Prevalence and prognosis of Alzheimer's disease at the mild cognitive impairment stage

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Running title: Comparing diagnostic research criteria

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Abstract

Three sets of research criteria are available for diagnosis of Alzheimer's disease in subjects with mild cognitive impairment: the International Working Group-1, International Working Group-2, and National Institute of Aging-Alzheimer Association criteria. We compared the prevalence and prognosis of Alzheimer's disease at the mild cognitive impairment stage according to these criteria.

1607 subjects with mild cognitive impairment were recruited from 13 cohorts, of whom 766 subjects had both amyloid and neuronal injury markers. We used cognitive test performance and available biomarkers to classify subjects as prodromal Alzheimer's disease according to International Working Group-1 and International Working Group-2 criteria and in the high-Alzheimer's disease-likelihood group, conflicting biomarker groups (Isolated Amyloid Pathology or Suspected Non-Alzheimer Pathophysiology), and low-Alzheimer's disease-likelihood group according to the National Institute of Aging-Alzheimer Association criteria. Outcome measures were the proportion of subjects with Alzheimer's disease at the mild cognitive impairment stage and progression to Alzheimer's disease-type dementia. We performed survival analyses using Cox proportional hazards models.

According to the International Working Group-1 criteria, 850 (53%) subjects had prodromal Alzheimer's disease. Their 3-year progression rate to Alzheimer's disease-type dementia was 50% compared to 21% for subjects without prodromal Alzheimer's disease. According to the International Working Group-2 criteria, 308 (40%) subjects had prodromal Alzheimer's disease. Their 3-year progression rate to Alzheimer's disease-type dementia was 61% compared to 22% for subjects without prodromal Alzheimer's disease. According to the National Institute of Aging-Alzheimer Association criteria, 353 (46%) subjects were in the high-Alzheimer's disease-likelihood group, 49 (6%) in the Isolated Amyloid Pathology group, 220 (29%) in the Suspected Non-Alzheimer Pathophysiology group, and 144 (19%) in the low-Alzheimer's disease-likelihood group. The 3-year progression rate to Alzheimer's disease-type dementia was 59% in the high-Alzheimer's disease-likelihood group, 22% in the Isolated Amyloid Pathology group, 24% in the Suspected Non-Alzheimer Pathophysiology group, and 5% in the low-Alzheimer's disease-likelihood group.

Our findings support the use of the proposed research criteria to identify Alzheimer's disease at the mild cognitive impairment stage. In clinical settings, the use of both amyloid and neuronal injury markers as proposed by the National Institute of Aging-Alzheimer Association criteria offers the most accurate prognosis. For clinical trials, selection of subjects in the National Institute of Aging-Alzheimer Association high-Alzheimer's disease-likelihood group or the International Working Group-2 prodromal Alzheimer's disease group could be considered.

Key words

Alzheimer's disease, mild cognitive impairment, biomarkers, diagnostic criteria, prognosis

Abbreviations

Aβ=Amyloid-beta; APOE=Apolipoprotein E; FDG=^{18}F-fluorodeoxyglucose; HR=Hazard Ratio; IWG-1=International Working Group-1; IWG-2=International Working Group-2; NIA-AA=National Institute of Aging - Alzheimer Association.

Introduction

In recent years three sets of research criteria for diagnosis of Alzheimer's disease in subjects with mild cognitive impairment have been proposed: the International Working Group (IWG)-1 (Dubois *et al.,* 2007, Dubois *et al.,* 2010), IWG-2 (Dubois *et al.,* 2014), and National Institute of Aging-Alzheimer Association (NIA-AA) criteria (Albert *et al.,* 2011). The criteria include biomarkers of Alzheimer's disease pathology to increase the confidence that subjects with mild cognitive impairment have Alzheimer's disease as underlying cause. However, they differ in the definition of mild cognitive impairment and biomarker abnormality (Visser *et al.,* 2012; Panel 1). A direct comparison between the criteria is lacking and it remains unclear which criteria are best to use.

The IWG criteria use the term prodromal Alzheimer's disease for diagnosis of Alzheimer's disease and were designed to serve as research criteria. The IWG-1 criteria require episodic memory impairment and at least one abnormal Alzheimer's disease biomarker. This biomarker can be a topographical marker (i.e. medial temporal lobe atrophy on MRI or parietotemporal hypoperfusion on FDG-PET) or a pathophysiological marker (i.e. decreased CSF Aβ1-42, increased CSF tau, or increased amyloid PET uptake; Dubois *et al.,* 2007, Dubois *et al.,* 2010). The updated IWG-2 criteria require cognitive impairment in any cognitive domain and either both decreased CSF Aβ1-42 and increased tau, or increased amyloid PET uptake (Dubois *et al.,* 2014). These criteria specify two subtypes: typical prodromal Alzheimer's disease if impairment on a memory test is present and atypical prodromal Alzheimer's if only impairment on a non-memory test is present. The NIA-AA criteria use the term mild cognitive impairment due to Alzheimer's disease and were designed for both clinical and research use. They require cognitive impairment in any cognitive domain and abnormal amyloid markers (i.e. decreased CSF Aβ1-42 or increased amyloid PET uptake) or neuronal injury markers (i.e. medial temporal lobe atrophy on MRI, increased CSF tau, or parietotemporal hypoperfusion on FDG-PET). They relate the number of abnormal biomarkers to

the likelihood that mild cognitive impairment is due to Alzheimer's disease (Albert *et al.,* 2011; Panel 1).

Preliminary studies have shown that the IWG-1 and NIA-AA criteria have a fair to good predictive ability for progression to Alzheimer's disease-type dementia in subjects with mild cognitive impairment (Bouwman *et al.,* 2010; Oksengard *et al.,* 2010; Petersen *et al.,* 2013; Prestia *et al.,* 2013). The validity of the IWG-2 criteria has not been tested yet. The aim of the present study is to compare the IWG-1, IWG-2, and NIA-AA criteria on prevalence and outcome of Alzheimer's disease at the mild cognitive impairment stage by means of a large multicenter study.

