Running title: Cognitive markers of Alzheimer's disease

Early neuropsychological detection of Alzheimer's disease

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Abstract

Lifestyle modification offers a promising way of preventing or delaying Alzheimer's disease (AD). In particular, nutritional interventions can contribute to decrease the risk of dementia. The efficacy of such interventions should be assessed in individuals thought to be prone to AD. It is therefore necessary to identify markers that may help detecting AD as early as possible. This review will focus on subtle neuropsychological changes that may already exist in the predementia phase, and that could point to individuals at risk of dementia. Episodic memory decline appears consistently as the earliest sign of incipient typical Alzheimer's disease. An episodic memory test that ensures deep encoding of information and assesses retrieval with free as well as cued recall appears as a useful tool to detect patients at an early stage of AD. Beyond the memory domain, category verbal fluency has been shown to decline early and to predict progression to AD. Moreover, in line with current diagnosis criteria for prodromal Alzheimer's disease, combining neuropsychological scores and neuroimaging data allows a better discrimination of future AD patients than neuroimaging or neuropsychological data alone. Altogether, the detection of cognitive changes that are predictive of the typical form of probable Alzheimer's disease already in the predementia stage points to at risk people who are the best target for therapeutic interventions, such as nutrition or physical exercise counseling or dietary interventions.

Keywords: Alzheimer's disease, mild cognitive impairment, neuropsychology, early diagnosis.

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Introduction

Alzheimer's disease (AD) is characterised by severe cognitive deficits, which worsen and affect an increasingly broad range of domains as the disease progresses. Although there exist some atypical forms starting with language, visuospatial or executive dysfunction, the most common syndromic presentation consists in memory impairment together with cognitive dysfunction in at least one other domain (language, reasoning, visuospatial abilities…) (1). Importantly, clinically evident dementia is preceded by a period lasting presumably one or more decades during which amyloid and tau proteins accumulate in the brain (2). Moreover, during the predementia period, cognitive deficits already exist. A recent study suggested that abnormal amyloid deposition could be detected about 17 years, hippocampal atrophy around 4 years, and cognitive impairment 3 years before a clinical diagnosis of Alzheimer's disease is made (3).

Given that neuropathology has reached a critical point when dementia occurs, the predementia period is considered the best target for therapeutic interventions (e.g., (4)). Among possible interventions, besides pharmaceutical treatment, cognitive rehabilitation and lifestyle modifications appear as promising avenues for preventing or delaying dementia onset. In particular, lifestyle modifications, such as nutritional interventions, physical activity training and stimulating leisure activities, have received an increasing interest in recent years. They are thought to contribute to build a reserve allowing individuals to resist longer to Alzheimer neuropathology (5) and to reduce AD risk factors such as hypertension, obesity, diabetes, oxidative stress… For instance, healthy nutritional habits, including the consumption of omega-3-based fatty acids and antioxidant vitamins, seem to reduce the risk of dementia in late life (6-8). Moreover, interventions proposing the adoption of the Mediterranean diet,

sometimes in combination with supplement nutrients, may lead to an attenuation of cognitive decline (9-11). As these promising preventive and/or therapeutic approaches become available, future work should evaluate their efficacy in individuals who are in the predementia phase of Alzheimer's disease.

Currently, research on the detection of the earliest signs of Alzheimer's disease points to several kinds of biomarkers: genetic biomarkers (e.g., APOEε4), neuroimaging biomarkers (e.g., cerebral atrophy, hypometabolism, amyloid deposition), cerebrospinal fluid (CSF) biomarkers (e.g., tau and amyloid levels) and cognitive markers (i.e., neuropsychological measures). In this review, we will focus on cognitive markers that may contribute to early detection of AD and hence to identify the best candidates to therapeutic interventions. It should be noted that the reviewed neuropsychological predictors apply to the typical form of Alzheimer's disease, that is dementia with prominent and initial memory deficits (1).

