ELSEVIER

Alzheimer's & Dementia ■ (2012) 1–11

Alzheimer's & Dementia

Prevalence of mild cognitive impairment subtypes in patients attending a memory outpatient clinic—comparison of two modes of mild cognitive impairment classification. Results of the Vienna Conversion to Dementia Study

Gisela Pusswald[a], Doris Moser[a], Andreas Gleiß[b], Stefan Janzek-Hawlat[b], Eduard Auff[a], Peter Dal-Bianco[a], Johann Lehrner[a,*]

[a]*University Clinic of Neurology, Medical University of Vienna, Vienna, Austria*
[b]*Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Vienna, Austria*

Abstract

Background: Early detection of dementia is becoming more and more important owing to the advent of pharmacologic treatment.
Objective: The goals of this study were to establish prevalence of mild cognitive impairment (MCI) subtypes in an outpatient memory clinic cohort using two different modes of MCI determination.
Design: Consecutive patients complaining of cognitive problems who came to the memory outpatient clinic for assessment of a possible cognitive disorder were included in the study.
Setting: Academic medical center.
Participants: Six hundred eighty consecutive patients complaining about cognitive problems who came to the memory outpatient clinic for assessment of a possible cognitive disorder and fulfilled the inclusion criteria were included in the study. For 676 patients, sufficient data for MCI classification were available.
Results: Categorizing MCI patients into MCI subtypes according to the minimum mode of MCI classification revealed the following results: 106 patients (15.7%) were categorized as cognitively healthy, whereas 570 patients (84.3%) met the criteria for MCI. MCI patients were subtyped as amnestic mild cognitive impairment (aMCI) single domain (31 patients; 4.6%), aMCI multiple domain (226 patients; 33.4%), non-aMCI single domain (125 patients; 18.5%), and non-aMCI multiple domain (188 patients; 27.8%). Categorizing MCI patients into MCI subtypes according to the mean mode of MCI classification revealed the following results: 409 patients (60.5%) were categorized as cognitively healthy, whereas 267 patients (39.5%) met the criteria for MCI. MCI patients were subtyped as aMCI single domain (47 patients; 6.9%), aMCI multiple domain (57 patients; 8.5%), non-aMCI single domain (97 patients; 14.3%), and non-aMCI multiple domain (66 patients; 9.8%).
Conclusion: MCI diagnosis frequencies are substantially affected by the criteria used for estimation of MCI. The effect of modifying the presence of impairment on a single cognitive measure versus the presence of impairment on a mean composite score of a certain domain differed considerably, ranging from 39.5% to 84.3%, indicating the importance of the development of guidelines for operationalizing MCI.

Keywords: Mild cognitive impairment subtypes; Neuropsychological testing; Dementia

1. Introduction

During the past decade, the interest in the concept of mild cognitive impairment (MCI), characterized as a clinical condition with memory impairment with or without cognitive

*Corresponding author. Tel.: 0043-1-40400-3109; Fax: 0043-1-40400-3141.
E-mail address: Johann.Lehrner@meduniwien.ac.at

1552-5260/$ - see front matter © 2012 The Alzheimer's Association. All rights reserved.
doi:10.1016/j.jalz.2011.12.009

impairment in other domains (amnestic mild cognitive impairment [aMCI] multiple domain vs aMCI single domain), has increased enormously [1,2]. Non-aMCI single domain and non-aMCI multiple domain based on impairments in attention, executive function, and language without memory impairment have also been reported [3,4].

The characterization of different subtypes is defined primarily through neuropsychological criteria. Because there is no standard protocol for cognitive assessment in diagnosing MCI, recent studies have operationally defined MCI criteria in different ways, and the neuropsychological batteries used in studies to date vary in a number of ways. The determination of abnormality on a neuropsychological test battery depends on a number of parameters, including the nature of the psychometric measures used, the number of test instruments to the cognitive domain being investigated, the reliability of individual measurers as compared with composite measures, the quality of the normative data, and the statistical threshold used to indicate impairment.

Currently, different procedures with differing numbers of tests for assessing cognitive functions are used. For assessing memory, different types of function (e.g., short-term memory vs long-term memory), different types of test material and learning/memory concepts (e.g., verbal vs nonverbal; verbal list learning and retention, prose paragraph recall, and memory for visually presented designs) are used. Other cognitive domains assessed beyond memory (e.g., language, executive function, visuospatial/perceptual ability, and attention) are tested by means of different measures. Additionally, some researchers use one measure within a domain, and others use more measures within a given domain [5]. Not surprisingly, differing criteria lead to major variations in the definition of MCI and its subtypes, and thus they produced a wide range of prevalence estimates and conversion rates in memory disorder clinics and in population-based studies [6,7].

The effect of changing a single factor, for example, the adjustment of the statistical threshold (−2 standard deviations [SDs], −1.5 SDs, −1 SD) used to establish impairment, has considerable effect on prevalence, progression rates, and stability of MCI diagnosis, depending on whether strict or liberal thresholds are implemented [5–8].

The effect of modifying other neuropsychological assessment factors, such as the number of impaired tests necessary, the type of score used (i.e., composite or single measures), and the number of tests administered, has only recently been investigated. Different criteria for determining impairment calculating *z*-scores (criteria for determining the presence of impairment on a single cognitive measure <1.5 SDs vs mean composite score of a domain <1.5 SDs) are used. The few studies that have examined the impact of these decisions have shown substantial effects on the frequency of diagnosed cases of MCI v5,6,8–13]. In addition, using published norms [8,14], as opposed to using norms of an own control group, produced different MCI estimates [5,9,14]. Furthermore, grouping tests variables into domains is most often done on subjective grounds, and analyses to identify shared underlying constructs in the neuropsychological tests were rarely performed [9]. The literature is further complicated by inherent differences in sample sizes and population demographics across studies [5]. These findings highlight the need for further detailed investigation of neuropsychological assessment parameters commonly used in population and clinical studies to operationalize MCI.

To explore suitable methods of defining MCI, the goals of the present study were to define a well-characterized, cognitively intact control group, grouping tests into domains (domain structure) using empirically validated methods; examine the distribution of impaired patients across neuropsychological measures using norms of this control group; and investigate two different approaches of MCI classification for MCI subtyping, namely, "minimum mode" of MCI classification and "mean mode" of MCI classification. To the best of our knowledge, these two modes of classification have not been directly compared yet. We further compared the two modes of MCI classification regarding MCI subtype prevalence in our cohort and the relationship to age and sex. We hypothesized that using the minimum mode of MCI classification will lead to a higher prevalence rate than using the mean mode of MCI classification. Another question was whether these MCI subtypes are different regarding cognitive status.

2. Methods

2.1. Subjects and procedure

The current data are part of a larger research project, the Vienna Conversion to Dementia Study. The Vienna Conversion to Dementia Study is a prospective cohort study encompassing consecutive, community-dwelling patients complaining of cognitive problems who come to the memory outpatient clinic for assessment of a possible cognitive disorder. The primary goal of the study was to determine the prevalence of four clinical MCI subtypes, and the secondary goal was to evaluate conversion rates from MCI to Alzheimer's disease (AD) using four clinical MCI subtypes. For the purpose of this article, we only present neuropsychological data regarding MCI subtypes. The study protocol was in accordance with the Helsinki Declaration, and the Ethical Committee of the Medical University of Vienna has approved it.

All patients received a complete neurological examination, standard laboratory blood tests, and psychometric testing. Information from the relatives/caregivers of the patients using standardized questionnaires was obtained. In most cases, a computed tomography scan or magnetic resonance imaging scan of the brain was obtained. In determining significant cerebrovascular disease, both neuroimaging and clinical patient features were used.

