Predictors of Alzheimer type dementia in subjects with mild cognitive impairments

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Voor Astrid

Altijd even bukken voordat we bloemen plukken (Toon Hermans)

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Prologue 0

CASE HISTORY

A 68-year old man A. was referred to a memory clinic by his physician because his wife complained that he forgot a lot of things. She was afraid that her husband was becoming demented. During the interview at the memory clinic, it appeared that A. himself had no problems at all. He had retired 5 years earlier and kept himself busy with many hobbies. He sang in the church choir and worked in the garden, although he had recently stopped playing bridge (too tiresome). He still went shopping and cooked every other day. His wife, however, remarked that the dinner did not taste as good as it used to. She said that he often went into the cellar to fetch something but came back with something else. He sometimes forgot who had visited him several days earlier. His wife considered her husband to be more introvert and sometimes a little sad, but he had also had these phases in the past. She hoped that some diagnosis could be made to take away her uncertainty.

The clinician at the memory clinic went through some clinical rating scales with the following results: the score on the Mini-Mental State examination (MMSE) was 28 out of 30 (he missed the day of the month and one word on the delayed recall item); the stage on the Global Deterioration Scale was 3 (mild cognitive impairment); and the score on the Hamilton Depression Rating Scale was 10 (mild depression). The clinician concluded that dementia was not present. He was uncertain, though, whether the cognitive complaints were the result of normal aging or depressed mood, or whether they were a very early manifestation of Alzheimer's disease. He wondered what to do next. Which diagnostic procedures would be helpful to make a stronger diagnosis?

The clinician decided to refer A. to a radiologist for an MRI scan of the brain and to a neuropsychologist for a neuropsychological examination. The following results were obtained. The radiologist reported on the basis of the MRI scan: 'no atrophy, no mass lesions'. The neuropsychologist remarked: 'A. is a friendly man, looks somewhat younger than his calendar age. Highly educated (university). He cooperates well but considers some of the tests as tiresome. His memory problems can partly be objectified: performance on the delayed recall of a word list is below the 10th percentile, while immediate recall and learning are good; recall of a story is unimpaired. The performance on tests assessing mental speed is variable but within

normal limits. High performance for the Trail-Making-Task, low performance on the Memory Scanning Task. Some suspectibility for interference (Stroop Color Word Test card 3). No language impairments. IQ is 130 (above average). Conclusion: impairment of delayed recall. This may be an early manifestation of Alzheimer's disease, but it can also be secondary to the depressed mood. Retest warranted after 1 year.'

The clinician made the diagnosis of aging-associated cognitive decline with a possible contribution of the depressed mood. A. and his wife were reassured that at present there was no dementia. The cognitive impairments may have been related to the depressed mood. He made an appointment for over 12 months.

After 12 months the situation at home was stable, although A. had made some errors in his handling of financial affairs. The MMSE score was 27. The neuropsychological examination revealed improvement of the delayed recall, a decline on some tests of cognitive speed and fluency, and an IQ of 125. No follow-up appointment was made.

After 36 months the wife of A. made a new appointment. Her husband forgot almost everything. He had stopped cooking meals and would sit for hours in front of the television even if there were no programs on it. The neuropsychological examination revealed deterioration on all cognitive measures. The diagnosis of probable AD type dementia was made.

Several questions arise from this case history:

- could AD not have been foreseen in this subject?
- which other diagnostic procedures would have improved the diagnosis at the first visit?
- was it likely that the cognitive impairment in this subject was related to the depressed mood?

These clinical questions formed the basis for the research described in this book.

Introduction 1

1.1 THE PRECLINICAL PHASE OF ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common type of dementia (Ott et al., 1995). The prevalence of AD in the general population increases with age: it is 0.2% in subjects between 55 and 64 years old, 0.9% in subjects between 65 and 74 years old, 7.4% in subjects between 75 and 84 years old, and 26.8% in subjects older than 85 years (Ott et al., 1995). The characteristic brain abnormalities in AD are beta amyloid deposits ('plaques') and abnormally phosphorylated tau protein ('tangles'). The diagnosis of AD is made usually according to the criteria of the NINCDS-ADRDA Work Group (McKhann et al., 1984). These criteria require that the subject is demented. Dementia is a clinical syndrome of multiple cognitive impairment that is severe enough to interfere with the activities of daily living (APA, 1994; WHO, 1992). Before the stage of dementia is reached, however, there is a period of 5 to 13 years in which the subject already experiences mild cognitive impairment that does not meet the criteria of dementia (Almkvist et al., 1998; Didic et al., 1998; Linn et al., 1995; Voskuil, 1999) (figure 1.1). This period is called the preclinical phase of AD (Almkvist et al., 1998; Bondi et al., 1994; Fabrigoule et al., 1998; Grober et al., 1997; Hock, 1998; Jacobs et al., 1995; Linn et al., 1995).[1]

An important challenge to psychogeriatricians is to identify subjects with developing AD in the preclinical stage of the disease. There are several reasons why this is of great interest. First, subjects in the preclinical stage of AD may benefit from drugs that have been shown to improve cognition in subjects with AD (Knapp et al., 1994; Rogers et al., 1998). Other drugs, which may slow down the progression of AD, such as antioxidants (Pitchumoni et al., 1998; Sano et al., 1997), non-steroidal anti-inflammatory drugs (Rogers et al., 1993), or estrogens (Felician et al., 1999), are probably most effective in the very earliest stages of AD. Second, subjects and their caregivers may benefit from counseling on how to handle the cognitive impairment. These psychosocial interventions can be particularly useful when they are administered early. It is also important for subjects with mild cognitive impairment to receive a prognosis with regard to their outcome. This may bring relief,

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[1] Synonyms are the subclinical (Persson et al., 1991), predementia (Reifler, 1997), subsyndromal, or prodromal phase of AD (Verhey, 1993). Some authors use the term 'preclinical' to refer to the period in which there are no clinical manifestations of cognitive impairment (Katzman, 1993). The term 'preclinical' used here, however, refers to the period before the clinical diagnosis of dementia is made but after the first clinical manifestation of cognitive impairment.

may end uncertainty about their cognitive impairment, and may give opportunities to anticipate the future (Robinson et al., 1998; Verhey, 1993).

