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Mild cognitive impairment diagnosed with the new DSM-5 criteria: prevalence and associations with non-cognitive psychopathology

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Objective: To contrast the prevalence of mild cognitive impairment (MCI) as diagnosed using DSM-5 criteria (DSM5-MCI) with MCI as diagnosed using Petersen's criteria (P-MCI) and to explore the association of both with non-cognitive psychopathological symptoms (NCPS).
Method: A two-phase epidemiological screening was implemented in a population-based sample of individuals aged 55+ (n = 4803). The Geriatric Mental State (GMS) was the main psychopathological instrument used, and AGECAT was used to make psychiatric diagnoses. Research psychiatrists diagnosed DSM5-MCI and P-MCI using operational criteria. Logistic regression models were then used to investigate the association of MCI with anxiety and depression and with NCPS.
Results: Weighted prevalence of DSM5-MCI and P-MCI was, respectively, 3.72% and 7.93% for the aged 65+. NCPS were common in both MCI categories, but negative-type symptoms such as 'anergia' and 'observed slowness' were considerably more frequent among persons with DSM5-MCI. Anxiety and depression diagnostic categories were associated with both P-MCI and DSM5-MCI, but affective-type symptoms were mainly associated with P-MCI. Some negative-type symptoms were inversely associated with P-MCI, and no association was observed with DSM5-MCI.
Conclusion: The prevalence of DSM5-MCI was half that of P-MCI. Negative-type NCPS were more frequently and typically associated with DSM5-MCI.

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Key words: mild cognitive impairment; prevalence; community study; DSM-5; non-cognitive psychopathological symptoms

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Significant outcomes

- The prevalence of MCI in this population was lower than has been reported typically elsewhere. The prevalence of DSM-5-MCI was half that according to classical, P-MCI diagnostic criteria.
- Non-cognitive, negative-type symptoms were more typically found in DSM-5-MCI, and affective-type symptoms are more typically found in P-MCI.
- The findings in this study do not suggest that one should expect a substantially higher rate of conversion to dementia for DSM-5-MCI than P-MCI.

Limitations

- The attrition rate in the study limits the generalizability of results.
- For the diagnosis of MCI, the research psychiatrists reviewed all the available information, but a full psychiatric examination was not performed in all cases.
- The lack, to date, of harmonization of the operational criteria used for MCI limits the comparability of results.

Introduction

There is increasing interest in preclinical diagnosis of Alzheimer's disease (AD) and other dementias, so that early interventions could be eventually implemented. (1) A number of syndromic descriptions have been proposed for characterization of memory and cognitive deficits that lead to dementia. Among these, the syndrome of 'mild cognitive impairment', MCI (2), has become the best known (3), and the validity of this construct has been supported by pathological findings (4) and brain imaging studies (5). However, several authors have suggested that MCI is a heterogeneous entity at the population level (6, 7), and this heterogeneity may partly explain the wide differences in the prevalence of MCI reported to date (8). In view of the typically high conversion rate of MCI to dementia (9), some authors have suggested that MCI is a transitional stage between aging and dementia, particularly dementia caused by AD. Notably, however, some population studies have shown that a considerable proportion of individuals with MCI do not progress to dementia, even after 10 years of follow-up (6, 10, 11). If MCI cases are sought as examples of subclinical dementia, then the MCI construct needs redefinition to increase its power to predict subsequent onset of fully expressed dementia.

The recently introduced DSM-5, with categories based largely on the consensus of expert panels, introduced a new concept of MCI (DSM-5-MCI) that appears to be more stringent, and its signs and symptoms more severe, than the widely used previous conception of MCI as described originally by R. Petersen (P-MCI) (2).

Because DSM-5-MCI allows for greater compromise in 'independence in functional activities' than its predecessor, DSM-5-MCI cases may include persons with more severe impairment in general, who might therefore be expected to show higher rates of subsequent 'conversion' to dementia. Contrariwise, the frequency with which P-MCI cases show an admixture of affective as well as cognitive symptoms (12) might also modify this condition's capacity to predict subsequent dementia. The evidence to support this last notion is mixed, because some studies have reported that comorbid depression in MCI leads to an increased rate of conversion to dementia, especially AD, in both clinical samples (13) and population studies (14). Other work has refuted this finding of an increased conversion rate (15), and at least one study showed a 'protective' role of depression in predicting subsequent dementia onset (16).

Still others have noted the presence of 'negative' psychopathology such as apathy in MCI (17), and this feature could have special interest because some workers have noted an association of apathy (but not depressive) symptoms with subsequent 'conversion' to dementia (16, 18). Our own prior work has noted an association of negative-type symptoms and dementia (19) and, in a preliminary study, a fourfold risk of subsequent dementia among MCI cases that exhibit psychomotor retardation. (20) These findings lead us to the prediction, to be tested in the future, that DSM-5-MCI would be a stronger predictor of subsequent dementia to the extent that it was associated more strongly with negative-type symptoms rather than anxiety and depression.

Aims of the study

In this context, the objectives of this study were, firstly, to document the age and sex prevalence of

mild cognitive impairment according to the new DSM-5 criteria, as well as to the classical Petersen et al.'s criteria and, second, to find support for the conjecture that, compared with the classical category, clinically relevant depression and anxiety will be less strongly associated with the DSM-5 new category, and clinically relevant negative-type symptoms will be more strongly associated with the DSM-5 new category.

Material and methods

Background, design, and sampling technique

The data for this study come from the baseline assessment in the Zaragoza Dementia and Depression (ZARADEMP) Project, a longitudinal, four-wave epidemiological study to eventually document the incidence rate of dementia (and depression). The objectives and general methodology of the project have been described elsewhere (21). The site of the study was Zaragoza, the fifth city by size in Spain (622 371 inhabitants). In the baseline study or ZARADEMP-I, a stratified random sample of individuals aged 55 and over, with proportional allocation by age and sex, was drawn from census lists. The refusal rate was 20.5%, and ultimately 4803 people were interviewed.