Inclusion and exclusion criteria were similar to other studies. Patients were excluded from the study if any of

the following conditions applied: (a) evidence of stroke, as determined by neuroradiologic and clinical examination; (b) history of severe head injury; (c) current psychiatric diagnosis according to International Classification of Diseases, tenth revision [15] (however, patients with (sub) depressive symptoms were included because (sub)depressive symptoms often occur in elderly patients); (d) any medical condition that leads to severe cognitive deterioration, including renal, respiratory, cardiac, and hepatic disease; and (e) diagnosis of dementia according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition [16].

2.2. MCI patients

Six hundred eighty consecutive patients complaining about cognitive problems who came to the memory outpatient clinic for assessment of a possible cognitive disorder and fulfilled the inclusion criteria were included in the study. Four patients had incomplete neuropsychological data owing to fatigue or motivational problems. Thus, for 676 patients, sufficient data for MCI classification were available. Patients were either referred by physicians or were self-referrals. The included area of the study was Vienna. Mean age of MCI patients was 66.9 ± 9.5 years. Altogether, 41.1% of the patients were male and 58.9% of the patients were female. Mean years of formal education were 11.7 ± 3.7. The median Mini-Mental State Examination (MMSE) performance of patients was 28 (range: 22–30).

2.3. Cognitively healthy control subjects

Great care was taken to enroll a sufficient number of cognitively healthy control subjects living independently at home. Control subjects were recruited by means of advertisements. They underwent a rigorous screening evaluation using standardized clinical interview and cognitive screening. Imaging procedures, neurological examination, standard laboratory blood tests, and informant reports were not included in the evaluation. They were assessed as being in good health. Criteria for healthy function were identified as being similar to those in the Mayo research studies [17,18]: (a) no active neurological or psychiatric disease, (b) no psychotropic medications, and (c) the subjects may have medical disorders but neither they nor their treatment compromises cognitive function. Cognitive status was given special attention, and cognitively healthy control subjects were screened for intact cognition. They were required to have an MMSE score $\geq$27 and a Montreal Cognitive Assessment score $\geq$26, adjusted for education. Control subjects did not complain about cognitive problems. Adequate normative data using cognitively healthy subjects (N = 250) for the neuropsychological measures were thus available. This normative sample will be used to estimate the dependence of neuropsychological test outcomes on age, education and gender as a basis of z-score computation (see below).

2.4. Neuropsychological measures

All participants were subjected to the Neuropsychological Test Battery Vienna (NTBV), which included attention, executive functioning, language, and memory domains [19–22]. The Alters-Konzentrations-Test [23], a geriatric cancellation test; the digit-symbol subtest of the German Wechsler Adult Intelligence Scale–Revised [24]; the symbol counting task from the cerebral insufficiency test [25]; the Trail Making Test B (TMTB) [26]; and the score difference of the Trail Making Test A (TMTA) and TMTB [26] were applied to assess attention. Executive functions were investigated using the TMTA [26], the Five-Point Test [27], the maze test from the Nürnberger Alters Inventar test battery [28], the Stroop test from the Nürnberger Alters Inventar test battery [28], and the interference test from the cerebral insufficiency test [25]. Naming as many words beginning with the letters b, f, and l that came to mind within 1 minute for each task was used to tap lexical verbal fluency. To test language functions, we used verbal fluency tasks and a confrontation naming task [29]. Naming as many animals, supermarket items, and tools that came to mind within 1 minute for each task was used to tap semantic verbal fluency. The modified Boston Naming Test [30] was used for assessing naming capabilities. Episodic memory was tested using the Verbal Selective Reminding Test [19] with the subtests of immediate recall, total recall, delayed recall, and recognition [31,32].

Cognitive testing for each patient lasted approximately 45 minutes. Testing was performed within one test session. Cognitive function tests were selected to assess a broad range of cognitive abilities commonly affected by AD and other forms of dementia.

The ability of the NTBV subtests to detect AD dementia has been established in a previous study, and we recently published results for sensitivity, specificity, positive predicted value, and negative predicted value, and found very good discrimination power for the NTBV in detecting AD dementia. Specifically, comparing the predictive accuracy using results from receiver operating characteristic curve analyses (area under the curve), we found very good discriminative power for single tests with an area under the curve ranging from 0.79 for the modified Boston Naming Test to 0.99 for the Verbal Selective Reminding Test–delayed recall [21] for patients with AD dementia versus cognitively healthy control subjects.

2.5. MCI classification procedure

To characterize the neuropsychological profile of MCI patients, a *z*-score for each variable was calculated that indicates the relative degree of impairment from healthy in SD units, thereby allowing direct comparison across different cognitive tests. As age, education, and sex effects on cognitive variables have been reported in the literature [33], *z*-scores for each neuropsychological variable were estimated as depending

on these demographic variables based on the cognitive healthy control sample. For this purpose, the flexible generalized additive models for location scale and shape (GAMLSS) model class was used [34]. Adequate distribution functions (normal, log-normal, Box-Cox power exponential, and others), corresponding link functions, as well as adequate transformations for age and years of formal schooling (linear, polynomial, cubic splines) were determined for each neuropsychological variable individually based on statistical information criteria (Akaike Information Criterion, Schwarz-Bayes Criterion) [34].

The domain structure of the NTBV was investigated empirically by means of cluster analysis based on the cognitively healthy subjects.The clustering into domains reflects the correlation structure of the z-scores as implemented in "proc varclus" of the software package SAS, version 9.2 (SAS Institute Inc., Cary, NC, 2002–2008). The variable clustering procedure revealed a six-cluster solution defining six domains for the 30 cognitive variables. The naming of the domains is not meant to be absolute and is oriented toward the most strongly correlated variables.

Table 1 presents the six clusters with cognitive variables and corresponding R^2 with its own cluster and R^2 with the next closest cluster.

Neurological examination, standard laboratory blood tests, and radiological evaluation were performed approximately 2 weeks before neuropsychological testing. After the completion of the evaluation, a consensus committee meeting was held involving the neurologists, neuropsychologists, and other study personnel who had evaluated the patients to determine cognitive status of the participants. The cognitive status of MCI subtypes was determined according to the Peterson criteria, and the cutoff score used was 1.5 SDs below age- and education-corrected norms using the cognitively healthy control subjects [18,35]. The attendees at this meeting were presented the raw data and the z-scores of the neuropsychological testing, but they were not informed about the minimum and mean modes of MCI classification.

Table 1
A variable clustering procedure based on 250 cognitively healthy subjects resulted in a six-cluster solution

Domain/Neuropsychological variable	R^2 with own cluster	R^2 with next closest
Domain 1/Attention		
AKT time	0.70	0.14
AKT total/time	0.69	0.14
Trail Making Test—TMTB	0.58	0.18
Digit-symbol test (WAIS-R)	0.44	0.24
TMTB − TMTA difference	0.43	0.07
Symbols counting (C.I.)	0.38	0.19
Domain 2/Executive function—phonematic verbal fluency		
Phonematic verbal fluency PWT total words	0.98	0.10
Phonematic verbal fluency PWT l-words	0.72	0.08
Phonematic verbal fluency PWT f-words	0.66	0.07
Phonematic verbal fluency PWT b-words	0.64	0.09
Domain 3/Executive function—interference		
Stroop color words	0.87	0.17
Stroop total/time	0.86	0.16
Interference (C.I.) time	0.68	0.30
Interference (C.I.) total/time	0.67	0.26
Stroop color words—colors	0.55	0.05
Stroop colors	0.55	0.24
Domain 4/Language		
Semantic verbal fluency SWT total words	0.66	0.22
Semantic verbal fluency SWT supermarket items	0.65	0.08
Semantic verbal fluency SWT animals	0.65	0.09
Semantic verbal fluency SWT tools	0.63	0.10
Boston Naming Test (mBNT)	0.05	0.02
Domain 5/Memory		
Verbal memory total recall (VSRT)	0.78	0.08
Verbal memory immediate recall (VSRT)	0.72	0.03
Verbal memory delayed recall (VSRT)	0.63	0.07
Verbal memory recognition (VSRT)	0.21	0.02
Domain 6/Executive function—planning and nonverbal fluency		
Planning maze test—NAI time	0.82	0.13
Planning maze test—NAI total/time	0.77	0.11
Nonverbal fluency five-point test—total correct	0.45	0.14
Trail Making Test—TMTA	0.43	0.19
Nonverbal fluency five-point test—perseverations	0.38	0.10

Abbreviations: AKT, Alters-Konzentrations-Test; WAIS-R, Wechsler Adult Intelligence Scale–Revised; TMTA, Trail Making Test version A; TMTB, Trail Making Test version B; NAI, Nürnberger Alters Inventar; C.I., cerebral insufficiency test; VSRT, Verbal Selective Reminding Test; mBNT, modified Boston Naming Test; PWT, Phonematische Wortflüssigkeit; SWT, Semantische Wortflüssigkeit.