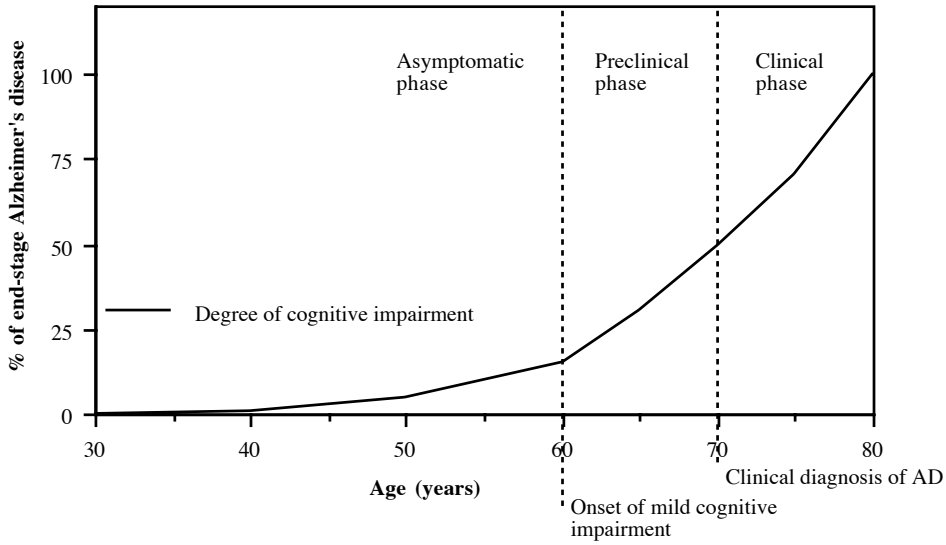

Figure 1.1 Hypothesized course of development of cognitive impairment in a subject with clinical diagnosis of AD at age 70.

1.2 PROBLEMS IN RECOGNIZING THE PRECLINICAL PHASE OF ALZHEIMER'S DISEASE

A major clinical problem is that although the preclinical stage of AD is characterized by mild cognitive impairment, not all subjects with mild cognitive impairment will progress to develop dementia (table 1.1). This diagnostic problem was illustrated in the case history in the prologue. The weighted percentage of mildly impaired subjects that progres to dementia is 31% (range 5-82%) (table 1.1). The differentiation between mildly cognitively impaired subjects with and without preclinical AD is an important clinical problem because many elderly people experience mild cognitive impairment. The prevalence of mild cognitive impairment varies from 6% to 85% (average 38%) in memory or dementia clinics (Ames et al., 1992; Bayer et al., 1987; Heuft et al., 1997; Kelly et al., 1995; Kopelman et al., 1996; Reding et al., 1985; Swanwick et al., 1996; Verhey et al., 1995; Walstra et al., 1992; Weiner et al., 1991), and from 1.5% to 27% in the general population (Graham et al., 1997; H-

änninen et al., 1996; Schröder et al., 1998). The main difficulty in predicting dementia in subjects with mild cognitive impairment is that the pathological hallmarks of AD, plaques and tangles, can not be visualized during life, and thus can not be used to predict dementia for that reason. The approaches that have been used to predict outcome in subjects with mild cognitive impairment have several limitations. First, the inclusion and exclusion criteria of studies investigating preclinical AD were often not well validated. For example, studies that excluded subjects with depression also excluded a substantial number of subjects with preclinical AD because depression is common in the early phase of AD (Devanand et al., 1996; Verhey, 1993; Verhey et al., in press). Similarly, studies that only included subjects with memory impairment may have missed a substantial number of subjects with preclinical AD who had no memory impairment. In order to formulate valid inclusion and exclusion criteria, studies are needed that describe the clinical characteristics of subjects with preclinical AD, but there are no such. Second, most studies that investigated predictors of dementia in subjects with mild cognitive impairment used a monodisciplinary approach and focussed on either cognitive symptoms, non-cognitive symptoms, brain abnormalities, genetic markers, or functional impairment, but not on a combination of these factors. This monodisciplinary approach often resulted in a low sensitivity and specificity for identifying subjects with preclinical AD.

From the above it can be concluded that multidisiciplinary studies are needed that describe the clinical characteristics of preclinical AD and the predictors of AD in subjects with mild cognitive impairment.

1.3 TERMINOLOGY

AD refers to a pathological process in the brain. In clinical practice, however, the term AD is used to describe a patient with dementia who fulfills the NINCDS-ADRDA clinical criteria of probable or possible AD. About 90% of the subjects who fulfill these criteria indeed have AD pathology in the brain on postmortem examination (Galasko et al., 1994; Klatka et al., 1996). In this thesis, we use the term ‘AD’ to refer to ‘probable or possible AD’. Thus, ‘predictors of AD’ means ‘predictors of the clinical diagnosis of probable or possible AD’. The term ‘preclinical AD’ is used to describe subjects who have mild cognitive impairment at the baseline assessment of a prospective study and who become demented and have AD during the follow-up period. As a consequence, the diagnosis of preclinical AD can only be made in retrospect. This means that the distinction between subjects with and without preclinical AD is based on the outcome at follow-up. Markers of preclinical AD are by definition also predictors of AD.

All subjects with probable or possible AD are by definition demented; however,

Table 1.1 Outcome of prospective studies of subjects with mild cognitive impairment. Legend see next page.

Study	MCI definition‡	N	Setting#	Age (years) (SD), range	MMSE baseline	FU (years)	% out-come	Demented			Improved	
								N	%	%AD	N	%
Hänninen 1995	AAMI	229	E	68, 60-78	26.8	3.6	77	16	9	81	26	15
O'Neill 1992	AAMI	8	C	72 (9)*	-	-	100	6	75	-	-	-
Bowen 1997	Amnesia	23	C	74 , 44-89	25.2	4	91	10	48	90	-	-
Coria 1995	Amnesia	56	C	71 (7), >60	-	3	100	30	54	-	-	-
Celsis 1997	ARCD	24	C	62 (9)	27.5	2	100	5	21	100	-	-
O'Brien 1992	BSF	68	C	67 (8), >50	28.7	3	94	6	10	83	-	-
Devanand 1997	CDR 0.5	49	C	66 (10), >40*	-	2.5*	60*	15	52	87	12	41
Rubin 1989b	CDR 0.5	16	R	72 (4), 64-81	-	6	100	11	73	100	1	7
Tierney 1996b	Complaints	178	C	72 (7)	27.8	2	81	35	24	97	-	-
Tuokko 1991	Complaints	45	C	69 (8)	-	1.3	100	18	40	100	-	-
Tröster 1994	Complaints	35	R	69 (8)	-	5*	86	4	13	100	21	70
Devanand 1997	Complaints	127	C	66 (10), >40	-	2.5	60	31	41	87	-	-
Reisberg 1986	GDS 2	48	R	71 (6)*	-	8.8	73*	2	8	-	-	-
de Leon 1993	GDS 3	32	C	71	25	4.1	100	23	72	100	-	-
Snowdon 1994	Guild score 2	41	E	74 (7), 65-95*	-	8	46	1	5	-	-	-
Snowdon 1994	Guild score 3	60	E	74 (7), 65-95*	-	8	43	5	19	-	-	-
Petersen 1995	MCI (Mayo)	78*	C	81, 73-86	26.2	2.8	85	25	38	100	-	-
Wolf 1998	MCI (Zaudig)	60*	C	68 (7), 51-84*	25.7	2.7	68	8	20	-	8	20
Johansson 1997	MCD	70	E	87, 84-90*	-	2.5	54	31	82	-	-	-
O'Connor 1991	Min Dem	44	E	85, >75*	-	2	55	12	50	-	5	21
Cooper 1996	Min Dem	67	E	80, >65	-	2	79	20	38	-	-	-
Devanand 1996	Mod CI	48	R	73 (7), >60*		2.5*	70*	30	63	93*	-	-
Ritchie 1997	Sub Cog Decl	397	E	75 (7), >60	-	2	71*	64	16	82	-	-
Copeland 1992	Sub-org GMS	46	E	>65	-	3	54	4	24	68	19	76

