risk of progression from MCI to AD dementia. Indication of anatomical and neuronal integrity, in combination with molecular and/or cellular alterations associated with the disease, could facilitate the differentiation of individuals with prospective cognitive decline from those with age-related late-onset memory impairment, as well as from those who will not develop progressive cognitive decline (stable MCI).

It should be emphasized that the clinico-descriptive MCI criteria proposed by Sachdev and co-investigators will need to be further refined in the future on the basis of evolving evidence. For example, biological markers should be integrated into the definition of MCI to establish a clinico-biological definition for the condition. Such continuous evidence-based harmonization and optimization of diagnostic criteria for the preclinical, prodromal and dementia stages of AD will substantially advance both accurate diagnosis and development of therapies.

Refinement and harmonization of criteria for MCI could improve future trials aimed at slowing down progression from MCI to dementia. The past clinical trials of anti-AD compounds that have included participants with MCI were considered unsatisfactory for several reasons. For example, a considerable proportion of individuals with MCI do not convert to clinically definite dementia over the trial periods. Another issue concerns the connection between AD pathology and dementia: about 30% of those individuals who develop dementia do not meet neuropathological criteria for AD; moreover, in trials recruiting individuals with amnestic MCI, the proportions of participants who have AD or AD pathology are unknown. Moreover, study design limitations — for example heterogeneous samples, lack of participants with a biomarker signature indicative of a risk of cognitive decline, suboptimal length of treatment, and ineffective indicators of disease progression — could count for the failure of past MCI trials[7]. Ongoing clinical trials with clearly defined participant populations (early AD, prodromal AD, or MCI owing to AD) are attempting to benefit from the advances in diagnostic criteria development.

It is worth noting that the refined, more-stringent criteria used by Sachdev and colleagues resulted in an MCI prevalence of 5.9%, which is lower than reported in the majority of the previous studies[2]. A number of potential confounders — including different sample sizes, methods of case identification, and the use of medication — could explain the different prevalences across studies. Despite the lower-than-expected MCI prevalence reported by



1. Preclinical stage: asymptomatic, at-risk
Duration: decades
- Amyloid-β accumulates in the brain
- Tau hyperphosphorylation gradually leads to neuronal loss
- Pathology does not yet noticeably affect cognition
- Biomarkers and genetic profile can indicate the risk of disease progression and reveal underlying AD

2. Prodromal stage: MCI
Duration: ~7 years
Subtypes:
- Progressive MCI
- MCI caused by AD
- Amnestic syndrome of the hippocampal type
- Deficits in memory and/or other cognitive domains noticeable to the person affected and/or others, but not severe enough to interfere with activities of daily living
- Biomarkers can determine the aetiological diagnosis

3. Syndromal stage: dementia
Duration: ~7 years; followed by total loss of independent function
- Notable loss of intellectual ability affecting memory and at least one other cognitive domain
- The impairment interferes with activities of daily living

Figure 1 | **Hypothetical staging model of sporadic Alzheimer disease (AD).** Although many individuals with mild cognitive impairment (MCI) progress to dementia, some remain stable or revert to normal cognitive function. The proposed staging is based on the progression of the disease and comprises two bits of information: AD stage as identified at diagnosis, and the current stage. The main categories in this system include the preclinical (or presymptomatic) phase (1), the prodromal stage, also known as MCI (2), and the dementia syndrome (3).

Sachdev *et al.*[2], a major decline in the incidence of dementia is unlikely to occur in the next few decades, as the converging risks associated with ageing, vascular risk factors and diabetes mellitus will continue to contribute to the increasing incidence of MCI and dementia.

On a positive note, improved access to education and effective lowering of vascular risk factors and depression are expected to dramatically delay the onset of cognitive impairment[8]. Indeed, a recent study evaluating cognitive function in >65-year-old individuals in England between 1991 and 2011 reported that over the study period, life expectancy at 65 years increased in both men (by 4.5 years) and women (by 3.6 years), as did the number of years free of any cognitive impairment (by 4.2 years in men and by 4.4 years in women)[9].

Because no disease-modifying treatment for AD is currently available, preventive measures are likely to be the key to mitigating the progressive global burden of MCI and dementia. Addressing modifiable risk factors as early as possible, preferably at the asymptomatic, preclinical stage of AD, could help turn back the rising tide of MCI and dementia[10]. Several large-scale randomized controlled trials have been established to evaluate the efficacy multidomain interventions that simultaneously target metabolic, vascular and lifestyle-related risk factors for dementia[10].

Substantial challenges still need to be addressed for successful AD prevention and development of disease-modifying drugs. A critical issue is the development of technologies to accurately screen and detect individuals at elevated risk among asymptomatic populations. The molecular and cellular mechanisms leading to prodromal and AD dementia commence decades before the onset of clinical symptoms of AD, providing a window of opportunity for disease-modifying treatments. Taking advantage of this opportunity, however, will require recognition and treatment of the earliest, asymptomatic stage of AD[10].

Even more importantly, we need initiatives that direct attention towards promoting and protecting cognitive health across the entire lifespan[10]. Moreover, we need to integrate and expand existing cohorts and registries to generate a worldwide database. Cooperation between different institutions and pooling of patient data would increase sample sizes, ensure replication, and strengthen the validity of the conclusions. With globally coordinated efforts by the academic research community, public and private institutions, and regulatory agencies to develop and implement internationally effective prevention starategies, curbing the escalating MCI and dementia epidemic might not be an unattainable goal. Refinement and harmonization of currently used clinical and research criteria for MCI presents the essential first milestone towards that goal.

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