2.6. *Modes of MCI classification for subtyping MCI: Minimum mode of MCI classification and mean mode of MCI classification*

For the minimum mode of MCI classification, MCI patients were divided into five groups of patients based on cognitive features as follows: cognitively healthy patients (z-scores of each single test were greater than −1.5 SDs), aMCI single domain patients (the z-score of at least one memory test was less than −1.5 SDs, all other z-scores were greater than −1.5 SDs), aMCI multiple domain (the z-score of at least one memory test was less than −1.5 SDs, and at least one other z-score of the remaining tests was less than −1.5 SDs), non-aMCI single domain patients (there is exactly one domain other than the memory domain where the minimum of the z-scores within this domain was less than −1.5 SDs), and non-aMCI multiple domain patients (at least two tests from different domains other than memory tests less than −1.5 SDs). Thus, basically each domain was assessed according to the minimum over the z-scores of all constituent tests.

For the mean mode of MCI classification, MCI patients were divided into five groups of patients based on cognitive features as follows: cognitively healthy patients (mean z-scores of each domain were greater than −1.5 SDs), aMCI single domain patients (mean z-score of the memory domain

was less than −1.5 SDs, all other mean *z*-scores of the remaining domains were greater than −1.5 SDs), aMCI multiple domain (the mean *z*-score of the memory domain was less than −1.5 SDs and at least one of the mean *z*-scores of the remaining domains was less than −1.5 SDs), non-aMCI single domain patients (there is exactly one domain other than the memory domain where the mean of the *z*-scores was less than −1.5 SDs), and non-aMCI multiple domain patients (mean *z*-scores of at least two domains other than memory domain were less than −1.5 SDs). Thus, each domain was assessed according to the mean over the *z*-scores of all constituent tests.

2.7. Statistical methods

Demographic variables are described by means and SDs, except MMSE scores, which are presented as median and range owing to the skewed distribution of this variable. *Z*-scores of the neuropsychological test variables are described by means and SDs.

To compare *z*-scores of neuropsychological variables between subtypes, 1-way analyses of variance have been computed. Uncorrected *P* values are given and significance according to the method of Bonferroni–Holm for multiplicity correction (for 30 neuropsychological variables) is indicated.

To test for a potential influence of age, sex, and years of formal schooling on the proportion of patients classified as MCI, a multivariate logistic regression model was used (with age and schooling treated as scale variables).

The reported *P* values are the results of two-sided tests. *P* values $\leq$.05 were considered to be statistically significant. All computations were performed using SAS software version 9.2, except GAMLSS estimation, which was done using R 2.11.1 (R Development Core Team, Vienna, Austria, 2010).

3. Results

Z-score values of the cognitive variables are presented as mean and SD in Table 2 for the total MCI patient sample. For

Table 2
Mean *z*-scores with standard deviations for each neuropsychological variable and corresponding frequency of patients showing performance less than −1.5 SDs in total MCI patients sample (N = 676)

Domain/Neuropsychological variable	*Z*-score ± SD	Number of impaired patients	Percentage of impaired patients
Domain 1/Attention			
AKT time	−0.05 ± 1.32	83	12.3
AKT total/time	−0.08 ± 1.28	85	12.6
Trail Making Test—TMTB	−0.59 ± 1.40	161	23.8
Digit-symbol test (WAIS-R)	−0.29 ± 1.07	81	12.0
TMTB − TMTA difference	−0.68 ± 1.63	170	25.2
Symbols counting (C.I.)	0.39 ± 1.23	44	6.5
Domain 2/Executive function—phonematic verbal fluency			
Phonematic verbal fluency PWT total words	−0.45 ± 1.56	131	19.4
Phonematic verbal fluency PWT l-words	−0.28 ± 1.43	97	14.4
Phonematic verbal fluency PWT f-words	−0.26 ± 1.32	115	17.1
Phonematic verbal fluency PWT b-words	−0.49 ± 1.48	147	21.8
Domain 3/Executive function—interference			
Stroop color words	0.13 ± 1.35	104	15.4
Stroop total/time	−0.25 ± 1.25	109	16.1
Interference (C.I.) time	−0.11 ± 1.29	87	12.9
Interference (C.I.) total/time	−0.13 ± 1.39	102	15.1
Stroop color words—colors	−0.25 ± 1.83	125	18.5
Stroop colors	−0.28 ± 1.28	79	11.7
Domain 4/Language			
Semantic verbal fluency SWT total words	−0.22 ± 1.34	96	14.2
Semantic verbal fluency SWT supermarket items	−0.16 ± 1.22	86	12.7
Semantic verbal fluency SWT animals	−0.29 ± 1.61	110	16.3
Semantic verbal fluency SWT tools	−0.03 ± 1.05	48	7.1
Boston Naming Test (mBNT)	−0.96 ± 0.88	169	25
Domain 5/Memory			
Verbal memory total recall (VSRT)	−0.44 ± 1.07	98	14.5
Verbal memory immediate recall (VSRT)	−0.50 ± 1.14	120	17.8
Verbal memory delayed recall (VSRT)	−0.57 ± 1.28	134	19.8
Verbal memory recognition (VSRT)	−0.89 ± 0.93	146	21.6
Domain 6/Executive function—planning and nonverbal fluency			
Planning maze test—NAI time	0.01 ± 1.36	81	12.0
Planning maze test—NAI total/time	0.03 ± 1.25	77	11.4
Nonverbal fluency five-point test—total correct	−0.21 ± 1.29	111	16.4
Trail Making Test—TMTA	−0.17 ± 1.18	98	14.5
Nonverbal fluency five-point test—perseverations	−0.49 ± 1.00	106	15.7

each cognitive variable, the frequency of patients showing impaired performance (defined as performing at least 1.5 SDs below of the age-, sex-, and schooling-specific healthy control medians) is also reported in Table 2.

Categorizing MCI patients into MCI subtypes according to the minimum mode of MCI classification revealed the following results: 106 patients (15.7%) were categorized as cognitively healthy, whereas 570 patients (84.3%) met the criteria for MCI. MCI patients were subtyped as aMCI single domain (31 patients; 4.6%), aMCI multiple domain (226 patients; 33.4%), non-aMCI single domain (125 patients; 18.5%), and non-aMCI multiple domain (188 patients; 27.8%). Figure 1A displays corresponding results for mean domain *z*-scores across MCI subtypes.

