

MRI and cerebrospinal fluid biomarkers for predicting progression to Alzheimer's disease in patients with mild cognitive impairment: a diagnostic accuracy study

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ABSTRACT

Objectives: To assess the incremental value of MRI and cerebrospinal fluid (CSF) analysis after a short memory test for predicting progression to Alzheimer's disease from a pragmatic clinical perspective.

Design: Diagnostic accuracy study in a multicentre prospective cohort study.

Setting: Alzheimer Disease Neuroimaging Initiative participants with complete data on neuropsychological assessment, MRI of the brain and CSF analysis.

Participants: Patients with mild cognitive impairment (MCI; n=181) were included. Mean follow-up was 38.9 months (range 5.5–75.9).

Main outcome measures: Diagnostic accuracy of individual instruments and incremental value of entorhinal cortex volume on MRI and p- τ /A β ration in CSF after administration of Rey's Auditory Verbal Learning Memory Test are calculated and expressed as the 'Net Reclassification Improvement' (NRI), which is the change in the percentage of individuals that are correctly diagnosed as Alzheimer or non-Alzheimer case.

Results: Tested in isolation, a short memory test, MRI and CSF all substantially contribute to the differentiation of those MCI patients who remain stable during follow-up from those who progress to develop Alzheimer's disease. The memory test, MRI and CSF improved the diagnostic classification by 21% (95% CI 15.1 to 26.9), 22.1% (95% CI 16.1 to 28.1) and 18.8% (95% CI 13.1 to 24.5), respectively. After administration of a short memory test, however, the NRI of MRI is +1.1% (95% CI 0.1 to 3.9) and of CSF is -2.2% (95% CI -5.6 to -0.6).

Conclusions: After administration of a brief test of memory, MRI or CSF do not substantially affect diagnostic accuracy for predicting progression to Alzheimer's disease in patients with MCI. The NRI is an intuitive and easy to interpret measure for evaluation of potential added value of new diagnostic instruments in daily clinical practice.

INTRODUCTION

Cognitive complaints are common in elderly populations and cognitive impairment and dementia are consistently rated among the

ARTICLE SUMMARY

Article focus

- Although often applied in practice, it is not well known to what extent MRI and cerebrospinal fluid (CSF) analysis improve diagnostic accuracy.
- Reports on diagnostic accuracy of MRI or CSF-analysis in dementia in general do not approach the topic from a pragmatic clinical perspective; the hierarchy of diagnostic information in everyday practice is ignored, importantly limiting the validity of the results for clinical practice.
- An improvement in diagnostic accuracy when adding a new test is often reported as area under the receiver-operator characteristics curve, which is hard to interpret; the Net Reclassification Improvement (NRI) is an attractive and easy to interpret measure for clinicians.

Key messages

- After the administration of a brief test of memory, MRI or CSF does not substantially affect diagnostic accuracy for Alzheimer's disease in patients with mild cognitive impairment.
- The NRI is an intuitive and easy to use measure that takes false-positive and false-negative findings into account when assessing added value of a new diagnostic instrument, thus increasing clinical applicability.

Strengths and limitations of this study

- Major strengths are the well characterised and relatively large sample size and the innovative methodological approach from a radically pragmatic clinical perspective using the NRI.
- Limitations are the selected population in ADNI, reducing the external validity of the results, and a certain degree of incorporation bias affecting the diagnostic accuracy of the memory test.

top concerns by older persons.¹ A timely and accurate diagnosis is important in patients presenting with cognitive complaints. A reliable diagnosis of Alzheimer's disease (AD)

provides a sound basis for counselling, planning of care and initiating symptomatic treatment. Similarly, the exclusion of AD in participants with memory complaints will offer immense relief and it may invite a search for other conditions that sometimes can be treated effectively, such as depression. MRI and cerebrospinal fluid (CSF) biomarkers have been advocated as diagnostic measures for diagnosing or excluding AD.^{2 3}

Studies comparing the discriminative power of diagnostic measures usually rely on statistical analyses that implicitly treat all potential predictors equally and in parallel, for example, by feeding data on all potential new diagnostic instruments into multivariate statistical models.⁴⁻⁷ This approach, however, does not reflect clinical reality very well. Also, other frequently used indices such as ORs or HRs from multivariate models or an area under the curve (AUC) as derived from a receiver-operator characteristics (ROC) curve have little intuitive appeal for physicians. Moreover, clinically relevant and statistically significant associations may not increase the AUC, rendering this measure to be less suitable for the evaluation of improvement of prediction models.^{8 9}