Material and methods

Subjects

Subjects were recruited from 5 multicenter studies (DESCRIPA (Visser *et al.,* 2008), AddNeuroMed (Lovestone *et al.,* 2009), German Dementia Competence Network (DCN; Kornhuber *et al.,* 2009), the European Alzheimer's Disease Consortium (EADC)-PET (Morbelli *et al.,* 2012), and American Alzheimer's Disease Neuroimaging Initiative (ADNI-1) study (Mueller *et al.,* 2005; Supplemental Text 1) and from 8 centers of the EADC (Amsterdam (van der Flier *et al.,* 2014), Antwerp (Van der Mussele *et al.,* 2014), Brescia (Frisoni *et al.,* 2009), Coimbra (Baldeiras *et al.,* 2008), Gothenburg (Eckerström *et al.,* 2010), Kuopio (Seppälä *et al.,* 2011), Liège (Bastin *et al.,* 2010), Lisbon (Maroco *et al.,* 2011)). If a subject participated in more than one study, we used data from the study with the longest follow-up.

Inclusion criteria of the present study were diagnosis of mild cognitive impairment, availability of at least one of the following biomarkers: Aβ1-42 and tau in CSF, qualitative or quantitative measures of medial temporal lobe atrophy on MRI (visual rating scale (medial temporal lobe atrophy score) or hippocampal volume), or cerebral glucose metabolism on brain FDG-PET; and at

least one clinical follow-up assessment. Exclusion criteria were diagnosis of dementia at baseline or any other vascular, somatic, psychiatric or neurological disorder that might have caused the cognitive impairment.

Clinical assessment

Clinical assessment was performed according to the routine protocol at each site, including a clinical interview, Mini-Mental State Examination scoring, and neuropsychological assessment.

Baseline diagnosis of mild cognitive impairment was made according to the criteria of Petersen *et al.,* 2004. Raw scores on neuropsychological tests were converted to Z-scores at each center. Cognitive impairment was defined as Z-score <-1.5 SD on at least one cognitive test (Supplemental Table 1). Subjects with a Z-score <-1.5 SD on a memory test were classified as having amnestic mild cognitive impairment. Subjects with a Z-score <-1.5 SD on a non-memory test only were classified as having non-amnestic mild cognitive impairment.

Primary outcome measures were the proportion of subjects with Alzheimer's disease at the mild cognitive impairment stage based on the IWG-1, IWG-2, and NIA-AA criteria and progression to Alzheimer's disease-type dementia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (APA, 1994) and National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association criteria (McKhann *et al.,* 1984). Secondary outcome measure was cognitive decline on the Mini-Mental State Examination.

The medical ethics committee at each center approved the study. All subjects provided informed consent.

Biomarker assessment

Biomarker assessment was performed according to the routine protocol at each site. PET scans were rated centrally. We used center-specific cut-offs to define abnormal biomarkers (Supplemental Table 2). Visual assessments of medial temporal lobe atrophy on MRI and cerebral glucose metabolism on FDG-PET were performed by experienced clinicians who were blinded to clinical and CSF biomarker data.

Subject classification

According to the IWG-1 criteria, subjects were classified as prodromal Alzheimer's disease if they had episodic memory impairment and at least one abnormal biomarker. This could be a topographical or pathophysiological marker (Panel 1). Although the IWG-1 criteria recommended a cued recall test to define memory impairment, such tests were not available for most studies and we used non-cued memory tests as well. According to the IWG-1 update of 2010, we defined atypical prodromal Alzheimer's disease as non-amnestic mild cognitive impairment with abnormal biomarkers in a post-hoc analysis.

According to the IWG-2 criteria, subjects were classified as prodromal Alzheimer's disease if they had impairment in memory (typical prodromal Alzheimer's disease) or non-memory domains (atypical prodromal Alzheimer's disease) and abnormal CSF Aβ1-42 and tau biomarkers (Panel 1). In the main analysis we pooled typical and atypical prodromal Alzheimer's disease but we also performed analyses for each subgroup separately.

According to the NIA-AA criteria, we distinguished between amyloid (i.e. CSF Aβ1-42) and neuronal injury markers (i.e. CSF tau, cerebral glucose metabolism on FDG-PET, medial temporal lobe atrophy score or hippocampal volume). Subjects with mild cognitive impairment in any domain were classified in the low-Alzheimer's disease-likelihood group if both amyloid and

neuronal injury markers were normal, in the high-Alzheimer's disease-likelihood group if amyloid and at least one neuronal injury marker were abnormal, and in one of the two conflicting biomarker groups if the amyloid marker was abnormal and neuronal injury markers normal (Isolated Amyloid Pathology group, i.e. IAP) or if at least one neuronal injury marker was abnormal and the amyloid marker normal (Suspected Non-Alzheimer Pathophysiology group, i.e. SNAP; Jack *et al.,* 2012, Petersen *et al.,* 2013, Vos *et al.,* 2013a). Of the subjects who had only one biomarker available, subjects were classified in the intermediate-Alzheimer's disease-likelihood group if the marker that was tested was abnormal and in the uninformative/inconclusive group if the marker was tested normal (Panel 1).

Statistical analyses

Statistical analyses were done with SPSS version 20.0 (Chicago, IL, USA) with significance set at $p<0.05$. Baseline differences between the biomarker subgroups were analyzed using ANOVA for continuous variables and χ^2 tests or logistic regression models for categorical variables. Cox proportional hazards models were used to test the predictive ability for Alzheimer's disease-type dementia. The relation of the criteria with change on the Mini-Mental State Examination was assessed by slope analyses with general linear mixed models including the baseline and last follow-up score. The model was specified with a random intercept and slope and with center as a random effect because this model provided the best -2 Log Likelihood compared with models with simpler covariance structures. All analyses were adjusted for age, gender, education, and center. Additionally, we calculated the sensitivity, specificity, positive and negative predictive value, and Youden index (sensitivity + specificity-1) for Alzheimer's disease-type dementia after 3 years.

