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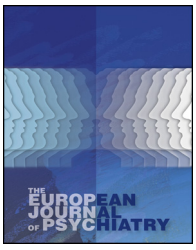

ORIGINAL ARTICLE

Different subpopulations of mild cognitive impairment are identified by using Petersen's or DSM-5 criteria

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Abstract
Objectives: In view of differences in the prevalence and conversion rate to dementia of Petersen's (P-MCI) and DSM-5's (DSM-5-MCI) categories of mild cognitive impairment, this paper is intended to examine the diagnostic agreement between the categories and to analyze clinical factors related to the potential discrepancies.
Method: A representative population cohort of 4580 dementia-free individuals 55+ years of age was examined in Zaragoza, Spain (ZARADEMP). Validated Spanish versions of instruments, including the Geriatric Mental State-AGECAT, were used for assessment. Research psychiatrists diagnosed DSM-5-MCI and P-MCI following operationalized criteria. Between-category differences were analyzed, and the statistical methods included the calculation of Cohen's Kappa coefficients of agreement, and the McNemar's test to compare the performance of the intermediate cognitive definitions.
Results: Diagnostic concordance in the classification of MCI cases was very limited. In the total sample, 2.7% of individuals did not meet the P-MCI criteria but met the DSM-5-MCI criteria; and 6.4% met the P-MCI criteria, but not the DSM-5-MCI criteria. Overlap of both categories was observed in only 0.6%. The overall Kappa (agreement between both MCI categories) was 0.08 (95% CI: 0.04–0.12; $p < 0.001$).

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While no between-category significant differences was observed in cognitive scores, relevant differences in the populations identified had to do with demographic, non-cognitive psychopathological factors, activities of daily living and general health factors.
Conclusions: This study shows 'poor' diagnostic agreement between the P-MCI and the DSM-5-MCI categories. The non-cognitive factors should receive special attention when trying to improve the validity of the MCI construct.

Introduction

The concept 'Mild Cognitive Impairment', MCI has received increasing attention from researchers, clinicians and administrators.[1] This construct was initially described by R. Petersen and colleagues.[2] It was intended to depict a clinical condition that could eventually result in dementia, so that the early identification could be followed by an early intervention. The condition was initially described as a category of patients with subjective memory loss verifiable by psychometric testing, but with no gross impairment in other aspects of cognition and no impairment in their usual activities of daily living (hence, no dementia).[3] This definition has been widely used, but the operational criteria have undergone several revisions over the course of the last decade. The International Working Group (IWG) criteria of MCI have also been influential,[4] as well as the National Institute of Aging-Alzheimer's Association (NIA-AA) criteria for MCI due to AD.[5] In fact, the category MCI remains an evolving diagnosis.[6]

The recent development of the DSM-5, the official classification of the American Psychiatric Association (APA), has included a category related to MCI, named 'Mild NeuroCognitive Disorder' (NCD),[7] which could have special relevance in view of the influence of this classificatory system. We expected this category would be similar to the original one described by Petersen et al.,[3] but were surprised to find out that the prevalence of MCI-DSM-5 in the general population was approximately half that of P-MCI.[8] These findings, as well as findings such as the ones by Ganguli et al.,[9] reporting wide disparity of prevalence rate of MCI in different studies, suggest that different subpopulations of MCI might be identified by using diverse diagnostic criteria. Other authors have also suggested that MCI is still an area of major debate, with no consensus on its classification.[10] Therefore, new studies are required to analyze the discrepancies detected, and efforts to homogenize the criteria applied should facilitate international comparisons.[11]

In support of the possibility that using P-MCI criteria or DSM-5-MCI criteria different subpopulations of MCI might be identified, we have also reported that the Conversion Rate (CR) to dementia of both categories is quite different.[12] Greater severity of DSM-5-MCI is suggested by the higher CR in this study. In support of this, we have also shown that the mortality rate is almost double in DSM-5-MCI individuals than in P-MCI individuals.[13] Moreover, the CR in our study, and similarly in the German, AgeCoDe study,[14] was much lower than previously expected. Both these studies were done in general population or primary care samples, and it seems to be clear that the CR is usually higher in settings such as dementia clinics.[15,16] Other methodological aspects could be invoked, but it is still intriguing to see that in studies such as the German and ours', the great majority of individuals diagnosed with MCI do not develop dementia in a reasonable period of time.[12]

Since it is obvious that the MCI construct could be important because of its potential for the early detection and therefore the potential prevention of dementia, it is evident that the construct should also be refined, trying to document its validity for specific purposes. Authors such as Matthews et al.[17] have discussed that it may be premature to rely on the diagnosis of MCI as presently characterized. In relation to this, we have argued,[18] as well as several other authors,[5,19] that maybe the MCI should be accompanied by genetic and/or other biomarkers. However, in the meantime, we believe it is also relevant to try to refine the clinical characteristics of MCI and, in this respect, the analysis of between-category discrepancies should facilitate the process.