Review methods

The process of selection of articles is illustrated in Figure 1. Articles dealing with predictors of Alzheimer's disease were searched for by means of an initial Pubmed search with the following criteria and keywords: [(memory AND longitudinal AND Alzheimer's disease) AND (prodromal OR conversion OR preclinical)], [mild cognitive impairment AND (Alzheimer's disease OR dementia) AND neuropsychology AND (prediction OR longitudinal)], and [Alzheimer's disease AND conversion AND neuropsychology]. Further search through the bibliography of reviews and meta-analyses led to 84 additional publications focusing on neuropsychological predictors of dementia. After excluding references related to animal studies, non-Alzheimer dementia, treatment outcomes, cognitively normal individuals with APOE ε4 genotype and depression, we reviewed 216 publications describing work on neuroimaging and/or neuropsychological indicators of

Alzheimer's disease. From these, the current review included those that describe longitudinal assessments (i.e., involving at least 2 neuropsychological assessments over a follow-up period of minimum 1 year) of healthy older subjects or patients with mild cognitive impairment (MCI), with statistics evaluating the predictive power of neuropsychological measures in the discrimination between subjects who progress to Alzheimer's disease and those who remained either cognitively normal or MCI.

Approaches for early neuropsychological detection of dementia

Two main approaches have been used to identify the cognitive markers of future development of Alzheimer's disease, both having in common the reliance on longitudinal assessments of participants. Whereas one approach consists in population-based studies that follow large cohorts of community-dwelling normal older participants, the other focuses on patients with mild cognitive impairment.

Large-scale population studies recruit healthy participants in the community and test them repeatedly with a more or less extensive neuropsychological battery. These longitudinal studies follow the participants for several years (e.g., from 4 years for the Bronx Aging Study (12) to 22 years for the Framingham study (13)). During the course of the follow-up, a proportion of the population develops Alzheimer's disease. It is therefore possible to identify the cognitive functions that were impaired in the prodromal phase in the future AD patients in comparison to participants who remained normal, and hence to picture the chronological sequence of these cognitive impairments (14, 15). Alternatively, researchers can point to the earliest cognitive changes in preclinical AD by detecting the point in time at which the slope of decline in a neuropsychological task becomes steeper in future AD patients than in stable healthy participants (16-18).

In the past fifteen years, research on the predementia stage of Alzheimer's disease has particularly focused on people with MCI. Initial criteria for MCI were the presence of subjective memory complaints and objective memory deficits, without other cognitive impairment, with relatively preserved functioning in daily life and no dementia (19). However, it soon appeared that MCI is a heterogeneous entity and that the different clinical MCI subtypes do not have the same prognosis. In particular, a distinction has been made between the amnestic forms of MCI (aMCI, either single domain if only memory is affected, or multiple domain if other cognitive functions are also deficient) and non-amnestic forms of MCI (single-domain or multiple domain) (20). Given that annual rate of progression to AD among patients with aMCI is much higher than in healthy older people (6.5% versus less than 1%, respectively (21)) whereas non-amnestic MCI patients more frequently progress to non-AD dementia (20), aMCI has been considered as a clinical manifestation of incipient AD or the prodromal phase of AD. Nevertheless, all aMCI patients are not to develop AD dementia symptoms. It is therefore necessary to find specific markers that would indicate whether a patient is likely or not to become demented in the near future. This motivated longitudinal studies that selected groups of MCI patients either in the community or in clinical settings and evaluated them regularly until they develop AD or for follow-up periods that typically vary between 1 year and 4 years. Performance from the initial cognitive assessment is then retrospectively analyzed to find the measure that best discriminates between MCI patients who remained stable throughout the follow-up period and those who progressed to AD.

Other studies have also investigated the issue of cognitive markers of AD in other at-risk people, such as carriers of the APOE ε4 allele (see (22) for a review). The current review will however focus on longitudinal studies in large cohorts from the population and in MCI patients.

Neuropsychological assessments that best predict Alzheimer's disease

Typically, longitudinal assessments of cohorts of healthy older adults or of patients with Mild Cognitive Impairment involve a more or less extensive battery of standard neuropsychological tests. The cognitive domains that are usually evaluated comprise episodic memory (memory for new information personally experienced in a specific context), working memory (to maintain a small quantity of information for a very brief period of time), executive functions (high-order functions that facilitate adaptation to new or complex situations, when highly practiced cognitive abilities no longer suffice), language and semantic memory (such as fluent word retrieval), and visuospatial abilities. Comparison between studies is made difficult because of the variety of tests that have been used, the heterogeneity of the population investigated (in terms of sample size, characterization of MCI patients, follow-up duration), the diversity of the cognitive testing (either several memory tests versus only one, the number of other neuropsychological scores) and the use of different statistical approaches (logistic regression analyses, survival analyses...). Therefore, only general trends can be drawn from current research on the earliest sign of cognitive decline in the predementia stage of Alzheimer's disease.