Results

Sample demographics

We included 1607 subjects with a mean follow-up of 2.4 (SD 1.3, range 0.5 to 9) years. 1511 subjects had a 1-year follow-up, 1069 a 2-year follow-up, 594 a 3-year follow-up, 170 a 4-year follow-up, 70 a 5-year follow-up, and 44 subjects had a follow-up longer than 5 years. 766 subjects had data on amyloid and neuronal injury markers (CSF Aβ1-42 with CSF tau, medial temporal lobe, or FDG-PET) and 841 subjects had data on only a neuronal injury marker (medial temporal lobe n=698; FDG-PET n=143). Supplemental Tables 3 and 4 show the number of subjects for each biomarker by center and the characteristics for the total sample and separate biomarker groups.

Prevalence and outcome

Table 1 shows the classification and characteristics of subjects according to the criteria and Table 2 shows the outcome according to the criteria classification. 850 (53%) subjects had prodromal Alzheimer's disease according to the IWG-1 criteria, and 308 (40%) subjects according to the IWG-2 criteria, either typical or atypical (Table 1). Subjects with prodromal Alzheimer's disease were more likely to progress to Alzheimer's disease-type dementia (Table 2, Fig. 1) and showed a larger decline on the Mini-Mental State Examination (Supplemental Table 5, Supplemental Fig. 1) than subjects without prodromal Alzheimer's disease.

According to the NIA-AA criteria, of the subjects with amyloid and injury markers available, 353 (46%) subjects were classified in the high-Alzheimer's disease-likelihood group, 49 (6%) in the Isolated Amyloid Pathology group, 220 (29%) in the Suspected Non-Alzheimer Pathophysiology group, and 144 (19%) in the low-Alzheimer's disease-likelihood group (Table 1). Of the subjects with only a neuronal injury marker available, 459 (55%) were classified in the intermediate-Alzheimer's disease-likelihood group and 382 (45%) in the inconclusive group. Subjects in the high-Alzheimer's disease-likelihood group were more likely to progress to Alzheimer's disease-type dementia than subjects in all other groups (Table 2, Fig. 1). When the NIA-AA categories were dichotomized, subjects with high-Alzheimer's disease-likelihood had a higher progression rate compared to subjects in the low-Alzheimer's disease-likelihood and conflicting biomarker groups

and subjects in the high-Alzheimer's disease-likelihood and conflicting biomarker groups had a higher progression rate than subjects in the low-Alzheimer's disease-likelihood group (Supplemental Table 5). The high-Alzheimer's disease-likelihood and intermediate-Alzheimer's disease-likelihood groups showed a larger decline on the Mini-Mental State Examination compared to all other groups (Supplemental Table 6, Supplemental Fig. 1).

Head-to-head comparison of criteria

In the subgroup of subjects with both amyloid and injury markers (n=766), the Cox regression prediction model showed a slightly better fit for the NIA-AA criteria than for the IWG-2 and IWG-1 criteria because the -2 Log Likelihood or deviance (a measure for unexplained variance) was lowest for the NIA-AA criteria (2906 versus respectively 2926 and 2982). Table 3 shows the overlap in classification between the criteria by outcome after 3 years. The requirement of memory impairment for IWG-1 prodromal Alzheimer's disease and the requirement of abnormal CSF Aβ1-42 and tau markers for IWG-2 prodromal Alzheimer's disease resulted in differences in classification compared to the NIA-AA criteria. Furthermore, the NIA-AA conflicting biomarker groups are considered prodromal Alzheimer's disease according to the IWG-1 criteria but not according to the IWG-2 criteria. In subsequent analyses, we dichotomized the NIA-AA criteria in two ways (A: high-Alzheimer's disease-likelihood group versus conflicting and low-Alzheimer's disease-likelihood groups and B: high-Alzheimer's disease-likelihood and conflicting groups versus low-Alzheimer's disease-likelihood group). Table 4 shows that the specificity and positive predictive value were highest for IWG-2, whereas the sensitivity and negative predictive value were highest for NIA-AA (B). NIA-AA (A) showed the highest Youden index.

In the subgroup of subjects with only a neuronal injury marker (n=841), the Cox regression model fit was slightly better for IWG-1 (-2 Log Likelihood 3000) than for NIA-AA (-2 Log Likelihood 3012). The specificity was higher for IWG-1 than NIA-AA (Table 4).

Typical versus atypical Alzheimer's disease

Of the subjects without IWG-1 prodromal AD, subjects with non-amnestic mild cognitive impairment and abnormal biomarkers (atypical prodromal Alzheimer's disease according to the IWG-1 update, n=231) were more likely to progress to Alzheimer's disease-type dementia (3-year progression rate 31%) than subjects with amnestic mild cognitive impairment or non-amnestic mild cognitive impairment with normal biomarkers (n=526, 3-year progression 17%, HR=1.9, 95% CI 1.3-2.7, p<0.0001; Supplemental Fig. 2). Subjects with IWG-2 atypical prodromal Alzheimer's disease (n=49) had a similar progression rate as subjects with IWG-2 typical prodromal Alzheimer's disease (n=259; 3-year progression rate 63 vs. 61%, p=0.78; Supplemental Fig. 2).