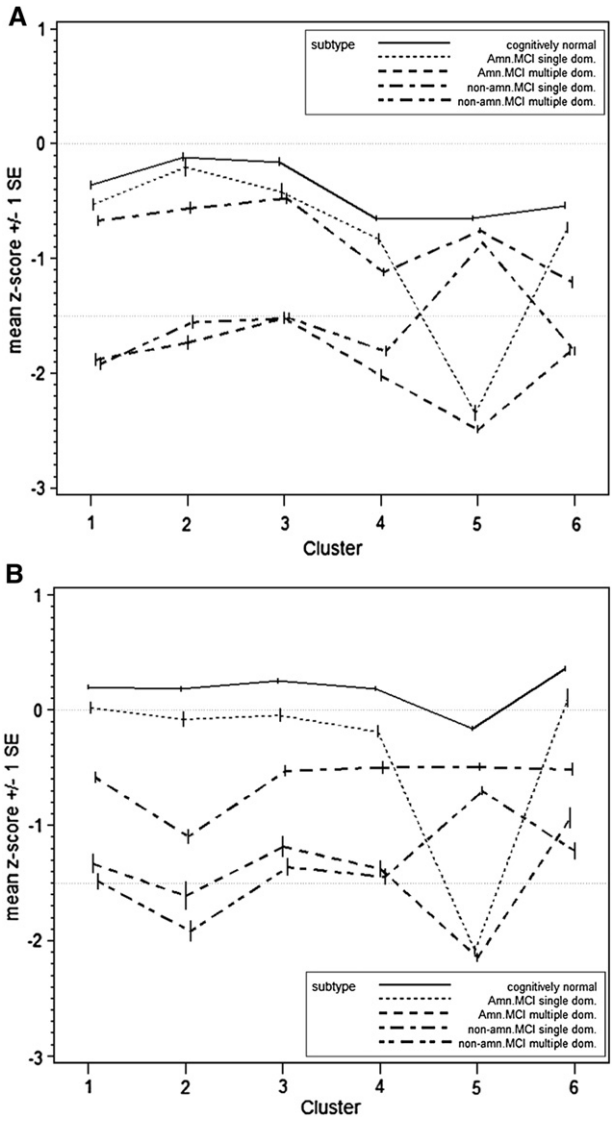

Fig. 1. Mean domain *z*-scores across mild cognitive impairment (MCI) subtypes for minimum mode classification and mean mode classification. (A) Minimum mode MCI classification across MCI subtypes. Each patient's individual minimum within a cluster is calculated, then mean and standard error of these minima are calculated across all patients. (B) Mean mode MCI classification across MCI subtypes. Each patient's individual mean within a cluster is calculated, then mean and standard error of these means are calculated across all patients.

Categorizing MCI patients into MCI subtypes according to the mean mode of MCI classification revealed the following results: 409 patients (60.5%) were categorized as cognitively healthy, whereas 267 patients (39.5%) met the criteria for MCI. MCI patients were subtyped as aMCI single domain (47 patients; 6.9%), aMCI multiple domain (57 patients; 8.5%), non-aMCI single domain (97 patients; 14.3%), and non-aMCI multiple domain (66 patients; 9.8%). Figure 1B displays corresponding results for mean domain *z*-scores across MCI subtypes.

For the minimum mode of MCI classification, statistical analyses for *z*-scores of all neuropsychological variables revealed significant subtype differences after Bonferroni–Holm correction (all corrected $P < .05$). See Table 3 for details of MCI subtypes.

For the mean mode of MCI classification, statistical analyses for *z*-scores of all neuropsychological variables revealed significant subtype differences after Bonferroni–Holm correction (all corrected $P < .05$). See Table 4 for details of MCI subtypes.

In the total sample the proportion of amnestic and non-amnestic subtypes was 38.0% and 46.3%, respectively, for the minimum mode of MCI classification and 15.4% vs. 24.1% for the mean mode. As can be seen from Figures 2A to 2D there is no clear trend over age with respect to subtype classification in either gender or mode of MCI classification. For the minimum mode of MCI classification, a logistic regression analysis showed no significant influence of age or years of formal schooling on the proportion of MCI patients ($P = .108$ and $P = .104$, respectively), whereas women showed a significantly higher risk for MCI (odds ratio = 1.60, $P = .032$). For the mean mode of MCI classification, a logistic regression analysis showed no significant influence of age, sex, or years of formal schooling on the proportion of MCI patients ($P = .097$, $P = .954$, and $P = .063$, respectively).

4. Discussion

In the present study, we examined different decision criteria on generating neuropsychological diagnoses of MCI in a large sample of elderly individuals participating in a longitudinal study of cognitive decline and dementia. We made a great effort to enroll a sufficient and well-characterized cognitively healthy control group who underwent a rigorous screening evaluation. We also used state-of-the-art statistical procedures (GAMLSS estimation) for calculating *z*-scores of the neuropsychological variables depending on age, sex, and education, and grouped these variables into cognitive domains by means of cluster analysis. In contrast to an a priori postulated domain structure, from a statistical point of view, our empirical approach optimally reflects the information contained in the data of the normative sample at hand.

We found that the percentage of impaired patients in single tests was rather low, ranging from 6.5% for the task of

Table 3
Z-scores with standard deviations for each neuropsychological variable for minimum mode MCI classification procedure