In everyday clinical reality, the order and hierarchy of diagnostic information is pivotal. Some information will be readily available during a first appointment, such as findings on brief cognitive testing in patients with suspected dementia. Other tests, however, will require to schedule new appointments and may be burdensome, invasive (eg, lumbar puncture), costly (eg, MRI) or both (eg, Positron Emission Tomography (PET)). Both clinical dogma and the societal perspective on costs encourage a diagnostic strategy that combines a high yield with low burden and costs.

The aim of the present study was to assess the incremental value of MRI and CSF biomarker analysis after the administration of a simple memory test in the differential diagnosis of patients with MCI. We aim to simulate the clinical reality of the consultation room as best as possible by first establishing diagnostic accuracy for a simple memory test as can be easily applied in daily practice. To quantify the performance of test additions, we use the Net Reclassification Improvement (NRI).¹ The NRI is simply the change in the percentage of individuals correctly diagnosed (as AD or non-AD, in this study) on the basis of any investigation that is added to the diagnostic information, that is, already available.^{9 10}

METHODS

Design and subjects

This is a case-control study within a prospective cohort study to evaluate the incremental value of MRI and CSF-analysis after a brief memory-test. We evaluate the diagnostic test accuracy of these instruments to diagnose which patients with mild cognitive impairment (MCI)

will progress to develop AD within several years. Data are obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://www.loni.ucla.edu/ADNI>; accessed 28 March 2013), a public-private partnership that was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and non-profit organisations. ADNI has the objective to investigate the role of serial MRI, PET, CSF and clinical and neuropsychological assessment in the measurement of the progression of MCI and early AD (see also <http://www.adni-info.org>).

We used data on individuals diagnosed with MCI of whom complete data on memory, MRI and CSF test results were available. At baseline, the diagnosis of MCI was based on the Petersen *et al's* criteria,¹¹ that is, memory complaints corroborated by an abnormal score on the delayed paragraph recall subtest of the Wechsler Memory Scale—Revised, a normal Mini Mental Status Examination score (>23), a Clinical Dementia Rating score of 0.5 and not satisfying consensus criteria for dementia. Participants who used drugs with anticholinergic or narcotic properties were excluded, but the use of a stable dose of cholinesterase inhibitors was allowed. Details on inclusion and exclusion criteria have been published before.^{11 12}

We analysed the diagnostic yield of different tests to differentiate between participants with MCI at baseline who remained stable (N=100) and participants who progressed to AD during follow-up (N=81). Mean follow-up of patients was 38.9 months (5.5–75.9).

Diagnostic tests

We based our analyses on the three most commonly used diagnostic instruments in cognitive impairment: memory tests, MRI and CSF. From the neuropsychological battery obtained in ADNI, we selected immediate recall of Rey's Auditory Verbal Learning Test (RAVLT) as memory test for the following reasons: (1) RAVLT results were not used in ADNI for defining diagnostic groups (in order to avoid circularity). (2) Immediate recall of RAVLT is easy to administer in routine clinical practice. (3) The RAVLT had one of the largest effect sizes in our previous analysis on differential diagnostic test characteristics in different age groups performed in the same dataset.¹³

Structural MRI scans (1.5 T) have been obtained using a standardised protocol described elsewhere and processed using voxel-based morphometry.¹⁴ We selected entorhinal cortex volume (part of the medial temporal lobe) as the best discriminating MRI measure, based on the same previous analysis, which was recently confirmed by others.^{5 13} Since an earlier study did not find significant differences between left and right volumes, we used the mean of left and right.¹⁵

CSF analysis of A β and phosphorylated τ (p- τ) in ADNI has been specified previously.^{16 17} We selected

¹Sometimes also referred to as 'Net Reclassification Index'.

Table 1 Patient characteristics

Characteristic	MCI-stable N=100	MCI-progression N=81
Age (years)	74.1 (7.6)	74.4 (7.4)
Sex (F) (%)	32	38.3
Education (years)	15.9 (3.0)	15.6 (3.0)
MMSE	27.2 (1.7)	26.6 (1.8)

Percentage or mean (SD).