Instruments

The ZARADEMP Interview has been used in this project. It incorporates several international instruments, previously standardized in Spain by our research group. For the purpose of this report, the following will be described:

- *Geriatric Mental State (GMS)*, the main instrument, is a semistructured standardized clinical interview for assessing the mental state of elderly persons (22). It includes neuropsychological items and a computerized diagnostic program, AGECAT, can be applied (23). The GMS-B, a shortened community version, was selected for this study. This interview is also a case finding instrument, particularly aimed at the most frequent disorders in the elderly population, namely dementia and depression, the 'threshold global score' discriminating between 'non-cases' and 'psychiatric cases'.
- Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) is a set of computer programs that analyze GMS data. The AGECAT groups the items of the GMS into components, which are gathered under eight diagnostic 'clusters' (or 'syndromes'), (dementia, depression, anxiety, etc.) (Stage I). Therefore, a given patient may be shown to simultaneously have more than one diagnostic 'cluster' or 'syndrome', for example, depression and anxiety syndromes. In the following stage (Stage II), a computer program compares syndrome clusters to reach a final diagnosis, recorded as either a diagnostic 'subsyndromal' (sub-case) (confidence levels 1 and 2) or a diagnostic 'case' (confidence levels $\geq$3). It has been found that levels of confidence of three and above correspond to what psychiatrists would usually recognize as a 'psychiatric case'. Experience with the GMS-AGECAT package includes community studies and international comparisons. The validity of the Spanish version has also been reported (24).
- *History and Aetiology Schedule (HAS)* is a standardized method of collecting history data from a caregiver, or directly from the respondent when he is judged to be reliable (25). The HAS is crucial to complete the GMS and facilitate a diagnostic process using the DSM system.
- *Mini-Mental Status Examination (MMSE)* (26, 27) is the screening instrument most frequently used internationally to detect cognitive decline.
- *Lawton & Brody scale* (28) and *Katz' index* (29) were used to assess instrumental and basic activities of daily living (ADL's), respectively, and to assess disability to complete DSM-IV-TR diagnostic criteria for dementia.

Procedure

A two-phase epidemiological screening design was used. In phase 1, trained senior medical students administered the ZARADEMP Interview to the elderly at home. Third-party caregivers were interviewed when the selected participant was considered to be unreliable. Medical reports, which are frequently available at participant's homes in Spain, were also used in the diagnostic process. The individuals were nominated as 'probable psychiatric cases' based on the GMS threshold 'global' score and/or Mini-Mental standard cutoff points. In phase 2, the individuals considered to be doubtful cases according to predetermined criteria were reassessed at home by the supervising, standardized research psychiatrists. The data on the remaining older people were thoroughly reviewed by the psychiatrists supervising individually the lay interviewers.

At the end of phase 2, a panel of psychiatrists diagnosed the cases of dementia when appropriate

using DSM-IV-TR criteria. Our previous studies have supported the validity of this diagnostic process performed by research psychiatrists in the elderly community (24). The identified cases of dementia have been excluded for subsequent analysis. The diagnosis of psychiatric disturbance and specifically the diagnosis of depression and anxiety were based on AGECAT criteria, Stage II.

The research psychiatrists reviewed all the information coming from the ZARADEMP Interview before individuals were classified as MCI 'cases' or 'non-cases' using both Petersen's et al. (2) and DSM-5 criteria (Table 1). Previously, the cognitive and ADL's items in the ZARADEMP Interview were operationalized to conform to the criteria in both categories of MCI. Following the official DSM-5 criteria, psychosis and specifically severe depression have been excluded from the MCI construct.

For the purpose of this study, GMS symptoms different from those included in the main 'cognitive' category in DSM-IV-TR were called 'non-cognitive psychopathological symptoms', NCPS. We selected 21 of these psychopathological symptoms, including the nuclear symptoms for each non-cognitive section of the GMS, and both affective-type symptoms and negative-type symptoms received special emphasis, because of their special relevance for this study. Following standard procedures, '0' was the score when the symptom was absent. However, scores '1' (symptom present, but mild or not frequent) and '2' (symptom frequent and/or severe) were collapsed for the calculation processes. Systematic checks on the reliability of the assessments were implemented to prevent the 'reliability-drift'.

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

Petersen's criteria	DSM-5 criteria
A. Subjective complaint of decline in memory on self- or informant report	A. 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in one or more cognitive domains (includes learning and memory, and other cognitive functions)
B. Isolated memory impairment on neuropsychological testing (below the standard threshold point)	And A. 2. A modest impairment in cognitive performance, documented by standardized cognitive assessment
C. General cognitive function preserved	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
D. Intact daily functioning in ADL scales	C. The cognitive deficits do not occur exclusively in the context of a delirium
E. Not meeting criteria for a diagnosis of dementia	D. The cognitive deficits are not better explained by another mental disorder (specifically: psychosis and severe depression)

Statistical analysis

Statistical analysis was performed using SPSS STATISTICS v.19 (IBM Corp., New York, NY, USA, 2010) for Windows. To compare sociodemographic features between non-cases and MCI cases (P-MCI and DSM-5-MCI), we used Pearson chi-square test and Student's *t*-test. We used $P < 0.05$ as the level of significance. Confidence intervals (95%) and standard deviations were also calculated. All statistical tests were two-tailed.

Weighted prevalence was estimated for the general population aged 55+ of the Zaragoza area using weights calculated based on the European population in January 1, 2013, (http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home/). To investigate the association of prevalent MCI (P-MCI and DSM-5-MCI) with psychiatric disturbances, logistic regression models were used (Table 4). Model 1 included terms for age, sex, and educational level. Model 2 additionally included the different diagnostic groups identified. In calculations related to DSM-5-MCI, severe depression was excluded.

Similarly, to explore mechanisms explaining the association of prevalent MCI (P-MCI and DSM-5-MCI) with NCPS, we used a series of models in which we gradually controlled for potential modifiers (Table 5). Model 1 included terms for age, sex and educational level, as well as negative-type symptoms. Model 2 additionally included anxiety/depression-type symptoms. Model 3 included all the NCPS incorporated in the previous models 1 and 2. A small amount of GMS data was missing (<5%).

Standard ethical principles have been maintained throughout the study. Participants were given a standard information sheet, and the Helsinki convention principles of written informed consent, privacy, confidentiality have been maintained throughout the project. The Ethics Committee of the University of Zaragoza and the *Fondo de Investigación Sanitaria* (FIS) approved the project according to Spanish law.