Progression to non-Alzheimer's disease dementia

Using the IWG-2 criteria, progression to non-Alzheimer's disease dementia was higher for subjects without prodromal Alzheimer's disease than for subjects with prodromal Alzheimer's disease (Table 1; 3-year progression rate 13% vs. 3%; HR=3.4, 1.3-8.8, p=0.011). Using the NIA-AA classification, progression to non-Alzheimer's disease dementia was higher in the low-Alzheimer's disease-likelihood (3-year progression rate 14%) and Suspected Non-Alzheimer Pathophysiology (3-year progression 13%) groups compared to the high-Alzheimer's disease-likelihood and inconclusive groups (3-year progression both 4%; Table 1; low: HR=3.0, 1.3-6.9, p=0.011 compared to high, HR=2.8, 1.2-6.5, p=0.016 compared to inconclusive; Suspected Non-Alzheimer Pathophysiology: HR=2.6, 1.2-5.6, p=0.013 compared to high, HR=2.5, 1.1-5.3, p=0.021 compared to inconclusive). Using the IWG-1 criteria, no difference in progression to non-Alzheimer's disease dementia was found between subjects without and with prodromal Alzheimer's disease (Table 1; 3-year progression rate 8% vs. 7%; HR=1.2, 0.8-1.9, p=0.35).

Effect of neuronal injury marker

Subject classification based on an amyloid marker in combination with CSF tau or with medial temporal lobe was generally the same (Table 5). Of the subjects with an abnormal amyloid marker and two neuronal injury markers, 29% had only one injury marker abnormal, with tau being more often abnormal than the medial temporal lobe (Table 6). Both these neuronal injury groups had a similar outcome. Subjects with abnormal CSF Aβ1-42 and both abnormal CSF tau and medial temporal lobe atrophy had a higher progression rate to Alzheimer's disease-type dementia than those with only one abnormal neuronal injury marker (68% vs. 36-41%, $p<0.0001$). Similar findings were obtained in subjects with a normal amyloid marker (Table 6).

SNAP characterization

Because the Suspected Non-Alzheimer Pathophysiology (SNAP) group showed a relatively high progression rate to Alzheimer's disease-type dementia, we investigated CSF Aβ1-42 levels between subjects with and without progression by comparing how much Aβ1-42 levels were above the cut-off. Analyses were restricted to subjects for whom biomarkers were analyzed by ELISA (n=185), as the number of subjects with Suspected Non-Alzheimer Pathophysiology for whom biomarkers were analyzed by xMAP was relatively small (n=35). Subjects with Suspected Non-Alzheimer Pathophysiology who progressed to Alzheimer's disease-type dementia had Aβ1-42 levels closer to the cut-off than subjects who did not progress and subjects who progressed to non-Alzheimer's disease dementia (158 [SD 142] above the cut-off vs. 336 [SD 257] and 381 [SD 259] pg/ml above the cut-off, $p<0.0001$; Fig. 2).

Discussion

This is the first large-scale multicenter study to compare the IWG-1, IWG-2, and NIA-AA criteria for prodromal Alzheimer's disease in subjects with mild cognitive impairment. We noted marked

differences between the criteria in Alzheimer's disease prevalence and predictive accuracy for Alzheimer's disease-type dementia.

The IWG criteria were designed to identify individuals with a high probability of having Alzheimer's disease for research purposes. Indeed, we found relatively high progression rates for Alzheimer's disease-type dementia in subjects with prodromal Alzheimer's disease but we found also that a substantial part of the subjects not meeting prodromal Alzheimer's disease criteria progressed to Alzheimer's disease-type dementia. For the IWG-1 criteria, we demonstrated that the high progression rate in subjects without prodromal Alzheimer's disease is likely due to the presence of subjects with non-amnestic mild cognitive impairment with abnormal biomarkers. For the IWG-2 criteria, we demonstrated that this is likely due to the inclusion of subjects with Isolated Amyloid Pathology and Suspected Non-Alzheimer Pathophysiology in this group. A remarkable finding was the similar predictive accuracy of IWG-2 typical and atypical prodromal Alzheimer's disease. This corroborates a previous study (Vos *et al.,* 2013b) and supports the use of non-amnestic mild cognitive impairment as Alzheimer's disease clinical phenotype.

The NIA-AA criteria were designed both for research and clinical purposes. The prognosis of the low, high, and intermediate Alzheimer's disease likelihood subgroups nicely fitted with the proposed terminology.

In the subsample with both amyloid and neuronal injury markers available, differences in sensitivity, specificity, positive predictive value, and negative predictive value between the criteria can be explained by whether one or two biomarkers needed to be abnormal. If both were required to be abnormal (as was the case for IWG-2 and NIA-AA high-Alzheimer's disease-likelihood versus low-Alzheimer's disease-likelihood and conflicting biomarker groups), positive predictive value and specificity were high and sensitivity and negative predictive value low, consistent with previous findings (van Rossum *et al.,* 2012). If one biomarker was required abnormal (as was the case for

IWG-1, NIA-AA high-Alzheimer's disease-likelihood and conflicting biomarker groups versus low-Alzheimer's disease-likelihood group), positive predictive value and specificity were low and sensitivity and negative predictive value high.

In the subsample with only a neuronal injury marker available, the higher specificity for IWG-1 compared to NIA-AA (intermediate-Alzheimer's disease-likelihood group versus inconclusive group) likely reflects the requirement of memory impairment for IWG-1 prodromal Alzheimer's disease. The progression rate to Alzheimer's disease-type dementia in the NIA-AA intermediate-Alzheimer's disease-likelihood group was similar to that of the high-Alzheimer's disease-likelihood group and suggests that many subjects also had abnormal amyloid markers

The relatively high progression rate (~20%) for subjects with Suspected Non-Alzheimer Pathophysiology is intriguing, as the biomarker profile suggests that non-Alzheimer's disease pathology is likely (Petersen *et al.,* 2013). We found that subjects with Suspected Non-Alzheimer Pathophysiology who progressed to Alzheimer's disease-type dementia had CSF Aβ1-42 levels just above the cut-off. This indicates that the Aβ1-42 cut-offs may have been too conservative, although using a more lenient cut-off would also lead to more false positives. Alternatively, it could be that these subjects have comorbidities so that less amyloid pathology is needed to progress to Alzheimer's disease-type dementia. Suspected Non-Alzheimer Pathophysiology could also be an atypical form of Alzheimer's disease with less pronounced amyloid pathology. It is also possible that these subjects have non-Alzheimer's disease pathology with minimal amyloid deposits and are misclassified as Alzheimer's disease-type dementia at follow-up.