In this background, the aims in this study were, first, to examine the diagnostic agreement between P-MCI and DSM-5-MCI criteria in a sample of the general population; and, second, to analyze clinical factors related to the potential discrepancies.

Method

Sample

The data presented here come from the Zaragoza Dementia and Depression (ZARADEMP) study, a longitudinal community study carried out in Zaragoza, Spain. The longitudinal design included a baseline, cross-sectional study (Wave I, starting in 1994) and four follow-up waves completed to date. This report presents data from the baseline study. Data collection and sample characteristics have been described elsewhere.[20] In short, a random sample of community dwelling persons aged 55 or more years, proportionally allocated by age and sex, was drawn from the census list of the city of Zaragoza (Spain) in 1991. Institutionalized individuals were also included. As a result, 4803 subjects underwent the baseline interview (Wave I).

The principles of the Declaration of Helsinki were followed throughout. The Ethics Committee of the University

of Zaragoza, and the Fondo de Investigación Sanitaria (FIS) approved the study protocol, according to Spanish Law. All individuals included in the study provided written informed consent.

Procedure

An epidemiological, longitudinal study was designed and a two-phase, diagnostic procedure was implemented. In the baseline interview, phase I, well-trained and regularly supervised lay interviewers conducted the 25- to 90-minute ZARADEMP interview at the subjects' home or place of residence. Research psychiatrists supervised the lay-interviewers, and re-examined in the elderly's homes all doubtful cases. Periodic re-training of interviewers was implemented to avoid the reliability decay. The ZARADEMP interview incorporates standardized Spanish versions of several international instruments, including the following ones.

Geriatric Mental State (GMS), a semi-structured standardized clinical interview for assessing the mental state of elderly persons,[21,22] accompanied by the AGECAT computer system, which uses an algorithm to analyze the GMS data and can have as outcome the psychiatric diagnosis.

The History and Aetiology Schedule (HAS), a standardized method of collecting history data from a caregiver, or directly from the respondent when he or she is judged to be reliable.[23]

Katz Index,[24,25] and Lawton and Brody Scale[26,27] to assess basic and instrumental activities of daily living, respectively; and a series of questions regarding medical and psychiatric history from the EURODEM (European Community Concerted Action on the Epidemiology and Prevention of Dementia) Study Risk Factors Questionnaire.[28]

In phase II, the trained, supervising research psychiatrists reassessed those individuals considered to be 'probable psychiatric cases', and/or the participants with information considered to be unreliable. These interviews were also conducted in the participants' place of residence, and the same instruments were used, as well as Hachinski's scale[29] and a brief, previously standardized neurological examination. Our previous studies support the validity of this case-finding procedure.[22] At the end of the baseline study, identified cases of dementia and subcases of dementia (GMS criteria) were excluded for the follow-up waves (Waves II and III), as well as for the present study.

MCI assessment and diagnosis

The process for the MCI assessment and diagnosis was as follows: first, blind to the results of the field work, a panel of research psychiatrists (and a psychologist) operationalized the relevant items in the ZARADEMP interview to comply with both Petersen et al.[3] and DSM-5 criteria[7] (see Table 1). Second, the research psychiatrists reviewed all the information from the ZARADEMP interview in Wave I and classified the individuals in the appropriate, operationalized categories of MCI 'cases' or 'non- cases'. Based on the DSM-5 criteria,[7] individuals with psychosis and severe depression (defined as an AGECAT case symptom level of 3 or above, Stage II) were excluded from the DSM-5-MCI construct. No exclusions were applied to Petersen et al. criteria.[3]

Statistical analysis

The Chi-square test was used to compare proportions across MCI groups. In normality continuous measures, an analysis of variance (ANOVA) test analysis was used to compare means. Bonferroni post hoc correction was also applied. Statistical significance was set at $p < 0.05$ and all tests were two-tailed.