Results

Table 2 compares demographic characteristics of individuals with MCI diagnosed according to both Petersen's (P-MCI) and DSM-5 criteria (DSM-5-MCI), with individuals identified as non-cases. The category 'non-cases' excludes cases of dementia, all the remaining psychiatric cases (AGECAT Stage II criteria), as well as cases of either MCI category. As can be seen, individuals with either MCI category are significantly older, and the proportion of

Table 2. Demographic characteristics of non-cases and individuals with mild cognitive impairment (MCI) diagnosed according to both Petersen's (P-MCI) and DSM-5 criteria (DSM5-MCI)

Demographic characteristics	Non-cases $n = 2053$	P-MCI cases $n = 323$	Statistic* (P value)	DSM-5-MCI cases $n = 154$	Statistic† (P value)
Women, n (%)	902 (43.93)	199 (61.60)	<0.001	107 (69.48)	<0.001
Age (year), mean (SD)	71.54 (8.97)	73.54 (8.69)	<0.001	80.53 (8.75)	<0.001
55–65, n (%)	557 (27.13)	55 (17.03)	<0.001	8 (5.19)	<0.001
65–79, n (%)	1077 (52.46)	177 (54.79)	0.470	57 (37.01)	<0.001
≥80, n (%)	419 (20.41)	91 (28.17)	0.002	89 (57.79)	<0.001
Education (year), mean (SD)	7.81 (3.97)	6.49 (3.29)	<0.001	6.32 (3.18)	<0.001
Illiterate, n (%)	141 (6.90)	36 (11.18)	0.009	18 (11.68)	0.038
Primary school, n (%)	1486 (72.80)	260 (80.74)	0.003	121 (78.57)	0.116
Secondary school or higher, n (%)	414 (20.28)	26 (8.07)	<0.001	15 (9.74)	0.002

*Non-cases vs. MCI according to Petersen's criteria (P-MCI).
†Non-cases vs. MCI according to DSM-5 criteria (DSM-5-MCI).

the oldest (aged 80+) was more than double among DSM-5-MCI individuals (57.79%) than in P-MCI individuals (28.17%). The proportion of women is significantly higher among MCI individuals and educational level is generally lower, the differences being statistically significant in most categories.

Table 3 shows the prevalence of P-MCI and DSM-5-MCI by age, by sex, and in the total sample. Three hundred and twenty-three individuals (7.05%) fulfilled P-MCI criteria and 154 DSM-5-MCI criteria (3.36%). As can be seen, the prevalence increases by age in all the subsamples until the age of 84 and then decreases. The prevalence is significantly higher in women in both diagnostic categories (weighted prevalence 8.33% for P-MCI and 3.29% for DSM-5-MCI) than in men (5.41% and 1.49%, respectively). Total weighted prevalence is more than double in P-MCI (6.93%) than in DSM-5-MCI (2.48%), but comparisons are not statistically adequate in view of the fact that some individuals are included in both MCI diagnostic categories. The prevalence in individuals aged 65+ has also been calculated for comparison with previous studies. The total weighted prevalence in this age group was 7.93% (95%CI 7.61–8.26%) for P-MCI and 3.72% (95%CI 3.39–4.06%) for DSM-5-MCI.

Among the P-MCI individuals, and according to AGECAT Stage II criteria, 12 individuals (3.7%) had a diagnosis of severe depression, 68 non-severe depression (21.0%), 33 sub-case depression (10.2%), 9 anxiety (2.7%), and 66 sub-case anxiety (20.4%). Among the DSM-5-MCI individuals, none had a diagnosis of severe depression (exclusion criterion by design), 32 non-severe depression (20.7%), 20 sub-case depression (12.9%), 6 anxiety (3.9%), and 31 sub-case anxiety (20.1%). In total, 58.2% individuals with P-MCI and 57.7% individuals with DSM-5-MCI had depression or anxiety. As some individuals are included in both MCI categories, no statistical differences are calculated. Conversely, the frequency of MCI among cases or sub-cases of depression and anxiety was also considerable, but the proportion of cases with P-MCI criteria (55.8%) was higher than with DSM-5-MCI (24.6%). The frequency of MCI among non-cases was considerable lower, and only 4.1% fulfilled P-MCI criteria and 1.9% DSM-5-MCI criteria.

Table 4 shows the results of calculations in two different logistic regression models of the association between MCI and the different diagnostic groups identified. In the final model, (model 2), measures of the association (OR) of depression with P-MCI (OR ranged from 3.13 for the severe to 4.34 for the non-severe) were higher than with DSM-5-MCI (OR = 3.00 for the non-severe and OR = 3.38 for the sub-cases). Measures of the association of anxiety at case level were higher with DSM-5-MCI (OR = 4.12) than with P-MCI (OR = 2.71), but sub-cases of anxiety were only associated with P-MCI.

Non-cognitive, psychopathological symptoms, NCPS of both depression–anxiety type and negative type, were common in MCI individuals. Among P-MCI, 87.9% had one or more symptoms, the median number being four symptoms. Among DSM-5-MCI, the corresponding figures were 94.2% and five symptoms. Figure 1 shows the psychopathological profiles of the main categories of GMS symptoms in P-MCI individuals and DSM-5-MCI individuals. It should be noted that negative-type symptoms and anxiety symptoms are very frequent in both MCI categories, the proportions for some being close to 50%. 'Dysphoric mood' was also observed in more than 30% of individuals in both categories. The profiles are quite different, however, the negative-type symptoms being considerably more frequent among DSM-5-MCI individuals, particularly 'subjective slowness', 'restriction of activities', 'anergia', and 'observed slowness'. 'Neurovegetative' symptoms (of anxiety/depression) and 'loneliness'

Table 3. Age and sex prevalence of mild cognitive impairment (MCI) diagnosed according to both Petersen's (P-MCI) and DSM-5 criteria (DSM5-MCI)

