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## The reliability and validity of Mini-Mental State Examination in elderly Croatian population

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Running title: Mini-Mental State Examination in elderly Croatian population

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## Abstract

**Aim:** The aim of this study was standardization and validation of the Mini-Mental Status Examination (MMSE) in the general Croatian aging population. **Methods:** Three-hundred forty-four participants underwent MMSE test, 217 cognitively healthy subjects without neurological and psychiatric disorders and 127 patients with mild cognitive impairment (MCI) or dementia. **Results:** The optimal cut-off point for screening of general Croatian population (cognitively healthy vs. MCI and dementia) is 26/27; in Croatian population aged  $\geq 65$  years the cut-off point is 24/25, whereas for screening of highly educated persons ( $\geq 14$  years of education) aged  $\geq 65$  years a higher cut-off point should be used (26/27). **Conclusions:** MMSE results when standardized and validated in certain population might better contribute to recognition of the individuals-at-risk that should be directed to dementia outpatient clinics.

## Introduction

The Mini-Mental Status Examination (MMSE) is the most commonly used screening test for the assessment of cognitive functioning [1]. Apart from bedside quantification of cognitive impairment, it is of great help in estimating the patients' cognitive change over time and also in monitoring therapeutic response in clinical trials [2]. During the years, the test was found to be relatively sensitive in diagnosing cases of overt dementia; however, its specificity decreases significantly when cognitively healthy individuals and patients with mild cognitive impairment (MCI) should be discriminated. Apart from evident advantages of MMSE test (e.g. short training required, quick and easy administration, good accessibility), there are also some disadvantages: 1.) dependence on demographic variables such as age [3,4] and education [4-6] where younger and highly educated persons score more, therefore, necessitating adjustment of the scores to these variables [7,8]; 2.) the effect of cultural differences, life style, head trauma, concomitant depression etc. on total scores [9]; 3.) neglecting important domains of cognitive functioning (e.g. executive function) that may be impaired early in dementia types other than Alzheimer's disease (AD).

MMSE was introduced in Croatia as a screening protocol for dementia shortly after its publication in 1975 [1]. Despite its widespread use in screening for cognitive impairment, there was no study so far with the aim of standardization and validation of MMSE in Croatian population; therefore, detailed guidelines for administration and interpretation of the test are missing. The aim of this study was to obtain standardization of MMSE in an ageing Croatian population with the emphasis on the effect of age, gender, and education on MMSE score and cut-off points as well as in different clinical settings (cognitively healthy individuals  $\geq 45$  years vs. MCI and demented patients  $\geq 45$  years, cognitively healthy individuals  $\geq 45$  years vs. demented patients  $\geq 45$  years, cognitively healthy individuals  $\geq 65$  years vs. demented patients  $\geq 65$  years, cognitively healthy individuals  $\geq 65$  years vs. AD patients  $\geq 65$  years). Finally, we interpreted our results in the context of previously published studies.

## Subjects and Methods

## Subjects

Subjects were recruited from general practitioners offices as well as Dementia Outpatient Clinic, Department of Cognitive Neurology, University Hospital Centre Zagreb from April 2009 to December 2011. Native Croatian speakers of 45 years of age or more were included in the study. Exclusion criteria were history of psychiatric illness (e.g. delirium, depression, and psychosis), history of head trauma, chronic alcohol intake, neurological illnesses with possible cognitive deficits (e.g. tumors and infections of the central nervous system), physical disorder or general medical condition affecting the CNS (e.g. hypothyroidism, multisystemic diseases).

## Methods

All eligible individuals underwent MMSE test. The original English version of MMSE test from 1975 [1] was translated into Croatian by two authors (M.B. and B.M.) with minor changes made based on different translations of verbal instructions. The original style of the MMSE was closely followed with 11 questions and maximum total score of 30. We used the word “TORBA” (“bag”) for the backwards spelling in question that estimates attention. Informed consent was obtained before administration of the tests from all subjects participating in the study or their legally assigned caregivers.

All subjects suspected of having cognitive impairment were referred to the Dementia Outpatient Clinic for additional routine evaluation: neurological examination, detailed neurocognitive and neuropsychological evaluation, blood tests analysis including complete blood count, electrolytes, thyroid function tests, vitamin B12 and folic acid levels, ECG and neuroimaging (brain MRI). The imaging studies were carried out on a 1.5 or 3 T scanner.