Cohen's Kappa[30] was used, which corrects for chance agreement, and the level of agreement between raters was assessed in terms of a simple categorical diagnosis (i.e., the presence or absence of a disorder). Kappa values range from −1.0 to 1.0, with values of 0 indicating agreement at only chance levels. Values above 0.75 are often considered good, values between 0.40 and 0.75 are fair, and values below 0.40 indicate poor agreement.[31]

McNemar's test[32] was performed to compare differences in percentage of MCI cases detected/diagnosed with either criteria. Confidence interval for the difference was also calculated.[33]

For all analyses, we used R software[34] with its *PropCIs* package to compute a difference of proportions with matched pairs.

Results

In the sample selected for this study ($n = 4580$), 7% of individuals were classified as P-MCI cases, but only 3.4% as DSM-5-MCI cases. Therefore, the proportion of cases of P-MCI was 3.6% higher than the proportion of DSM-5-MCI cases (CI 2.8–4.6; $p < 0.001$). A diagnostic concordance in the classification of MCI cases was observed in a total of 4163 participants: 4133 of them were classified as non-cases and the overlap of P-MCI and DSM-5-MCI was observed in only 30 individuals (Table 2). On the contrary, 124 participants (2.7% of total sample) did not meet the P-MCI criteria but met the DSM-5-MCI criteria; and 293 participants (6.4% of total sample) met the P-MCI criteria, but did not meet the DSM-5-MCI criteria. The overall percentage agreement was 90.8% and overall kappa was 0.08 (95% CI: 0.04–0.12; $p < 0.001$), indicating ''poor'' agreement between both MCI categories.

Table 3 compares demographic and clinical characteristics of non-cases, ''pure cases'' of both P-MCI and DSM-5-MCI (those with no overlap), and ''overlap cases'' (those fulfilling both diagnostic criteria). Compared with P-MCI cases, the proportion of women, the oldest and those with poor general health were significantly higher among DSM-5-MCI cases. Similarly, the scores in iADL's were significantly higher and a trend for lower MMSE scores (not statistically significant) was observed in DSM-5-MCI cases. The frequency of cases of depression was lower, but was higher the frequency of cases of anxiety among the DSM-5-MCI cases.

In the ''overlap cases'', the most notable characteristics were the frequency of the oldest old, the higher proportion of the illiterate and of cases of both depression and anxiety, and the highest proportion of individuals with poor general health.

Discussion

As we anticipated in view of previously reported, wide differences in the prevalence of P-MCI and DSM-5-MCI in

Table 1 Diagnostic criteria for mild cognitive impairment (MCI) used in the study.

Petersen's criteria	DSM-5's criteria
A. Subjective complaint of decline in memory on self or informant report Subjective memory complaint, Geriatric Mental State, GMS, specific item (dichotomized, affected)	A.1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; Subjective complaint (GMS item) (dichotomized, affected) OR The informant reports cognitive problems (GMS item) (dichotomized, affected) OR The interviewer observes memory difficulties (GMS item) (dichotomized, affected) AND A.2. A modest impairment in cognitive performance, documented by standardized cognitive assessment. MMSE total score 24–29
B. Isolated memory impairment on neuropsychological testing (below the standard threshold point) MMSE total score normal (cut score 23/24) AND MMSE memory item low (cut score 1/2)	B. The cognitive deficits do not interfere with capacity for independence in everyday activities (as measured by ADL scales), but greater effort, compensatory strategies, or accommodation may be required. Intact Basic ADL's (Katz's index) AND Can do normal activities, caregiver's opinion (GMS item) ((dichotomized, unaffected)) AND Mild difficulty in Instrumental ADL's (Lawton & Brody scale) (scores 1–3)
C. Intact daily functioning in ADL scales Normal function in both, Lawton & Brody and Katz's scales	C. The cognitive deficits do not occur exclusively in the context of a delirium
D. Not meeting criteria for a diagnosis of dementia No dementia according to either GMS-AGECAT criteria or DSM-IV criteria.	D. The cognitive deficits are not better explained by another mental disorder (specifically: psychosis and severe depression). Absence of other mental disorder, GMS-AGECAT criteria

the general population,[8] as well as marked differences in the conversion rate to dementia,[12] this article confirms the limited agreement between both diagnostic categories, since the overall kappa was only 0.08. To some extent, between-category differences might be expected, in view that signs and symptoms of the DSM-5-MCI construct may be more severe than those captured in the P-MCI definition, which was developed with a different philosophical approach.[35] Still, it is remarkable that the diagnostic agreement occurred in only 30 cases (9.3% of P-MCI cases; 19.5% of DSM-5-MCI cases).