		P-MCI			DSM-5-MCI		
		No. of cases	Prevalence (%)	95% CI	No. of cases	Prevalence (%)	95% CI
Men	55–59	2	2.60	0.31–9.07	0	0.00	0.00–4.67
	60–64	21	4.78	2.67–6.89	3	0.68	0.14–1.98
	65–69	16	4.13	2.02–6.27	1	0.26	0.01–1.43
	70–74	23	6.74	3.93–9.55	11	3.23	1.20–5.25
	75–79	17	7.08	3.62–10.54	4	1.67	0.46–4.21
	80–84	22	12.22	7.16–17.29	7	3.89	0.79–6.99
	85–89	19	7.79	4.22–11.35	16	6.56	3.25–9.87
	90+	4	6.06	1.67–14.80	5	7.58	2.50–16.80
	Total	124	6.28	5.19–7.38	47	2.38	1.68–3.08
Weighted prevalence*			5.41	5.06–5.75		1.49	1.13–1.84
Women	55–59	8	9.09	2.51–15.66	1	1.14	0.03–6.17
	60–64	24	6.74	3.93–9.55	4	0.83	0.23–2.11
	65–69	48	10.17	7.34–13.00	9	1.91	0.57–3.25
	70–74	40	8.37	5.78–10.96	13	2.72	1.16–4.28
	75–79	33	9.09	5.99–12.19	19	5.23	2.80–7.66
	80–84	26	9.77	6.02–13.53	19	7.14	3.86–10.43
	85–89	17	5.45	2.77–8.13	32	10.25	6.73–13.78
	90+	3	2.06	0.43–5.89	10	6.85	2.41–11.29
	Total	199	7.90	6.83–8.98	107	4.25	3.44–5.06
Weighted prevalence*			8.33	7.83–8.84		3.29	2.77–3.80
Total	55–59	10	6.06	2.11–10.00	1	0.61	0.01–3.33
	60–64	45	4.89	3.44–6.34	7	0.76	0.14–1.38
	65–69	64	7.45	5.64–9.27	10	1.16	0.39–1.94
	70–74	63	7.69	5.81–9.58	24	2.93	1.71–4.15
	75–79	50	8.29	6.01–10.58	23	3.81	2.20–5.43
	80–84	48	10.76	7.77–13.75	26	5.83	3.54–8.12
	85–89	36	6.48	4.34–8.61	48	8.63	6.21–11.06
	90+	7	3.30	0.66–5.94	15	7.07	3.39–10.76
	Overall	323	7.05	6.30–7.80	154	3.36	2.83–3.89
Weighted prevalence*			6.93	6.54–7.32		2.48	2.08–2.88

*The weighted prevalence has been obtained from the prevalence in each age stratum, weighted by the proportion of individuals according to the European population in January 1st, 2013 (http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home/).

were considerably more frequent among P-MCI individuals.

Table 5 shows the results of calculations in three different logistic regression models of the association between MCI and the NCPS most frequently observed. In the final model (model 3), all the NCPS were included in the calculations. Contrary to DSM-5-MCI, P-MCI was significantly associated with symptoms of anxiety and depression ('sleep problems', 'neurovegetative symptoms', and 'dysphoric mood'). However, in relation to negative-type symptoms, the measures of the association of subjective slowness and 'restriction of activities' with DSM-5-MCI (OR = 1.81 and 1.71, respectively) were higher than with P-MCI (OR = 1.62 and 1.42, respectively). Significant, inverse associations were observed with 'anergia' and 'observed slowness' in P-MCI, but no association was observed in DSM-5-MCI individuals.

Discussion

This study shows that the weighted prevalence of MCI diagnosed according to the criteria in the recently approved DSM-5, and DSM-5-MCI (3.72% for individuals for the aged 65 or more) was approximately half that according to classical, P-MCI diagnostic criteria (7.93% for the aged 65 or more). We also found partial support for the hypothesis that the association of clinically relevant depression and anxiety is weaker, and the association of clinically relevant negative-type symptoms is stronger in DSM-5-MCI when compared with P-MCI. Our study has several strengths, such as the use of a representative population sample, including institutionalized individuals; the use of the GMS, a standardized psychiatric interview incorporating both subjective reports and interviewer observations, revalidated in the same population; and the use of AGECAT diagnostic criteria, which are considered to be valid to document clinically significant cases in community samples. The lower prevalence of DSM-5-MCI, when compared with P-MCI, may partially be explained by the more stringent criteria for the cognitive deficit in the former and by the exclusion of psychiatric disorder such as major depression, which has frequently been associated with cognitive problems (30).

Table 4. Results of calculations in two different logistic regression models of the association between mild cognitive impairment (MCI) and the different diagnostic groups identified*

	Petersen's criteria (P-MCI)							
	Model 1 $n = 4542$				Model 2 $n = 4123$			
		OR 95% CI				OR 95% CI		
	OR	Lower	Upper	*P* value	OR	Lower	Upper	*P* value
Sex (ref. man)	1.14	0.90	1.44	0.276	0.88	0.67	1.16	0.389
Age (ref. 55–65)								
65–79	**1.56**	**1.14**	**2.14**	**0.005**	1.38	0.99	1.91	0.051
80+	**1.47**	**1.03**	**2.09**	**0.030**	1.21	0.83	1.77	0.313
Education (ref. Secondary or higher)								
Illiterate	**1.97**	**1.16**	**3.34**	**0.012**	1.71	0.95	3.07	0.073
Primary school	**2.10**	**1.39**	**3.18**	**<0.001**	**1.80**	**1.17**	**2.77**	**0.007**
Non-cases								
Severe depression	–	–	–	–	**3.13**	**1.63**	**5.98**	**0.001**
Non-severe depression	–	–	–	–	**4.34**	**3.05**	**6.18**	**<0.001**
Sub-case depression	–	–	–	–	**3.37**	**2.19**	**5.19**	**<0.001**
Anxiety	–	–	–	–	**2.71**	**1.31**	**5.62**	**0.007**
Sub-case anxiety	–	–	–	–	**1.58**	**1.13**	**2.20**	**0.006**
	DSM-5 criteria (DSM-5-MCI)							
	Model 1 $n = 4542$				Model 2 $n = 4432$			
		OR 95% CI				OR 95% CI		
	OR	Lower	Upper	*P* value	OR	Lower	Upper	*P* value
Sex (ref. man)	**1.65**	**1.15**	**2.35**	**0.006**	1.42	0.95	2.11	0.080
Age (ref. 55–65)								
65–79	**3.35**	**1.59**	**7.06**	**0.001**	**2.94**	**1.38**	**6.25**	**0.005**
80+	**10.51**	**5.06**	**21.85**	**<0.001**	**9.75**	**4.64**	**20.48**	**<0.001**
Education (ref. Secondary or higher)								
Illiterate	0.99	0.48	2.02	0.979	0.88	0.38	2.05	0.781
Primary school	1.36	0.78	2.36	0.275	1.34	0.74	2.44	0.325
Non-cases								
Non-severe depression	–	–	–	–	**3.00**	**1.83**	**4.91**	**<0.001**
Sub-case depression	–	–	–	–	**3.38**	**1.92**	**5.93**	**<0.001**
Anxiety case	–	–	–	–	**4.12**	**1.66**	**10.22**	**0.002**
Sub-case anxiety	–	–	–	–	1.39	0.86	2.24	0.172