Legend table 1.1 MCI=mild cognitive impairment, FU=follow-up; AD=Alzheimer's disease; ‡AAMI= Age Associated Memory Impairment; ARCD= Age Related Cognitive Decline; BSF= Benign senescent forgetfulness; CDR=Clinical Dementia Rating Scale; GDS=Global Deterioration Scale; MCI=mild cognitive impairment; MCD=Mild cognitive dysfunction; Min Dem=Minimal dementia; Mod CI=Moderate Cognitive Impairment; Sub Cog Decl=Subclinical cognitive decline; Sub-org GMS=sub-case organic disorder Geriatric Mental State schedule. For a description of the definitions of mild cognitive impairment see Appendix A.
#Setting: E=Epidemiological; R=Research (subjects that were recruited by advertisements, or were spouses or siblings of patients); C=Clinical.
*Data on the subjects with mild cognitive impairment were not available; the presented data are from the total study population.

not all demented subjects have AD.[2] Most of the prospective studies on mild cognitive impairment used dementia as an endpoint, and not AD (table 1.1). About 90% (range 68-100%) of these subjects have AD-type dementia (table 1.1). Since AD is by far the most common cause of dementia in subjects with mild cognitive impairment, we equate dementia with AD when we discuss the findings of the studies. The limitations of this approach are discussed in the general discussion.

The term 'mild cognitive impairment' is used to describe subjects with cognitive impairment that is not severe enough to meet the criteria of dementia and in whom the cognitive impairment is not related to cerebro-vascular events, neurodegenerative diseases (e.g., Parkinson's disease), brain neoplasm, head trauma, drug intoxication, alcohol abuse, hypothyroid or hyperthyroid function, or vitamin deficiency. Mild cognitive impairment does not refer to any specific definition unless specified otherwise.

1.4 AIM OF THE STUDY

The aim of the present study is to identify subjects with preclinical AD among subjects with mild cognitive impairment. We will try to answer the following questions:

- what are the clinical characteristics of preclinical AD?
- what are the advantages of a multidisciplinary approach compared with a monodisciplinary approach in predicting AD in subjects with mild cognitive impairment?
- how can a multidisciplinary approach be implemented in the diagnostic work-up of subjects with mild cognitive impairment?

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2 The diagnosis of dementia is made regardless of any underlying pathology. Other common causes of dementia are vascular dementia, Lewy-body disease, and frontotemporal dementia. As in AD, the cause of other types of dementia is determined according to clinical criteria because the pathological substrate of these dementing disorders can not be visualised during life. The dementias other than AD are also refered to as non-AD-type dementia.

We used a multidisciplinary approach with cognitive, non-cognitive, functional, genetic, and brain imaging variables. The variables selected as predictors were chosen because they were predictive of AD in a monodisciplinary approach. These variables are listed below and some issues concerning these variables that still need to be clarified are discussed.

- *age and educational level*. Many population-based studies have indicated that high age and low educational level are risk factors for AD (for example Launer et al. (1999)). It is not clear whether age and education are also risk factors for AD in clinical samples.

- *the apolipoprotein E (apoE) genotype*. The apoE genotype is coded by different alleles (e2,e3, and e4). Subjects with AD have one or two e4 alleles more often than do control subjects (Corder et al., 1993; Saunders et al., 1993). The apoE-e4 allele is associated with an increased incidence of AD (Coria et al., 1995; Devanand et al., 1996; Evans et al., 1997; Myers et al., 1996; Petersen et al., 1995; Slooter et al., 1998; Tierney et al., 1996b) and of cognitive decline (Feskens et al., 1994; Hyman et al., 1996; O'Hara et al., 1998) in the general population and in clinical samples of subjects with mild cognitive impairment. Most of these studies have been performed in populations older than 60 years and it is not known whether the apoE-e4 allele is predictive of AD in younger subjects.

- *the degree of cognitive impairment*. Most studies indicate that cognitive impairment, especially memory impairment, is predictive of AD in population-based studies or in clinical samples of subjects with mild cognitive impairment (see Almkvist et al. (1998) for a review). However, it is not clear whether all subjects with memory impairment will develop AD, and whether the absence of memory impairment excludes subsequent AD.

- *the Mini-Mental State Examination (MMSE) score*. The MMSE is a simple cognitive test that is a measure of global cognitive impairment. Population-based and clinical studies have yielded conflicting results concerning the question whether the MMSE score is predictive of AD or not (Braekhus et al., 1995; Celsis et al., 1997; Devanand et al., 1997; O'Brien et al., 1992; Petersen et al., 1995; Schmand et al., 1997; Small et al., 1997a; Tierney et al., 1996a; Wolf et al., 1998). It is important to evaluate the predictive accuracy of the MMSE because the MMSE is widely used.

- *the degree of functional impairment*. Some studies indicated that functional impairment is predictive of AD (Barberger-Gateau et al., 1993; Brayne et al., 1997; Peter-

sen et al.,1993; Ritchie et al.,1997), but other studies did not (Devanand et al., 1997).

- *the extent of medial temporal lobe atrophy*. Atrophy of the medial temporal lobe increases the risk for subsequent AD (de Leon et al., 1993a; Fox et al., 1996; Jack et al., 1999; Kaye et al., 1997). No studies have compared qualitative and quantitative methods to assess medial temporal lobe atrophy. Quantitative assessment is accurate and has a good inter- and intra-observer variability but is time-consuming to perform. Qualitative assessment is quick to perform but is less accurate and has a lower inter- and intra-observer variability. Since medial temporal lobe atrophy correlates with memory performance (Deweer et al., 1995; Golomb et al., 1994) it needs to be determined whether assessment of the medial temporal lobe increases the predictive accuracy of delayed recall performance for AD in subjects with mild cognitive impairment. It is also important to find out whether medial temporal lobe atrophy is specific for preclinical AD or whether it is also present in other disorders with memory impairment. To address this issue, we investigated the brain substrate of the memory impairment seen in patients with Korsakoff's syndrome.