Only a small group of subjects was classified in the Isolated Amyloid Pathology group, likely because most subjects with Alzheimer's disease already have neuronal injury at the mild cognitive impairment stage. ~20% of the subjects with Isolated Amyloid Pathology progressed to Alzheimer's disease-type dementia. A previous mild cognitive impairment study did not find any

converters with Isolated Amyloid Pathology, although this could be due to their relatively short follow-up (1 year; Petersen *et al.,* 2013). Studies with longer follow-up are needed to see whether all subjects with Isolated Amyloid Pathology will eventually progress to Alzheimer's disease-type dementia or have some amyloid pathology unrelated to Alzheimer's disease.

Availability of only one biomarker is a common clinical situation. As amyloid assessment is relatively invasive and expensive, often only neuronal injury markers will be measured. In subjects with only injury markers, the prognostic accuracy of the NIA-AA intermediate-Alzheimer's disease-likelihood and inconclusive groups was very similar to that of the IWG-1 groups.

A higher progression rate to non-Alzheimer's disease dementia was found in subjects without IWG-2 prodromal AD compared to those with prodromal AD and in subjects in the NIA-AA low-Alzheimer's disease-likelihood and Suspected Non-Alzheimer Pathophysiology groups compared to the high-Alzheimer's disease-likelihood group. This is in line with what is expected based on the biomarker profiles. In general, the progression rate to non-Alzheimer's disease dementia at follow-up was rather low, which could be because the cohorts were designed to study Alzheimer's disease.

We found that 29% of the subjects with abnormal CSF Aβ1-42 and two neuronal injury markers (CSF tau and MTL) had only one of the injury markers abnormal. This is likely because the neuronal injury biomarkers measure different pathophysiologies and abnormality in one does not always mean that the other is abnormal as well, at least at the MCI stage. Subjects with both injury markers abnormal had higher Alzheimer's disease progression rates compared to those with only one abnormal injury marker in combination with amyloid pathology. This is in line with previous studies (Scott *et al.,* 2010; van Rossum *et al.,* 2012) and suggests that the former group is further in the disease process or has a more aggressive form of Alzheimer's disease.

The lack of standardized biomarker cut-offs is a known drawback in the field. We applied center-specific biomarker cut-offs to correct for possible differences in lab procedures. Use of the same CSF ELISA cut-off for all centers would have led to essentially the same results (Supplemental Table 7). Although the use of predefined cut-offs likely resulted in somewhat lower sensitivities and specificities compared to other studies that used cut-offs defined within the sample, our study may better reflect the real diagnostic accuracy of biomarkers/the criteria.

This study has several limitations. Because the findings were based on memory clinic or research populations, they may not be generalizable to other settings. For some subjects a MRI assessment was not performed or data was not provided to us, although this is normally part of clinical routine. No autopsy data were available, which might have led to misclassification of Alzheimer's disease. Furthermore, we used retrospective data so centers used different cognitive tests and biomarker protocols. While this reflects current clinical practice, it could have introduced variability. Analyses for the largest cohorts separately showed some variability in prevalence and outcome of Alzheimer's disease in subjects with mild cognitive impairment (Supplemental Table 8 and 9). However, as this variability is typically random, pooling data of all centers is likely to balance out on average. Furthermore, as our main aim was to compare the sets of criteria, variability in operationalization will affect each of the criteria similarly. Standardization of cognitive tests and biomarkers will be an important goal to achieve in the future and many initiatives have been started working on this. But even after standardization the criteria may still perform differently in specific settings. Because we used retrospective data, access to tests that measure non-memory domains was limited. Our operationalization of atypical prodromal Alzheimer's disease may therefore not entirely reflect the clinical variants described in the IWG-2 criteria and may be less sensitive to detect atypical cognitive profiles. While the IWG-1 criteria recommended a cued recall test to define memory impairment, such tests were not available for most studies and we used non-cued memory tests as well. New prospective studies should include a wider range of cognitive tests to improve operationalization of the criteria. We used CSF Aβ1-42 as amyloid marker while use of

amyloid-PET could have led to different results and would be interesting in light of the IWG-2 criteria. The major strengths of our study include the large sample size of well-characterized subjects and relatively long follow-up.

Our findings have several implications. While the IWG-1, IWG-2 and NIA-AA criteria for prodromal Alzheimer's disease can all be used to select subjects for therapeutic trials or clinical follow-up as they all predict cognitive decline with reasonable accuracy, a certain set of criteria may be preferred for specific purposes. In clinical trials, a high conversion rate is needed. If both amyloid and neuronal injury markers are available one could best select subjects according to the IWG-2 prodromal Alzheimer's disease group or NIA-AA high-Alzheimer's disease-likelihood group. This means that subjects with any mild cognitive impairment can be included. If only neuronal injury markers are available, the IWG-1 criteria should be considered rather than the NIA-AA criteria because of the higher specificity due to requirement of amnestic mild cognitive impairment for prodromal Alzheimer's disease. In clinical settings, a refined prognosis is needed and exclusion of the disease is important to reassure patients. The NIA-AA criteria will then offer the most accurate prognosis. As Alzheimer's disease at the mild cognitive impairment stage can manifest as non-memory impairment, a broad definition of mild cognitive impairment should be applied.

Isolated Amyloid Pathology and Suspected Non-Alzheimer Pathophysiology are heterogeneous conditions with subgroups progressing to Alzheimer's disease-type dementia and further studies are needed to characterize these subjects' prognosis and underlying pathophysiology.

