ABSTRACT: The status of Mild Cognitive Impairment (MCI) as a valid construct is controversial. The term encompasses people with heterogeneous clinical profiles, and invites sub-classifications that still require validation. Still, much evidence suggests that, properly selected, many people with MCI — especially Amnestic MCI — are at a high risk of dementia. This paper considers the validity of the construct of MCI as a high-risk state for progression and a target for treatment. We conclude that the status of MCI as an entity remains controversial. On the one hand, it can be argued that the careful section of cases at high risk of developing dementia means that it is a valid target, with the goal being the prevention of dementia. Advocates of this view see a linear progression that they are trying to arrest, but studies have yet to show that this can be done. On the other hand, it can be argued that the patients who progressed did not develop dementia: they actually had a very early form of it. By this view, people without the progressive form will be needlessly exposed to anti-dementia drugs, and the others should be treated anyway. Why some people progress and others do not is not clear, but the variable rates of progression — between clinic-based and population-based samples and between very similar clinical trials with slightly different inclusion criteria — suggests that MCI is a heterogeneous entity. The phenomenon of slowing or non-progression itself should be investigated, and such investigations likely should extend to people now classified as having mild dementia.

RÉSUMÉ: Le déficit cognitif léger est-il une cible de traitement valide? Le statut du déficit cognitif léger (DCL) en tant que concept valide est controversé. Le terme désigne des individus qui ont des profils cliniques hétérogènes et il ouvre la voie à des sous-classifications qui n’ont pas été validées. Cependant il existe beaucoup de données indiquant que, s’ils sont choisis adéquatement, plusieurs individus ayant un DCL, spécialement le DCL amnésique, sont à haut risque de démence. Cet article examine la validité du concept du DCL comme un état à haut risque de progression et une cible de traitement. Nous concluons que le statut du DCL comme entité demeure controversé. D’une part, on peut considérer qu’une sélection précise des cas à haut risque de développer une démence indique qu’il s’agit d’une cible valide, le but étant la prévention de la démence. Ceux qui défendent cette position considèrent qu’il s’agit d’une progression linéaire qu’ils veulent tenter d’arrêter. Cependant les études n’ont pas démontré qu’il est possible de le faire jusqu’à maintenant. D’autre part, on peut considérer que les patients qui ont progressé n’ont pas développé une démence : ils avaient en fait une forme très précoce de démence. Si on adopte ce point de vue, les individus qui n’ont pas la forme progressive seront exposés inutilement aux médicaments anti-démence et les autres devraient être traités de toute façon. On ne sait pas pourquoi le déficit cognitif progresse chez certains individus et pas chez d’autres, mais le taux variable de progression - entre des échantillons recrutés en clinique et des échantillons recrutés dans la population, et entre des essais cliniques très similaires ayant des critères d’inclusion légèrement différents - suggère que le DCL est une entité hétérogène. Le phénomène de la progression lente ou de l’absence de progression devrait faire l’objet d’études et ces études devraient inclure des individus qu’on classifie actuellement comme ayant une démence légère.

The validity of a construct can be evaluated in several ways, but a three-part approach distinguishes between content, construct and criterion validity. Content validity refers to whether an idea is valid on its face. Although at least one careful study, which employed neuropsychological comparison, has called it into question, both broad camps (of advocates and skeptics) agree that many patients with dementia pass through a transitional stage. Still, there is considerable nuance, even in areas of apparent agreement. For example, the advocates of the MCI as high-risk state now recognize subgroups - an amnestic MCI type which progresses to dementia, and other types (e.g. frontotemporal MCI) that progress to other dementias. In this way, some sense can be made of the considerable heterogeneity that is noted in people with MCI. Clearly, content validity is a weak form of validation, but can be a useful starting point. Here it illustrates a central feature of MCI as now constituted, which is its heterogeneity. It is the resolution of heterogeneity which will be important to how MCI is viewed as a target for therapy.