- *depression*. Several studies involving elderly subjects from the general population have indicated that depression is a risk factor for AD (Buntinx et al., 1996; Devanand et al., 1996; Jorm et al., 1991; Speck et al., 1995; Yaffe et al., 1999). However, it is not clear from the literature whether depression can predict AD in subjects with mild cognitive impairment. Some studies reported that most depressed subjects with cognitive impairment develop AD, but these studies lacked a control group of non-depressed subjects with mild cognitive impairment (Alexopoulos et al., 1993; Copeland et al., 1992; Kral et al., 1989; Reding et al., 1985). Other studies indicated that depression itself can cause cognitive impairment that mimics the cognitive impairment seen in AD (see Christensen et al. (1997a) for a review), and that the cognitive impairment in depressed subjects was reversible after the improvement of the depression (Abas et al., 1990; Hill et al., 1992). Cognitive impairment secondary to depression is called depression-related cognitive impairment. One important question is, therefore, how subjects with preclinical AD can be differentiated from subjects with depression-related cognitive impairment.

1.5 SET-UP OF THE STUDY

The predictors of AD were investigated in a clinical and in a epidemiological population. The clinical population was selected from the Maastricht Memory Clinic. The Maastricht Memory Clinic is a university hospital-affiliated outpatient clinic for

subjects with cognitive impairment (Verhey et al., 1993a). It is imbedded in the department of Psychiatry and Neuropsychology and the department of Neurology of the Academic Hospital Maastricht, The Netherlands. Patients are referred to it by general practitioners (53%), neurologists (28%), and psychiatrists (19%). The epidemiological population was selected from the Amsterdam Study of the Elderly (AMSTEL). AMSTEL is a population-based study of elderly subjects older than 65 years (Jonker et al., 1990). We chose these two populations because while a clinical setting has the advantage that the results of the clinical study can be applied in a clinical setting, it has the disadvantage of referral bias in that only a selection of patients with mild cognitive impairment are referred to the Maastricht Memory Clinic. While referral bias is avoided in a population-based setting, the results for these samples can not be translated to clinical practice because not all subjects with mild cognitive impairment in the general population will be seen in a clinical setting.

The thesis is organized as follows. In chapter 2, we investigate the course of objective memory impairment and predictors of outcome in subjects from the Maastricht Memory Clinic. The predictors tested in this chapter were age, education, performance on memory tests, MMSE score, apoE genotype, depression, and degree of functional impairment. In chapter 3, we investigate predictors of dementia in subjects with minimal dementia from the AMSTEL study. We use dementia as the main outcome measure so that we can compare the results with those of other prospective studies of subjects with minimal dementia; however, we also provide analyses with AD as outcome. The predictors tested in this chapter were age, education, performance on cognitive tests, MMSE score, apoE genotype, and depression. In chapter 4, we describe how often depression is present in subjects with preclinical AD from the Maastricht Memory Clinic and we investigate how depressed subjects with preclinical AD can be differentiated from subjects with depression-related cognitive impairment. In chapter 5, we compare the predictive value of medial temporal lobe atrophy with that of age and memory impairment in subjects with mild cognitive impairment from the AMSTEL study. We also compare different methods for assessing medial temporal lobe atrophy. In chapter 6, we assess the predictive value of medial temporal lobe atrophy for AD in subjects with mild cognitive impairment from the Maastricht Memory Clinic. In chapter 7, we describe the brain substrate of the memory impairment seen in patients with Korsakoff's syndrome. In chapter 8, we describe the clinical characteristics of subjects with preclinical AD from the Maastricht Memory Clinic. In chapter 9, we summarize the main findings of the study and propose the Preclinical AD scale (PAS): a multidisciplinary approach to predict AD in subjects with mild cognitive impairment. We conclude with suggestions for future research in the field of preclinical AD and with recommendations for clinical practice.

Course of objective memory impairment in non-demented subjects attending a memory clinic and predictors of outcome

2

SUMMARY

OBJECTIVE: To investigate the course of objective memory impairment in non-demented subjects who attended a memory clinic and to test predictors for outcome.
METHODS: Non-demented subjects (N=74) were included when they were older than 40 years and had a baseline score on the delayed recall of a word learning test below the tenth percentile. The subjects were reassessed after 2 and 5 year.
RESULTS: At the 5-year follow-up, 42% of the subjects had no memory impairment, 19% of the subjects had memory impairment without dementia, and 39% of the subjects had Alzheimer type dementia (AD). Predictors at baseline of reversible memory impairment in a multivariate analysis were age, scores on the MMSE and delayed recall, and the degree of functional impairment. Predictors at baseline of AD in a multivariate analysis were age and the score on the MMSE. The apolipoprotein E genotype and the presence of depression at baseline were not predictors of outcome. The positive predictive value was 72% for reversible memory impairment and 81% for AD.
CONCLUSION: Memory impairment is often reversible and therefore its presence alone is not sufficient to consider subjects as preclinically demented. Predictive accuracy can be increased by including simple measures such as age, the scores on the MMSE and delayed recall, and the degree of functional impairment.

INTRODUCTION

Objective memory impairment in non-demented elderly individuals is an important riskfactor for Alzheimer-type dementia (AD) (Bowen et al., 1997; Linn et al., 1995), but cognitive impairment may also be reversible (Alexopoulos et al., 1993; O'Connor et al., 1990). While several studies have investigated the relation between subjective or objective memory impairment and subsequent dementia (Bowen et al., 1997; Coria et al., 1995; O'Brien et al., 1992), there have been no studies on how often objective memory impairment in non-demented subjects is reversible and on factors that are associated with the reversibility of memory impairment. It is impor-

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tant to distinguish subjects with reversible memory impairment from those who are at high risk for AD because high-risk subjects may be candidates for treatment with drugs that are becoming available for AD. In addition, the caregivers of these patients may benefit from counselling on how to handle the cognitive impairment of their partners.

The aim of the present longitudinal study was to investigate the course of memory impairment and to identify predictors of outcome. Outcome was defined as reversible memory impairment, persistent memory impairment without dementia, or AD. We also developed post-hoc decision rules that can be used in clinical practice to predict outcome. We selected variables that have been demonstrated to be associated with an increased risk for AD or cognitive decline in non-demented elderly subjects e.g. the severity of the memory impairment (Jacobs et al., 1995; Linn et al., 1995), age (Ott et al., 1998), the apolipoprotein E (apoE) -e4 allele (Coria et al., 1995; Petersen et al., 1995; Slooter et al., 1998), the score on the Mini-Mental State Examination (MMSE) (Braekhus et al., 1995), and the degree of interference by the cognitive impairment with the activities of daily living (Brayne et al., 1997). We also selected depression as a predictor because depression may cause cognitive impairment that is reversible after improvement of the depression (Alexopoulos et al., 1993; Hill et al., 1992).

