Eur Arch Psychiatry Clin Neurosci (2013) 263:325–333
DOI 10.1007/s00406-012-0349-0

ORIGINAL PAPER

The National Institute on Aging-Alzheimer's Association research criteria for mild cognitive impairment due to Alzheimer's disease: predicting the outcome

Liang-Hao Guo · Panagiotis Alexopoulos · Tamara Eisele · Stefan Wagenpfeil · Alexander Kurz · Robert Perneczky

Received: 22 May 2012 / Accepted: 10 August 2012 / Published online: 30 August 2012

Abstract The National Institute on Aging-Alzheimer's Association (NIA-AA) clinical research criteria for mild cognitive impairment (MCI) due to Alzheimer's disease (AD) incorporate the use of biomarkers to classify patients according to the likelihood of the presence of AD pathology. The aim of the study was to compare the risk of progression to AD dementia between the four NIA-AA MCI subgroups using data from the AD Neuroimaging Initiative. Patients with MCI were categorised according to the NIA-AA criteria into subgroups with high, intermediate, and low likelihood of the presence of AD pathology (MCI-high, MCI-intermediate, and MCI-unlikely, respectively) or into a group of patients that only met the MCI-core clinical criteria (MCI-core). Data of follow-up visits conducted 6–60 months after baseline were used to compare the relative risk of future AD dementia between the four subgroups employing a Cox regression model. The MCI-high subgroup ($N = 22$) had a 2.3 times higher risk of developing AD dementia compared with the MCI-core subgroup ($N = 327$; $P = 0.002$), while there was a trend for a higher risk in the MCI-high subgroup in contrast to the MCI-intermediate subgroup ($N = 31$, $P = 0.08$). No patients in the MCI-unlikely subgroup ($N = 17$) progressed to AD dementia. Patients with MCI-high have a higher risk for developing AD dementia. The new NIA-AA MCI criteria represent a valuable research instrument that could be incorporated into the diagnostic process of the MCI syndrome after optimisation and refinement.

Keywords Mild cognitive impairment · Alzheimer's disease · Dementia · Diagnostic criteria

Liang-Hao Guo and Panagiotis Alexopoulos contributed equally to the manuscript.

This study is conducted for the Alzheimer's Disease Neuroimaging Initiative.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). The investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wpcontent/uploads/how_to_apply/ADNI_Authorship_List.pdf.

L.-H. Guo · P. Alexopoulos (✉) · T. Eisele · A. Kurz · R. Perneczky (✉)
Department of Psychiatry and Psychotherapy, Klinikum rechts der Isar der Technischen Universität München, Ismaninger Str. 22, 81675 Munich, Germany
e-mail: panos.alexopoulos@lrz.tum.de

R. Perneczky
e-mail: robert.perneczky@lrz.tum.de

S. Wagenpfeil
Institute of Medical Statistics and Epidemiology, Technische Universität München, Ismaninger Str. 22, 81675 Munich, Germany

Introduction

Mild cognitive impairment (MCI) refers to the transitional stage between physiological cognitive ageing and mild dementia. It is heterogeneous with regard to aetiology, clinical appearance and prognosis [2, 5, 13, 33, 34, 37]. Progressive MCI with prominent memory deficits often represents a pre-dementia stage of Alzheimer's disease (AD) [3, 15, 34]. For this particular form of minor cognitive deterioration, the term "MCI due to AD" has been recently proposed [1].

Progress in the field of AD biomarkers [10, 25] enabled a workgroup of the National Institute on Aging and the Alzheimer's Association (NIA-AA) to develop a novel set of clinical criteria for MCI. MCI-core clinical criteria for healthcare providers without access to advanced imaging techniques or cerebrospinal fluid (CSF) analyses were proposed in addition to research criteria incorporating biomarkers, which were recommended for clinical research settings including clinical trials [1]. The new set of research criteria allows the classification of MCI into three subgroups according to the alleged probability that the MCI syndrome is caused by AD pathology and into an additional subgroup with less-well-established probability.

The current study aimed to retrospectively apply the NIA-AA MCI criteria to a large sample from the AD Neuroimaging Initiative (ADNI) and to explore how the stratification into subgroups with different putative likelihood of AD pathology was associated with the rate of progression to AD dementia.

Materials and methods

The data used in this study were obtained from the ADNI database on 27 October 2011. ADNI is based on a broad collaboration of approximately 50 academic institutions and private corporations across the USA and Canada. It is supported by the NIA, non-profit organisations and private pharmaceutical companies. The primary goal of ADNI is to explore whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological data can be combined to assess the progression of MCI and early AD dementia. The study was approved by the institutional review boards of all participating centres, and written informed consent was obtained from all participants or authorised representatives after extensive description of ADNI.

Participants

Information on 397 patients with MCI was obtained. The new MCI-core clinical criteria only minimally deviate from the criteria defined by Petersen et al. [14, 32], which were applied in ADNI. Even though the NIA-AA criteria do not explicitly exclude deficits in cognitive domains other than memory, they are still focused on memory impairment since pre-dementia AD is most frequently characterised by an amnestic syndrome [1]. Thus, all patients with MCI included in ADNI also fulfil the new MCI-core clinical criteria.