Logistic regression model, odds ratios (OR), confidence intervals (CI), and P-values (P) based on Wald chi-square test with 1 degree of freedom are shown for all variables analyzed. Boldface entries in the table mean that the OR is statistically significant.

*Logistic regression models were calculated to investigate the association between MCI and depression (sub-case and non-severe) and anxiety (case and sub-case). Model 1 included terms for age, sex, and educational level. Model 2 additionally included the former diagnostic groups considered. In calculations related to DSM-5-MCI, severe depression was excluded.

The rate of P-MCI reported here is lower than in most studies in the international literature, between 11% and 19% in individuals aged 65 or more (3, 31), but low prevalence rates have also been reported in other studies in Southern Europe (15, 32). Geographical differences might be suspected in view of low incidence rates of dementia and AD observed in Southern European countries (21, 33). However, comparisons of the prevalence of MCI are difficult, in view of sampling differences between studies. Furthermore, the operational criteria of MCI used in this report have not been harmonized for comparative studies.

As observed in previous reports (34, 35), this study shows an association of MCI with age. However, contrary to what we have observed in AD in the same population (21), the prevalence of MCI did not increase in the oldest old. Conversion into dementia (10), and the increased mortality rate, might partially explain the decreased prevalence in the oldest old, but also the fact that MCI is a heterogeneous syndrome and the ultimate outcome may be influenced by some of its components, such as reversible medical illnesses influencing cognitive performance or affective syndromes comorbid with the cognitive syndrome (36).

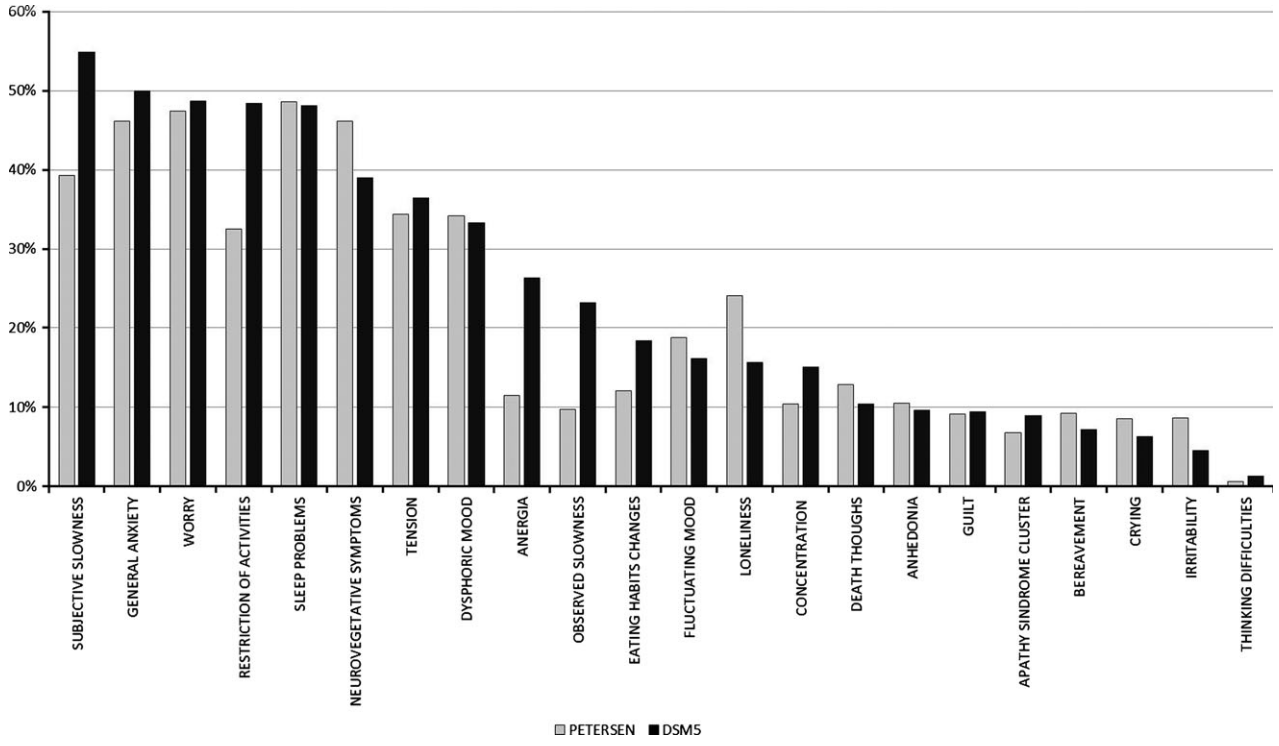

Fig. 1. Psychopathological profiles of the most frequent categories of GMS symptoms in individuals with mild cognitive impairment (MCI) diagnosed according to both Petersen's (P-MCI) and DSM-5 criteria (DSM5-MCI); the graph is organized by frequency of DSM5-MCI symptoms.