METHODS

Subjects

The patients were selected from the Maastricht Memory Clinic, a university affiliated outpatient clinic for subjects with cognitive impairment (Verhey et al., 1993a). All patients complained about memory dysfunction and were referred by a general practitioner (51%), a neurologist (27%), or a psychiatrist (22%). Subjects were included when they were older than 40 years and when they had memory impairment. Memory impairment was defined as an impairment on the delayed recall of a word learning test because several studies indicated that especially impairment on the delayed recall is predictive of subsequent dementia (Almkvist et al., 1998; Bowen et al., 1997; Linn et al., 1995; Tierney et al., 1996a). Impairment was defined as a score below the 10th percentile because this cut-off is commonly used in clinical practice and is similar to the cut-off used in criteria of mild cognitive impairment (Levy, 1994; Smith et al., 1996). This definition of memory impairment excluded most subjects with age related cognitive decline (ARCD) (APA, 1994), because the memory impaiment was outside the normal limits given the person's age. We excluded subjects with dementia, a score on the MMSE below 24, a score on the Global Deterioration Scale (GDS) (Reisberg et al., 1982) higher than 3, severe

sensory impairment, psychosis, panic disorder, post-traumatic stress disorder, bipolar disorder, or cognitive problems in relation to cerebro-vascular events neurodegenerative diseases (e.g., Parkinson's disease), brain neoplasm, head trauma, drug intoxication, alcohol abuse, hypothyroid or hyperthyroid function, or vitamin deficiency. The study cohort consisted of 74 subjects. After the study was explained to them, subjects gave their written informed consent.

Baseline assessment and clinical diagnosis

All subjects underwent a standardized assessment at baseline which included a detailed history provided by the patient and a significant other, a psychiatric, neurological, and physical examination, appropriate laboratory tests, a neuropsychological assessment, and neuroimaging as described elsewere (Verhey et al., 1993a). In addition, the MMSE (Folstein et al., 1975), as a measure of global cognitive impairment, the GDS (Reisberg et al., 1982), which is a scale for staging levels of cognitive impairment, the Hamilton Depression Rating Scale-17 items (HDRS) (Hamilton, 1960), and the Blessed Dementia Rating Scale (BDRS) part I (Blessed et al., 1968) were administered. From the BDRS we used the total score on the first 11 items as a measure of impairment in functioning in daily living (BDRS-DL). Psychiatric diagnoses were made according to DSM-IV criteria (APA, 1994). Depression was diagnosed when the subjects fulfilled the criteria of minor or major depression. The diagnosis of depression was made regardless of a possible underlying aetiology such as bereavement, co-morbid conditions or pain. Since cognitive impairment in depression is associated with the severity of the depression (Christensen et al., 1997a), we have used the term depression in the present study to refer to subjects with a score on the HDRS higher than 13. None of these subjects were severely depressed as HDRS scores were lower than 26. All subjects were treated according to clinical standards with no specific treatment protocol. The clinical standard treatment of depressed subjects consisted of drug therapy and/or psychotherapy.

Follow-up procedure

After 2 years and 5 years the subjects were invited for a follow-up assessment. This consisted of a standardized questionnaire about medical history and cognitive complaints, the MMSE, the GDS, the HDRS, the BDRS, and a neuropsychological test protocol. The diagnosis of dementia and AD was made according to the DSM-IV and NINCDS-ADRDA criteria (McKhann et al., 1984) by a neuropsychiatrist and a neuropsychologist, who were unaware of the results of the baseline assessment and who made their diagnosis independently of each other. If there was disagreement about the clinical diagnosis, a consensus meeting was held and if no agreement was reached the subject was considered not demented. No neuropsychological testing was

done at follow-up in two subjects who were demented at follow-up because one subject was too impaired and the other had died after the diagnosis of dementia was made but before the neuropsychological test was carried out. Subjects who were demented at the 2-year follow-up were not invited for the 5-year follow-up. When separate analyses were performed with subjects who had completed the 5-year follow-up, only the demented subjects were included whose baseline assessment was at least 5 years ago.

Delayed recall measure

The delayed recall measure was selected from a neuropsychological assessment that consisted of a series of standard clinical tests covering the cognitive domains of memory, language, attention, praxis, executive functions, and intelligence, as described elsewhere (Jolles, 1986; Verhey et al., 1993a). Delayed recall was tested with the Dutch version of the Auditory Verbal Learning Test (AVLT) (Brand et al., 1985; Lezak, 1995). Fifteen unrelated monosyllabic words were presented five times and after each presentation the subject was asked to reproduce as many words as possible. After 20 minutes, during which non-verbal tests were performed, delayed recall was tested. If the neuropsychologist considered that a subject could not perform the 15-word version of the AVLT appropriately, a 10-word version of the test was administered (in 2 subjects at the 2-year follow-up and 1 subject at the 5-year follow-up). This score was multiplied by 1.5 to make it comparable to the others. A parallel version of the AVLT was used at follow-up.

Correction of MMSE and delayed recall for age, sex, and education

Since the MMSE and the delayed recall scores correlate with age, sex and education, we corrected the scores for these variables. The correction was based on a reference population of 1870 cognitively normal subjects older than 40 years randomly selected from a registry of general practitioners (Jolles et al., 1995; van Boxtel et al., 1998). In this population, multiple linear regression was performed with age, sex, and education entered in the first step, using $p<0.05$ as the criterion for remaining in the model. In the next step, non-linear terms and interaction terms for the significant main effects were entered. On the basis of the resulting model, an expected test score for each subject was calculated. This score was subtracted from the observed score. The residue of the delayed recall was divided by the standard deviation of the residue in the reference population to give a z-score. A z-score below zero indicated below average performance. A z-score of -1.28 or lower corresponds with a memory performance below the tenth percentile of the reference population. The residue of the MMSE was added to the expected MMSE of a subject with average age, sex, and education in the study population (MMSE=28.2). Both the uncorrected and corrected

MMSE scores are listed in the tables but only the corrected MMSE scores were used for the analyses. The MMSE score was not available for three subjects at baseline and these subjects were given the average MMSE score of the study population (Small et al., 1997a). We chose to substitute the data in order to retain these subjects in the multivariate analysis. The analyses with and without the subjects with substituted MMSE scores yielded similar results. The three subjects without an MMSE score tended to be younger (49 years versus 61 years, p=0.07) at baseline, and had a lower GDS score (p=0.01) compared to the subjects with an MMSE score. The other variables at baseline (including the z-score of the delayed recall and the HDRS score) were not different between the subjects with or without MMSE score at baseline.

APOE genotyping

The apoE genotyping was performed with a polymerase chain reaction (Slooter et al., 1998; Wenham et al., 1991). Blood samples for genotyping were taken at the follow-up assessment from 1995 onwards. Therefore, no samples were available for subjects seen before 1995 or without follow-up. One subject refused to give blood. The apoE genotype was available for 44 subjects (70% of the subjects who were seen at follow-up). Compared with the subjects who were apoE genotyped, the subjects who were not apoE genotyped had a lower score on the MMSE at baseline (26.9 vs 28.0, p=0.01), and were more frequently demented at follow-up (42% vs 18%, p=0.004). On the basis of the apoE genotype we defined a group with the apoE-e4 allele (apoE-e4+) including the genotypes e4e4 (N=3) and e3e4 (N=20), and a group without a apoE-e4 allele (apoE-4-) including the genotypes e2e3 (N=2) and e3e3 (N=19).