MCI, mild cognitive impairment; MMSE, Mini Mental Status Examination.

one of the CSF-marker profiles ($p\text{-}\tau/A\beta$) that was previously shown to distinguish well between AD and controls and patients with MCI who remain stable versus those who progress to AD.^{4 13}

We have followed the STARD guidelines for the reporting of diagnostic test accuracy studies. Data on the study design, participants and diagnostic test procedures provided by ADNI were of sufficient quality to allow for a diagnostic test accuracy study.¹⁸

Statistical analyses

All test variables were corrected for age, sex and education based on regression weights in the control group as previously described.¹³

For each of the three diagnostic measures (RAVLT, entorhinal cortex volume on MRI and $p\text{-}\tau/A\beta$ in CSF), we then calculated the ROC curves and the respective AUCs. Based on these curves, we selected the cut-off values with the highest value for the combined sensitivity and specificity as a proxy for the optimal cut-off value (Youden index).

First, we performed univariate Cox regression analyses with the time to diagnosis of dementia as the dependent variable, and RAVLT, entorhinal cortex volume on MRI and $p\text{-}\tau/A\beta$ in CSF as covariates, dichotomised at the optimal cut-off values. In the multivariate analysis, we first entered the RAVLT. We then added entorhinal

cortex volume on MRI and $p\text{-}\tau/A\beta$ in CSF using a step-wise forward procedure in order to determine the effect of each variable on the overall performance of the model. We performed the same analyses with RAVLT, entorhinal cortex volume on MRI and $p\text{-}\tau/A\beta$ in CSF as continuous variables.

Since many clinicians find HR from Cox models difficult to interpret and translate into daily practice decisions, we subsequently did the analysis from a clinician's perspective. The percentage of participants with the disease (MCI who progressed to AD) reflects the a priori chance of correct classification, without application of any diagnostic test. Next, the performance of the memory test, MRI and CSF measures were assessed with the NRI which gives the proportion of participants correctly (re-)classified as either control or case. Finally, we recalculated the NRI values for the MRI entorhinal cortex volume and CSF $p\text{-}\tau/A\beta$ ratio following the classification by the RAVLT. All analyses were carried out with PASW V.18.0.

RESULTS

Characteristics of the study sample are specified in table 1. Cognitive impairment in the patients was mild, as expected in an MCI population. Using the Cox regression analysis as a conventional way of analysis, the dichotomised score on the RAVLT, entorhinal cortex volume on MRI and CSF $p\text{-}\tau$ /amyloid ratio, significantly predicted progression to AD (table 2). When entorhinal cortex volume and CSF were added to the model with only the RAVLT, the model significantly improved in its ability of predicting progression to AD (χ^2 14.2, df 1, $p<0.001$ for MRI and χ^2 9.1, df 1, $p=0.003$ for CSF). When using the continuous variables, these results were attenuated and not significant for CSF (χ^2 10.6, df 1, $p=0.003$ for MRI and χ^2 2.6, df 1, $p=0.11$ for CSF).

We subsequently did the analysis using the NRI. Figure 1 shows the ROC curves for the three diagnostic measures. The resulting AUCs and overlapping CIs of

Table 2 Performance of the Cox regression models with the three diagnostic instruments as dichotomised variables (univariate model) and the performance of the models in which entorhinal cortex volume on MRI and $p\text{-}\tau/A\beta$ ratio in CSF were added to the model after performance on the RAVLT (multivariate models)

Diagnostic instrument	HR	95% CI	p Value	Improvement of the model
Univariate model				
RAVLT	4.9	2.5 to 9.5	<0.001	
MRI	2.8	1.8 to 4.4	<0.001	
CSF	2.9	1.7 to 5.2	<0.001	
Multivariate model				
RAVLT+MRI				χ^2 14.2, 1 df, $p=0.001$
RAVLT	4.2	2.2 to 8.3	<0.001	
MRI	2.4	1.5 to 3.7	<0.001	
RAVLT+CSF				χ^2 9.1, 1 df, $p=0.003$
RAVLT	4.1	2.1 to 8.0	<0.001	
CSF	2.3	1.3 to 4.0	0.005	

CSF, cerebrospinal fluid; RAVLT, Rey's Auditory Verbal Learning Test.