The expected high frequency of affective-type disorder among MCI cases was confirmed in this study, because more than half of the individuals with MCI were classified as cases or sub-cases of depression or anxiety by the AGECAT program, no matter the diagnostic criteria used. Previous studies in the literature (12, 14, 17), including few studies using clinically significant diagnosis (37, 38), have also reported that depression and/or anxiety is common in MCI. Conversely, and suggesting a bidirectional association as previously reported by Hidaka et al. (38), among cases or sub-cases of depression or anxiety, the frequency of MCI was quite considerable, but was less than half in DSM-5-MCI (24.6%) than in P-MCI (55.8%). Furthermore, although direct statistical comparisons are not possible here, in the final logistic regression model, P-MCI was associated with all diagnostic categories of anxiety and depression, but DSM-5-MCI was not associated with sub-cases of anxiety; anxiety–depression-type symptoms ('neurovegetative' symptoms, 'dysphoric mood', and 'sleep problems') were associated with P-MCI, but not with DSM-5-MCI. These findings tend to support our hypothesis that the association of affective-type psychopathology and MCI is weaker in DSM-5-MCI when compared with P-MCI. While lesser contamination by affective-type symptoms might stimulate conjectures about an increased power of DSM-5-MCI, in relation to P-MCI, to predict conversion into dementia, the literature is controversial in this respect. Some clinical (13, 39) and population reports suggest that the presence of depression or anxiety may herald the conversion of MCI into dementia (40), but other studies suggested the protective effect of depression (16).

In relation to our initial conjectures about the association of NCPS negative-type symptoms with P-MCI and DSM-5-MCI, we have found the following. Firstly, the negative-type symptoms were more frequent in DSM-5-MCI. Secondly, the measures of the association of some negative-type symptoms (subjective slowness and restriction of activities) were higher in DSM-5-MCI than in P-MCI. And thirdly, the association of symptoms such as 'anergy' and 'observed slowness' with P-MCI was inverse and statistically significant, but no significant association of these symptoms with DSM-5-MCI was observed. Again, while no direct statistical comparisons are possible here, the higher frequency of negative-type symptoms in DSM-5-MCI, when compared with P-MCI, and also the differences in the pattern of the associations found tend to support our conjectures about the association of negative-type psychopathology with DSM-5-MCI, better than with P-MCI.

Table 5. Results of calculations in three different logistic regression models of the association between mild cognitive impairment (MCI) and the non-cognitive psychopathological symptoms most frequently observed*

	Petersen's criteria (P-MCI)											
	Model 1 $n = 4372$				Model 2 $n = 4359$				Model 3 $n = 4224$			
		OR 95% CI				OR 95% CI				OR 95% CI		
	OR	Lower	Upper	*P* value	OR	Lower	Upper	*P* value	OR	Lower	Upper	*P* value
Sex (ref. man)	1.08	0.85	1.38	0.489	0.86	0.66	1.10	0.243	0.86	0.66	1.11	0.255
Age (ref. 55–65)												
65–79	**1.55**	**1.12**	**2.13**	**0.007**	**1.63**	**1.17**	**2.26**	**0.003**	**1.66**	**1.19**	**2.31**	**0.003**
80+	1.42	0.99	2.05	0.056	**1.46**	**1.01**	**2.11**	**0.042**	**1.55**	**1.06**	**2.28**	**0.023**
Education (ref. Secondary or higher)												
Illiterate	**2.03**	**1.19**	**3.47**	**0.009**	1.63	0.94	2.83	0.081	1.66	0.95	2.91	0.073
Primary school	**2.12**	**1.39**	**3.21**	**<0.001**	**1.96**	**1.29**	**2.98**	**0.002**	**1.96**	**1.29**	**2.98**	**0.002**
Subjective slowness	**1.75**	**1.21**	**2.54**	**0.003**	–	–	–	–	**1.62**	**1.11**	**2.36**	**0.012**
Restriction of activities	**1.75**	**1.17**	**2.61**	**0.006**	–	–	–	–	1.42	0.94	2.14	0.089
Anergia	**0.62**	**0.40**	**0.97**	**0.037**	–	–	–	–	**0.53**	**0.33**	**0.85**	**0.009**
Observed slowness	**0.58**	**0.37**	**0.92**	**0.023**	–	–	–	–	**0.56**	**0.35**	**0.92**	**0.022**
General anxiety	–	–	–	–	0.95	0.73	1.23	0.704	0.93	0.72	1.22	0.635
Tension	–	–	–	–	1.07	0.83	1.39	0.575	1.25	0.94	1.68	0.117
Worry	–	–	–	–	**1.33**	**1.02**	**1.72**	**0.030**	1.07	0.82	1.40	0.573
Sleep problems	–	–	–	–	**1.63**	**1.26**	**2.11**	**<0.001**	**1.32**	**1.01**	**1.71**	**0.036**
Neurovegetative symptoms	–	–	–	–	**1.41**	**1.07**	**1.85**	**0.013**	**1.65**	**1.27**	**2.14**	**<0.001**
Dysphoric mood	–	–	–	–	**1.52**	**1.14**	**2.02**	**0.004**	**1.50**	**1.13**	**2.00**	**0.005**
	DSM-5 criteria (DSM-5-MCI)											
	Model 1 $n = 4372$				Model 2 $n = 4359$				Model 3 $n = 4224$			
		OR 95% CI				OR 95% CI				OR 95% CI		
	OR	Lower	Upper	*P* value	OR	Lower	Upper	*P* value	OR	Lower	Upper	*P* value
Sex (ref. man)	**1.46**	**1.01**	**2.10**	**0.041**	1.41	0.97	2.05	0.067	1.33	0.91	1.94	0.136
Age (ref. 55–65)												
65–79	**3.12**	**1.48**	**6.59**	**0.003**	**3.29**	**1.56**	**6.95**	**0.002**	**3.09**	**1.46**	**6.54**	**0.003**
80+	**7.98**	**3.79**	**16.80**	**<0.001**	**10.26**	**4.90**	**21.46**	**<0.001**	**8.08**	**3.81**	**17.13**	**<0.001**
Education (ref. Secondary or higher)												
Illiterate	1.04	0.51	2.15	0.902	0.93	0.45	1.92	0.839	0.98	0.47	2.05	0.962
Primary school	1.33	0.76	2.32	0.318	1.30	0.75	2.27	0.352	1.28	0.73	2.24	0.389
Subjective slowness	**1.85**	**1.09**	**3.15**	**0.023**	–	–	–	–	**1.81**	**1.06**	**3.09**	**0.029**
Restriction of activities	**1.89**	**1.09**	**3.26**	**0.022**	–	–	–	–	1.71	0.99	2.97	0.054
Anergia	1.04	0.63	1.72	0.849	–	–	–	–	0.98	0.58	1.64	0.950
Observed slowness	0.80	0.48	1.32	0.388	–	–	–	–	0.78	0.46	1.30	0.348
General anxiety	–	–	–	–	1.36	0.94	1.97	0.093	1.28	0.88	1.86	0.186
Tension	–	–	–	–	1.14	0.79	1.64	0.471	1.06	0.71	1.58	0.765
Worry	–	–	–	–	1.16	0.81	1.67	0.407	1.03	0.71	1.50	0.850
Sleep problems	–	–	–	–	1.09	0.75	1.58	0.647	1.11	0.77	1.60	0.571
Neurovegetative symptoms	–	–	–	–	1.42	0.97	2.07	0.065	1.08	0.73	1.57	0.689
Dysphoric mood	–	–	–	–	1.18	0.79	1.76	0.409	1.17	0.78	1.75	0.444