Data were available from clinical follow-up visits conducted 6–60 months after baseline. Patients diagnosed with AD dementia at follow-up met National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD [27, 32]. No patient progressed to any other form of dementia, such as frontotemporal dementia or dementia with Lewy bodies. Biomarker values were not used as indicators of clinical disease progression. The date of the progression to AD dementia was defined by the time when the diagnosis of probable AD was established as the intervals between the follow-up assessments were relatively short (6 months), and since AD is a slowly progressive disorder [1] with no clear clinical severity thresholds.

PET acquisition and analysis

PET scan methods and analysis protocols were previously described in detail [19]. For the ^{18}F-fluorodeoxyglucose (FDG) PET analyses, a group of regions of interest (ROI) based on areas that typically show hypometabolism in patients with AD was generated (bilateral angular gyrus, posterior cingulate/precuneus and inferior temporal cortex of both hemispheres). Mean FDG counts were extracted from each ROI. The ROI mean counts were subsequently averaged to form a single 'composite' FDG ROI to be included in all FDG PET analyses as previously described [20].

From ^{11}C-labelled Pittsburgh compound B (PiB), PET data standardised uptake ratio (SUVR) images were created [24]. A mean cortical PiB SUVR encompassing averaged bilateral cortical ROIs in which PiB uptake has been previously detected in AD dementia was used (anterior cingulate, prefrontal, lateral temporal and parietal cortex and posterior cingulate/precuneus) [20]. Baseline PiB-PET data were available from 15 patients whilst scans from 39 patients were initially obtained at the 12-month follow-up visit. Taking into consideration the slow progression of amyloid pathology over years, as determined by annual change in PiB uptake [9, 20], PiB-PET scans acquired at the 12-month follow-up visit were also included in the analysis. No MCI patient with the initial PiB-PET scan acquired at the 12-month follow-up visit was diagnosed with AD dementia at the time of the scan.

MRI acquisition and analysis

Structural MRI scans (1.5 tesla) were acquired according to a standard protocol described elsewhere [17]. Briefly, 3-dimensional sagittal magnetisation prepared rapid gradient-echo (MPRAGE) scans were obtained. Total brain volumes and bilateral hippocampal volumes were extracted using FreeSurfer software, an atlas-based approach that has been validated for use in subjects with a great variability in brain morphology [6, 22].

CSF acquisition and analysis

The CSF concentrations of β-amyloid 1–42 ($A\beta_{42}$), total tau (tTau), and phosphorylated tau ($pTau_{181}$) were measured using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX, USA) with Innogenetics immunoassay kit-based reagents (INNO-BIA AlzBio 3; Ghent, Belgium) [21].

APOE genotyping

APOE genotypes were determined for all ADNI participants through analysis of blood samples using standard polymerase chain reaction methods [38].

Cut-offs for subject classification

Cut-offs to differentiate between normal and pathological findings were selected from previous ADNI publications. The cut-offs were determined by using receiver operating characteristic (ROC) analyses with AD dementia and cognitively normal ADNI participants. Regarding the CSF parameters, $A\beta_{42}$, tTau and $pTau_{181}$ concentrations of less than 193 pg/mL, greater than 93 pg/mL, and greater than 23 pg/mL, respectively, were regarded as abnormal [22, 39]. PiB-PET SUVR values greater than 1.46 [29] and FDG PET composite ROI values less than 1.22 [20] were considered positive for AD pathology. Furthermore, hippocampal volumes lower than 3,260.40 mm^3 indicated AD pathology [22].

In order to determine the optimal cut-off for the annual whole brain atrophy rate, an ROC analysis was performed on all ADNI controls (191) versus patients with AD dementia (126) with MRI scans from the baseline and the 12-month follow-up visits. The threshold value of the ratio $(\text{Brain volume at 12-month follow-up} - \text{brain volume at baseline})/\text{Brain volume at baseline}$ was -0.01 with a sensitivity of 86.40 % and a specificity of 50.80 % (area under the curve: 0.74). Patients with AD dementia had a mean atrophy rate of -0.012 ± 0.024 while controls had a rate of -0.006 ± 0.037.

Stratification of patients with MCI

The availability of biomarkers varied between the individual patients. Since missing information and incomplete datasets are typical for clinical settings and are also compatible with the NIA-AA criteria, patients were not excluded from the analysis in case of missing values. The NIA-AA MCI criteria distinguish between biomarkers indicating Aβ deposition (CSF $A\beta_{42}$ and PiB-PET) and biomarkers reflecting neuronal injury (CSF $tTau/pTau_{181}$, hippocampal volume, rate of whole brain atrophy and FDG PET). Equal weight is assigned to different markers within the same category in the allocation of patients to one of the following four categories:

- MCI due to AD—high likelihood (MCI-high): If both Aβ and neural injury biomarkers are suggestive of AD, the highest probability that the MCI syndrome is due to AD pathology is assigned.
- MCI due to AD—intermediate likelihood (MCI-intermediate): If biomarkers suggesting Aβ deposition are positive and biomarkers of neuronal injury are untested or vice versa, an intermediate likelihood that the patient suffers from AD pathology is assumed.
- MCI—unlikely due to AD (MCI-unlikely): Biomarkers both of Aβ deposition and neuronal injury are negative. This MCI subgroup is considered to have the lowest likelihood of underlying AD pathology.
- MCI—core clinical criteria (MCI-core): Patients are classified into the MCI-core subgroup if biomarker analyses yield conflicting results within one biomarker category or between two biomarker categories; or if biomarkers are entirely missing or if biomarkers of only one category are available and they are not indicative of AD. The MCI-core category is still compatible with the possibility that the patient has underlying AD pathology [1] but no likelihood level can be assigned.