Subjects included in the study were finally divided into two groups: 1.) cognitively healthy individuals (without subjective and objective cognitive deficits; recruited from general practitioners offices, or family members and caregivers of patients), and 2.) patients with cognitive impairment (MCI or overt dementia). The diagnoses were established by a team of experienced neurologists and psychiatrists according to the currently recognized clinical criteria for different types of dementia. The diagnosis of “probable” AD was made according to the criteria of the National Institute of

Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorder Association (NINCDS-ADRDA) [10]. Among patients who fulfilled Roman's criteria for vascular dementia [11], we included only those with subcortical vascular dementia with specific MRI changes (T2-weighted subcortical vascular changes without finding of cortical lesions). These patients were included in the group of subcortical vascular cognitive impairment (VCI). The diagnosis of frontotemporal lobar degeneration (FTLD) was made according to the Neary's criteria [12]. The diagnosis of diffuse Lewy body disease (DLBD) was made according to the clinical criteria of the consortium on DLBD [13]. The diagnosis of Parkinson's disease dementia (PDD) was made according to the clinical diagnostic criteria for PDD [14]. The diagnosis of MCI was made according to the Petersen's criteria and criteria of the International Working Group on Mild Cognitive Impairment [15,16]. Final diagnoses were based on additional results of diagnostic work-up and prolonged follow-up period up to 12 months. The study was approved by the ethical committee of the University Hospital Center Zagreb. All patients were naive for specific therapy for dementia (e.g. acetylcholinesterase inhibitors and memantine) at the time of inclusion to the study. To quantify severity of dementia we used clinical dementia rating scale classifying patients in very mild (MCI), mild, moderate, or severe stages of dementia [17].

#### Statistical analysis

Subjects were divided according to the cognitive status (with or without cognitive impairment or dementia), type and severity of dementia as well as age, gender and education. Subjects with MCI were divided according to the primary cognitive deficit: memory (amnesic type MCI, aMCI) or other (non-amnesic type of MCI, naMCI). Data are presented as mean  $\pm$  standard deviation (SD) and median with range. Sensitivities, specificities, positive predictive values (PPV), and negative predictive values (NPV) were calculated at different cut-off points (23/24, 24/25, 25/26, 26/27) between subjects without cognitive impairment and different subsets of cognitively impaired patients (e.g. MCI plus demented patients  $\geq$  45 years, demented patients  $\geq$  45 years, demented patients  $\geq$  65 years, AD patients  $\geq$  65 years). The final cut-off points on the MMSE were derived from the receiver operating characteristic (ROC) curve analysis when the sum of sensitivity and specificity was

maximized for each subset of patients. Correlations between MMSE scores and severity of dementia as well as other demographic data were assessed by calculating Spearman's rank correlation coefficients (r). Statistical analysis was performed using SPSS v.11.0.1. P values lower than 0.05 were considered statistically significant.

## Results

Of the 344 participants recruited in the study, 217 subjects had no cognitive impairment and 127 patients had MCI or dementia. In the dementia group, there were 53 patients with AD, 41 with VCI, 14 with FTLD, 7 with DLBD, 5 with PDD, 29 with aMCI, 16 with naMCI, 7 patients with other types of dementia (3 with posterior cortical atrophy, 2 with corticobasal degeneration, and 2 with normal pressure hydrocephalus). Except significantly younger ages of subjects without cognitive impairment as well as of FTLD and MCI patients, there were no other statistically significant differences in age, education and gender among groups. Stratification and demographic data of participants are shown in Table 1. The mean MMSE score of subjects without cognitive impairment was  $27.9 \pm 2.1$  points; median 28.0 with range of 6.0; whereas MMSE scores of MCI, mild, moderate and severe dementia patients were  $26.9 \pm 2.3$ ,  $23.9 \pm 2.5$ ,  $18.3 \pm 2.7$ , and  $10.0 \pm 3.2$  points respectively. Medians with interquartile ranges (25<sup>th</sup>-75<sup>th</sup> percentile) of MMSE scores are graphically presented in Figure 1. Additionally, mean values and SD as well as medians with ranges of MMSE scores are presented in Table 1. Mean MMSE scores for subjects  $\geq 65$  years were as follows:  $27.1 \pm 2.7$  in subjects without cognitive impairment,  $24.0 \pm 2.5$  in a group of mildly demented patients,  $17.6 \pm 2.9$  in a group of moderately demented patients, and  $9.7 \pm 2.8$  in a group of severely demented patients. There was no statistically significant difference in education, gender, or age among groups. Additionally, no statistical difference was found in MMSE scores between female and male subjects without cognitive impairment ( $28.03 \pm 2.3$  for women,  $27.8 \pm 1.7$  for men). Distribution of MMSE scores in subjects  $\geq 65$  years stratified by the presence of cognitive impairment/dementia and severity of dementia (mild, moderate, severe) is shown as medians and interquartile ranges (25<sup>th</sup> to 75<sup>th</sup> percentile) in Figure 2. Medians with interquartile ranges of MMSE scores of cognitively healthy