The persistence of heterogeneity of who is included in various MCI definitions, and what outcomes they experience is at the heart of the MCI controversy, but variable outcomes are not unique to MCI. People with MCI come from a larger pool of people who have cognitive states that, while impaired, do not meet criteria for dementia. For example, the alcohol amnestic syndrome, post-stroke cognitive impairment, congenital cognitive abnormalities, chronic schizophrenia, depression, post-infectious syndromes and traumatic brain injury were each designated as belonging to the group “Cognitive Impairment, No Dementia” (CIND). The CIND group was the single largest entity in the population, according to the Canadian Study of Health and Aging, and people with many CIND syndromes showed improvement over five years of follow-up.

The setting of MCI in a wider context of CIND is key. The various sets of criteria can be read as a progressive refinement from the most heterogenous category of CIND to a purer ‘AMCI’ as confounders (alcohol amnestic syndrome, depression, etc.) are eliminated. From a construct standpoint, there are two problems – what is the nature of what is left over? Is it AMCI or very early Alzheimer’s disease? In addition, what is the nature of the conditions that have been excluded? Are they actually confounders, or are they – as might be argued about depression that presents chiefly with cognitive features – variants of an underlying process such as Alzheimer’s disease?

Much of the evidence for and against the validity of MCI comes from studies of construct validity, in which MCI is evaluated in its correlation with standard measures. A host of studies point to patients with MCI having scores on a variety of tests that are “in between” patients with no cognitive impairment and those with dementia. Some of this is inevitable from the way that MCI is defined. In consequence, it is important to understand the extent to which the memory impairment (in the case of amnestic MCI) correlates with impairment in other domains. This is important because if patients with AMCI have scores “in between” MCI and dementia in memory, but not in other cognitive domains, then it would be easy to accept that AMCI is an isolated memory problem that might herald subsequent dementia. But the common observation that AMCI patients also have “in between” scores on language, attention and concentration, and function can further be taken as evidence that these patients have very mild dementia. The reasoning is that they have global cognitive impairment (memory and at least one other domain) likely with some functional impairment, which thereby would meet the definition of dementia. In short, one important objection to MCI is that it really is early Alzheimer’s disease. The counter-argument from clinicians hinges on two points. First, the definition of dementia stresses that deficits must be “significant”, and the “in-between” deficits do not meet this clinically crucial but conceptually ephemeral level of impairment. Secondly, in practice, clinicians must hesitate in concluding or communicating that patients have what is usually an untreatable condition (i.e., dementia), when that individual may be reclassified within three years as being normal! By its very nature MCI in most settings is heterogeneous and any MCI cohort contains individuals who will not progress to dementia and therefore it would be wrong to tell patients that MCI is really just early Alzheimer’s Disease. How to distinguish clinically between people who will progress (and thus are legitimate targets of therapy) and those who will not is not yet established.

For people who subscribe to the view that what we really need is better diagnosis of very early dementia, then how might investigations proceed? Some feel that the state could be quickly clarified by better testing - for example, by better neuropsychological batteries, and specifically, better tests of executive function or of neuroimaging, making the diagnosis less dependent on clinical judgment. Others, however, are less persuaded that more “objective” testing (either neuropsychological or neuroimaging) would substantially improve diagnosis. There is also disagreement about the same data. For example, even amongst people who meet all of the MCI criteria, the time for progression to dementia varies by many years between patients. Mild Cognitive Impairment advocates see this as confirming the high risk state, making it distinct from early dementia. Mild Cognitive Impairment skeptics call it unacceptable heterogeneity, likely reflecting very early dementia. On the other hand, proponents of (A)MCI as a high risk state might argue that this is a misuse of the term dementia - akin to saying that someone with a rectal temperature of 37.6 (in a setting where infection is suspected) has very early fever. (This too can be countered by pointing out the need to know not just a single observation, but its course.) In such a circumstance, a question that merits consideration is what to call the earliest clinical expression of Alzheimer’s disease.