Logistic regression model, odds ratios (OR), confidence intervals (CI), and P-values (P) based on Wald chi-square test with 1 degree of freedom are shown for all variables analyzed. Boldface entries in the table mean that the OR is statistically significant.

*Logistic regression models were calculated to explore mechanisms explaining the association of prevalent MCI (P-MCI and DSM-5-MCI) with NCPS. Model 1 included terms for age, sex, and educational level, as well as negative-type symptoms. Model 2 additionally included anxiety/depression-type symptoms. Model 3 included all the NCPS incorporated in the previous models 1 and 2.

We have previously argued about the possibility that negative-type NCPS, and not only cognitive symptoms are also core psychopathology of dementia, and specifically of the most common types found in the community, namely AD and vascular dementia (VD) (19). Additionally, several authors have previously shown in clinical studies (16, 18, 41), but also in population studies (20, 42), that symptoms such as apathy or slowness increase the risk and/or are associated with the most common types of dementia. Therefore, in view of the association with negative-type symptoms shown in

this study, we now speculate that DSM-5-MCI may be a better predictor of conversion into dementia, when compared with P-MCI. However, the 'negative-type symptoms' (i.e., apathy or depression related) and similarly depression (in relation to time of onset, etiology, etc.) might be heterogeneous and therefore merit detailed studies in relation to MCI, because this heterogeneity may have implications on observed relationships.

The validation of the DSM-5-MCI construct needs new studies, including longitudinal studies to test its ability to predict the conversion into dementia. The amnestic vs. non-amnestic subtype of cognitive deficit may be a predictor of dementia outcomes (43); specifically, the amnestic subtype of MCI has been shown to be more related to AD and a non-amnestic subtype more related to VD (44), but the DSM-5 construct might comprise both subtypes of MCI, because it incorporates in the definition the decline in one or more cognitive domains, including memory, but also other cognitive functions.

The ability of the DSM-5-MCI construct to predict subsequent onset of dementia might be improved in relation to P-MCI, because signs and symptoms are more severe and allow for greater compromise in 'independence in functional activities' (2). Based on the results in this study, we might speculate that the ability of DSM-5-MCI as presently characterized to predict subsequent onset of dementia would also be incremented because of the association with NCPS negative-type symptoms. However, such increment would not be drastic, because the associations found were not strong. The incorporation of biomarker assessments in future studies, in addition to the clinical assessment of MCI, may lend added clarity to our understanding of the meaning of MCI as diagnosed by either method (45).

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References

1. Stephan BC, Kurth T, Matthews FE, Brayne C, Dufouil C. Dementia risk prediction in the population: are screening models accurate? Nat Rev Neurol 2010;**6**:318–326.
2. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;**56**:303–308.
3. Sachdev PS, Brodaty H, Reppermund S et al. The Sydney Memory and Ageing Study (MAS): methodology and baseline medical and neuropsychiatric characteristics of an elderly epidemiological non-demented cohort of Australians aged 70–90 years. Int Psychogeriatr 2010;**22**:1248–1264.
4. Gaser C, Franke K, Klöppel S et al. BrainAGE in mild cognitive impaired patients: predicting the conversion to Alzheimer's disease. PLoS One 2013;**8**:e67346.
5. Nickl-Jockschat T, Kleiman A, Schulz JB et al. Neuroanatomic changes and their association with cognitive decline in mild cognitive impairment: a meta-analysis. Brain Struct Funct 2012;**217**:115–125.
6. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia–meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand 2009;**119**:252–265.
7. Werner P, Korczyn AD. Mild cognitive impairment: conceptual, assessment, ethical, and social issues. Clin Interv Aging 2008;**3**:413–420.
8. Ganguli M, Chang CC, Snitz BE, Saxton JA, Vanderbilt J, Lee CW. Prevalence of mild cognitive impairment by multiple classifications: the Monongahela-Youghiogheny Healthy Aging Team (MYHAT) project. Am J Geriatr Psychiatry 2010;**18**:674–683.
9. Modrego PJ, Fayed N, Pina MA. Conversion from mild cognitive impairment to probable Alzheimer's disease predicted by brain magnetic resonance spectroscopy. Am J Psychiatry 2005;**162**:667–675.
10. Gao S, Unverzagt FW, Hall KS et al. Mild cognitive impairment, incidence, progression, and reversion: findings from a community-based cohort of elderly African Americans. Am J Geriatr Psychiatry 2013;**22**:670–681.
11. Brodaty H, Heffernan M, Kochan NA et al. Mild cognitive impairment in a community sample: the Sydney Memory and Ageing Study. Alzheimers Dement 2013;**9**:310–317.
12. Shahnawaz Z, Reppermund S, Brodaty H et al. Prevalence and characteristics of depression in mild cognitive impairment: the Sydney Memory and Ageing Study. Acta Psychiatr Scand 2013;**127**:394–402.
13. Modrego PJ, Ferrández J. Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: a prospective cohort study. Arch Neurol 2004;**61**:1290–1293.