Among the cognitive domains that are evaluated with standard neuropsychological batteries, episodic memory was consistently identified as the first domain to decline in population-based studies of preclinical Alzheimer's disease (see Table 1). In the majority of longitudinal studies of MCI patients, measures of episodic memory also emerge as the best predictors of progression to AD (23-51). This seems to be true for verbal episodic memory as well as for visual episodic memory, when the latter is evaluated. The memory decline initiates many years before the clinical diagnosis of Alzheimer's disease. For instance, future AD patients may present with subtle episodic memory deficits compared to stable healthy individuals for as long as 9 to 10 years before the emergence of the first clinical symptoms

(13, 15, 52). Furthermore, it has been suggested that, although episodic memory is affected very early, performance plateaus for several years before showing an abrupt decline 2 or 3 years before dementia onset (53).

Standard tests of episodic memory consist in presenting a list of items (e.g., words or pictures) and subsequently evaluating memory for these items by either asking the participants to recall as many studied items as possible or to identify among propositions those items that were studied (recognition). For recall tests, participants may have to retrieve studied items without any support (free recall) or to retrieve studied items on the basis of some cue, such as the semantic category to which the item belongs (cued recall). Several tests assess recall immediately after the study phase (immediate recall) and then again after 20 or 30 minutes (delayed recall). Recall measures are more often cited as good cognitive markers of future AD than recognition scores. Moreover, many population-based studies and MCI follow-up studies point toward the usefulness of scores of delayed recall as excellent predictors of progression to AD (12-15, 23, 25, 34, 36, 39, 41, 43, 45, 47, 48, 54-57).

As mentioned above, the question of which memory test and which measure are the best has currently no definitive answer given the heterogeneity of the tests that have been used in the different studies. Nevertheless, assuming that the different memory tests do not have the same sensitivity and specificity, a few studies have tried to compare the predictive accuracy of several memory tests, in an attempt to find the one that would be particularly appropriate for identifying early AD among MCI patients (27, 37, 42). The Free and Cued Selective Reminding test (and its longer versions avoiding ceiling effects in healthy subjects, the Double Memory test (58) and the RI-48 test in French language (59)) was found to best discriminate between AD or MCI patients and healthy subjects, and also between MCI patients who will progress to AD and MCI patients who will remain stable, when compared to other standard memory tests. In the Free and Cued Selective Reminding test, participants are

shown 16 items (e.g., grapes) presented four at a time on a card. For each card, the participants have to point and name aloud each item after its unique category cue (e.g., fruit) has been provided. When all four items of a card have been identified, immediate cued recall of those four items is tested. Once all four items have been successfully recalled (or for a maximum of three trials), the next card is presented following the same procedure until all 16 items have been studied. After a brief retention interval of 20 seconds, three recall trials are proposed, each consisting of free recall followed by cued recall (e.g., what was the fruit?) for items that have not been spontaneously recalled. After 30 minutes, free and cued delayed recall is assessed. The advantage of the Free and Cued Selective Reminding test (and RI48 test) has been explained by the fact that it provides cognitive support at both encoding and retrieval. Indeed, in these tests, cognitive support consists in controlled encoding of materials by relating the items to their respective semantic category followed by a cued recall test where the categories serve as cues. This would facilitate performance of participants whose main difficulties concern the initiation of memory strategies (e.g., healthy older participants, demented patients with frontal lesion), but not performance of participants who have genuine difficulties with memory encoding and storage (e.g., AD patients) (60, 61). Consistently, cued recall in the Free and Cued Selective Reminding test (as well as Double Memory test and RI48) is better than free recall in differentiating AD from healthy aging and other forms of dementia like fronto-temporal dementia, Huntington's disease or Parkinson's disease (62). Building upon these findings, a revision of the research criteria for MCI has been proposed in order to better define prodromal Alzheimer's disease (63): an episodic memory deficit taking the form of "recall deficit that does not improve significantly or does not normalise with cueing or recognition testing and after effective encoding of information has been previously controlled" is considered the core diagnostic criteria.