individuals and AD patients (stratified by severity of dementia)  $\geq 65$  years are graphically presented in Figure 3.

Table 2 presents sensitivities, specificities, PPVs, and NPVs for four different settings (cognitively healthy individuals  $\geq 45$  years vs. MCI plus demented patients  $\geq 45$  years, cognitively healthy individuals  $\geq 45$  years vs. demented patients  $\geq 45$  years, cognitively healthy individuals  $\geq 65$  years vs. demented patients  $\geq 65$  years, cognitively healthy individuals  $\geq 65$  years vs. AD patients  $\geq 65$  years) with marked values of sensitivities, specificities, PPVs and NPVs for specific (“ideal”) cut-off points. The cut-off point was 26/27 when comparing cognitively healthy individuals  $\geq 45$  years to the group of demented patients alone or together with MCI patients of the same age group. When comparing cognitively healthy individuals  $\geq 65$  years to demented patients  $\geq 65$  years the cut-off point was 24/25, while comparing cognitively healthy individuals  $\geq 65$  years to strictly AD patients  $\geq 65$  years the cut-off point was 23/24. PPVs were extremely high in all above mentioned clinical settings at cut-off points; however, NPVs were not satisfactory in two situations: when comparing cognitively healthy individuals  $\geq 45$  years to the joint group of MCI and demented patients  $\geq 45$  years (NPV = 71.32%), and when comparing cognitively healthy individuals  $\geq 65$  years to demented patients  $\geq 65$  years (NPV = 60.71%). The results are presented in Table 2. When comparing the cognitively healthy and AD groups  $\geq 65$  years, there was gender difference in cut-off points (23/24 for men, 24/25 for women). In a cohort of highly educated patients ( $\geq 14$  years of education), the cut-off point was 26/27 with sensitivity of 72.73%, specificity of 96.67%, PPV of 96% and NPV of 76.32% when comparing cognitively healthy individuals to MCI and demented patients  $\geq 65$  years. At the cut-off point of 23/24 the sensitivity and specificity were 45,45% and 100% respectively with PPV of 100 and NPV of 62.5% for the same clinical setting. The cut-off point was the same (26/27) when comparing solely highly educated AD patients to cognitively healthy individuals with very high sensitivity, specificity, PPV and NPV (95.45%, 96.67%, 95.45% and 96.67%). At the cut-off point of 23/24 the sensitivity and specificity were 68.18% and 100%, respectively with PPV of 100% and NPV of 81.08% (data not shown).

Correlations between MMSE scores, age, education, and disease stage in select groups of patients or cognitively healthy individuals are presented in Table 3. There was no statistically

significant correlation between MMSE score and age or level of education in a cognitively healthy group of subjects. Significantly negative correlation between MMSE score and age and MMSE score and disease stage was found in a joint group of cognitively impaired patients (MCI patients and patients with overt dementia). In two other groups (patients with overt dementia and AD patients), as expected there was significantly negative correlation between MMSE score and stage of the disease. Positive correlation between MMSE score and level of education was found only in group of patients with overt dementia.