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Panel 1. Classification according to the IWG-1, IWG-2, and NIA-AA criteria

Criteria	Definition
IWG-1 (2007)	
No prodromal Alzheimer's disease	No memory impairment or normal biomarkers
Prodromal Alzheimer's disease	Memory impairment, at least one abnormal Alzheimer's disease biomarker
IWG-2 (2014)	
No prodromal Alzheimer's disease	Any cognitive impairment, normal CSF Aβ1-42 and/or tau or normal amyloid PET scan[a]
Prodromal Alzheimer's disease	Any cognitive impairment, abnormal CSF Aβ1-42 and tau or abnormal amyloid PET scan[a]
NIA-AA (2011)	
Low-Alzheimer's disease-likelihood group	Any cognitive impairment, normal amyloid and neuronal injury markers
High-Alzheimer's disease-likelihood group	Any cognitive impairment, abnormal amyloid and neuronal injury markers
Conflicting Isolated Amyloid pathology group	Any cognitive impairment, abnormal amyloid and normal neuronal injury marker
Conflicting Suspected non-Alzheimer's disease Pathophysiology group	Any cognitive impairment, normal amyloid and abnormal neuronal injury marker
Intermediate-Alzheimer's disease-likelihood group	Any cognitive impairment, one marker tested[b] and abnormal
Inconclusive/uninformative group	Any cognitive impairment, one marker tested[b] and normal

Amyloid marker=CSF Aß1-42, neuronal injury marker=CSF tau/medial temporal lobe atrophy score/hippocampal volume/FDG-PET, cognitive impairment is defined as Z-score < -1.5 (see methods). [a]In our study, CSF data is used for subject classification; [b]In our study, only neuronal injury markers were tested.

IWG=International Working Group, NIA-AA=National Institute of Aging and Alzheimer's Association, CSF=cerebrospinal fluid, Aß=amyloid beta.

Table 1. Demographics and clinical outcome according to the IWG-1, IWG-2, and NIA-AA criteria

	IWG-1 criteria		IWG-2 criteria		NIA-AA criteria					
	No prodromal Alzheimer's disease	Prodromal Alzheimer's disease	No prodromal Alzheimer's disease	Prodromal Alzheimer's disease	Low Alzheimer's disease likelihood	High Alzheimer's disease likelihood	Conflicting A: Isolated Amyloid Pathology	Conflicting B: Suspected Non-Alzheimer Pathophysiology	Intermediate Alzheimer's disease likelihood	Uninformative /inconclusive
	Normal markers or no amnestic mild cognitive impairment N=757	Amnestic mild cognitive impairment & at least 1 marker + N=850	CSF markers - N=458	CSF markers + N=308	Amyloid - Injury - N=144	Amyloid + Injury + N=353	Amyloid + Injury - N=49	Amyloid - Injury + N=220	Amyloid ? Injury + N=459	Amyloid ? Injury - N=382
Age, y	68.6 (8.7)[P]	71.3 (7.9)	67.2 (8.9)[P]	71.4 (7.6)	62.9 (9.0)[H,A,B,I,U]	71.4 (7.6)[L,A,B,I,U]	66.1 (7.7)[L,H,B,I,U]	69.4 (8.3)[L,H,A,I]	72.8 (7.3)[L,H,A,B,U]	69.0 (8.4)[L,H,A,I]
Female, n	406 (54%)[P]	402 (47%)	206 (45%)	147 (48%)	63 (44%)[U]	165 (47%)[U]	21 (43%)[U]	104 (47%)[U]	223 (49%)[U]	232 (61%)[L,H,A,B,I]
Education, y	10.3 (4.4)[P]	11.2 (4.2)	10.6 (3.9)[P]	11.9 (4.1)	10.5 (3.2)[H]	11.7 (4.3)[L,B,I,U]	11.0 (4.0)	10.5 (4.0)[H]	10.7 (4.4)[H]	10.3 (4.8)[H]
Amnestic mild cognitive impairment, n	357 (47%)[P]	850 (100%)	310 (68%)[P]	259 (84%)	98 (68%)[H,I]	293 (83%)[L,A,B,U]	30 (61%)[H,I]	148 (67%)[H,I]	379 (83%)[L,A,B,U]	259 (68%)[H,I]
Follow-up, y	2.4 (1.3)	2.3 (1.3)	2.4 (1.3)	2.3 (1.2)	2.4 (1.1)	2.3 (1.2)	2.7 (1.5)[I]	2.5 (1.3)[I]	2.2 (1.3)[A,B,U]	2.4 (1.4)[I]
APOE-ε4	218 (37%)[P]	342 (53%)	137 (33%)[P]	190 (66%)	36 (28%)[H,A,I]	207 (63%)[L,A,B,I,U]	22 (46%)[L,H]	62 (32%)[H,I]	144 (51%)[L,H,B,U]	89 (35%)[H,I]
MMSE at baseline	27.5 (2.2)[P]	26.4 (2.3)	27.1 (2.3)[P]	26.2 (2.5)	27.7 (2.3)[H,B,I]	26.2 (2.4)[L,A,B,I,U]	27.6 (1.9)[H,B,I]	26.7 (2.3)[L,H,A,U]	26.7 (2.2)[L,H,A,U]	27.6 (2.2)[H,B,I]
MMSE at last follow-up	26.2 (3.9)[P]	23.3 (4.5)	25.8 (3.9)[P]	22.4 (5.0)	27.0 (3.2)[H,B,I]	22.5 (4.9)[L,A,B,I,U]	26.3 (4.0)[H,I]	25.7 (4.0)[L,H,I]	24.2 (3.8)[L,H,A,B,U]	26.2 (4.0)[H,I]
Progression to Alzheimer's disease-type dementia at last follow-up	134 (18%)[P]	405 (48%)	84 (18%)[P]	186 (60%)	5 (4%)[H,A,B,I,U]	207 (59%)[L,A,B,I,U]	11 (22%)[L,H,I]	47 (21%)[L,H,I]	201 (44%)[L,H,A,B,U]	68 (18%)[L,H,I]
Time to Alzheimer's disease-type dementia, y	2.4 (1.3)	2.3 (1.3)	2.5 (1.7)	2.3 (1.2)	2.9 (1.1)	2.3 (1.2)	3.1 (1.8)	2.6 (1.8)	2.3 (1.3)[U]	2.7 (1.5)[I]
Progression to non-Alzheimer's disease dementia at last follow-up	45 (6%)	40 (5%)	43 (9%)[P]	5 (2%)	15 (10%)[H,U]	10 (3%)[L,B]	2 (4%)	21 (10%)[H,U]	26 (6%)	11 (3%)[L,B]
Diagnosis of non-Alzheimer's disease dementia										
Frontotemporal dementia	15	9	13		7			6	8	3
Lewy body dementia	12	4	7		5			2	8	1
Vascular dementia	7	1	4	1	2	1	1	2	2	1
Parkinson's disease dementia		2	2			1				
Progressive supranuclear	1									1