In a context of great interest in the subject of MCI, because of the potential of this construct for the early identification of individuals at risk of dementia, the discrepancies in the diagnostic classification should alert both clinicians and researchers. However, we should consider

Table 2 Concordance in the distribution of P-MCI and DSM-5-MCI in the general population of individuals aged 55+ years.

		Petersen's criteria		Total
		No case	Case	
DSM-5 criteria	No case	4133 (90.2%)	293(6.4%)	4426 (96.6%)
	Case	124 (2.9%)	30 (0.6%)	154 (3.4%)
	Total	4257(92.9%)	323 (7.0%)	4580

Table 3 Differences of demographic and clinical characteristics between three categories of 'Mild Cognitive Impairment cases' and 'non-cases'.

Demographic and clinical characteristics	Non-cases $n = 4133$	P-MCI 'pure' cases $n = 293$	DSM5-MCI 'pure' cases $n = 124$	'Overlap' cases $n = 30$	*p* value
Women, n (%)	2318 (56.1)	181 (61.8)	89 (71.8)[a]	18 (60.0)	0.002[¥]
Age, n (%)					
≤65	1023 (24.8)	54 (18.4)	7 (5.6)	1 (3.3)	<0.001[¥]
65–79	2059 (49.8)	165 (56.3)	45 (36.3)	12 (40.0)	
≥80	1051 (25.4)	74 (25.3)	72 (58.1)[a,b]	17 (56.7)[a,b]	
Education, n (%)					0.004[¥]
Illiterate	424 (10.4)	31 (10.6)	13 (10.5)	5 (16.7)	
Primary school	3.003 (73.3)	237 (81.2)[a]	98 (79.0)	23 (76.7)	
Secondary school or higher	669 (16.3)	24 (8.2)[a]	13 (10.5)	2 (6.7)	
MMSE score, mean (SD)	26.4 (3.8)	26.2 (2.1)	25.9 (2.3)	25.4 (2.4)	0.176[*]
Depression, n (%)					<0.001[¥]
No case	3112 (82.6)	155 (60.8)	70 (64.2)	9 (40.9)	
Subcase	213 (5.7)	31 (12.2)[a]	18 (16.5)[a]	2 (9.1)	
Case	444 (11.8)	69 (27.1)[a]	21 (19.3)	11 (50.0)[a,c]	
Anxiety, n (%)					<0.001[¥]
No case	2333 (56.4)	116 (39.6)	51 (41.1)	9 (30.0)	
Subcase	1.621 (39.2)	158 (53.9)[a]	62 (50.0)	18 (60.0)	
Case	179 (4.3)	19 (6.5)	11 (8.9)	3 (10.0)	
Basic ADLs score, mean (SD)	0.2 (1.1)	0.1 (0.3)	0.1 (0.5)	–	0.021[*]
Instrumental ADLs score, mean (SD)	0.6 (2.1)	0.0 (0.2)	2.4 (2.6)[a,b]	1.3 (0.6)[b]	<0.001[*]
Poor general health, n (%)	2.160 (52.3)	175 (59.7)	94 (75.8)[a,b]	24 (80.0)[a]	<0.001[¥]

P-MCI 'pure' cases: 'Mild Cognitive Impairment cases' without overlap with DSM-5-MCI cases.
DSM-5-MCI 'pure' cases: 'Mild Cognitive Impairment cases' without overlap with P-MCI cases.
'Overlap' cases: 'Mild Cognitive Impairment cases' with overlap P-MCI/DSM-5-MCI.
[*] ANOVA test.
[¥] Chi-square test.
[a] $p < 0.05$ (reference: non-cases MCI).
[b] $p < 0.05$ (reference: P-MCI 'pure' cases).
[c] $p < 0.05$ (reference: DSM5-MCI 'pure' cases).

special characteristics in this paper. First, this study was conducted in the general population and the results might be different in clinical samples.[36] Both the prevalence of MCI and the conversion rate to dementia[15] have been reported to be considerably higher in clinical samples, suggesting that conclusions in the general population could not necessarily be transferred to the clinical settings.

Second, while we were careful in the diagnosis of MCI, the conjecture may be that in clinical practice discrepancies in the application of diagnostic criteria observed in this community study might be minimized. In relation to this, we have previously argued strongly that the category ''Mild NeuroCognitive Disorder'' in DSM-5, which we adapted for the DSM-5-MCI criteria, needs a more careful operationalization for research purposes.[12]

Third, we have previously argued that the DSM-5-MCI criteria allows for some functional deficit among the diagnostic criteria[8] and suggested that this could be a crucial factor to explain the different results reported in P-MCI vs DSM-5-MCI.[13] We now show some evidence to support this conjecture, since the scores in iADL's were significantly higher among DSM-5-cases when compared with P-MCI cases.