Statistical analysis

The statistical analyses were performed using SPSS v19.0 for Windows (IBM Corp., Somers, NY, USA). The normal distribution of data was checked using the Kolmogorov–Smirnov test. Differences between the MCI subgroups regarding age, education and Mini-Mental-State Examination (MMSE) [11] scores were tested by analysis of variance (ANOVA) or Kruskal–Wallis test; pairwise comparisons were performed using the Scheffe's test or the Mann–Whitney test, as appropriate. χ^2 tests were employed for testing differences regarding sex distribution, presence of the *APOE* $\varepsilon 4$ allele and progression rates to AD dementia. Differences in the hazard rate of progression to AD dementia between the MCI subgroups were analysed using Cox regression models, adjusting for patient characteristics that significantly differed between the groups. Two-sided P values less than 0.05 were considered statistically significant.

Results

The characteristics of the study sample ($N = 397$) are presented in Table 1. The MCI subgroups significantly

Table 1 Description of the study sample

	MCI-high	MCI-intermediate	MCI-unlikely	MCI-core
N	22	31	17	327
Age, years*	73.64 (7.10) [55:87]	75.45 (6.79) [64:86]	71.06 (9.02) [56:86]	75.01 (7.43) [55:90]
Men/women ratio	9:13[#]	14:17[†]	9:8	224:103
Education, years*	15.36 (2.70) [9:20]	14.19 (3.45) [4:20] †	15.18 (3.25) [8:20]	15.86 (2.99) [6:20]
MMSE score*	26.50 (1.74) [24:29]	27.00 (1.84) [24:30]	27.71 (1.80) [24:30]	27.03 (1.77) [23:30]
APOE ε4 carriers	17[#]	19	4[‡¶§]	172
CSF Aβ_{42}, ng/L*	(*N* = 21) 137.05 (17.85) [96.77:171.70]	(*N* = 0)	(*N* = 15) 239.63 (32.07) [194.18:281.91]	(*N* = 164) 159.61 (51.56) [50.66:282.70]
CSF pTau$_{181}$, ng/L*	(*N* = 21) 47.17 (13.18) [25.00:77.00]	(*N* = 0)	(*N* = 15) 16.93 (4.18) [8.00:22.00]	(*N* = 163) 35.56 (17.85) [12.00:115.00]
CSF tTau, ng/L*	(*N* = 21) 151.89 (54.17) [94.69:327.31]	(*N* = 0)	(*N* = 15) 52.72 (16.38) [12.74:71.56]	(*N* = 164) 101.34 (60.10) [18.39:479.13]
Composite FDG PET ROI*	(*N* = 3) 1.28 (0.05) [1.23:1.34]	(*N* = 9) 1.29 (0.05) [1.21:1.37]	(*N* = 2) 1.15 (0.09) [1.08:1.21]	(*N* = 189) 1.21 (0.14) [0.78:1.63]
Cortical PiB-PET SUVR*	(*N* = 2) 2.03 (0.18) [1.90:2.16]	(*N* = 0)	(*N* = 1) 1.18	(*N* = 51) 1.80 (0.40) [1.12:2.45]
Atrophy Rate, 10^{-3}*	(*N* = 14) −24.53 (20.91) [−94.64:−13.45]	(*N* = 15) -21.68 (8.49) [−40.94:−13.71]	(*N* = 9) -4.39 (4.95) [-11.12:4.84]	(*N* = 252) −3.81 (47.50) [-193.24:336.41]
Hippocampal volume, mm^3*	(*N* = 20) 2,932.17 (179.23) [2,513.00:3,230.00]	(*N* = 25) 2,958.54 (231.34) [2,382.00:3,222.00]	(*N* = 14) 3,818.82 (355.89) [3,366.50:4,653.50]	(*N* = 294) 3,256.80 (533.70) [1,735.50:4,640.50]
Duration of follow-up, months	16.36 (8.52) [6:36][#]	17.81 (12.91) [0:36][†]	34.94 (10.44) [12:48][‡¶§]	25.21 (13.94) [0:60]
Time to AD dementia, months	14.12 (5.59) [6:24][#]	15.50 (9.03) [6:36]	NA	20.28 (10.81) [6:60]
Ratio of AD dementia to no AD dementia	17:5[#]	12:15**	0:17[‡¶§]	134:181
Ratio of AD dementia to no AD dementia at 12-month follow-up	10:12[#]	7: 20**	0:17[‡¶]	49:316
Ratio of AD dementia to no AD dementia at 24-month follow-up	17:5[#]	11:16**	0:17[‡¶§]	112:203