palsy										
Alcohol related dementia		1	1					1		
Not available	10	23	16	4	1	8	1	10	8	5

Results are mean (SD) for continuous variables or frequency (%). *APOE*=Apolipoprotein E, MMSE=Mini-Mental State Examination (range 0-30), IWG=International Working Group, NIA-AA=National Institute of Aging and Alzheimer's Association. *APOE* genotype was only available in a subgroup of the sample: IWG-1 no prodromal Alzheimer's disease N=593 and prodromal Alzheimer's disease N=641; IWG-2 no prodromal Alzheimer's disease N=410 and prodromal Alzheimer's disease N=289; NIA-AA Low N=128, High N=327, Isolated Amyloid Pathology N=48, Suspected Non-Alzheimer Pathophysiology N=196, Intermediate N=281, Inconclusive N=254. $^{L}p<0.05$ compared to low Alzheimer's disease likelihood, $^{H}p<0.05$ compared to high Alzheimer's disease likelihood, $^{A}p<0.05$ compared to conflicting A group IAP, $^{B}p<0.05$ compared to conflicting B group SNAP, $^{I}p< 0.05$ compared to intermediate Alzheimer's disease likelihood, $^{U}p<0.05$ compared to uninformative/inconclusive group.

Table 2. Alzheimer's disease-type dementia survival probability by the IWG-1, IWG-2 & NIA-AA criteria

	3-year progression rate to Alzheimer's disease-type dementia*	Hazard Ratio** (95% CI)	P-value
IWG-1			
No prodromal Alzheimer's disease	21%	Reference	
Prodromal Alzheimer's disease	50%	3.0 (2.4-3.7)	<0.0001
IWG-2			
No prodromal Alzheimer's disease	22%	Reference	
Prodromal Alzheimer's disease	61%	4.0 (3.0-5.2)	<0.0001
NIA-AA			
Low-Alzheimer's disease-likelihood group	5%	Reference	
High-Alzheimer's disease-likelihood group	59%	14.4 (5.9-35.2)	<0.0001
Conflicting Isolated Amyloid Pathology group	22%	4.6 (1.6-13.2)	0.0050
Conflicting Suspected Non-Alzheimer pathophysiology group	24%	4.7 (1.8-11.9)	0.0011
Intermediate-Alzheimer's disease-likelihood group	49%	10.2 (4.1-25.2)	<0.0001
Uninformative/inconclusive group	21%	3.5 (1.4-8.8)	0.0079

*Estimated 3-year progression (cumulative incidence) rate to Alzheimer's disease-type dementia, **Hazard ratios (95% CI) for progression to Alzheimer's disease-type dementia calculated using Cox regression analyses and corrected for baseline age, gender, education and center. IWG=International Working Group, NIA-AA=National Institute of Aging and Alzheimer's Association.

Table 3. Overlap in subject classification according to the IWG-1, IWG-2, and NIA-AA criteria by outcome after 3 years

		NIA-AA					
		Amyloid and neuronal injury markers (N=766)				Only a neuronal injury marker (N=841)	
		Low Alzheimer's disease likelihood (N=144)	High Alzheimer's disease likelihood (N=353)	Conflicting: Isolated Amyloid pathology (N=49)	Conflicting: Suspected Non-Alzheimer pathophysiology (N=220)	Intermediate Alzheimer's disease likelihood (N=459)	Uninformative/ Inconclusive (N=382)
IWG-1	No prodromal Alzheimer's disease	144 (2%)	60 (45%)	19 (11%)	72 (11%)	80 (19%)	382 (12%)
	Prodromal Alzheimer's disease	-	293 (49%)	30 (23%)	148 (20%)	379 (39%)	-
IWG-2	No prodromal Alzheimer's disease	144 (2%)	45 (42%)	49 (18%)	220 (17%)	NA	NA
	Prodromal Alzheimer's disease	-	308 (49%)	-	-	NA	NA

Results are total number of subjects (% of subjects with Alzheimer's disease-type dementia after 3 years of follow-up).

NA=not applicable, IWG=International Working Group, NIA-AA=National Institute of Aging and Alzheimer's Association.