Domain/Neuropsychological variable	CN N = 106	aMCI SD N = 31	aMCI MD N = 226	Non-aMCI SD N = 125	Non-aMCI MD N = 188	*P* value
Domain 1/Attention						
AKT time[c,e,f,h,i,k]	0.78 ± 1.01	0.41 ± 0.79	−0.43 ± 1.42	0.44 ± 0.90	−0.48 ± 1.31	<.001*
AKT total/time[c,e,f,h,i,k]	0.75 ± 0.96	0.40 ± 0.75	−0.47 ± 1.37	0.42 ± 0.86	−0.50 ± 1.24	<.001*
Trail Making Test–TMTB[c,e,f,h,i,k]	0.45 ± 0.92	0.16 ± 0.80	−1.04 ± 1.44	0.01 ± 1.02	−1.15 ± 1.34	<.001*
Digit-symbol test (WAIS-R)[c,e,f,h,i,k]	0.37 ± 0.94	0.21 ± 0.74	−0.60 ± 1.18	0.15 ± 0.85	−0.67 ± 0.85	<.001*
TMTB − TMTA difference[c,e,f,h,i,k]	0.29 ± 1.12	0.09 ± 0.90	−1.11 ± 1.76	−0.13 ± 1.10	−1.21 ± 1.70	<.001*
Symbols counting (C.I.)[c,e,f,i,k]	0.95 ± 0.89	0.79 ± 0.81	−0.05 ± 1.38	0.95 ± 0.93	0.19 ± 1.15	<.001*
Minimum score attention†	−0.36 ± 0.70	−0.53 ± 0.50	−1.88 ± 1.47	−0.67 ± 0.90	−1.91 ± 1.38	
Domain 2/Executive function—phonematic verbal fluency						
Phonematic verbal fluency PWT total words[c,e,f,h,i,k]	0.60 ± 0.87	0.45 ± 0.98	−1.08 ± 1.72	0.22 ± 1.08	−0.88 ± 1.46	<.001*
Phonematic verbal fluency PWT l-words[c,e,f,h,i,k]	0.57 ± 0.77	0.34 ± 0.87	−0.80 ± 1.67	0.27 ± 0.86	−0.61 ± 1.42	<.001*
Phonematic verbal fluency PWT f-words[c,e,f,h,i,k]	0.55 ± 1.13	0.57 ± 1.18	−0.70 ± 1.24	0.17 ± 1.26	−0.62 ± 1.20	<.001*
Phonematic verbal fluency PWT b-words[c,e,f,g,h,i,k]	0.37 ± 0.86	0.37 ± 0.79	−1.07 ± 1.58	0.08 ± 1.26	−0.79 ± 1.44	<.001*
Minimum score phonematic verbal fluency†	−0.11 ± 0.72	−0.20 ± 0.82	−1.73 ± 1.69	−0.56 ± 1.03	−1.55 ± 1.43	
Domain 3/Executive function—interference						
Stroop color words[c,e,f,h,i,k]	0.55 ± 0.88	0.24 ± 0.92	−0.75 ± 1.34	0.34 ± 1.09	−0.69 ± 1.14	<.001*
Stroop total/time[c,e,f,h,i,k]	0.60 ± 0.99	0.20 ± 0.95	−0.67 ± 1.20	0.30 ± 1.17	−0.68 ± 1.11	<.001*
Interference (C.I.) time[c,e,f,h,i,k]	0.68 ± 0.98	0.72 ± 0.57	−0.50 ± 1.39	0.42 ± 0.99	−0.60 ± 1.17	<.001*
Interference (C.I.) total/time[c,e,f,h,i,k]	0.72 ± 1.08	0.77 ± 0.67	−0.53 ± 1.48	0.42 ± 1.09	−0.64 ± 1.27	<.001*
Stroop color words—colors[c,e,i,k]	0.29 ± 0.83	0.21 ± 1.20	−0.58 ± 1.82	0.23 ± 2.01	−0.54 ± 2.05	<.001*
Stroop colors[c,e,f,i,k]	0.92 ± 1.28	0.45 ± 1.02	−0.29 ± 1.37	0.64 ± 1.00	−0.20 ± 1.30	<.001*
Minimum score interference†	−0.16 ± 0.68	−0.42 ± 0.70	−1.52 ± 1.34	−0.48 ± 0.95	−1.52 ± 1.10	
Domain 4/Language						
Semantic verbal fluency SWT total words[c,e,f,h,i,k]	0.73 ± 0.92	0.25 ± 0.77	−0.83 ± 1.41	0.41 ± 1.01	−0.54 ± 1.24	<.001*
Semantic verbal fluency SWT supermarket items[c,e,f,i,k]	0.58 ± 1.09	−0.01 ± 0.92	−0.59 ± 1.20	0.29 ± 1.14	−0.38 ± 1.12	<.001*
Semantic verbal fluency SWT animals[c,e,f,i,j,k]	0.76 ± 1.15	0.22 ± 0.88	−1.01 ± 1.83	0.32 ± 1.13	−0.52 ± 1.43	<.001*
Semantic verbal fluency SWT tools[c,e,f,i,k]	0.48 ± 0.93	0.20 ± 0.76	−0.35 ± 1.02	0.37 ± 0.98	−0.23 ± 1.04	<.001*
Boston Naming Test (mBNT)[c,d,e,f,h,k]	−0.47 ± 0.48	−0.51 ± 0.58	−1.11 ± 0.93	−0.89 ± 0.76	−1.17 ± 0.99	<.001*
Minimum score language†	−0.65 ± 0.46	−0.83 ± 0.48	−2.02 ± 1.35	−1.12 ± 0.66	−1.81 ± 1.11	
Domain 5/Memory						
Verbal memory total recall (VSRT)[b,c,d,g,h,i,j]	0.16 ± 0.93	−0.84 ± 1.15	−1.21 ± 0.95	0.06 ± 0.83	−0.10 ± 0.83	<.001*
Verbal memory immediate recall (VSRT)[b,c,e,f,g,h,i,j,k]	0.40 ± 0.79	−0.99 ± 0.91	−1.48 ± 1.03	0.13 ± 0.78	−0.16 ± 0.70	<.001*
Verbal memory delayed recall (VSRT)[b,c,d,e,g,h,i,j]	0.38 ± 0.87	−1.35 ± 1.11	−1.59 ± 1.28	0.04 ± 0.86	−0.17 ± 0.76	<.001*
Verbal memory recognition (VSRT)[b,c,g,h,i,j]	−0.42 ± 0.50	−1.69 ± 0.93	−1.60 ± 1.02	−0.49 ± 0.50	−0.45 ± 0.51	<.001*
Minimum score memory†	−0.65 ± 0.45	−2.35 ± 0.70	−2.49 ± 0.91	−0.76 ± 0.47	−0.87 ± 0.40	
Domain 6/Executive function–planning and nonverbal fluency						
Planning maze test—NAI time[c,e,f,h,i,k]	0.77 ± 0.91	0.50 ± 0.98	−0.32 ± 1.43	0.39 ± 1.28	−0.34 ± 1.33	<.001*
Planning maze test—NAI total/time[c,e,f,h,i,k]	0.73 ± 0.97	0.54 ± 1.07	−0.26 ± 1.25	0.37 ± 1.22	−0.34 ± 1.21	<.001*
Nonverbal fluency five-point test—total correct[c,e,f,h,i,k]	0.35 ± 0.95	0.36 ± 0.95	−0.58 ± 1.43	0.24 ± 1.04	−0.49 ± 1.24	<.001*
Trail Making Test—TMTA[c,d,e,f,h,i,k]	0.60 ± 0.96	0.31 ± 0.89	−0.49 ± 1.25	0.17 ± 0.89	−0.53 ± 1.12	<.001*
Nonverbal fluency five-point test—perseverations[c,d,e]	−0.17 ± 0.60	−0.27 ± 0.64	−0.57 ± 1.08	−0.58 ± 1.09	−0.57 ± 1.03	.003*
Minimum score planning and nonverbal fluency†	−0.54 ± 0.59	−0.73 ± 0.45	−1.81 ± 1.02	−1.20 ± 1.00	−1.81 ± 0.90	

Abbreviations: CN, cognitively healthy; aMCI SD, amnestic MCI single domain; aMCI MD, amnestic MCI multiple domain; non-aMCI SD, nonamnestic MCI single domain; non-aMCI MD, nonamnestic MCI multiple domain.

NOTE. Significant pairwise comparisons after Tukey correction: [b]CN vs. a-MCI SD; [c]CN vs. a-MCI MD; [d]CN vs. Non a-MCI SD; [e]CN vs. Non a-MCI MD; [f]a-MCI SD vs. a-MCI MD; [g]a-MCI SD vs. Non a-MCI SD; [h]a-MCI SD vs. Non a-MCI MD; [i]a-MCI MD vs. Non a-MCI SD; [j]a-MCI MD vs. Non a-MCI MD; [k]Non a-MCI SD vs. Non a-MCI MD.

*Significant difference between subtypes after multiplicity correction according to the method by Bonferroni and Holm.

†Each patient's individual minimum within a cluster is calculated, then mean and SD of these minima are calculated across all patients.

symbol counting to 25.2% for the TMTB minus TMTA score. Memory tasks were in between, indicating that patients did not show impairments only in memory but also in other cognitive tasks. Thus, selective memory impairment is rather rare, with patients reporting memory problems showing a wide range of cognitive impairments. This result corroborates previous reports [4].

To investigate the effect of different MCI criteria on MCI subtype prevalence, we investigated two different approaches to MCI subtype classification. One method classified MCI when the *z*-score of at least one single cognitive test (variable) was less than −1.5 SDs, the so-called minimum mode. In the other approach, the mean mode, the criteria were qualified as MCI when the *z*-score of the mean of all cognitive variables within one specific domain, for example, memory, was less than −1.5 SDs. Not surprisingly, based on the definition of the subtyping procedure, different MCI classifications resulted. By means of minimum mode,

Table 4
Z-scores with standard deviations for each neuropsychological variable for mean mode MCI classification procedure