* Data presented as mean (SD) [minimum:maximum] as appropriate; *MCI* mild cognitive impairment, *MCI-high* MCI due to AD-high likelihood, *MCI-intermediate* MCI due to AD-intermediate likelihood, *MCI-unlikely* MCI unlikely due to AD, *MCI-core* MCI-core clinical criteria, *AD* Alzheimer's disease, *MMSE* mini-mental state examination, *Aβ42* β-amyloid 1–42, *pTau181* tau phosphorylated at threonine 181, *tTau* total tau, *FDG PET* [18F] fluorodeoxyglucose positron emission tomography, *ROI* region of interest, *PiB-PET SUVR* [11C] Pittsburgh compound B positron emission tomography standardised uptake ratio, *NA* not applicable. Atrophy rate = (Brain volume at 12-month follow-up − brain volume at baseline)/Brain volume at baseline

† Statistically significant differences between MCI-intermediate and MCI-core, $P < 0.05$

‡ Statistically significant differences between MCI-intermediate and MCI-unlikely, $P < 0.05$

§ Statistically significant differences between MCI-unlikely and MCI-core, $P < 0.05$

¶ Statistically significant differences between MCI-high and MCI-unlikely, $P < 0.05$

Statistically significant differences between MCI-high and MCI-core, $P < 0.05$

** Statistically significant differences between MCI-high and MCI-intermediate, $P < 0.05$

differed with regard to education, *APOE* ε4 allele carrier status, sex distribution, and proportion of patients that had progressed to AD dementia (Kruskal–Wallis test $P = 0.036$, Pearson χ^2 $P = 0.007$; 0.003 and <0.001, respectively). Cognitive performance as determined by the MMSE at baseline (Kruskal–Wallis test $P = 0.218$) did not differ between the subgroups. Four patients with MCI-intermediate and twelve with MCI-core were lost to follow-up. Follow-up data of patients diagnosed with AD dementia were not taken into account after a diagnosis of AD dementia had been established. Follow-up periods differed between the MCI subgroups (Kruskal–Wallis test $P < 0.001$, $N = 381$). The time to the diagnosis of AD dementia was significantly different between the subgroups (Kruskal–Wallis test $P < 0.029$, $N = 163$). The results of the pairwise analyses are presented in Table 1.

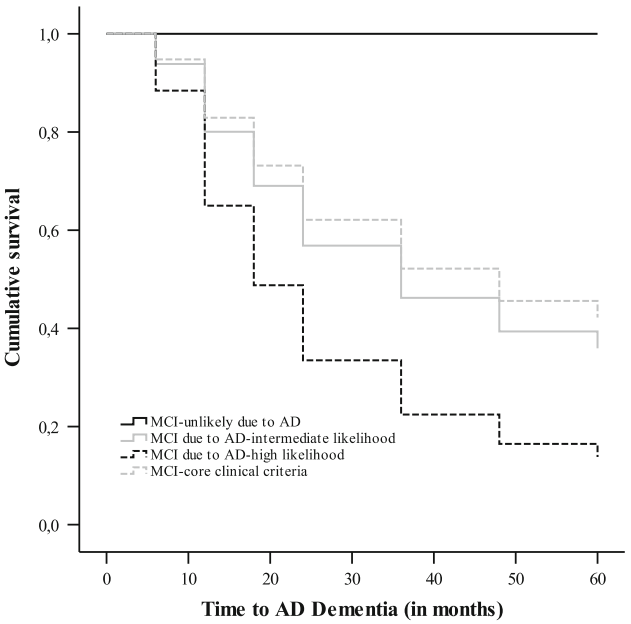

Fig. 1 Cox regression survival curves in patients with mild cognitive impairment (MCI) due to Alzheimer's Disease (AD), according to the NIA-AA research criteria

The Cox regression models included education, presence of the *APOE* ε4 allele, sex, and MCI subgroup as prognostic factors (Fig. 1; Table 2). The risk of progressing to AD dementia was 2.3 times higher in patients with MCI-high compared with the MCI-core subgroup ($P < 0.01$); this means an approximately 82 % elevation in the risk of developing AD dementia after adjustment for the other explanatory variables in the model. Patients with MCI-high tended to have a significantly higher hazard (approximately 0.52 times) to develop AD dementia in comparison with the MCI-intermediate subgroup ($P = 0.08$). No patients in the MCI-unlikely subgroup progressed to dementia within the follow-up period. No further significant differences were detected between the groups ($P > 0.05$). Between the baseline and the 12-month follow-up visits, 17 % of all patients progressed to AD dementia. The proportion of patients who progressed to AD dementia was largest in patients with MCI-high (45 %), followed by MCI-intermediate (26 %) and MCI-core (16 %); the differences in progression rates attained statistical significance ($P < 0.001$, $N = 381$). Between baseline and 24-month follow-up, 77 % of patients with MCI-high, 41 % of patients with MCI-intermediate and 36 % of patients with MCI-core progressed to AD dementia ($P < 0.001$, $N = 381$). Moreover, according to the Cox regression models, carriers of an *APOE* ε4 allele had a 1.8 times higher or a 59 % increase in the hazard of developing AD dementia than non-carriers.