Table 4. Predictive accuracy of the IWG-1, IWG-2, and NIA-AA criteria for Alzheimer's disease-type dementia after 3 years

Sample	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Youden index
Amyloid & neuronal injury markers					
IWG-1	0.82 (0.77-0.87)	0.47 (0.43-0.51)	0.38 (0.34-0.43)	0.86 (0.83-0.90)	0.29 (0.22-0.35)
IWG-2	0.69 (0.63-0.75)	0.71 (0.67-0.75)	0.49 (0.43-0.55)	0.85 (0.82-0.88)	0.40 (0.33-0.47)
NIA-AA (A) high vs. conflicting/low	0.77 (0.72-0.83)	0.66 (0.63-0.70)	0.48 (0.43-0.53)	0.88 (0.85-0.91)	0.44 (0.37-0.51)
NIA-AA (B) conflicting/high vs. low	0.99 (0.97-1.00)	0.26 (0.22-0.29)	0.35 (0.31-0.39)	0.98 (0.96-1.00)	0.24 (0.20-0.28)
Only a neuronal injury marker					
IWG-1	0.71 (0.64-0.77)	0.63 (0.60-0.67)	0.39 (0.34-0.44)	0.87 (0.83-0.90)	0.34 (0.27-0.41)
NIA-AA inconclusive vs. intermediate	0.78 (0.72-0.83)	0.53 (0.49-0.57)	0.36 (0.31-0.40)	0.88 (0.84-0.91)	0.31 (0.24-0.38)

Results are predictive accuracy for Alzheimer's disease-type dementia after 3-year follow-up according to the criteria for the subgroup with amyloid and neuronal injury markers (n=766) and for the subgroup with only a neuronal injury marker (n=841). For the IWG-1 and IWG-2 criteria, groups are defined as no prodromal Alzheimer's disease versus prodromal Alzheimer's disease. Youden index= sensitivity + specificity-1. IWG=International Working Group, NIA-AA=National Institute of Aging and Alzheimer's Association.

Table 5. Classification based on amyloid marker and CSF tau or medial temporal lobe neuronal injury marker

	IWG-1 criteria		NIA-AA criteria			
	Normal group	Amnestic mild cognitive impairment and at least 1 marker +	Amyloid - Injury -	Amyloid + Injury +	Amyloid + Injury -	Amyloid - Injury +
CSF Aß1-42 & tau, N=766						
Prevalence	327 (43%)	439 (57%)	198 (26%)	308 (40%)	94 (12%)	166 (22%)
Progression to Alzheimer's disease-type dementia at last follow-up	55 (17%)	215 (49%)	12 (6%)	186 (60%)	32 (34%)	40 (24%)
CSF Aß1-42 & MTL, N=544						
Prevalence	240 (44%)	304 (56%)	156 (29%)	191 (35%)	102 (19%)	95 (18%)
Progression to Alzheimer's disease-type dementia at last follow-up	42 (18%)	158 (52%)	14 (9%)	122 (64%)	28 (28%)	36 (38%)

Results are prevalence and progression rate for subject classifications based on CSF Aß1-42 and tau versus CSF Aß1-42 and medial temporal lobe. Aß=amyloid-beta, CSF=cerebrospinal fluid, IWG=International Working Group, MTL=medial temporal lobe, NIA-AA=National Institute of Aging and Alzheimer's Association.

Table 6. Classification based on amyloid marker and two neuronal injury markers

Amyloid marker	Amyloid + (N=286)				Amyloid - (N=258)			
Neuronal injury markers	Tau - MTL -	Tau + MTL -	Tau - MTL +	Tau+ MTL +	Tau - MTL -	Tau + MTL -	Tau - MTL +	Tau+ MTL +
Prevalence within amyloid subgroup	37 (13%)	58 (20%)	25 (9%)	168 (58%)	91 (35%)	65 (25%)	39 (15%)	63 (24%)
Prevalence in total group	37 (7%)	58 (11%)	25 (5%)	166 (31%)	91 (17%)	65 (12%)	39 (7%)	63 (12%)
Progression to Alzheimer's disease-type dementia at last follow-up	12 (32%)	24 (41%)	9 (36%)	113 (68%)	4 (4%)	10 (15%)	5 (13%)	23 (37%)

Results are prevalence and progression rate for subject classifications based on CSF Aß1-42, tau and MTL.

Aß=amyloid-beta, CSF=cerebrospinal fluid, MTL=medial temporal lobe.

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Figure legends

Figure 1. Alzheimer's disease-type dementia survival probability by the IWG-1, IWG-2, and NIA-AA criteria

The graphs represent the Alzheimer's disease-type dementia survival probability according to the IWG-1 (left), IWG-2 (middle), and NIA-AA (right) criteria, adjusted for age, gender, education, and center.

IWG-1: The group without prodromal Alzheimer's disease represents subjects without memory impairment and/or abnormal biomarker(s). The prodromal Alzheimer's disease group represents subjects with memory impairment and at least one abnormal biomarker. IWG-2: The group without prodromal Alzheimer's disease represents subjects with normal CSF Aβ1-42 and/or tau. The prodromal Alzheimer's disease group represents subjects with abnormal CSF Aβ1-42 and tau. NIA-AA: The low-Alzheimer's disease-likelihood group represents subjects with normal amyloid and neuronal injury markers, the high-Alzheimer's disease-likelihood group represents subjects with both abnormal amyloid and neuronal injury markers, the IAP group is a conflicting biomarker group with an abnormal amyloid marker and normal neuronal injury marker, the SNAP group is a conflicting biomarker group with an abnormal neuronal injury marker and normal amyloid marker, the intermediate-Alzheimer's disease-likelihood group represents subjects with an abnormal neuronal injury marker without information on amyloid pathology, the inconclusive group represents subjects with a normal neuronal injury marker without information on amyloid pathology. AD=Alzheimer's disease, IWG=International Working Group, NIA-AA=National Institute of Aging and Alzheimer's Association, IAP=isolated Alzheimer pathology, SNAP=suspected non-Alzheimer pathophysiology.

Figure 2. CSF Aß1-42 levels above the cut-off in the SNAP group by outcome

Results are CSF Aß1-42 levels above the cut-off of subjects with SNAP who had Alzheimer's disease-type dementia, no dementia or non-AD dementia at follow-up. As Aß1-42 cut-offs were different for different studies, we compared the Aß1-42 levels above the cut-off (deviation from the cut-off) and not overall Aß1-42 levels. The bold line represents the mean CSF Aß1-42 levels above the cut-off. AD=Alzheimer's disease, Aß=amyloid beta, SNAP=Suspected Non-Alzheimer Pathophysiology.