Statistical Analysis

In groups with more than 10 subjects, continuous variables were compared by means of a t-test. In groups with 10 or fewer subjects, continuous variables were analyzed with the Mann-Whitney test corrected for ties. This test was also used to analyze the BDRS-DL data. Categorical data were analyzed with a Chi square test with continuity correction. When two or more cells had 5 cases or less, the twotailed Fisher's exact test was applied. Logistic regression analysis was performed to identify variables that were predictors of outcome. At the first step age, the presence or absence of depression, and the scores on the BDRS-DL, MMSE, and delayed recall were entered and with backward step selection variables were selected that were significantly associated with outcome. The apoE genotype was not entered in the multivariate analysis because the genotype was not available for all subjects. All statistical tests were two-tailed. The significance level was set at 0.05.

RESULTS

Of the 74 subjects included at baseline, 11 subjects (15%) had no assessment at follow-up because they were untraceble (*N*=2), refused to participate (*N*=5), had died (*N*=3), or had multiple system atrophy at follow-up (*N*=1). Twenty-seven subjects (36%) had a 2-year follow-up, 33 subjects (45%) had both a 2-year and 5-year follow--up, and three subjects (4%) had only a 5-year follow-up. The subjects without a follow-up assessment had similar baseline characteristics as the subjects with a follow-up assessment except for the uncorrected MMSE score (table 2.1). Nineteen subjects were demented at follow-up; they all had probable AD.

Table 2.1 Baseline characteristics

	Follow-up (*N* = 63)	No-follow-up (*N* = 11)	*P*-value
Age	60.1 (10.4)	66.9 (12.8)	0.06
Education (years)	10.3 (3.0)	11.5 (3.5)	0.16
Sex Male/ Female	34/29	5/6	0.85
HDRS	11.1 (6.3)	10.3 (6.1)	0.69
GDS			1.0
-2 (%)	20 (32)	4 (36)	
-3 (%)	43 (69)	7 (64)	
BDRS-DL	0.88 (0.71)	1.1 (1.2)	1.0
MMSE	27.4 (1.7)	26.8 (1.1)	0.03
MMSE (corrected)	27.7 (1.6)	27.4 (1.1)	0.64
Delayed recall baseline*	-2.0 (0.6)	-2.2 (0.5)	0.34
Depressed/Not depressed (% depressed)	22/41 (35)	4/7 (36)	1.0

All data are mean (SD) unless specified otherwise.
* Data expressed as z-score. A z-score below zero indicates below average performance.

Course of memory impairment

The course of the memory impairment is shown in figure 2.1. In the 60 subjects with a 2-year follow-up, the memory performance had improved in 21 (35%) and remained stable in 23 (38%) Sixteen subjects (27%) had AD at the 2-year follow-up. In the 36 subjects with a 5-year follow-up, the memory performance had improved in 15 (42%) and remained stable in 7 (19%). Fourteen subjects (39%) had AD at the 5-year follow-up. One subject of the ten subjects (10%) who had improved at the 2-year follow-up, showed memory impairment at the 5-year follow-up. Seven of the 23 (33%) subjects with persistent memory impairment but no dementia at the 2-year follow-up showed improved memory function at the 5-year follow-up, while 10 (42%) of these subjects remained impaired and 6 (25%) had become demented.

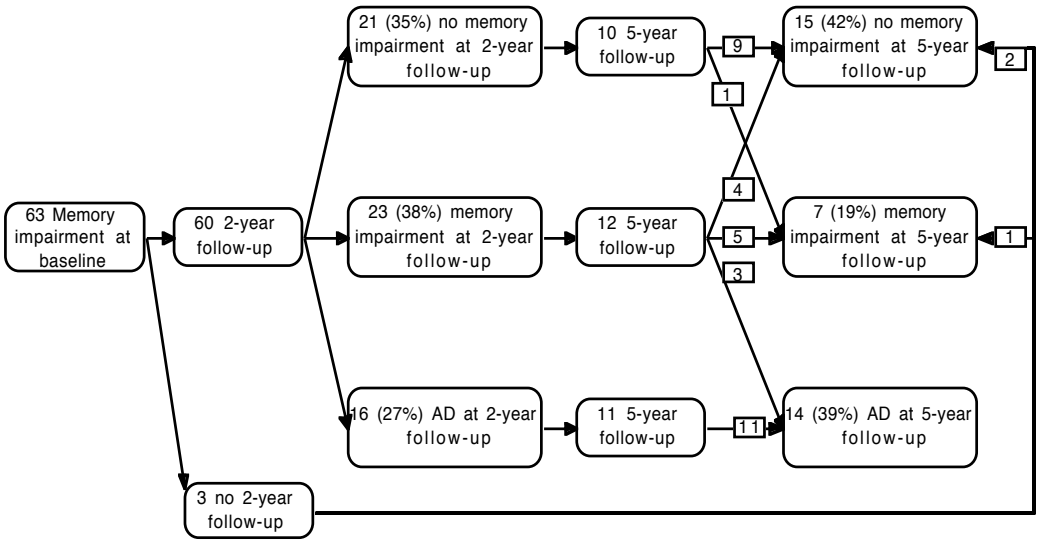

Figure 2.1 Course of memory impairment. Note that subjects who had AD at the 2-year follow-up were considered to have a 5-year follow-up if the baseline assessment of these subjects was at least 5 years ago.

Predictors of outcome

We classified the subjects according to the outcome at the most recent follow-up assessment (table 2.2) because the differences in baseline characteristics between the groups with reversible memory impairment, persistent memory impairment, and AD at the 2-year follow-up were similar to the differences in baseline characteristics between these groups at the 5-year follow-up. Compared to non-demented subjects with persistent memory impairment, subjects with reversible memory impairment had higher MMSE and the delayed recall scores at follow-up, and were less frequently depressed at follow-up. Subjects with reversible memory impairment had a lower age at baseline, lower GDS and BDRS-DL scores at baseline, and higher MMSE and delayed recall scores at both baseline and follow-up than did the subjects who had AD at follow-up. Subjects who were impaired but not demented at follow-up were younger and had lower GDS and BDRS-DL scores at baseline than did the subjects who had AD at follow-up. The frequency of the apoE-e4 allele or the frequency of depression at baseline was not different between the three groups.