## Discussion

The aim of this study was to standardize the MMSE test for the elderly Croatian population with the main focus on finding cut-off points for different clinical settings. According to Folstein's et al. first study in 1975, the cut-off point for differentiation between demented patients and non-demented individuals was 23/24 [1]; however, this result was obviously biased toward the lower MMSE score due to inclusion of solely demented psychiatric in-patients (patients in severe stages of the disease). Later results had shown that MMSE was less accurate in distinguishing cognitively healthy individuals and patients with dementia in the community populations, especially if MCI patients were included. In our study, at the cut-off point of 23/24 (proposed by Folstein) the sensitivity was 75.51% and specificity was 100% with a PPV of 100% for differentiation of cognitively healthy individuals and patients with overt dementia. These results are in concordance with the previously published articles with sensitivity ranging mostly between 76% and 87% and specificities around 90-95% [18-22]; however, lower sensitivities were also reported (around 50-65%) [23,24].

By extending group of overt dementia patients with MCI patients the optimal cut-off point in our study raised to 26/27 with the sensitivity of 73.47% and specificity of 95.10%. The same cut-off point were suggested in study published by O'Bryant et al. [25] with roughly similar sensitivity and specificity (69% and 91% respectively) and some other publications (latest MMSE guidelines reported sensitivity of 83% and specificity of 66%) [22,26,27]. Additionally, in our study the optimal cut-off point for discrimination between cognitively healthy individuals and patients with overt dementia was

26/27 with sensitivity of 93.88% and specificity of 95.10%. The high cut-off points found in our study might be explained by more frequent recruitment of patients in the initial stages of dementia as well as higher percentage of highly educated persons than in the general population. However, the cut-off point significantly decreased to 24/25 with inclusion of patients/cognitively healthy individuals  $\geq 65$  years old with the sensitivity of 87.06% and specificity of 94.44%. The limitation of MMSE test is that it neglects certain domains of cognitive functioning (e.g. executive function) that are damaged in early stages of dementia types other than AD meaning that some patients may achieve a very high MMSE score despite significant cognitive impairment. Therefore, we evaluated only patients with AD to determine the accuracy of MMSE in distinguishing AD and cognitively healthy patients  $\geq 65$  years. The cut-off point was 23/24 as Folstein proposed in 1975 with sensitivity of 92.50% and specificity of 100% [1]. The cut-off point of 24/25 was proposed by Morales et al. [28] with a sensitivity of 85% and specificity of 90% for distinguishing the same cohort. This cut-off point reached high sensitivity (95%) and specificity (94.44%) in our study as well. Additionally, higher cut-off points were proposed for screening of highly educated individuals. O'Bryant et al. [25] suggested a cut-off point of 26/27 with optimal ratio of sensitivity (89%) and specificity (91%) and overall correct classification rate of 90%. The same cut-off point for screening highly educated individuals of  $\geq 65$  years was optimal in our study with sensitivity of 72.73%, specificity of 96.67%, PPV of 96%, and NPV of 76.32%.

The latest MMSE guidelines proposed a cut-off point of 26/27 for screening the general population [26]. In our study, the cut-off level was the same for screening the general population irrespective of inclusion of MCI patients; however, as expected sensitivity and specificity was significantly lower when MCI cases were included. Additionally, the same cut-off was found for screening of highly educated individuals.

To the best of our knowledge, except a Slovenian study [24] there are no similar studies in Croatia and surrounding South East European countries that share comparable cultural, educational and historic backgrounds. Our results were very similar to those of Slovenian group [24]. Additionally, education level of cognitively healthy population in our study was comparable to the last population registration in Croatia (52.9% individuals who finished secondary school in our cohort compared to 47% in Croatian population). Higher percentage of highly educated individuals in our

cohort was probably due in part to the criterion of inclusion of only patients who are  $\geq 45$  years, and not all age groups.

In conclusion, the result of our study shows that the optimal cut-off point for screening the Croatian population overall is 26/27. For screening of population of  $\geq 65$  years the cut-off level is 24/25, whereas, for screening of highly educated persons ( $\geq 14$  years education) of  $\geq 65$  years, a higher cut-off point should be used (26/27). The aim of this study is not to encourage the diagnosis of cognitive impairment based solely on MMSE score, but rather to direct individuals-at-risk with subjective or objective cognitive complaint to the dementia outpatient clinic for an additional neurocognitive and neuropsychological evaluation.

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Conflict of interest statement: There is no conflict of interest.