The predominance of episodic memory deficits as cognitive markers of incipient typical AD has been interpreted as reflecting the early pathological involvement of the medial temporal lobe in the course of Alzheimer's dementia (64). In line with this view, the cued recall score of the Free and Cued Selective Reminding test was related to medial temporal glucose metabolism (65) and total recall score (i.e., free + cued recall) of the Free and Cued Selective Reminding test was found to correlate with hippocampal volume in patients with Alzheimer's disease (66). Also, tasks like Paired Associates Learning and face-name associative memory, that rely on the hippocampus for encoding relational bounds between pieces of information (67), have a very good discriminative power for detecting MCI patients who will develop AD (24, 26, 44). This is consistent with the idea that hippocampus-dependent tasks are sensitive to early cerebral changes in AD.

As stressed by Gainotti et al. (68), in order to propose an operational criteria of the best neuropsychological predictors of conversion to AD, one needs not only to identify specific memory tests that are the most efficient predictors, but also to define the most appropriate cut-off scores for discriminating at-risk individuals. Ideally, stringent cut-off scores should be used, as stricter measures seem to provide better prediction of conversion (69). As an illustration, in addition to showing the adequacy of the Free and Cued Selective Reminding test as predictor of AD, Sarazin et al. (37) proposed a free recall score of 17/48 (corresponding to the sum of free recall scores for the 3 trials) together with a total score over the three trials of 40/48 as optimal cut-off score to discriminate MCI patients with a high probability of progressing to AD within 36 months (90%).

Beyond the episodic memory domain, poor verbal fluency performance is put forward as a good predictor of future AD in several population-based studies (Table 1) and a few MCI follow-up studies (25, 31, 43, 49). In particular, category verbal fluency (e.g., to provide as many animals exemplars as possible in 2 minutes) predicts significantly progression to AD

(12, 14, 15, 17, 52, 70, 71), while phonemic verbal fluency (e.g., to provide as many words starting with the letter F as possible in 2 minutes) was less frequently identified as a cognitive marker of Alzheimer's disease (57, 72). The relative sequence of the decline of episodic memory and category fluency is controversial, as some studies indicated that memory impairment arises first (14, 15, 17), while another work reported initial disruption of category fluency preceding memory decline by a few years (70). Category fluency tasks are multi-determined, involving mainly semantic memory and executive functions like flexibility and inhibition. So it is not clear whether predementia impairment in these tasks reflect early emergence of executive or semantic difficulties. In favor of an early executive impairment is the observation that category fluency has been found to decline together with a measure of flexibility (Trail Making Test) (14, 17). Moreover, a qualitative analysis of response production during a category fluency task in individuals who were to develop AD 5 years later showed that difficulties concerned switching between subcategories during word production (e.g., to cite farm animals, then insects, birds…) which is an executive ability rather than accessing many items within one subcategory which measures semantic memory storage (73). However, given that an executive decline would also affect phonemic fluency, the semantic account has sometimes been favored (68, 74), notably in light of the severe semantic memory deficits found in MCI patients (74). Moreover, Wilson et al. (18) suggested that semantic memory deficits may even precede episodic memory decline in the predementia period, a finding paralleling the very initial decline of category fluency put forward by Amieva et al. (70).

Other early neuropsychological predictors of AD have also been described, such as visuospatial abilities (57, 71, 75), abstract reasoning (13, 52, 70, 76), recognition memory of objects (48, 77, 78) or short term memory for conjunctions of features (79-81). Even though controlled episodic memory tests and category fluency tasks emerge as the most discriminant

measures that allow pointing at future AD patients, most studies found actually that the predementia stage of AD can involve subtle deficits in a broad range of neuropsychological tests. Indeed, a combination of cognitive measures often provides greater predictive accuracy than a single score (15, 26, 28, 38, 49, 50, 82). Thus, in the face of the variety of measures that was found to be sensitive and specific to early AD, future search for the best predictors should probably consider combination of tasks assessing episodic memory, semantic memory, executive functioning, visuospatial processing and abstract reasoning.