Domain/Neuropsychological variable	CN N = 409	aMCI SD N = 47	aMCI MD N = 57	Non-aMCI SD N = 97	Non-aMCI MD N = 66	*P* value
Domain 1/Attention						
AKT time[c,e,f,h,i,k]	0.36 ± 1.01	0.22 ± 0.93	−1.05 ± 1.47	−0.38 ± 1.37	−1.50 ± 1.44	<.001*
AKT total/time[c,e,f,h,i,k]	0.33 ± 0.98	0.12 ± 0.93	−1.06 ± 1.45	−0.44 ± 1.30	−1.45 ± 1.37	<.001*
Trail Making Test—TMTB[c,d,e,f,h,i,k]	−0.10 ± 1.13	−0.11 ± 1.04	−2.02 ± 1.41	−1.10 ± 1.30	−1.98 ± 1.24	<.001*
Digit-symbol test (WAIS-R)[c,e,f,h,i,k]	0.05 ± 0.94	−0.19 ± 1.06	−1.37 ± 1.11	−0.65 ± 0.85	−1.04 ± 0.94	<.001*
TMTB − TMTA difference[c,e,f,h,i,k]	−0.22 ± 1.28	−0.05 ± 1.44	−2.06 ± 1.77	−1.15 ± 1.83	−2.07 ± 1.60	<.001*
Symbols counting (C.I.)[c,e,f,g,h,i,k]	0.77 ± 1.03	0.06 ± 1.26	−0.42 ± 1.31	0.24 ± 0.96	−0.78 ± 1.40	<.001*
Mean score attention†	0.20 ± 0.77	0.02 ± 0.66	−1.33 ± 1.13	−0.59 ± 0.86	−1.49 ± 0.96	
Domain 2/Executive function—phonematic verbal fluency						
Phonematic verbal fluency PWT total words[c,e,f,h,i,k]	0.21 ± 1.03	−0.09 ± 0.88	−1.91 ± 1.97	−1.27 ± 1.36	−2.30 ± 1.65	<.001*
Phonematic verbal fluency PWT l-words[c,e,f,h,i,k]	0.25 ± 0.91	0.02 ± 0.90	−1.54 ± 2.13	−0.92 ± 1.39	−1.81 ± 1.62	<.001*
Phonematic verbal fluency PWT f-words[c,e,f,h,i,k]	0.20 ± 1.23	−0.06 ± 1.02	−1.18 ± 1.18	−0.95 ± 1.05	−1.46 ± 0.87	<.001*
Phonematic verbal fluency PWT b-words[c,e,f,h,i,k]	0.07 ± 1.13	−0.19 ± 0.94	−1.74 ± 1.82	−1.21 ± 1.34	−2.03 ± 1.44	<.001*
Mean score phonematic verbal fluency†	0.18 ± 0.87	−0.08 ± 0.78	−1.61 ± 1.59	−1.10 ± 1.09	−1.92 ± 1.28	
Domain 3/Executive function—interference						
Stroop color words[c,e,f,h,i,k]	0.16 ± 1.07	−0.23 ± 0.86	−1.49 ± 1.43	−0.63 ± 1.08	−1.50 ± 1.24	<.001*
Stroop total/time[c,e,f,h,i,k]	0.15 ± 1.14	−0.26 ± 0.88	−1.36 ± 1.26	−0.64 ± 0.98	−1.24 ± 1.17	<.001*
Interference (C.I.) time[c,e,f,h,i,k]	0.32 ± 1.06	0.10 ± 0.93	−0.97 ± 1.45	−0.55 ± 1.07	−1.60 ± 1.35	<.001*
Interference (C.I.) total/time[c,e,f,h,i,k]	0.33 ± 1.15	0.13 ± 1.05	−1.01 ± 1.50	−0.62 ± 1.21	−1.66 ± 1.44	<.001*
Stroop color words—colors[c,e,i,k]	0.09 ± 1.75	−0.16 ± 1.54	−1.45 ± 1.45	−0.48 ± 1.73	−1.00 ± 2.25	<.001*
Stroop colors	0.51 ± 1.21	0.22 ± 1.27	−0.74 ± 1.29	−0.16 ± 1.16	−1.09 ± 1.36	<.001*
Mean score interference†	0.25 ± 0.90	−0.04 ± 0.73	−1.18 ± 1.21	−0.53 ± 0.85	−1.36 ± 1.06	
Domain 4/Language						
Semantic verbal fluency SWT total words[c,e,f,g,h,i,k]	0.27 ± 1.11	−0.12 ± 0.88	−1.64 ± 1.19	−0.52 ± 1.19	−1.71 ± 1.21	<.001*
Semantic verbal fluency SWT supermarket items[c,e,i,k]	0.22 ± 1.15	−0.22 ± 1.02	−1.22 ± 0.92	−0.41 ± 1.13	−1.18 ± 0.85	<.001*
Semantic verbal fluency SWT animals[c,e,f,h,i,j,k]	0.26 ± 1.20	−0.11 ± 0.97	−1.95 ± 1.80	−0.64 ± 1.51	−1.95 ± 1.94	<.001*
Semantic verbal fluency SWT tools[c,e,f,g,i,k]	0.26 ± 0.97	−0.11 ± 0.97	−0.66 ± 0.86	−0.25 ± 1.09	−0.88 ± 0.86	<.001*
Boston Naming Test (mBNT)[c,d,e,f,h,k]	−0.85 ± 0.79	−0.89 ± 0.74	−1.20 ± 0.95	−1.02 ± 1.02	−1.39 ± 1.08	<.001*
Mean score language†	0.19 ± 0.85	−0.19 ± 0.66	−1.37 ± 0.96	−0.50 ± 0.97	−1.44 ± 0.95	
Domain 5/Memory						
Verbal memory total recall (VSRT)[b,c,e,f,g,h,i,j,k]	−0.08 ± 0.94	−1.57 ± 0.86	−1.90 ± 0.74	−0.45 ± 0.84	−0.53 ± 0.86	<.001*
Verbal memory immediate recall (VSRT)[b,c,e,g,h,i,j]	−0.03 ± 0.88	−2.09 ± 1.07	−2.20 ± 0.78	−0.53 ± 0.75	−0.79 ± 0.74	<.001*
Verbal memory delayed recall (VSRT)[b,c,d,e,g,h,i,j,k]	−0.10 ± 0.98	−2.60 ± 1.25	−2.45 ± 0.96	−0.40 ± 0.79	−0.72 ± 0.80	<.001*
Verbal memory recognition (VSRT)[b,c,g,h,i,j]	−0.67 ± 0.70	−2.12 ± 1.12	−1.96 ± 0.96	−0.66 ± 0.71	−0.83 ± 0.95	<.001*
Mean score memory†	−0.16 ± 0.69	−2.08 ± 0.46	−2.14 ± 0.50	−0.49 ± 0.56	−0.70 ± 0.55	
Domain 6/Executive function—planning and nonverbal fluency						
Planning maze test—NAI time[c,e,f,h,i,k]	0.41 ± 1.08	0.18 ± 1.22	−0.83 ± 1.62	−0.46 ± 1.36	−1.15 ± 1.55	<.001*
Planning maze test—NAI total/time[c,e,f,h,i,k]	0.39 ± 1.08	0.20 ± 1.22	−0.68 ± 1.27	−0.44 ± 1.19	−1.01 ± 1.33	<.001*
Nonverbal fluency five-point test—total correct[c,e,f,h,i,k]	0.21 ± 1.10	−0.27 ± 1.11	−1.11 ± 1.57	−0.64 ± 1.08	−1.41 ± 1.16	<.001*
Trail Making Test—TMTA[c,d,e,f,h,i,k]	0.18 ± 1.03	0.04 ± 1.02	−1.11 ± 1.31	−0.53 ± 0.98	−1.15 ± 1.17	<.001*
Nonverbal fluency five-point test—perseverations[c,d,e]	−0.53 ± 1.05	−0.79 ± 0.93	−0.42 ± 1.03	−0.45 ± 0.89	−0.17 ± 0.76	.003*
Mean score planning and nonverbal fluency†	0.36 ± 0.88	0.10 ± 0.95	−0.94 ± 1.24	−0.51 ± 0.95	−1.22 ± 1.06	

NOTE. Significant pairwise comparisons after Tukey correction: [b]CN vs. a-MCI SD; [c]CN vs. a-MCI MD; [d]CN vs. Non a-MCI SD; [e]CN vs. Non a-MCI MD; [f]a-MCI SD vs. a-MCI MD; [g]a-MCI SD vs. Non a-MCI SD; [h]a-MCI SD vs. Non a-MCI MD; [i]a-MCI MD vs. Non a-MCI SD; [j]a-MCI MD vs. Non a-MCI MD; [k]Non a-MCI SD vs. Non a-MCI MD.

*Significant difference between subtypes after multiplicity correction according to the method by Bonferroni and Holm.

†Each patient's individual mean within a cluster is calculated, then mean and SD of these means are calculated across all patients.

84.3% of patients met the criteria for MCI, and by means of the mean mode, only 39.5% met the MCI criteria. Nevertheless, the relation of amnestic to non-amnestic MCI subtypes was similar for the two subtyping procedures (38.0% vs. 46.3% for the minimum mode and 15.4% vs. 24.1% for the mean mode).