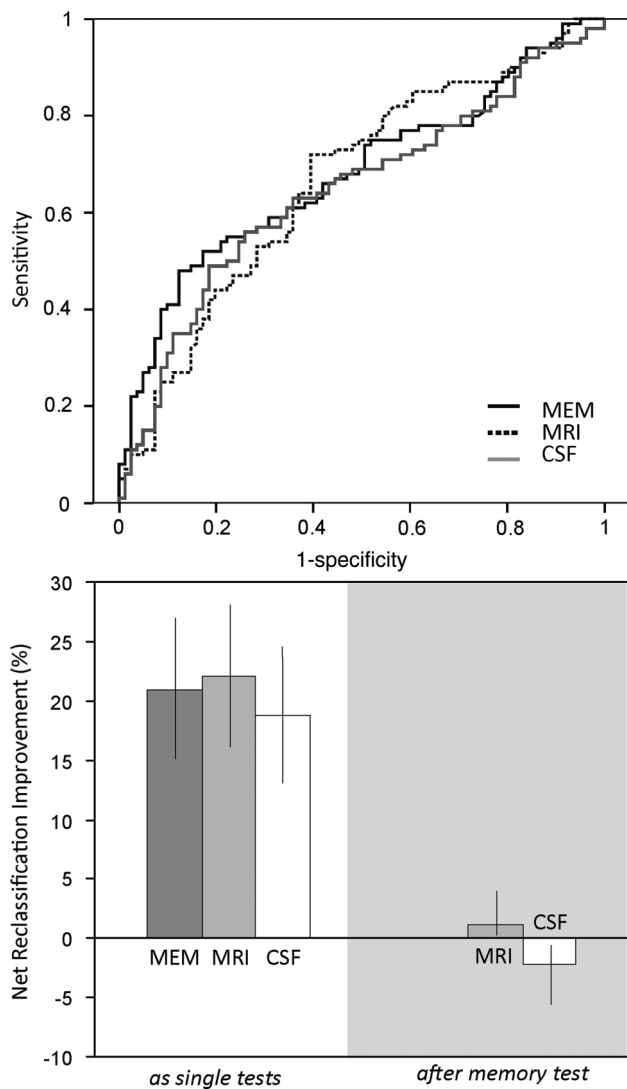


Figure 1 Receiver-operator characteristic-curves (ROC; upper panel) and Net Reclassification Improvements (lower panel) of Rey's Auditory Verbal Learning memory test (RAVLT), entorhinal cortex volume on MRI and p- τ /A β ratio in cerebrospinal fluid (CSF) in participants with mild cognitive impairment (MCI). The upper panel depicts the ROC curves for the RAVLT test of memory (MEM), entorhinal cortex volumetry (MRI) and the p- τ /A β ratio in CSF contrasting MCI participants without progression to dementia on follow up (N=100) and those progression to Alzheimer's disease (N=81). The corresponding area under curves are provided in table 2. The lower panel shows the net reclassification improvement for the same comparisons as a result of performing a single test (left) or on the right, in the grey area, for the MRI and CSF examination, *after* having incorporated the result of memory testing.

the three diagnostic tests illustrate that their performance was largely comparable (table 3).

To calculate the NRIs, the a priori correct classification rates were based on the percentage of participants with the disease for each comparison (table 4). When the NRI for all diagnostic measures is calculated in

isolation, all diagnostic tests substantially improve diagnostic classification (table 4). Participants who were incorrectly reclassified to the wrong diagnostic category are taken into account by this method, thus specifying the resulting *false-positive* and *false-negative* cases following a diagnostic test.

If the same analyses are repeated after first incorporating the RAVLT results, the contributions of entorhinal cortex volume on MRI and p- τ /A β ratio in CSF testing to diagnostic accuracy change dramatically (right panel of figure 1): MRI hardly affects diagnostic accuracy (NRI after MRI is +1.1 (95% CI 0.1 to 3.9), while CSF testing tends to actually *decrease* diagnostic accuracy in this study population as a result of reclassification to the wrong diagnostic category (NRI after CSF biomarker testing is -2.2 (95% CI -5.6 to -0.6). In figure 2, we illustrate this process for reclassification according to MRI and CSF results. MRI often results in false-negative conclusions, that is, in patients who do have AD entorhinal cortex volumes are in the normal range. CSF analysis on the other hand, often elicits false-positive findings.