Combining neuropsychology and neuroimaging for prediction of dementia

Current research criteria for MCI due to Alzheimer's disease (83) and the recent recommendations for defining preclinical Alzheimer's disease (84) incorporated biomarkers like cerebrospinal fluid (CSF) measures of amyloid and tau pathology, medial temporal atrophy on MRI images and reduction of glucose metabolism in the temporoparietal and medial posterior cortices or cerebral accumulation of amyloid on PET scans. In this context, it seems advisable to combine several markers of Alzheimer's disease as this may improve prediction accuracy.

Actually, several studies have reported good predictive power for classifying MCI patients as future AD versus stable MCI when using combination of neuropsychological measures and biomarkers (medial temporal atrophy, temporoparietal glucose metabolism, CSF amyloid, cortical thickness) (see Table 2). Some argued that combining neuroimaging and neuropsychological markers improved discrimination accuracy compared to each kind of predictor alone. This was in fact based on mere inspection of classification accuracies. For instance, Visser et al. (85) used logistic regression analyses to assess the predictive power of a memory measure and the manually-drawn volume of the medial temporal lobe to classify subjects with mild cognitive impairment as a function of whether they developed dementia or

not in a 3-year follow-up period. They observed that the highest classification accuracy was obtained by combining the memory score and the medial temporal lobe volume (96%). Memory or cerebral atrophy alone correctly classified respectively 88% and 77% of the patients. In the same vein, in Schmand et al. (47), combining a verbal episodic memory score, hippocampal volume and CSF amyloid measure correctly predicted progression from MCI to AD with an accuracy of 70%, whereas classification accuracy was below 70% for each individual measure. Similarly, Peters et al. (86) indicated that cortical thickness of the anterior cingulate gyrus combined to specific memory measures yielded a classification accuracy of 87.5% in the discrimination between stable MCI versus MCI who developed AD. This was considered more accurate predictions than those based on neuroimaging (75%) or cognitive measures (82.5%) alone.

In an attempt to provide support to this observation, we recently assessed the statistical significance of the improvement in predictive accuracy from individual predictors to combined markers (87). As hypothesized, combining well-known neuropsychological markers of AD (RI48 and verbal fluency scores) and measures of cerebral glucose metabolism (FDG-PET) allowed to discriminate stable and progressor MCI patients significantly better (89%) than using neuroimaging data alone (74%) (permutation test, $p < .001$).

Conclusions

Individuals who will develop Alzheimer's disease present with specific cognitive difficulties several years before any clinical sign of pathology are detected. When they exhibit mild cognitive impairment, it is possible to predict whether they have a high risk of progressing to the typical form of Alzheimer's disease (amnesic presentation) on the basis of performance in some neuropsychological tests. Prediction of AD achieves high sensitivity and specificity for a measure of verbal cued recall following controlled encoding (Free and Cued Selective

Reminding test, RI48). This measure is thought to be particularly sensitive to early hippocampal neuropathological changes in AD and their cognitive consequence, namely a specific deficit of memory encoding and consolidation, as opposed to a deficit in elaborative encoding and retrieval strategies like in normal aging and other forms of dementia. Future AD onset is also well predicted by category verbal fluency scores. These neuropsychological measures significantly improve predictive accuracy when they are added to neuroimaging biomarkers. This finding has been incorporated in recent revisions of diagnostic criteria for the prodromal phase of Alzheimer's disease (63, 83). Thus, specific neuropsychological deficits involving encoding of new information into episodic memory and word retrieval into semantic memory, combined with neuroimaging biomarkers, may allow to point at older individuals with greater risk to develop Alzheimer's disease in coming years. Importantly, these markers alert about an increased *probability* of dementia, but should not be taken as definitive sign of future dementia. As stressed in the revised diagnostic criteria, the combination of neuropsychological profile and biomarkers should be used for research purposes rather than for the sake of clinical diagnosis. Indeed, one of the main goals of detecting at risk individuals is the identification of targets for testing therapeutic interventions that have the potential of attenuating the rate of cognitive decline, such as individualized cognitive rehabilitation programs or modification of lifestyle, including nutritional interventions.