A recent article by Tay et al.[37] has studied the diagnostic agreement between IWG, which uses diagnostic criteria similar to the P-MCI, and DSM-5's criteria for MCI. While the objectives in this study were different from ours' and comparisons are difficult because they assessed a memory clinic sample, they also found a much higher prevalence of IWG-MCI (86/234), than DSM-5-MCI (40/234). Therefore, their study coincides with ours and supports our findings of low agreement between both categories of MCI, as well as the lower prevalence of the DSM-5 category, suggesting that the diagnostic criteria in the American classification are more restrictive.[37]

In relation to the second objective in this study, in trying to analyze the characteristics of the discrepant cases to eventually refine the MCI concept, other relevant differences between P-MCI and DSM-5-MCI have been found. While no significant differences were observed in cognitive, MMSE scores, the proportion of women, the oldest old and those with poor general health were significantly higher among DSM-5-MCI cases. It might be argued that the oldest age might be a common denominator to all these factors, but we have previously discussed that age is not the only factor to explain the important differences found in subjects such

as the conversion rate to dementia.[12] New research, including studies using multifactorial analysis would be required to determine the specific weight of individual factors. Other factors to consider in trying to explain the differences found relate to non-cognitive psychopathological symptoms. As expected, the frequency of depression was lower among DSM-5-MCI cases, since severe depression is one of the exclusion criteria for this category. On the contrary, anxiety was more frequent among the DSM-5-MCI cases than among P-MCI cases.

Special interest may have the description of characteristics in the ''overlap cases'', which were a minority in this study. Among the individuals fulfilling both diagnostic criteria, the most notable characteristics were the frequency of the oldest old, the higher proportion of the illiterate and of cases of both depression and anxiety, and the highest proportion of individuals with poor general health.

In view of the between-category differences found in this study, it is also remarkable that no significant differences have been observed in global, MMSE cognitive scores, since the DSM-5-MCI category is suggested to capture more severe cases. As a consequence of this, it is possible to speculate that MCI, as presently characterized, might be influenced by factors such as non-cognitive psychopathology or poor general health, even more than cognitive impairment. This is relevant in relation to a construct intended to predict the development of dementia.

Some authors have argued that the MCI construct has stood the test of time, and expected that using DSM-5-MCI criteria it would be possible to predict the development of dementia with greater accuracy.[38] However, the same authors claim that new empirical studies are required to validate this consensus category. Ganguli et al.[9] have also emphasized the need to validate research criteria at the community level before incorporation into clinical practice. It is intriguing that, in view of evidence provided in the articles reviewed here, the predictive power of DSM-5-MCI, while being improved in relation to P-MCI criteria, seems to be limited. Moreover, this increased predictive power might be at the cost of decreased sensitivity, which is important in studies such as those conducted in general population settings. The critical relevance and the power of the MCI construct is that it might allow the early identification of individuals at risk of dementia and, therefore, the detection of potentially treatable cases. In view of the studies reviewed, it seems that it is premature to recommend the MCI concept for wider use in population-based settings. Studies such as the present one should help in the task of developing a construct with improved validity and predictive power.

We have argued in previous studies in this series about the strengths of the ZARADEMP project, conducted in a large, representative sample in a typical city population in Spain, which included institutionalized individuals and had a limited proportion of drop-outs.[12,13] We have also discussed potential limitations such as the ones related to the diagnostic process in the community; or the diagnosis of MCI by the panel of research psychiatrist. However, as this study makes clear, the MCI categories used merit more careful validity studies before the results are generalizable.

In conclusion, the diagnostic concordance between the P-MCI and the DSM-5-MCI categories is quite limited, and the discrepancies in the MCI sub-populations identified should alert both clinicians and researchers. While no significant differences were observed in cognitive, global scores, relevant differences in the populations identified had to do with demographic, non-cognitive psychopathological factors and general health factors. If MCI is intended to predict dementia, the non-cognitive factors should receive special attention in future studies to improve the predictive validity of the MCI construct. Multifactorial methods should be used to determine the specific weight of the risk factors. Biomarkers may be certainly important, but may be not sufficient. The findings in this study should help in the way to improve the MCI construct.

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