Rates of progression are of particular importance, because predictive validity is an aspect of criterion validation, which is held as the highest form of validity. In a systematic review of 19 longitudinal studies, Bruscoli and Lovestone concluded that heterogeneity reflected not just how patients were recruited for MCI studies (on this, there is widespread agreement) but also how the criteria were employed. Specifically, they noted that more stringent measurement of deficits resulted in better prediction of conversion, raising the possibility that highly specified MCI represents very early dementia. Similar disagreements about interpretation exist in considering biological markers, such as CSF beta-amyloid and tau. For example, of 52 patients with MCI, those with elevated levels of tau had a higher...
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<td>Petersen et al., 1999</td>
<td>Y</td>
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<td>N</td>
<td>Y</td>
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<td>Morris et al., 2001</td>
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<td>Y</td>
<td>Not indicated</td>
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<td>Bennett et al., 2002</td>
<td>N</td>
<td>Y</td>
<td>Not indicated</td>
<td>Extensive neuropsychological battery</td>
<td>Population specific cut-offs used</td>
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<td>Darby et al., 2002</td>
<td>Y</td>
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<td>N</td>
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<td>CERAD word list recall</td>
<td>=&lt;0.5</td>
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<td>Hassinen et al., 2002</td>
<td>N</td>
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<td>N</td>
<td>Not indicated</td>
<td>MMSE&gt;22</td>
<td>&gt;1SD below mean of cohort</td>
</tr>
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<td>Kalaria et al., 2002</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Not indicated</td>
<td>CDR-Y</td>
<td>&gt;2SD below age adjusted norms</td>
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<tr>
<td>Larrieu et al., 2002</td>
<td>Y</td>
<td>Y</td>
<td>MMSE&gt;1SD</td>
<td>Hinton Visual Retention Test</td>
<td>&gt;2SD below age &amp; ed. Adjusted means</td>
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<tr>
<td>Fusse et al., 2003</td>
<td>Examed as a clinical variable</td>
<td>Y</td>
<td>N</td>
<td>Structured Mental Status (SfMAM)</td>
<td>&gt;1SD below age &amp; ed. + Assoc norms on sub-tests of SfMAM</td>
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<tr>
<td>Risk et al., 2003</td>
<td>Examed as a clinical variable</td>
<td>N</td>
<td>Not indicated</td>
<td>No cut-offs set; Dx based on clinical consensus</td>
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<td></td>
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<td>Lambon et al., 2003</td>
<td>Y</td>
<td>N</td>
<td>MMSE&lt;24</td>
<td>Logical Memory (immediate) - DMS (memory)</td>
<td>&gt;1.5 SD below means of cohort</td>
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<tr>
<td>Lopez et al., 2003</td>
<td>Necessary for ‘probable’ MCI, but not ‘possible’ MCI</td>
<td>Y</td>
<td>Y</td>
<td>n/a</td>
<td>&gt;1.5 SD below a sample of 250 unpaired subjects</td>
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<tr>
<td>Faterow et al., 2004</td>
<td>(InDDEx study)</td>
<td>Y</td>
<td>Y</td>
<td>Not indicated</td>
<td>CERD NYU paragraph recall</td>
<td>&lt;0.5</td>
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<td>Feldman et al., 2004</td>
<td>N</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>CERD NYU paragraph recall</td>
<td>&lt;10</td>
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<td>Gianguli et al., 2004</td>
<td>Y</td>
<td>Not indicated</td>
<td>N</td>
<td>MMSE&gt;10 word list delayed recall</td>
<td>&gt;1SD below mean of cohort</td>
<td></td>
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<tr>
<td>Grundman et al., 2004</td>
<td>(ADCS-MIS study)</td>
<td>Y</td>
<td>Examed as a clinical variable</td>
<td>&lt;9</td>
<td>Logical Memory II</td>
<td>&gt;12</td>
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<td>Royall et al., 2004</td>
<td>Not indicated</td>
<td>Examined as a clinical variable</td>
<td>Y</td>
<td>Not indicated</td>
<td>MMSE- CLOX-1,2 (clock drawing test) - COWA (verbal fluency) - EXIT 25 (executive interview) - Trail A + B - CVLT (verbal memory) - DRS- MMSE</td>
<td>&gt;1.5 SD below average score of the sample on each measure</td>
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<td>Ridofrano et al., 2004</td>
<td>Not indicated</td>
<td>Examined as a clinical variable</td>
<td>&lt;9</td>
<td>Habit Recall Story Recall Test</td>
<td>score in the lowest 10% percentile of the cohort</td>
<td></td>
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<td>DeJager et al., 2005</td>
<td>Not indicated</td>
<td>N</td>
<td>Y</td>
<td>Not indicated</td>
<td>CERAD 10 word list free and delayed recall</td>
<td>&gt;1.5 SD below means of cohort</td>
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<td>Devanand et al., 2005</td>
<td>Y</td>
<td>Y</td>
<td>MMSE&gt;22</td>
<td>MMSE-Delayed recall</td>
<td>&gt;2 of 3 items recalled</td>
<td>&gt;1SD below norms</td>
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<td>Cicchetti et al., 2005</td>
<td>Not indicated</td>
<td>N</td>
<td>Not indicated</td>
<td>WAIS-R similarities or digit symbol</td>
<td>&gt;10 points below WAIS-R verbal IQ score. If no deficits on objective tests, memory complaint + informant’s confirmation of decline and functional decline</td>
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**Table: MCI criteria used in earlier studies**
Table: continued