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Conflict of interest

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635

636 Figure captions.

637

638 Figure 1. Selection of reports included in the review.

639

640 Table 1. Population-based longitudinal studies testing for the cognitive measures that predict
641 future development of Alzheimer's disease.

Study	Cohort name	N	Follow-up duration	Earlier emerging cognitive impairments
Masur et al. (1994) (12)	Bronx Aging Study	317 (64)	4 years	Verbal and visual episodic memory, working memory, category fluency (2 years before diagnosis)
Linn et al. (1995) (88)	Framingham study	1045 (55)	13 years	Verbal episodic memory, working memory
Jacobs et al. (1995) (76)	North Manhattan Aging Project	443 (41)	4 years	Verbal episodic memory, language, abstract reasoning
Howieson et al. (1997) (54)		139 (16)	5 years	Verbal episodic memory (2.8 years before diagnosis)
Small et al. (1997) (72)	Kungsholmen project	205 (26)	3 years	Verbal and visual episodic memory; phonemic fluency (3 years before diagnosis)
Small et al. (2000) (55)	Kungsholmen project	532 (73)	6 years	Verbal episodic memory (6 years before diagnosis)
Elias et al. (2000) (13)	Framingham Study	1043 (106)	22 years	Verbal episodic memory and abstract reasoning (10 years before diagnosis)

Grober et al. (2000) (61)	Einstein Aging Study	264 (32)	10 years	Verbal episodic memory (5 years before diagnosis)
Chen et al. (2000) (56)	Monongahela Val-ley Independent Elders Survey	603 (120)	10 years	Verbal episodic memory, executive function (1.5 year before diagnosis)
Chen et al. (2001) (89)	Monongahela Val-ley Independent Elders Survey	551 (68)	10 years	Verbal episodic memory and executive function (decline between 3.5 and 1.5 years before diagnosis)*
Hall et al. (2001) (16)	Bronx Aging Study	488 (75)	19 years	Verbal episodic memory (7-8 years before diagnosis); Performance IQ (2 years before diagnosis)*
Bäckman et al. (2001) (90)	Kungsholmen project	120 (15)	6 years	Verbal episodic memory (6 years before diagnosis)
Saxton et al. (2004) (14)	Cardiovascular Health Study	693 (72)	8 years	Verbal and visual episodic memory (5-8 years before diagnosis); category fluency and executive function (3.5-5 years before diagnosis)
Rapp et al.	Berlin Aging	187 (15)	4 years	Attention, executive

(2005) (91)	Study			function, verbal episodic memory
Tierney et al. (2005) (15)	Canadian Study of Health and Aging	5-years: 551 (77) 10 years: 263 (47)	5 and 10 years	5 years before diagnosis: verbal episodic memory, category fluency, information. 10 years before diagnosis: verbal episodic memory
Amieva et al. (2005) (52)	PAQUID	1255 (215)	9 years	Visual episodic memory, category fluency, abstract reasoning, global cognition (9 years before diagnosis)*
Amieva et al. (2008) (70)	PAQUID	3777 (350)	14 years	Category fluency; abstract reasoning (12 years before diagnosis)*
Grober et al. (2008) (17)	Baltimore Longitudinal Study of Aging	1006 (92)	15 years	Verbal episodic memory (7 years before diagnosis); executive function (2-3 years before diagnosis)*
Johnson et al. (2009) (92)		444 (134)	25 years	Visuospatial function (3 years before diagnosis), global cognition (2 years), memory (1 year)*
Auriacombe et al. (2010) (93)	3C study	1160 (60)	5 years	Verbal episodic memory

Wilson et al. (2011) (18)	Religious Orders Study & Rush Memory and Aging Project	2071 (462)	16 years	Semantic memory, working memory (6 years before diagnosis)*
Riley et al. (2011) (71)	UK-ADC	121 (32)	7.5 years	Constructional praxis, verbal episodic memory, category fluency*
Rabin et al. (2012) (94)	Einstein Aging study	627 (48)	12 years	Verbal episodic memory
Schmid et al. (2013) (57)	BASEL	825 (29)	13 years	Verbal and visual episodic memory, verbal fluency, visuospatial ability