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Table 1. Demographic data of participants

	Subjects without cognitive impairment (n=217)	Subjects with cognitive impairment (MCI + dementia) (n=127)							
		AD (n=53)	VCI (n=41)	FTLD (n=14)	DLBD (n=7)	PDD (n=5)	aMCI (n=29)	na-MCI (n=16)	Other (n=7)
Age at evaluation (years)	66.2 ± 9.6 63.5 (38.0)	76.0 ± 5.6 77.0 (24.0)	72.4 ± 9.6 75.0 (42.0)	65.7 ± 9.8 69.6 (32.0)	76.3 ± 6.5 77.5 (23.0)	75.3 ± 5.3 76.0 (15.0)	68.4 ± 10.0 68.0 (40.0)	72.1 ± 10.6 70.5 (38.0)	65.5 ± 11.3 67.5 (27.0)
45 - 64	55	3	5	4	0	0	12	5	2
65 - 74	107	14	13	8	2	2	10	5	3
≥ 75	42	36	23	2	5	3	7	6	2
Education (years)	13.3 ± 2.6 12.5 (14.0)	11.4 ± 5.0 12.0 (18.0)	10.8 ± 5.3 12.0 (20.0)	10.8 ± 3.5 11.5 (12.0)	12.2 ± 7.4 13.5 (23.0)	10.7 ± 2.4 11.0 (6.0)	11.8 ± 3.8 12.0 (19.0)	12.1 ± 3.7 12.0 (13.0)	11.8 ± 4.0 13.0 (9.0)
No primary school or partial	1	13	9	2	2	0	7	2	2
Primary school	34	6	8	2	1	1	0	0	2
Secondary school	117	17	13	8	0	4	11	9	3
Higher and university education	65	17	11	2	4	0	11	5	0
Sex (total number)									
Male	98	22	24	8	4	3	17	9	4
Female	119	31	17	6	3	2	12	7	3
MMSE	27.9 ± 2.1 28.0 (6.0)	18.1 ± 4.9 20.0 (23.0)	19.6 ± 5.3 12.0 (20.0)	19.9 ± 6.9 21.5 (19.0)	19.6 ± 5.5 21.0 (15.0)	21.4 ± 5.7 22.0 (5.0)	27.0 ± 2.1 27.0 (10.0)	26.8 ± 2.6 27.0 (7.0)	24.8 ± 4.6 26.5 (10.0)

Data are presented as mean ± SD and median (range).

AD = Alzheimer's disease; VCI = vascular cognitive impairment; FTLD = frontotemporal lobar degeneration; DLBD = Diffuse Lewy body disease; PDD = Parkinson's disease dementia;

aMCI = amnesic mild cognitive impairment; na-MCI = non-amnesic mild cognitive impairment



Table 2. Sensitivities, specificities, positive predictive values (PPV) and negative predictive values (NPV) in different settings of cut-off values

MMSE cut-off	Sensitivity				Specificity				PPV				NPV			
	≥45 y (D+MCI)	≥45 y (D)	≥65 y (D)	≥65 y (AD)	≥45 y (D+MCI)	≥45 y (D)	≥65 y (D)	≥65 y (AD)	≥45 y (D+MCI)	≥45 y (D)	≥65 y (D)	≥65 y (AD)	≥45 y (D)	≥65 y (D)	≥65 y (AD)	≥65 y (AD)
23/24	53,74	75,51	77,65	92,50	100	100	100	100	100	100	100	100	60,00	80,95	48,65	85,71
24/25	60,64	84,69	87,06	95,00	99,02	99,02	94,44	94,44	98,89	98,81	98,67	97,44	63,52	87,07	60,71	89,47
25/26	67,35	88,76	91,76	97,50	97,06	97,06	83,33	83,33	97,06	97,06	96,30	92,86	67,35	90,00	68,18	93,75
26/27	73,47	93,88	96,47	100	95,10	95,10	83,33	83,33	95,58	94,85	96,47	93,02	71,32	91,51	83,33	100

Data are presented in percentages.