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<tr>
<th>Ref.</th>
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<th>Sparse</th>
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<th>CVLT</th>
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<td>Kumar et al., 2005</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Key Auditory Verbal Learning Test 2 subjects of WAIS (Delayed Visual reproduction and logical memory)</td>
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<tr>
<td>Nasreddine et al., 2005</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>At least 1SD below norms</td>
</tr>
<tr>
<td>Visser et al., 2005</td>
<td>Not indicated</td>
<td>Y</td>
<td>Y</td>
<td>Not indicated</td>
<td>Global Deterioration Scale 20 item story recall</td>
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<tr>
<td>Hill-Ingall 11 (as described in Visser et al., 2005)</td>
<td>Not indicated</td>
<td>Y</td>
<td>Y</td>
<td>Not indicated</td>
<td>CDR NYU Paragraph recall</td>
<td></td>
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<tr>
<td>Aminokine study (as described in Visser et al., 2005)</td>
<td>Not indicated</td>
<td>Y</td>
<td>Y</td>
<td>MMSE&gt;24</td>
<td>CDR Logical Memory II Goniometric Dep. Scale</td>
<td></td>
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<tr>
<td>Piactenium Study (as described in Visser et al., 2005)</td>
<td>Not indicated</td>
<td>Y</td>
<td>Y</td>
<td>Not indicated</td>
<td>CDR Logical Memory I Logical Memory II HDRS</td>
<td></td>
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<tr>
<td>Rofecoxib Study (as described in Visser et al., 2005)</td>
<td>Not indicated</td>
<td>Y</td>
<td>Y</td>
<td>MMSE&gt;23</td>
<td>CDR RAVLT total learning HDRS</td>
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<tr>
<td>Vergheese et al., 2006</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Verbal IQ&gt;84</td>
<td>Blessed test 5 item memory phrase</td>
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</table>

In consequence, it is not yet evident dementia, evidential dementia, they varied importantly in the proportions who carried an ApoE4 allele. As clinical correlative studies- even with neuropathology - an inadequate test of validity. In dementia studies, there is a strong tradition of considering criterion validity chiefly in the form of referent validation, with the referent being a so-called “gold standard”. The "gold standard" was held to be neuropathology, although the existence of several sets of neuropathological criteria that can yield conflicting results diminishes the luster of this approach somewhat. Importantly, all studies show a dose response between putative pathogenic factors and NCI, MCI and AD. On the other hand, neurocompensatory responses might be more specific, so that static levels might not reflect dynamic changes, making simple correlative studies- even with neuropathology - an inadequate test of validity.