642 N. Number of participants (number of progression to AD). AD. Alzheimer's disease.

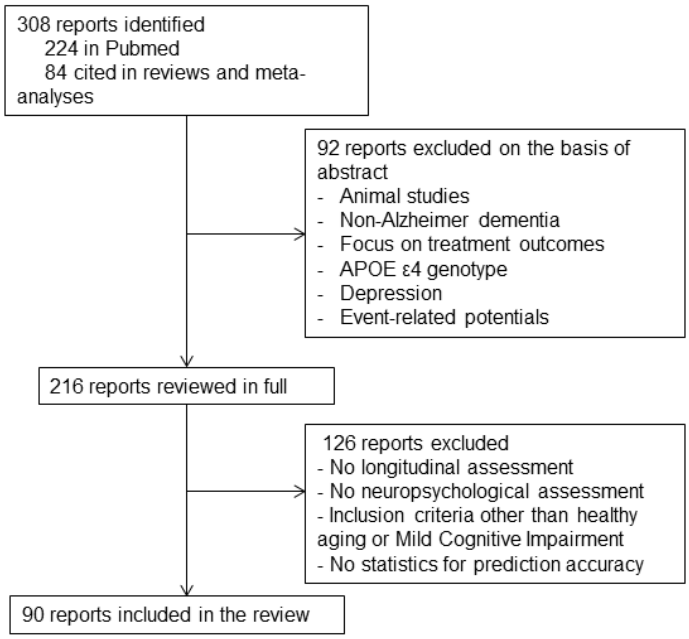
643 * Analysis of change point (time at which the rate of decline changes).

644 Table 2. Predictive accuracy of cognitive measures, neuroimaging or CSF biomarkers, and
645 combination of markers for detecting progression to AD in longitudinal studies of MCI
646 patients.

Study	N	Follow-up duration	Measures	Classification accuracy
Visser et al. (1999) (85)	27 (9)	3 years	- Episodic memory	88 %
			- MRI	77 %
			- Neuropsychology + MRI	96 %
Arnaiz et al. (2001) (75)	20 (9)	3 years	- Visuospatial ability	65 %
			- FDG-PET	75 %
			- Neuropsychology + FDG-PET	90 %
Borroni et al. (2006) (95)	31 (18)	2 years	Neuropsychology battery + SPECT	77.8 %
Devanand et al. (2008) (82)	148 (39)	3 years	- Neuropsychology battery	89.6 %
			- MRI	80.5 %
			- Neuropsychology + MRI	92.5 %
Gomar et al. (2011) (96)	320 (116)	2 years	- Neuropsychology battery + MRI	71.9 %
Venneri et al. (2011) (97)	25 (11)	3 years	Neuropsychology battery + MRI	Sensitivity 91 %
Schmand et al. (2012) (47)	175 (81)	1.6 years	- Neuropsychology battery	64 %
			- MRI	66 %
			- CSF	63 %
			- FDG-PET	57 %

			- Neuropsychology + MRI + CSF	70 %
			- Neuropsychology + MRI + CSF + FDG-PET	65 %
Peters et al. (2014) (86)	40 (18)	2 years	- Neuropsychology battery	82.5 %
			- MRI	75 %
			- Neuropsychology + MRI	87.5 %
Segovia et al. (2014) (87)	46 (26)	3 years	- Neuropsychology battery	85 %
			- FDG-PET	74 %
			- Neuropsychology + FDG-PET	89 %

N. Number of MCI patients (number of patients who progressed to AD). MRI. Measure of cerebral grey matter volume or cortical thickness. FDG-PET. Measure of cerebral glucose metabolism. SPECT. Measure of cerebral perfusion. CSF. Measure of tau and Aβ1-42 levels in CSF.


308 reports identified
224 in Pubmed
84 cited in reviews and meta-analyses
92 reports excluded on the basis of abstract
- Animal studies
- Non-Alzheimer dementia
- Focus on treatment outcomes
- APOE ε4 genotype
- Depression
- Event-related potentials
216 reports reviewed in full
126 reports excluded
- No longitudinal assessment
- No neuropsychological assessment
- Inclusion criteria other than healthy aging or Mild Cognitive Impairment
- No statistics for prediction accuracy
90 reports included in the review

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