D = demented; MCI = mild cognitive impairment; AD = Alzheimer's disease

Table 3. Correlations between MMSE scores, age, education and stage of the disease in selected groups of patients/cognitively healthy individuals

	MMSE
Subjects without cognitive impairment	Age -0,072
	Education 0,079
MCI + demented patients	Age -0,272**
	Education 0,208 *
	Disease stage -0,871**
Only demented patients	Age -0,210*
	Education 0,246
	Disease stage -0,838**
Only AD patients	Age -0,229
	Education 0,128
	Disease stage -0,710**

\*\*Correlation is significant at the 0.01 level (2-tailed)

\*Correlation is significant at the 0.05 level (2-tailed)

## Legends to figures

Figure 1. MMSE scores in cognitively healthy individuals, subjects with mild cognitive impairment (MCI) and subjects with mild, moderate, and severe dementia  $\geq 45$  years. Data are presented as box plots. Boxes represent the 25th, 50th (median), and 75th percentiles. Circles represent mild outliers.

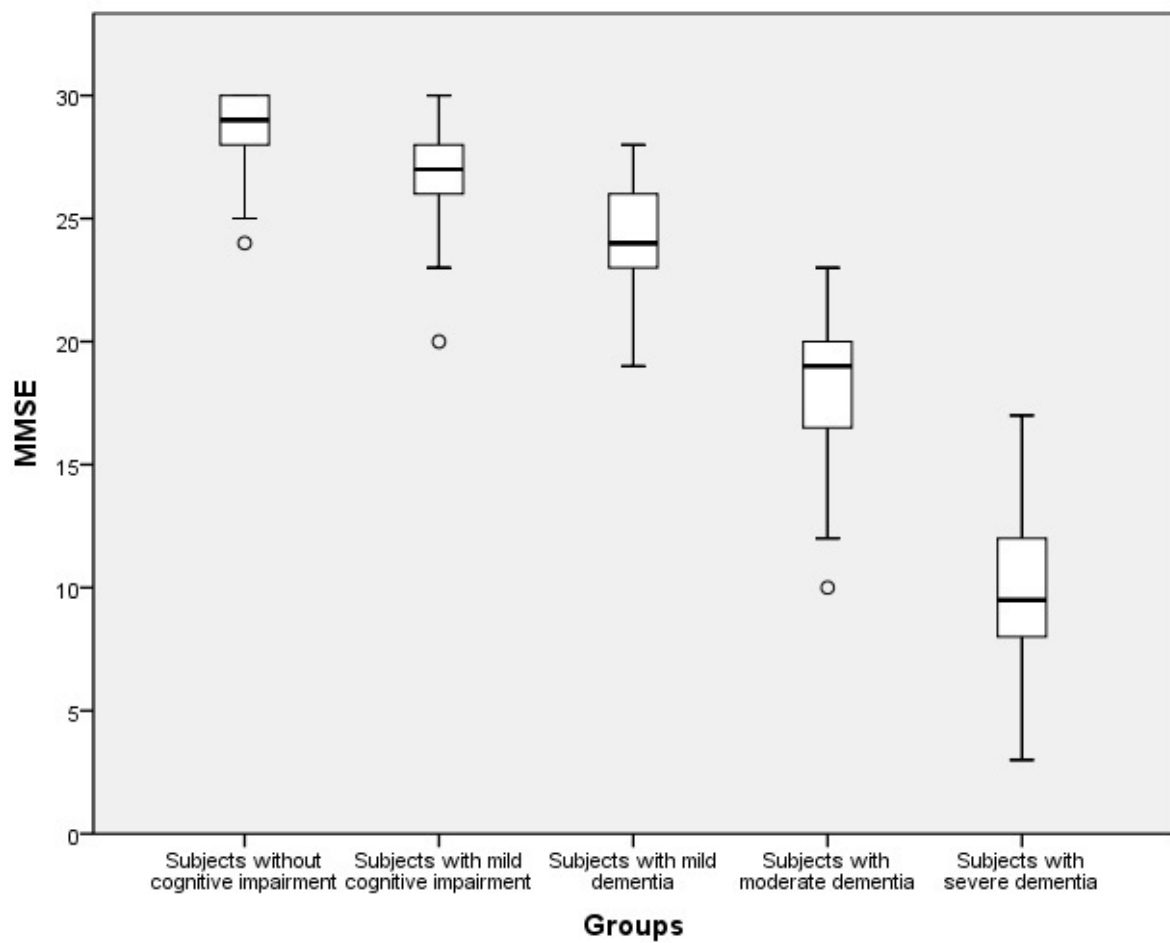


Figure 2. MMSE scores in cognitively healthy individuals and subjects with mild, moderate and severe dementia  $\geq 65$  years. Data are presented as box plots. Boxes represent the 25th, 50th (median), and 75th percentiles.