Explorative analyses using alternative cut-off points for all the three diagnostic tests did not importantly change our findings on the relative strengths of the resulting NRIs, as can be expected since more sensitive cut-offs by definition lead to reduced specificities and vice versa. As expected on the basis of the relative strength of associations between neuroimaging and CSF parameters in the ADNI dataset,^{13 19} the use of other MRI parameters (eg, hippocampal atrophy) or CSF measures (total- τ or A β levels or the total- τ /A β -ratio) did also not importantly affect the results.

DISCUSSION

When considered as single tests, a short memory test, MRI and CSF biomarker analysis all perform at a comparable level, independent of the statistical analysis used. All three diagnostic instruments have AUCs around 0.65 for distinguishing which patients with MCI will progress to AD with an average follow-up of 39 months. However, when MRI and CSF testing are evaluated *after* incorporating the results of a brief test of memory, both diagnostic methods fail to substantially improve diagnostic accuracy when assessed from a clinician's perspective using the intuitive NRI.

Implications for clinical practice and research

Different diagnostic guidelines from both Europe and the USA recommend that all patients with cognitive impairment should undergo structural imaging.²⁰ European guidelines for the diagnosis of AD identify alterations of A β and p- τ in CSF as supportive for the diagnosis.²¹ The recently revised recommendations from the National Institute on Aging-Alzheimer's Association workgroup add some nuance and do not advocate the use of CSF biomarkers for routine diagnostic purposes.²² The present findings suggest that from a pragmatic

Table 3 Area under the curves (AUC) of receiver-operator characteristics curves

	Stable MCI (n=100) vs MCI participants progressing to AD (n=81)	
	AUC	Absolute cut-off value
Memory testing with RAVLT (words)	0.680 (0.603–0.757)	34.59
MRI entorhinal cortex volumetry (ml)	0.666 (0.587–745)	0.41
CSF p- τ /A β ratio	0.646 (0.566–0.727)	0.079

AD, Alzheimer's disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; RAVLT, Rey's Auditory Verbal Learning test.

perspective, neither MRI nor CSF-analysis does importantly increase diagnostic accuracy for progression to AD in MCI patients, if a brief test of memory is administered first. From a societal perspective, this may have important implications, for example, with respect to referral patterns in uncomplicated cases. The role of neuroimaging using CT or MRI does remain undisputed in selected patients with suspected cerebrovascular damage and to rule out surgically treatable conditions, which account for up to 1% of all cases of dementia.^{23 24} Similarly, CSF analysis remains valuable in the occasional patient with an atypical clinical presentation of cognitive impairments who is suspected of (meningo-) encephalitis or prion disease.

Our analysis from a pragmatic clinical point of view does not warrant any conclusion concerning the value of MRI or CSF-analysis for research into disease mechanisms in dementia. Test characteristics of these CSF biomarkers are very different in older persons compared with younger persons.^{13 25} The better CSF test characteristics in early-onset AD may point to a potentially useful indication for CSF analysis in patients with young-onset dementia. Future studies will learn if neuroimaging and CSF studies will live up to the expectations concerning their potential roles in prognostication of disease course or as valid surrogate endpoints in clinical trials of new therapies. However, in general, the effect of biomarker assessments in subsequent studies and daily practice tends to be lower than in the initial reports fuelling current recommendations.^{2 26}

Evaluation of new diagnostic instruments

Gluud and Gluud²⁷ have made a plea for diagnostic test research that investigates if patients really fare better with a new test, after the test characterises of a new diagnostic method have been established. Whereas new drugs are evaluated in the context of available drugs, new diagnostic instruments are frequently evaluated in isolation. Data as presented here that specify how new information affects the diagnostic accuracy based on clinical information from other sources can be a first step towards a more rigorous evaluation of new diagnostic methods. Based on the present findings, it is not very likely that randomisation to a diagnostic routine including MRI and CSF examination will offer important benefits compared with diagnostic evaluation without these measurements in future studies.