Table 2 Estimates of variables in Cox regression

Variable	Regression coefficient (b)	Standard error SE (b)	*P* value	Estimated hazard	95 % Confidence interval for hazard ratio
MCI subgroups			0.023		
MCI subgroups (0 = MCI-core[a], 1 = MCI-unlikely)	−11.998	140.241	0.932	<0.001	0.000–1.45 × 10^{-117}
MCI subgroups (0 = MCI-core[a], 1 = MCI-intermediate)	0.171	0.306	0.576	1.187	0.651–2.164
MCI subgroups (0 = MCI-core[a], 1 = MCI-high)	0.832	0.269	0.002	2.297	1.355–3.894
MCI subgroups (0 = MCI-high[a], 1 = MCI-intermediate)	−0.660	0.379	0.082	0.517	0.246–1.087
APOE ε4 (0 = ε4 non carriers[a], 1 = ε4 carriers)	0.588	0.172	0.001	1.800	1.285–2.523
Sex (0 = female[a], 1 = male)	−0.177	0.166	0.288	0.838	0.605–1.161
Education	−0.008	0.027	0.769	0.992	0.941–1.046

Patients classified into mild cognitive impairment (MCI) due to Alzheimer's disease (AD) subgroups according to the NIA-AA research criteria and their biomarker profiles

MCI mild cognitive impairment, *MCI-high* MCI due to AD-high likelihood, *MCI-intermediate* MCI due to AD-intermediate likelihood, *MCI-unlikely* MCI-unlikely due to AD, *MCI-core* MCI-core clinical criteria, *AD* Alzheimer's disease, *MMSE* mini-mental state examination

[a] Reference category

Discussion

The present study compared the hazard of developing AD dementia between MCI groups with a different likelihood of underlying AD pathology according to the NIA-AA diagnostic criteria; we report that the risk of future AD dementia increased with the growing probability of AD pathology. The MCI-high subgroup had a significantly higher hazard of progression to AD dementia compared with the MCI-core subgroup and tended to have a significantly higher risk to develop AD dementia than patients with MCI-intermediate, whilst no patients with MCI-unlikely progressed to AD dementia. Hence, classifying patients with MCI according to the probability of underlying AD pathology seems to provide important prognostic information [16]. The detected prognostic differences between the individual subgroups suggest that the NIA-AA diagnostic criteria may provide clinically meaningful information. It is noteworthy that the baseline MMSE scores did not differ across the MCI groups; thus, the different risks of developing AD dementia cannot be simply explained by differences in clinical disease severity. In the present sample, the observed overall progression rate to AD dementia in the first year after the initial visit (17 %) was in line with previous reports on samples recruited in specialised centres [33]. Nonetheless, progression rates observed in community-based cohorts are mostly lower [5, 23].

The mean duration of follow-up differed significantly across the MCI subgroups. Follow-up was shorter in the MCI-high and in the MCI-intermediate subgroups than in the MCI-core group. The MCI-unlikely subgroup had the longest follow-up period. These deviations can be attributed to differences in progression to AD, since follow-up data of patients with MCI who had progressed to AD dementia were not taken into account after a diagnosis of AD dementia had been established. As clearly illustrated by the differences in the time to AD dementia, patients with MCI-high progressed more rapidly compared with MCI-core, whilst the differences in time to AD dementia between the former MCI subgroup and patients with MCI-intermediate did not attain statistical significance.

APOE ε4 allele carrier status is a further factor, affecting the progression to AD dementia. In addition to the prognostic differences between the MCI subgroups, the Cox regression model revealed that the *APOE* ε4 allele was associated with a faster progression of MCI to AD dementia, which is line with previous reports [4]. Patients with MCI carrying the *APOE* ε4 allele seem to have a higher hazard of progressing to AD dementia within a short period of time compared with non-carriers [1, 8].

Accurate prognostic information and reliable risk appraisal are of high clinical relevance. Evidence in support of a high risk of imminent cognitive decline may offer patients with MCI and their relatives the opportunity to plan ahead and may also enable clinicians to anticipate potential management problems. Furthermore, once disease-modifying therapies become available, patients with a high likelihood of AD could be treated at the earliest possible disease stage without the risk of exposing unaffected individuals to potentially harmful side effects [31].

In the current study, biomarker values were dichotomized as either normal or abnormal without taking into account that values close to the cut-off points might be less informative. The interpretation of such borderline biomarker findings and their diagnostic and prognostic impact still remains elusive. Similarly, the relevance of contradicting biomarker findings, such as a positive PiB-PET and a normal CSF Aβ_{42} in the same individual, has yet to be determined. The NIA-AA MCI criteria treat such findings as if the information were not available. This is a viable strategy to exclude unreliable information, but it is also associated with information losses. In addition, different markers of the same type of pathology (for example CSF tau and hippocampal atrophy) are treated as if they represented exactly the same pathomechanism. In fact, distinct biomarkers track different aspects of the AD pathophysiological process, which may or may not evolve simultaneously [18, 29, 42]. Consequently, the diagnostic value of biomarkers may differ according to the disease stage. Therefore, the refinement of biomarker algorithms for the NIA-AA criteria constitutes a further challenge [12].

The small size of both the MCI-high and the MCI-unlikely subgroups in comparison with the other two groups illustrates how rarely all biomarkers either argue for or against the presence of AD pathology. In addition, the largest group of the present study was MCI-core. It consisted of 257 patients in whom biomarker analyses yielded conflicting results within one biomarker category and 12 patients with conflicting results between the biomarker categories, as well as of 16 patients in whom biomarkers were missing and 42 patients with biomarkers of only one category available that were not indicative of AD. The aforementioned categories of patients, who were encompassed within the MCI-core subgroup, did not differ with regard either to demographic variables or to progression to AD dementia between baseline and 12- and 24-month follow-up (data not shown). It is noteworthy that in routine clinical settings more than one biomarker in each category will seldom be obtained due to budgetary restrictions. Cost-effectiveness is of paramount importance for a widespread use of biomarkers in MCI diagnostics and ought to be taken into account in the development of diagnostic criteria.