When comparing the MCI prevalence rate of our cohort, considering both modes in the prevalence of MCI in population-based epidemiological and clinic-based studies, we found a wide range of prevalence rates. Prevalence rates of MCI varied widely depending on the impairment criteria ranging from 4% to 70% and were strongly affected by the choice of neuropsychological assessment parameters [12,14].

Nordlund et al [36] found that memory impairment alone or impairment in one cognitive domain alone is a rather benign condition. However, the 2-year outcome of patients with impairment in several cognitive domains is associated with more severe progression to dementia. Furthermore, they showed that subjects who progressed to dementia did not always show memory problems at the baseline. Therefore, a clinical examination including

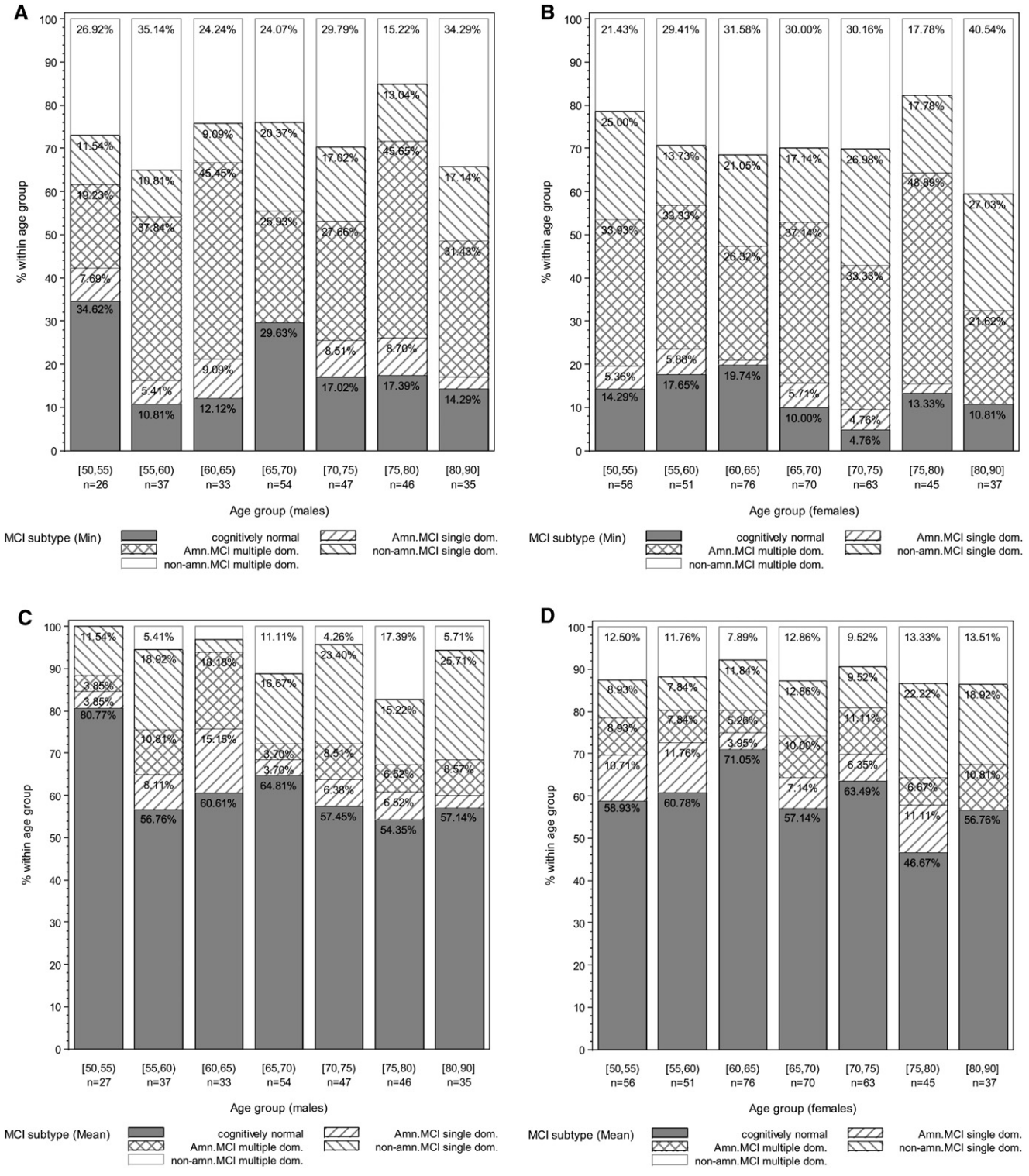

Fig. 2. Prevalence of MCI subtypes across mode of MCI subtype classification, age-group, and sex. (A) Prevalence of MCI subtypes in males across age-group using minimum mode MCI subtype classification. (B) Prevalence of MCI subtypes in females across age-group using minimum mode MCI subtype classification. (C) Prevalence of MCI subtypes in males across age-group using mean mode MCI subtype classification. (D) Prevalence of MCI subtypes in females across age-group using mean mode MCI subtype classification.

neuropsychological standard tests of multiple domains is indispensable for detecting individuals at high risk of converting to dementia.

Recently, computerized cognitive assessment was introduced for MCI [37]. Such assessment offers a briefer, more objective, and precise alternative to traditional testing.

Moreover, comparison to age- and education-appropriate norms may be computed automatically. Specifically, an Excel-based program to compute *z*-scores is available from the authors.

We also explored the relation of mode of MCI classification, age, and sex on prevalence of MCI subtypes in our cohort of memory clinic outpatients. We only found a higher prevalence of MCI in women when using the minimum mode of classification. This result is in stark contrast to a recent population-based study [38]. Differences in study population may account for that result. We can only speculate that men came later to the clinic for evaluation and therefore are more progressed and perhaps have received the AD diagnosis more often. That could be one reason why we found a lower male MCI prevalence than other research groups investigating populations samples. Another explanation for that effect could be that women and men have sex-specific cognitive reserve. For example, females performed better on verbal episodic memory tasks, whereas males showed better results in visuospatial episodic memory [39]. We detected no effect of age and years of formal schooling on MCI prevalence. This finding comes rather unexpected and needs to be investigated further. One reason could possibly be that our patients had not been sampled from the general population but from a memory outpatient clinic where the distribution of MCI subtypes could approximately be more similar between subgroups of same age and education.

As in most clinical studies, the current study has also some limitations that should be addressed. Our cohort is very specific, and the results may not be generalizable to the general population. Population studies outside specialized memory clinics are necessary to ensure ecological validity of the results. The definition of high-risk populations is of utmost importance. Incidence rates of dementia are highly elevated among cases with MCI compared with the general population, confirming that MCI comprises a high-risk population [40]. The characterization of MCI subtypes is very important because they can help understand the natural progression of patients perceiving cognitive problems. Visuospatial processing is an important domain in the assessment of MCI, and results for such measures have not been reported in this article because such measurers had been introduced at a later time point in the formal process of neuropsychological assessment at our institution, and therefore not enough data are yet available to perform meaningful statistical analyses.

Finally, follow-up studies determining conversion to dementia should be performed to investigate the usefulness of different modal MCI classification schemes and to establish best cutoff scores for neuropsychological testing and effects of age, sex, and education on the development of dementia in MCI patients.

In a previous study with a small sample size [20], we found for the measurers of sensitivity, specificity, positive and negative predicted values, percentage of correctly predicted patients using the minimum mode of MCI classification for the categorical variable of aMCI versus a cognitively healthy control group, a sensitivity of 0.64, a specificity of 0.86, a positive predicted value of 0.41, a negative predicted value of 0.94, and percentage correctly predicted of 83.0. Further study regarding the predictive validity of different MCI classifications in terms of dementia prediction is necessary. Such an investigation is being currently performed at our institution.

In conclusion, patients reporting cognitive problems and seeking help in a memory outpatient clinic, albeit having no clinical dementia, show a wide range of cognitive impairments.