Strengths and limitations

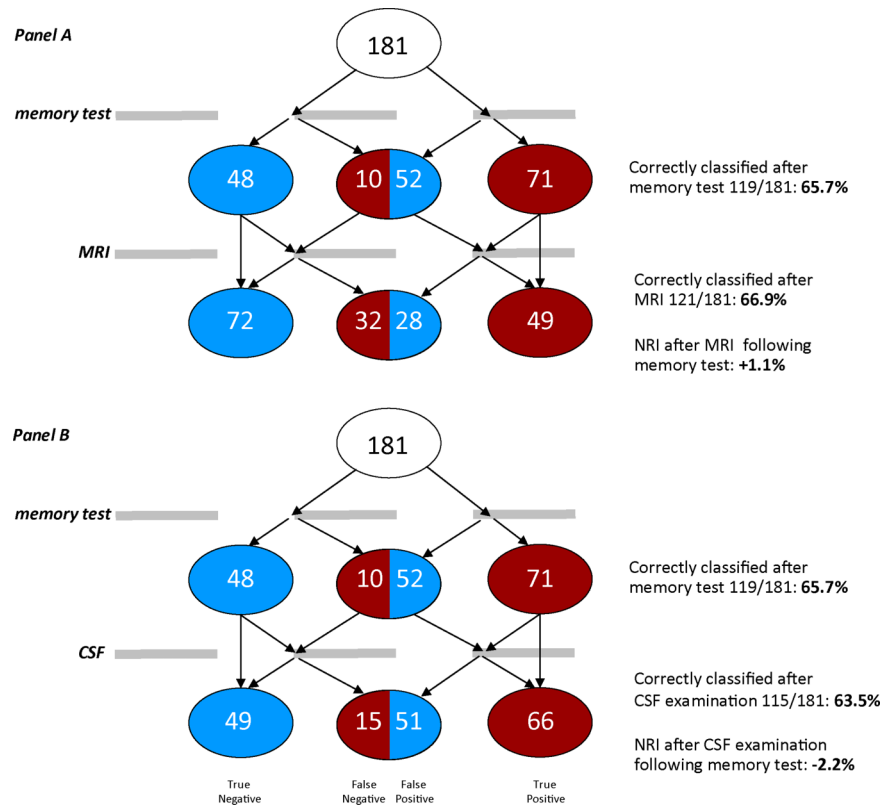
A major strength of our study is that it combines data on clinical characteristics, neuroimaging and CSF biomarkers from a cohort of older persons who were all examined in the same way according to a well-defined protocol. The results of the use of different statistical techniques show largely the same results. In the Cox model, the addition of the entorhinal cortex volume significantly improved the model after incorporating the RAVLT results first, whereas in the NRI the added value of the MRI was negligible, suggesting that smaller entorhinal cortex volume on MRI does contribute significantly to the prediction *how soon* an MCI patient

Table 4 Results of memory testing, neuroimaging and CSF investigations

	Participants with stable MCI vs MCI participants progressing to AD						
	Prior probability of correct classification, before any testing: 44.8%*						
	MCI stable n=100		MCI progression n=81		Posterior probability (%)	NRI (%)	95% CI NRI
True negative	False positive	True positive	False negative				
Memory testing with RAVLT	48	52	71	10	65.7	21.0	15.1 to 26.9
MRI entorhinal cortex volumetry	72	28	49	32	66.9	22.1	16.1 to 28.1
CSF p- τ /A β ratio	49	51	66	15	63.5	18.8	13.1 to 24.5

*The prior probability of correct classification is calculated assuming that all participants progress from mild cognitive impairment (MCI) to AD. AD, Alzheimer's disease; CSF, cerebrospinal fluid; NRI, net reclassification improvement.