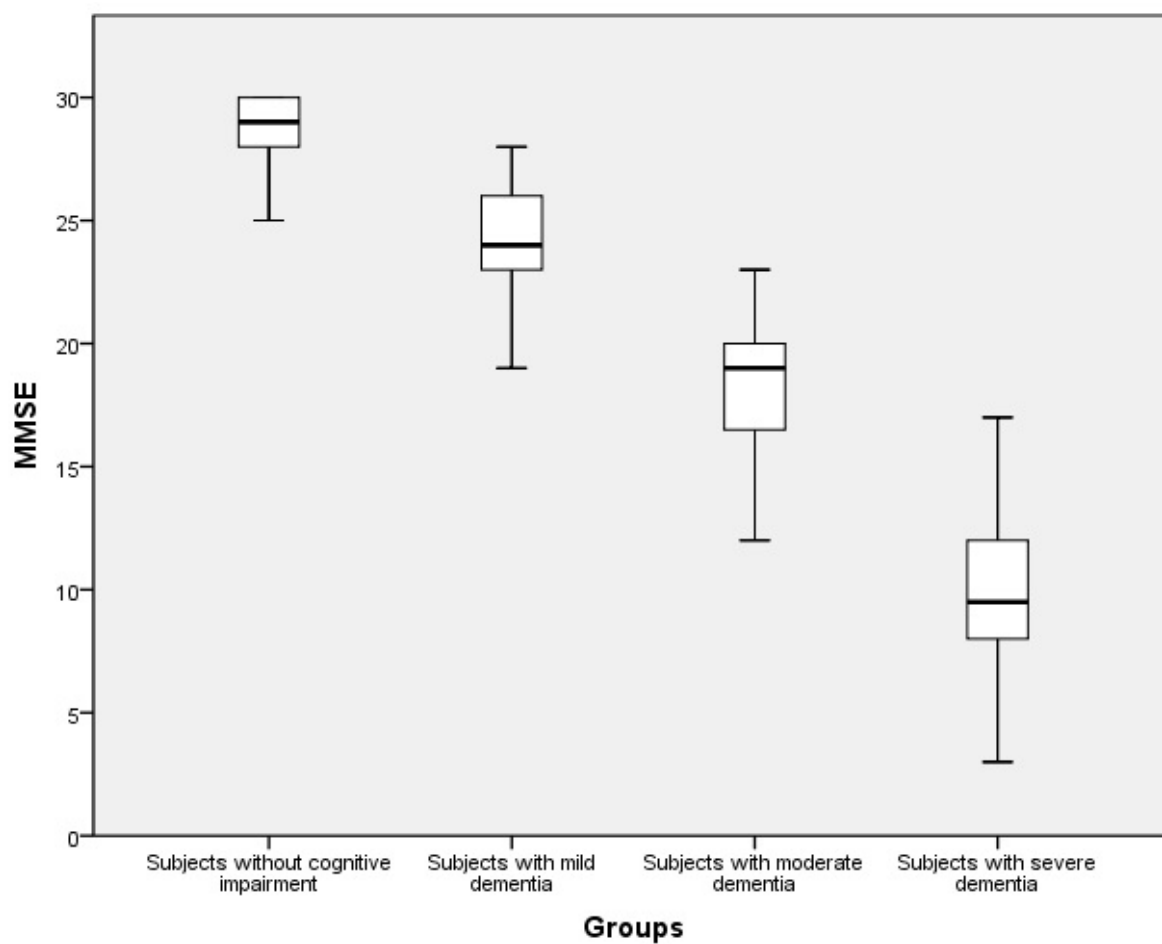


Figure 3. MMSE scores in cognitively healthy individuals and subjects with mild, moderate, and severe Alzheimer's disease  $\geq 65$  years. Data are presented as box plots. Boxes represent the 25th, 50th (median), and 75th percentiles. The circle represents a mild outlier.