Acknowledgements

The authors thank Arinya Eller for proofreading this manuscript.

References

[1] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–8.

[2] Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1133–42.

[3] Petersen RC, Roberts RO, Knopman DS, Boeve BF, Geda YE, Ivnik RJ, et al. Mild cognitive impairment: ten years later. Arch Neurol 2009;66:1447–55.

[4] Petersen RC. Clinical practice. Mild cognitive impairment. N Engl J Med 2011;364:2227–34.

[5] Ganguli M, Blacker D, Blazer DG, Grant I, Jeste DV, Paulsen JS, et al. Classification of neurocognitive disorders in DSM-5: a work in progress. Am J Geriatr Psychiatry 2011;19:205–10.

[6] Busse A, Angermeyer MC, Riedel-Heller SG. Progression of mild cognitive impairment to dementia: a challenge to current thinking. Br J Psychiatry 2006;189:399–404.

[7]. Stephan BC, Savva GM, Brayne C, Bond J, McKeith IG, Matthews FE. Optimizing mild cognitive impairment for discriminating dementia risk in the general older population. Am J Geriatr Psychiatry 2010; 18:662–73.

[8] Schink JA, Loewenstein DA, Raj A, Schoenberg MR, Banko JL, Potter H, et al. Defining mild cognitive impairment: impact of varying decision criteria on neuropsychological diagnostic frequencies and correlates. Am J Geriatr Psychiatry 2010;18:684–91.

[9] Teng E, Becker BW, Woo E, Cummings JL, Lu PH. Subtle deficits in instrumental activities of daily living in subtypes of mild cognitive impairment. Dement Geriatr Cogn Disord 2010;30:189–97.

[10] Loewenstein DA, Acevedo A, Ownby R, Agron J, Barker WW, Isaacson R, et al. Using different memory cutoffs to assess mild cognitive impairment. Am J Geriatr Psychiatry 2006;14:911–9.

[11] Jak AJ, Bangen KJ, Wierenga CE, Delano-Wood L, Corey-Bloom J, Bondi MW. Contributions of neuropsychology and neuroimaging to understanding clinical subtypes of mild cognitive impairment. Int Rev Neurobiol 2009;84:81–103.

[12] Jak AJ, Bondi MW, Delano-Wood L, Wierenga C, Corey-Bloom J, Salmon DP, et al. Quantification of five neuropsychological approaches to defining mild cognitive impairment. Am J Geriatr Psychiatry 2009; 17:368–75.

[13] Busse A, Bischkopf J, Riedel-Heller SG, Angermeyer MC. Subclassifications for mild cognitive impairment: prevalence and predictive validity. Psychol Med 2003;33:1029–38.
[14] Kochan NA, Slavin MJ, Brodaty H, Crawford JD, Trollor JN, Draper B, et al. Effect of different impairment criteria on prevalence of "objective" mild cognitive impairment in a community sample. Am J Geriatr Psychiatry 2010;18:711–22.
[15] Dilling H, Mombour W, Schmidt MH, eds. Internationale klassifikation pychischer Störungen. ICD-10 Kapitel V (F): Klinisch -diagnostische Leitlinien. 4th ed. Bern, Switzerland: Huber; 2000.
[16] Saß H, Wittchen HU, Zaudig M, Houben I. Diagnostisches und statistisches manual psychischer störungen–textrevision–DSM-IV-TR. Göttingen, Germany: Hogrefe Verlag für Psychologie; 2003.
[17] Greenaway MC, Smith GE, Tangalos EG, Geda YE, Ivnik RJ. Mayo older Americans normative studies: Factor analysis and expanded neuropsychological battery. Clin Neuropsychol 2009;23:7–20.
[18] Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med 2004;256:183–94.
[19] Lehrner J, Gleiß A, Maly J, Auff E, Dal-Bianco P. Der verbale Selektive Reminding Test (VSRT). Ein verfahren zur überprüfung verbaler gedächtnisfunktionen. Neuropsychiatrie 2006;20:204–14.
[20] Lehrner J, Gufler R, Guttmann G, Maly J, Gleiß A, Auff E, et al. Annual conversion to Alzheimer's disease among patients with memory complaints attending an outpatient memory clinic: the influence of amnestic mild cognitive impairment and the predictive value of neuropsychological testing. Wien Klin Wochenschr 2005;117:629–35.
[21] Lehrner J, Maly J, Gleiß A, Auff E, Dal-Bianco P. The Vienna Neuropsychological Test Battery (VNTB) for detecting dementia—standardization, norms, and validation. Psychol Österreich 2007;4(5):358–65.
[22] Lezak MD. Neuropsychological assessment. New York, NY: Oxford University Press; 1995.
[23] Gatterer G. Alters-Konzentrations-Test (AKT). 2., neu normierte Auflage. Göttingen, Germany: Hogrefe; 2008.
[24] Tewes U. Hamburg-Wechsler-Intelligenztest für Erwachsene–Revision 1991 (HAWIE-R). Bern, Switzerland: Verlag Hans Huber; 1994.
[25] Lehrl S, Fischer B. Kurztest für cerebale Insuffizienz (c.I.-Test). Ebersberg, Germany: Vless; 1997.
[26] Reitan R. Trail Making Test (TMT). Tucson, AZ: Reitan Neuropsychology Laboratory; 1979.
[27] Regard M, Strauss E, Knapp P. Children's production on verbal and non-verbal fluency tasks. Percept Mot Skills 1982;55:839–44.
[28] Oswald WD, Fleischmann UM. Das Nünberger-Alters-Inventar. Göttingen, Germany: Hogrefe Verlag; 1997.
[29] Goodglass H, Kaplan E. The assessment of aphasia and related disorders. 2nd ed. Philadelphia, PA: Lea & Fabinger; 1983.
[30] Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I: clinical and neuropsychological assessment of Alzheimer's disease. Neurology 1989;39:1159–65.
[31] Crook T, Salama M, Gobert J. A computerized test battery for detecting and assessing memory disorders. In: Bes A, Cohn J, Hoyer S, Marc-Vergenes JP, Wisniewski HM, eds. Senile Dementias: Early Detection. London-Paris: John Libbey Eurotext; 1986. p. 79–85.
[32] Youngjohn JR, Larrabee GJ, Crook TH. First-last names and the grocery list selective reminding test: two computerized measures of everyday verbal learning. Arch Clin Neuropsychol 1991;6:287–300.
[33] Chandler MJ, Lacritz LH, Hynan LS, Barnard HD, Allen G, Deschner M, et al. A total score for the CERAD neuropsychological battery. Neurology 2005;65:102–6.
[34] Stasinopoulus DM, Rigby RA. Generalized additive models for location scale and shape (GAMLSS). J Stat Softw 2007;23:1–46.
[35] Petersen RC, Morris J. Mild cognitive impairment as a clinical entity and treatment target. Arch Neurol 2005;62:1160–3.
[36] Nordlund A, Rolstad S, Klang O, Edman A, Hansen S, Wallin A. Two-year outcome of MCI subtypes and aetiologies in the Goteborg MCI study. J Neurol Neurosurg Psychiatry 2010;81:541–6.
[37] Dwolatzky T, Whitehead V, Doniger GM, Simon ES, Schweiger A, Jaffe D, Chertkow H. Validity of a novel computerized cognitive battery for mild cognitive impairment. BMC Geriatr 2003;3:4–16.
[38] Petersen RC, Roberts RO, Knopman DS, Geda YE, Cha RH, Pankratz VS, et al. Prevalence of mild cognitive impairment is higher in men. The Mayo Clinic Study of Aging. Neurology 2010; 75:889–97.
[39] Beinhoff U, Tumani H, Brettschneider J, Bittner D, Riepe MW. Gender-specificities in Alzheimer's disease and mild cognitive impairment. J Neurol 2008;255:117–22.
[40] Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. Lancet 2006;367:1262–70.