Predictors for reversible memory impairment in the multivariate analysis were evaluated by comparing group I (reversible memory impairment) in table 2.2 with group II (memory impairment at follow-up) and group III (AD at follow-up). The

Table 2.2 Baseline characteristics and follow-up scores according to outcome at the latest available follow-up assessment

	Outcome at Follow-up		
	No memory impairment	Memory impairment	
		Not demented	AD
	group I	group II	group III
	(*N* = 26)	(*N* = 18)	(*N* = 19)
Age Range	55.2 (6.9) 40-68	57.9 (11.3) 40-77	69.0 (7.9)[a,b] 48-81
Age below 65/above 65 (% below 65)	24/2 (92)	12/6 (67)	4/15 (21)[a,b]
Education (years)	9.7 (2.8)	11.2 (2.6)	10.3 (3.6)
Sex Male/ Female	16/10	10/8	8/11
APO-e4+/ APO-e4- (% e4+)	8/11 (42)	9/8 (53)	6/2 (75)
HDRS at baseline	10.8 (6.5)	13.0 (7.0)	9.7 (5.3)
GDS at baseline -2 (%) -3 (%)	 10 (38) 16 (62)	 8 (44) 10 (56)	 2 (11)[b] 17 (89)
BDRS-DL at baseline	0.88 (0.8)	0.47 (0.47)	1.2 (0.61)[a,b]
MMSE at baseline	28.0 (1.6)	27.7 (1.5)	26.5 (1.8)[a,b]
MMSE (corrected) at baseline	28.0 (1.5)	27.7 (1.7)	27.2 (1.7)
MMSE (corrected) at follow-up	28.4 (1.3)	25.4 (2.5)[a]	23.4 (5.4)[a]
Delayed recall at baseline*	-1.85 (0.34)	-2.1 (0.53)	-2.2 (0.80)[a]
Delayed recall at follow-up*	-0.27 (0.63)	-2.54 (0.73)[a]	-2.32 (1.1)[a]
Depressed/Not depressed at baseline (% depressed)	8/18 (31)	9/9 (50)	5/14 (26)
Depressed**/Not depressed at follow-up (% depressed)	1/25 (4)	5/12 (29)[a]	1/14 (7)

All data are means (SD) unless specified otherwise.
* Data expressed as z-score. A z-score below zero indicates below average performance.
** Subjects with depression at both baseline and follow-up
[a] Different from group I with *p*-value <0.05
[b] Different from group II with *p*-value <0.05

variables age, baseline delayed recall score, and baseline BDRS-DL score were retained in the model after backward step selection (table 2.3). The BDRS-DL score was associated with reversibility in the unexpected direction. The sensitivity of the

model was 58%, the specificity 74%, the positive predictive value (PPV) (i.e. the chance that subjects with a predicted probability for reversible memory impairment larger than 0.50 had reversible memory impairment) was 60%, and the negative predictive value (NPV) (the chance that subjects with a predicted probablity for reversible memory impairment lower than 0.50 did not have reversible memory impairment) was 73%. Since the accuracy of the analysis could have been influenced by the fact that not all subjects completed the 5-year follow-up, we repeated the logistic regression analysis with subjects with only a 5-year follow-up. The variables age, baseline delayed recall backward step selection (table 2.3). Again, the BDRS-DL score was associated with reversibility in the unexpected direction. The predictive accuracy was better than that of the model with all subjects (table 2.3).

Predictors of AD in the multivariate analysis were evaluated by comparing group III (AD at follow-up) in table 2.2 with group I (reversible memory impairment) and group II (memory impairment at follow-up). The variables age, baseline delayed recall score, and baseline MMSE score were retained in the model after backward step selection (table 2.3). The sensitivity of the model was 76%, the specificity 89%, the PPV 76%, and the NPV 85%. When the analysis was repeated with only subjects with a 5-year follow-up, the variables age and baseline MMSE score were retained in the model after backward step selection and the predictive accuracy was higher than that of the model with all subjects (table 2.3).

Table 2.3 Predictors of outcome after logistic regression with backward step selection

Outcome	Selected variables (OR, 95% CI, *p*-value)	Sensitivity	Specificity	PPV	NPV
Reversible memory impairment	Age (0.87, 0.8-0.9, 0.001) Delayed recall (4.4, 1.2-16.4, 0.03) BDRS-DL (3.2, 1.1-9.5, 0.03)	54	73	58	69
Reversible memory impairment (only subjects with a 5-year follow-up)	Age (0.84, 0.7-1.0, 0.01) Delayed recall (11.3, 1.0-120, 0.05) BDRS-DL (6.8, 0.9-3.7, 0.07) MMSE (1.8, 0.9-52.5, 0.09)	87	76	72	89
AD	Age (1.2, 1.1-1.3, 0.001) Delayed recall (0.35, 0.1-1.2, 0.09) MMSE (0.65, 0.4-1.0, 0.07)	74	89	74	89
AD (only subjects with a 5-year follow-up)	Age (1.3, 1.1-1.5, 0.003) MMSE (0.40, 0.2-1.0, 0.04)	93	86	81	95

OR=Odds ratio per unit change, CI=Confidence interval, PPV=positive predictive value, NPV=negative predictive value.

Decision rules for identifying subjects with reversible memory impairment and subjects with dementia at follow-up

In order to develop decision rules that can be easily used in clinical practice to predict outcome we dichotomized all variables. The cut-off points were established such that the outcome could be predicted with a high positive predictive value. Twenty-two of the 26 subjects (85%) with reversible memory impairment were younger than 65, had a delayed recall score between the first and the tenth percentile, and a corrected MMSE score above 26.5. Also six subjects with persistent memory impairment or AD fulfilled these criteria (the PPV was 79%). Thirteen of the 19 subjects (68%) with AD at follow-up were older than 65 and had a BDRS-DL score at baseline ≥1. Three non-demented subjects fulfilled these criteria (the PPV was 81%).

The decision rules for reversible memory impairment were based on corrected MMSE and the delayed recall scores. Since these corrected scores may not be available we also used uncorrected scores. Fourteen of the 26 subjects (54%) with reversible memory impairment were younger than 65 years, had a delayed recall of ≥4 words, and had a MMSE score ≥28. Four subjects with persistent memory impairment or AD at follow-up fulfilled these criteria (the PPV was 78%).

DISCUSSION

The main conclusion of this study is that objective memory impairment in non-demented subjects is reversible (42%) as often as it is a precursor of subsequent AD (39%). Age and the baseline MMSE and delayed recall scores were the best predictors of outcome.

Our study is unique for several reasons. First, there have been no previous longitudinal studies that focussed on the prediction of reversible memory impairment. Second, we followed memory-impaired subjects for up to 5 years, which is longer than in most other studies. Third, we also included younger subjects in the age range 40 to 60 years, which enables us to generalize the results more than in other studies. Fourth, we investigated not only cognitive measures and age as predictors but also a functional measure, a genetic marker, and the presence of depression.