14. Richard E, Reitz C, Honig LH et al. Late-life depression, mild cognitive impairment, and dementia. JAMA Neurol 2013;**70**:374–382.
15. Panza F, Capurso C, D'introno A et al. Impact of depressive symptoms on the rate of progression to dementia in patients affected by mild cognitive impairment. The Italian Longitudinal Study on Aging. Int J Geriatr Psychiatry 2008;**23**:726–734.
16. Vicini Chilovi B, Conti M, Zanetti M, Mazzù I, Rozzini L, Padovani A. Differential impact of apathy and depression in the development of dementia in mild cognitive impairment patients. Dement Geriatr Cogn Disord 2009;**27**: 390–398.
17. Peters ME, Rosenberg PB, Steinberg M et al. Prevalence of neuropsychiatric symptoms in CIND and its subtypes: the Cache County Study. Am J Geriatr Psychiatry 2012; **20**:416–424.
18. Palmer K, di Iulio F, Varsi AE et al. Neuropsychiatric predictors of progression from amnestic-mild cognitive impairment to Alzheimer's disease: the role of depression and apathy. J Alzheimers Dis 2010;**20**:175–183.
19. Saz P, López-Antón R, Dewey ME et al. Prevalence and implications of psychopathological non-cognitive symptoms in dementia. Acta Psychiatr Scand 2009;**119**: 107–116.
20. Lobo A, López-Antón R, De-La-cámara C et al. Non-cognitive psychopathological symptoms associated with incident mild cognitive impairment and dementia. Alzheimer's type. Neurotox Res 2008;**14**:263–272.
21. Lobo A, Lopez-Anton R, Santabárbara J et al. Incidence and lifetime risk of dementia and Alzheimer's disease in a Southern European population. Acta Psychiatr Scand 2011;**124**:372–383.
22. Copeland JR, Dewey ME, Griffiths-Jones HM. A computerized psychiatric diagnostic system and case nomenclature for elderly subjects: GMS and AGECAT. Psychol Med 1986;**16**:89–99.
23. Copeland JR, Dewey ME, Wood N, Searle R, Davidson IA, McWilliam C. Range of mental illness among the elderly in the community. Prevalence in Liverpool using the GMS-AGECAT package. Br J Psychiatry 1987;**150**: 815–823.
24. Lobo A, Saz P, Marcos G, Día JL, De-La-cámara C. The prevalence of dementia and depression in the elderly community in a southern European population. The Zaragoza study. Arch Gen Psychiatry 1995;**52**:497–506.
25. Dewey ME, Copeland JR. Diagnosis of dementia from the history and aetiology schedule. Int J Geriatr Psychiatry 2001;**16**:912–917.
26. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;**12**: 189–198.
27. Lobo A, Saz P, Marcos G et al. Revalidation and standardization of the cognition mini-exam (first Spanish version of the Mini-Mental Status Examination) in the general geriatric population. Med Clin (Barc) 1999;**112**:767–774.
28. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;**9**:179–186.
29. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function. JAMA 1963;**185**:914–919.
30. Gracia-García P, De-La-cámara C, Santabárbara J et al. Depression and incident Alzheimer disease: the impact of disease severity. Am J Geriatr Psychiatry 2013; doi: 10.1016/j.jagp.2013.02.011. [Epub ahead of print].
31. Katz MJ, Lipton RB, Hall CB et al. Age-specific and sex-specific prevalence and incidence of mild cognitive impairment, dementia, and Alzheimer dementia in blacks and whites: a report from the Einstein Aging Study. Alzheimer Dis Assoc Disord 2012;**26**:335–343.
32. Ravaglia G, Forti P, Montesi F et al. Mild cognitive impairment: epidemiology and dementia risk in an elderly Italian population. J Am Geriatr Soc 2008;**56**:51–58.
33. Fratiglioni L, Launer LJ, Andersen K et al. Incidence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000;**54**: S10–S15.
34. Petersen RC, Roberts RO, Knopman DS et al. Prevalence of mild cognitive impairment is higher in men. The Mayo Clinic Study of Aging. Neurology 2010;**75**:889–897.
35. Lipnicki DM, Sachdev PS, Crawford J et al. Risk factors for late-life cognitive decline and variation with age and sex in the Sydney Memory and Ageing Study. PLoS One 2013;**8**:e65841.
36. Alexopoulos GS, Borson S, Cuthbert BN et al. Assessment of late life depression. Biol Psychiatry 2002;**52**:164–174.
37. Gabryelewicz T, Styczynska M, Pfeffer A et al. Prevalence of major and minor depression in elderly persons with mild cognitive impairment–MADRS factor analysis. Int J Geriatr Psychiatry 2004;**19**:1168–1172.
38. Hidaka S, Ikejima C, Kodama C et al. Prevalence of depression and depressive symptoms among older Japanese people: comorbidity of mild cognitive impairment and depression. Int J Geriatr Psychiatry 2012;**27**:271–279.
39. Lee GJ, Lu PH, Hua X et al. Depressive symptoms in mild cognitive impairment predict greater atrophy in Alzheimer's disease-related regions. Biol Psychiatry 2012;**71**: 814–821.
40. Palmer K, Berger AK, Monastero R, Winblad B, Bäckman L, Fratiglioni L. Predictors of progression from mild cognitive impairment to Alzheimer disease. Neurology 2007; **68**:1596–1602.
41. Richard E, Schmand B, Eikelenboom P et al. Symptoms of apathy are associated with progression from mild cognitive impairment to Alzheimer's disease in non-depressed subjects. Dement Geriatr Cogn Disord 2012;**33**:204–209.
42. Peters ME, Rosenberg PB, Steinberg M et al. Neuropsychiatric symptoms as risk factors for progression from CIND to dementia: the Cache County Study. Am J Geriatr Psychiatry 2013;**21**:1116–1124.
43. Luck T, Riedel-Heller SG, Luppa M et al. A hierarchy of predictors for dementia-free survival in old-age: results of the AgeCoDe study. Acta Psychiatr Scand 2014;**129**: 63–72.
44. Hughes TF, Snitz BE, Ganguli M. Should mild cognitive impairment be subtyped? Curr Opin Psychiatry 2011;**24**:237–242.
45. Lobo A, Quintanilla MA. The search of new biomarkers to identify Alzheimer's disease: an editorial comment to T Vanmierlo et al. 'The plant sterol brassicasterol and additional CFS biomarker in Alzheimer's Disease' (1). Acta Psychiatr Scand 2011;**124**:163–164.