Biomarker changes considered typical for AD by the NIA-AA criteria are not exclusively observed in patients

with AD pathology, but they have also been detected in other brain disorders such as dementia with Lewy bodies, amyloid angiopathy, or frontotemporal dementia [7, 35, 41]. Otherwise, AD pathology is often not the only reason for cognitive deterioration and the MCI syndrome but other co-pathologies including cerebrovascular changes or the occurrence of Lewy bodies also contribute to the clinical presentation [28]. Therefore, the genesis of AD dementia is probably more complex than suggested by current diagnostic criteria.

The incorporation of biomarkers into the diagnostic process of MCI is recommended for research use only because of lacking standardised operating procedures [1]. For example, the reproducibility of CSF measurements between laboratories is relatively poor [26] and universally applicable standard values are urgently needed [40]. In order to be useful for population-based settings, research will have to be conducted in less selected population samples and diagnostic biomarker thresholds will have to be adjusted accordingly. Nevertheless, the use of the new criteria will contribute to advancing the field to a point where biomarkers can be used in routine clinical care [36].

The present study should be viewed in the light of a number of limitations. The size of the MCI-unlikely and MCI-high groups was relatively small, and some patients were lost before the follow-up, which, however, does not affect the results of the Cox regression model since lost patients are treated as censored cases. The observed tendency of the MCI-high subgroup to have a significantly higher risk to progress to AD dementia compared with MCI-intermediate subgroup may imply that in larger samples statistically significant differences could possibly be detected. Further drawbacks of the present investigation are its retrospective nature and the total absence of CSF biomarker values in patients with MCI-intermediate. However, it should be underscored that according to the NIA-AA criteria the MCI-intermediate group is per definition characterised by an untested biomarker category, whilst the available biomarkers of the other category are indicative of AD. Prospective studies investigating differences in the progression to AD dementia between the four NIA-AA MCI subgroups are warranted. The study also included a sample that had been recruited at specialised university centres; hence, the results may not be readily transferred to the general population. Finally, no pathological verification of the diagnoses was available, but current diagnostic criteria for AD have been proven to be very accurate for populations recruited at specialised centres [30].

To conclude, the new NIA-AA criteria constitute a valuable tool for the stratification of patients with MCI according to the risk of short-term progression to AD dementia, which is crucial both for patient counselling and for the selection of treatment study populations. Nevertheless, a refinement of the way biomarkers are treated within this diagnostic framework is urgently needed to maximise the clinical relevance of the new criteria. In addition to the establishment of standardised procedures, this refinement process will also have to explore the incremental value of different candidate biomarkers.

Acknowledgments Data collection and sharing for this project were funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904). ADNI is funded by the NIA, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Abbott, AstraZeneca AB, Bayer Schering Pharma AG, Bristol-Myers Squibb, Eisai Global Clinical Development, Elan Corporation, Genentech, GE Healthcare, GlaxoSmithKline, Innogenetics, Johnson and Johnson, Eli Lilly and Co., Medpace, Inc., Merck and Co., Inc., Novartis AG, Pfizer Inc, F. Hoffman-La Roche, Schering-Plough, Synarc, Inc., as well as non-profit partners including the Alzheimer's Association and Alzheimer's Drug Discovery Foundation, with participation from the U.S. Food and Drug Administration. Private sector contributions to ADNI are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organisation is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at University of California San Diego. ADNI data are disseminated by the Laboratory for Neuroimaging at University of California Los Angeles. This research was also supported by NIH grants P30AG010129 and K01 AG030514 as well as the Dana Foundation. The sponsors did not have any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The authors wish to thank S. M. Landau PhD and Prof. W. J. Jagust from the Helen Wills Neuroscience Institute of the University of California, Berkeley, USA, for their invaluable advice concerning the application of the new MCI research criteria and for providing information about ADNI image analysis. They also express their gratitude to Dorottya Ruisz for proofreading.

Conflict of interest None.

References

1. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the national institute on ageing-Alzheimer's Association Workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:270–279
2. Alexopoulos P, Grimmer T, Perneczky R, Domes G, Kurz A (2006) Do all patients with mild cognitive impairment progress to dementia? J Am Geriatr Soc 54:1008–1010
3. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E (2011) Alzheimer's disease. Lancet 377:1019–1031
4. Bertram L (2008) The genetics of alzheimer's disease. Handb Clin Neurol 89:223–232
5. Busse A, Bischkopf J, Riedel-Heller SG, Angermeyer MC (2003) Mild cognitive impairment: Prevalence and incidence according to different diagnostic criteria. Results of the leipzig longitudinal study of the aged (leila75+). Br J Psychiatry 182:449–454

6. Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ (2006) An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31:968–980
7. Dickson DW, Kouri N, Murray ME, Josephs KA (2011) Neuropathology of frontotemporal lobar degeneration-tau (FTLD-tau). J Mol Neurosci 45:384–389
8. Drzezga A, Grimmer T, Riemenschneider M, Lautenschlager N, Siebner H, Alexopoulus P, Minoshima S, Schwaiger M, Kurz A (2005) Prediction of individual clinical outcome in MCI by means of genetic assessment and (18)F-FDG PET. J Nucl Med 46:1625–1632
9. Engler H, Forsberg A, Almkvist O, Blomquist G, Larsson E, Savitcheva I, Wall A, Ringheim A, Langstrom B, Nordberg A (2006) Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. Brain 129:2856–2866
10. Falkai P, Moller HJ (2010) Understanding mental disorders from neuronal networks to glial cells and proteomics. Eur Arch Psychiatry Clin Neurosci 260:441–442
11. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198
12. Frisoni GB, Winblad B, O'Brien JT (2011) Revised NIA-AA criteria for the diagnosis of Alzheimer's disease: a step forward but not yet ready for widespread clinical use. Int Psychogeriatr 23:1191–1196
13. Ganguli M, Snitz BE, Saxton JA, Chang CC, Lee CW, Vander Bilt J, Hughes TF, Loewenstein DA, Unverzagt FW, Petersen RC (2011) Outcomes of mild cognitive impairment by definition: a population study. Arch Neurol 68:761–767
14. Gomar JJ, Bobes-Bascaran MT, Conejero-Goldberg C, Davies P, Goldberg TE (2011) Utility of combinations of biomarkers, cognitive markers, and risk factors to predict conversion from mild cognitive impairment to alzheimer disease in patients in the Alzheimer's disease neuroimaging initiative. Arch Gen Psychiatry 68:961–969
15. Grundman M, Petersen RC, Ferris SH, Thomas RG, Aisen PS, Bennett DA, Foster NL, Jack CR Jr, Galasko DR, Doody R, Kaye J, Sano M, Mohs R, Gauthier S, Kim HT, Jin S, Schultz AN, Schafer K, Mulnard R, van Dyck CH, Mintzer J, Zamrini EY, Cahn-Weiner D, Thal LJ (2004) Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. Arch Neurol 61:59–66
16. Heister D, Brewer JB, Magda S, Blennow K, McEvoy LK (2011) Predicting MCI outcome with clinically available MRI and CSF biomarkers. Neurology 77:1619–1628
17. Jack CR Jr, Bernstein MA, Fox NC, Thompson P, Alexander G, Harvey D, Borowski B, Britson PJ, Whitwell JL, Ward C, Dale AM, Felmlee JP, Gunter JL, Hill DL, Killiany R, Schuff N, Fox-Bosetti S, Lin C, Studholme C, DeCarli CS, Krueger G, Ward HA, Metzger GJ, Scott KT, Mallozzi R, Blezek D, Levy J, Debbins JP, Fleisher AS, Albert M, Green R, Bartzokis G, Glover G, Mugler J, Weiner MW (2008) The Alzheimer's disease neuroimaging initiative (ADNI): MRI methods. J Magn Reson Imaging 27:685–691
18. Jack CR Jr, Lowe VJ, Senjem ML, Weigand SD, Kemp BJ, Shiung MM, Knopman DS, Boeve BF, Klunk WE, Mathis CA, Petersen RC (2008) 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment. Brain 131:665–680
19. Jagust WJ, Bandy D, Chen K, Foster NL, Landau SM, Mathis CA, Price JC, Reiman EM, Skovronsky D, Koeppe RA (2010) The Alzheimer's disease neuroimaging initiative positron emission tomography core. Alzheimers Dement 6:221–229
20. Jagust WJ, Landau SM, Shaw LM, Trojanowski JQ, Koeppe RA, Reiman EM, Foster NL, Petersen RC, Weiner MW, Price JC, Mathis CA (2009) Relationships between biomarkers in aging and dementia. Neurology 73:1193–1199
21. Kim S, Swaminathan S, Shen L, Risacher SL, Nho K, Foroud T, Shaw LM, Trojanowski JQ, Potkin SG, Huentelman MJ, Craig DW, Dechairo BM, Aisen PS, Petersen RC, Weiner MW, Saykin AJ (2011) Genome-wide association study of CSF biomarkers a{beta}1–42, t-tau, and p-tau181p in the ADNI cohort. Neurology 76:69–79
22. Landau SM, Harvey D, Madison CM, Reiman EM, Foster NL, Aisen PS, Petersen RC, Shaw LM, Trojanowski JQ, Jack CR Jr, Weiner MW, Jagust WJ (2010) Comparing predictors of conversion and decline in mild cognitive impairment. Neurology 75:230–238
23. Larrieu S, Letenneur L, Orgogozo JM, Fabrigoule C, Amieva H, Le Carret N, Barberger-Gateau P, Dartigues JF (2002) Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. Neurology 59:1594–1599
24. Lopresti BJ, Klunk WE, Mathis CA, Hoge JA, Ziolko SK, Lu X, Meltzer CC, Schimmel K, Tsopelas ND, DeKosky ST, Price JC (2005) Simplified quantification of Pittsburgh compound b amyloid imaging pet studies: a comparative analysis. J Nucl Med 46:1959–1972
25. Martins-de-Souza D (2010) Is the word 'biomarker' being properly used by proteomics research in neuroscience? Eur Arch Psychiatry Clin Neurosci 260:561–562
26. Mattsson N, Andreasson U, Persson S, Arai H, Batish SD, Bernardini S, Bocchio-Chiavetto L, Blankenstein MA, Carrillo MC, Chalbot S, Coart E, Chiasserini D, Cutler N, Dahlfors G, Duller S, Fagan AM, Forlenza O, Frisoni GB, Galasko D, Galimberti D, Hampel H, Handberg A, Heneka MT, Herskovits AZ, Herukka SK, Holtzman DM, Humpel C, Hyman BT, Iqbal K, Jucker M, Kaeser SA, Kaiser E, Kapaki E, Kidd D, Klivenyi P, Knudsen CS, Kummer MP, Lui J, Llado A, Lewczuk P, Li QX, Martins R, Masters C, McAuliffe J, Mercken M, Moghekar A, Molinuevo JL, Montine TJ, Nowatzke W, O'Brien R, Otto M, Paraskevas GP, Parnetti L, Petersen RC, Prvulovic D, de Reus HP, Rissman RA, Scarpini E, Stefani A, Soininen H, Schroder J, Shaw LM, Skinningsrud A, Skrogstad B, Spreer A, Talib L, Teunissen C, Trojanowski JQ, Tumani H, Umek RM, Van Broeck B, Vanderstichele H, Vecsei L, Verbeek MM, Windisch M, Zhang J, Zetterberg H, Blennow K (2011) The Alzheimer's Association external quality control program for cerebrospinal fluid biomarkers. Alzheimers Dement 7:386-395 e386
27. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. Neurology 34:939–944
28. Middleton LE, Grinberg LT, Miller B, Kawas C, Yaffe K (2011) Neuropathologic features associated with Alzheimer disease diagnosis: age matters. Neurology 77:1737–1744
29. Mormino EC, Kluth JT, Madison CM, Rabinovici GD, Baker SL, Miller BL, Koeppe RA, Mathis CA, Weiner MW, Jagust WJ (2009) Episodic memory loss is related to hippocampal-mediated beta-amyloid deposition in elderly subjects. Brain 132:1310–1323
30. Morris JC, McKeel DW Jr, Fulling K, Torack RM, Berg L (1988) Validation of clinical diagnostic criteria for Alzheimer's disease. Ann Neurol 24:17–22
31. Orgogozo JM, Gilman S, Dartigues JF, Laurent B, Puel M, Kirby LC, Jouanny P, Dubois B, Eisner L, Flitman S, Michel BF, Boada M, Frank A, Hock C (2003) Subacute meningoencephalitis in a subset of patients with ad after abeta42 immunization. Neurology 61:46–54

32. Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, Jack CR Jr, Jagust WJ, Shaw LM, Toga AW, Trojanowski JQ, Weiner MW (2010) Alzheimer's disease neuroimaging initiative (ADNI): Clinical characterisation. Neurology 74:201–209
33. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B (2001) Current concepts in mild cognitive impairment. Arch Neurol 58:1985–1992
34. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E (1999) Mild cognitive impairment: clinical characterisation and outcome. Arch Neurol 56:303–308
35. Quigley H, Colloby SJ, O'Brien JT (2011) Pet imaging of brain amyloid in dementia: a review. Int J Geriatr Psychiatry 26:991–999
36. Reiman EM, McKhann GM, Albert MS, Sperling RA, Petersen RC, Blacker D (2011) Alzheimer's disease: implications of the updated diagnostic and research criteria. J Clin Psychiatry 72:1190–1196
37. Ritchie K, Artero S, Touchon J (2001) Classification criteria for mild cognitive impairment: a population-based validation study. Neurology 56:37–42
38. Saykin AJ, Shen L, Foroud TM, Potkin SG, Swaminathan S, Kim S, Risacher SL, Nho K, Huentelman MJ, Craig DW, Thompson PM, Stein JL, Moore JH, Farrer LA, Green RC, Bertram L, Jack CR Jr, Weiner MW (2010) Alzheimer's disease neuroimaging initiative biomarkers as quantitative phenotypes: genetics core aims, progress, and plans. Alzheimers Dement 6:265–273
39. Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, Blennow K, Soares H, Simon A, Lewczuk P, Dean R, Siemers E, Potter W, Lee VM, Trojanowski JQ (2009) Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol 65:403–413
40. Vanderstichele H, Bibl M, Engelborghs S, Le Bastard N, Lewczuk P, Molinuevo JL, Parnetti L, Perret-Liaudet A, Shaw LM, Teunissen C, Wouters D, Blennow K (2012) Standardization of preanalytical aspects of cerebrospinal fluid biomarker testing for Alzheimer's disease diagnosis: a consensus paper from the Alzheimer's Biomarkers Standardization Initiative. Alzheimers Dement 8:65–73
41. Viswanathan A, Greenberg SM (2011) Cerebral amyloid angiopathy in the elderly. Ann Neurol 70:871–880
42. Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, Green RC, Harvey D, Jack CR, Jagust W, Liu E, Morris JC, Petersen RC, Saykin AJ, Schmidt ME, Shaw L, Siuciak JA, Soares H, Toga AW, Trojanowski JQ (2012) The Alzheimer's disease neuroimaging initiative: a review of papers published since its inception. Alzheimers Dement 8(1 Suppl):S1–S68