Figure 2 Reclassification and Net Reclassification Improvement (NRI) of participants as no progression to Alzheimer's disease (AD) or progression to AD after a basic memory test (Rey's Auditory Verbal Learning memory test) followed by MRI (A) or cerebrospinal fluid (B) Illustration of the effects of memory testing and subsequent MRI on diagnostic classification of a group of 181 participants belonging either to a group of stable MCI patients (blue, N=100) or patients with MCI who progressed to AD during follow-up (red, N=81). For reasons of typographical clarity not all possible changes of diagnostic category are delineated.



progresses to AD, but not much to the *cumulative probability* of progression to AD after the complete observation period, that is, 39 months on average in this study. For CSF, the added value was less clear, since the model using the continuous variables did not significantly improve after adding CSF to the RAVLT results. Although the ADNI database is probably the best prospective dataset currently available in dementia research, it has some important limitations. Owing to its focus on the diagnosis of AD, participants with depression, cerebrovascular disease, major psychiatric disease and alcohol or substance abuse have been excluded while these conditions are certainly relevant to the differential diagnosis in clinical practice.²⁸ This selection limits the external validity of the present results. In daily practice, the single test of immediate recall as used in the present analysis will often be insufficient and a more comprehensive examination of affect and cognition will be required in patients representing a broader spectrum of differential diagnoses.²³ Although the average follow-up of 38.9 months in the MCI group is considerable, progression to AD can still occur after an even longer time-interval. The current hypothesis that CSF changes long precede cognitive impairment could have led to an underestimation of the predictive value of CSF biomarkers, although the predictive value of CSF many years before dementia onset has not been documented to date in patients visiting memory clinics.^{29 30} The amyloid cascade hypothesis holds that AD starts with amyloid deposition decades before dementia symptoms

appear.³¹ This process is revealed by low CSF A β concentrations and high signal in A β scanning with PET. Next, progressive neuronal cell death results in elevated CSF τ concentrations, and in decreased medial temporal lobe (MTL) function and MTL atrophy at neuroimaging. Only in this stage of the process, cognitive impairments are presumed to arise. Given that cognitive symptoms are used to classify people as MCI patients, and given that only part of all MCI cases are due to AD, one would expect that CSF and neuroimaging variables were the better predictors of conversion from MCI to AD, which apparently is not the case in this population.

Another important caveat of the present analysis is that the NRI treats false-positive and false-negative results equally. Depending on the clinical setting, a more sensitive test (also implying more false-positive results) or a highly specific test (with more false-negative findings) may be preferred. The present analysis does, however, provide proof of the general principle that in patients with cognitive complaints, cheap and relatively simple clinical examinations can importantly reduce the incremental value of subsequent invasive, burdensome, expensive and time-consuming technical investigations.

An important concern is the possible circularity in the logic of the presented comparison of diagnostic techniques. Special care was taken that the specific clinical test that was evaluated here, the RAVLT, did not play any role in the final diagnostic classification that was used as gold standard in ADNI. However, a certain degree of incorporation bias is inevitable since participants in ADNI were

selected on having an amnesic disorder. Moreover, in the ADNI cohort exclusion of patients with cerebrovascular disease, space-occupying lesions, evidence of infections or other signs of systemic disease may also have affected the interpretation of MRI and CSF test results. These limitations indicate that the findings of the present analysis should be rigorously tested in the clinical setting of a regular memory clinic.²⁷

Conclusions and future directions

The present results highlight the importance of the order of tests in evaluating individuals with cognitive complaints. After administration of a brief test of memory, MRI or CSF does not substantially improve diagnostic accuracy in patients with MCI. Clinical guidelines for the timely diagnosis of AD have much to gain from considering the incremental value of new tests added to the existing instruments that are widely used, cheap and associated with a low burden for patients. Ultimately, it may stimulate a more individualised approach in the diagnostic evaluation of older persons with cognitive complaints. Independent studies on the diagnostic value and cost-effectiveness of an individualised diagnostic approach in more diverse cohorts with cognitive complaints are warranted.

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Contributors ER and WAvG have carried out all statistical analyses. ER and WAvG have drafted the manuscript. BAS has contributed to the statistical analyses. ER, BAS, PE and WAvG are responsible for the intellectual content. BAS and PE have critically revised the manuscript. All authors had full access to the data and can take responsibility for the integrity of the data and the accuracy of the data analysis. ER is the guarantor of the study. The paper was prepared according to the STARD criteria for diagnostic research papers. All authors have read and approved the final manuscript.

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Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The dataset of ADNI is freely available to scientific researchers under the conditions of ADNI at <http://www.loni.ucla.edu/ADNI>. Participants gave informed consent, data are anonymised and risk of identification is minimal.

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