**CONCLUSIONS**

In general, it seems logical to propose that cholinesterase inhibitors having not been demonstrably effective reflects either that: the MCI concept is valid, but the drugs are ineffective, or; MCI is valid, the drugs are effective, but the outcome measures used to detect treatment effects have been insensitive to clinically important change, or; the MCI concept is not valid enough to select operational criteria which pick out people with demonstrable memory impairment who might respond to treatment with a cholinesterase inhibitor. The present data do not readily allow for these possibilities to be distinguished, but they do show that even small differences in clinical trials enrollment criteria appear to make big differences in the rates of progression, even if attempting to have more rigorous criteria in population studies does not affect progression (or recovery). An important policy consideration in knowing whether MCI is a valid target of treatment is that, as we have seen, MCI is not the only form of cognitive impairment that falls between normal cognitive function and dementia. In consequence, it is clear that questions about definition - which is central to the current controversies about MCI as a therapeutic target - are essential features and not regulatory niceties. Definitional nuances also have policy implications in that minor changes in how MCI is defined can result in three-fold differences in prevalence. If MCI is to become a treatable “disease” then careful attention needs to be paid to criteria, lest it become a rapidly spreading epidemic!
We note that MCI is potentially a target of therapy not just for cholinesterase inhibitors. There is now a set of publications which demonstrate a lack of depletion of choline acetyltransferase in MCI, or in mild AD brains, for that matter.\textsuperscript{34, 49, 50} Unimpressive symptomatic trials of ChEIs would support this view. Additionally, MCI is being evaluated as an entity driven by cerebrovascular disease, suggesting that it might also be a target for vascular risk factor modification.\textsuperscript{51} Other compounds that have been evaluated for use among current MCI criteria include rofecoxib\textsuperscript{52} and Vitamin E.\textsuperscript{33}

Many of the controversies about how to conceptualize MCI are amenable to pragmatic research programs, and should motivate better funding for systematic inquiry. Future studies might well make the controversy obsolete. For example, if an anti-amyloid compound that is potentially disease-modifying — that might, in fact, prevent dementia — were to be studied, then it might well be studied in people who were genetically at risk, even if they did not have MCI/very early Alzheimer’s disease. On the other hand, unless prevention of dementia is completely effective, it might well be that future ‘prevented dementia’ would look more like MCI (or CIND) than like normal cognitive function.

If many people with MCI actually have early dementia, which increasingly seems likely,\textsuperscript{53} then how to identify this group needs better attention. It is likely that clinically sensible tests of executive function will be of particular value.\textsuperscript{26} It might also be that the comparatively little attention paid to behavioural manifestations has lessened the sensitivity and specificity of the MCI construct.\textsuperscript{51, 54-56} In this regard, an epidemiological and clinical research program that evaluated MCI in relation to depression would be of particular value.\textsuperscript{27} Further specification of the number and types of domains that are affected might also yield greater specificity.\textsuperscript{58} Hypotheses such as these – and the hypothesis that intervention can delay progression in very early dementia - merit specific testing, using both standard tests, and more sensitive measures than those now generally employed. Such a program would require a much more sophisticated evaluation of patients than is now routinely available outside of the academic research setting in Canada. In consequence, it appears that MCI as a high-risk state putatively distinct from very early dementia is best understood as an entity that requires additional research, including at the level of concept validation.\textsuperscript{59} Intervention studies should therefore be undertaken with a view to clarifying the concept, targets of treatment and identification of potential responder groups.

**DECLARATION**

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Within the past 2 years Howard H. Feldman has served as a consultant, received grant funding or participated in CME programs sponsored by Astra Zeneica, Pfizer, Eisai, Novartis, Janssen, Servier, Sanofi Synthelabo, Lilly, GlaxoSmithKline, Myriad, Targacept, Forest, Lundbeck and Aponyx.

**REFERENCES**