This is the first study that shows that in a clinical setting the severity of the memory impairment, age, a low score on the MMSE, and the degree of functional impairment are associated with an increased risk of AD in non-demented elderly subjects with memory impairment. These findings corroborate the findings from population-based studies (Braekhus et al., 1995; Brayne et al., 1997; Jacobs et al., 1995; Linn et al., 1995; Ott et al., 1998). The finding that functional impairment was associated with reversibility of memory impairment in the wrong direction in

the multivariate analysis problably resulted from the fact that the BDRS-DL score tended to be lower in subjects with persistent memory impairment than in subjects with reversible memory impairment (table 2.2). The relation between depression and the outcome of memory impairment was not straightforward. In one third of the subjects who were depressed at baseline, the depression improved together with the memory impairment (N=7), in one third both the depression and the memory impairment persisted at follow-up (N=6), and in one third the depression improved while the cognitive impairment remained or progressed to AD (N=6). The latter group was at baseline older than the other groups (66 years vs 55 years (p=0.04) and 56 years (p=0.15) respectively). Thus, when both moderately severe depression and memory impairment are present, the memory impairment is not necessarily secondary to the depression, and this is probably especially true in elderly subjects (O'Connor et al., 1990). We expected that the apoE-e4 allele would be strongly related with AD or persistent memory impairment. However, a substantial number of the subjects with reversible memory impairment appeared to be carriers of the apoE-e4 allele. All these subjects were younger than 65 years. This finding is of interest because it suggests that only in subjects older than 65 years is the apoE-e4 allele associated with persistent memory impairment or AD (Coria et al., 1995; Petersen et al., 1995). The apoE-e4 allele was frequently found in subjects who developed dementia at follow--up, but the apoE-e4 allele frequency in the demented was not significantly different from that of the other groups, probably because the apoE genotype was not determined in all demented subjects.

In almost 50% of the subjects with reversible memory impairment, the improvement of cognitive functioning may have resulted from improvement of depression. In the other subjects, the improvement could be due to improvement of subsyndromal depression or stress, that was caused, for example, by bereavement, co-morbid disorders, or pain. We did, however, not investigate these possible causes of reversible memory impairment. In addition, improvement could also have resulted from learning effects or regression to the mean. Nineteen percent of the subjects continued to have memory impairment after 5 years but had not developed AD. These subjects were relatively young and had little functional impairment at baseline. Depression was common at baseline and persisted in more than 50% of the subjects. This may indicate that in these subjects the memory impairment is related to depression but it can not be excluded that these subjects would develop AD later on. The apoE-e4 allele frequency was high, suggesting that some of the subjects would develop AD after the follow-up period. In AD, severe memory impairment can exist up to 13 years before other cognitive deficits develop (Didic et al., 1998).

In order to translate these findings to clinical practice, we tried to formulate some decision rules. Clearly, these rules need cross-validation in our own population

and in different settings. The decision rules were not based on the same variables that were selected by the multivariate analyses. This probably resulted from the fact that we made use of dichotomized scores in formulating the decision rules. One of the most important factors in predicting outcome was age. Typically, subjects with reversible memory impairment were younger than 65 years and subjects with AD at follow-up were older than 65 years. When subjects older than 65 years also experienced difficulties with activities of daily living there was a high risk (81%) of subsequent AD. The combination of age below 65, a delayed recall of ≥4 words, and a MMSE score ≥28 indicated a high chance (78%) that the memory impairment was reversible. The sensitivity of these decision rules was low (less than 70%) which means that the baseline characteristics of subjects with reversible memory impairment or AD at follow-up are heterogeneous. This lack of a simple profile of subjects with reversible memory impairment or AD at follow-up implies that information from different sources is important to predict outcome. The sensitivity and positive predictive value may be further increased by using biological markers of AD such as hippocampal atrophy (de Leon et al., 1993a; Visser et al., 1999b).

A limitation of the study is the fact that not all subjects completed the 5-year follow-up. The reason why not all subjects had a 5-year follow-up was that not all subjects were long enough in the study. As can be seen in figure 2.1, the outcome of some subjects who had memory impairments but who were not demented after 2 years changed after 5 years. We therefore repeated the analyses with only subjects with 5-year follow-up data. This had the disadvantage that there were few subjects. The outcome of the logistic regression model and the decision rules are sample dependent and may therefore not apply in other settings. There may be other causes of reversible memory impairment such as medications, hypothyroid or hyperthyroid function, or vitamin deficiency but these conditions were excluded at baseline.

In conclusion, memory impairment is often reversible, and for this reason memory impairment alone is not sufficient cause to consider a subject as preclinically demented. Predictive accuracy can be increased by taking into consideration simple measures such as age, the scores on the MMSE and delayed recall, and the degree of functional impairment. When both depression and memory impairment are present, the memory impairment is not necessarily secondary to the depression but both can be the first symptoms of AD. Memory impairment may even be reversible in carriers of the apoE-e4 allele.

Course of minimal dementia and predictors of outcome

3

SUMMARY

OBJECTIVE: Previous studies have indicated that not all subjects who meet the CAMDEX criteria of 'minimal dementia' progress to dementia. In the present study predictors of outcome in minimally demented subjects were tested.
METHODS: Forty-five subjects with minimal dementia who were participating in a population-based study were followed-up for on average 2.3 years. Variables tested as predictors of outcome were age, the apolipoprotein E (apoE) genotype, and the baseline scores on the MMSE, CAMCOG memory subscale, and fluency. Depression at baseline was tested as a predictor of reversible minimal dementia.
RESULTS: At follow-up, minimal dementia turned out to be reversible in 11 subjects (24%), and persistent in 10 subjects (22%). Fourteen subjects (31%) had become demented after 1 year, and 10 subjects (22%) after 2 or 3 years. Predictors at baseline of reversible minimal dementia in a multivariate analysis were age, score on the CAMCOG memory subscale, and the apoE genotype. Predictors at baseline of dementia after 1 year in a multivariate analysis were also age, score on the CAMCOG memory subscale and the apoE genotype. Subjects with persistent minimal dementia and dementia after 2 or 3 years could not be differentiated from each other at baseline. The positive predictive value was 67% for reversible minimal dementia and 83% for dementia after 1 year.
CONCLUSIONS: The diagnosis of minimal dementia is made in mildly cognitively impaired subjects who form a heterogenous group with respect to clinical outcome. Age, the score on the CAMCOG memory subscale, and the apoE genotype can improve predictive accuracy in these subjects. Other diagnostic tests, such as assessment of medial temporal lobe atrophy, may further improve predictive accuracy.

INTRODUCTION

The Cambridge Mental Disorders of the Elderly Examination (CAMDEX) uses the term 'minimal dementia' for subjects with mild cognitive impairment at high risk for dementia (Roth et al., 1986). Previous studies, however, indicated that not all

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This chapter has been submitted as PJ Visser, FRJ Verhey, J Jolles, C Jonker, 'Course of minimal dementia and predictors of outcome'.

subjects with minimal dementia progress to dementia (Cooper et al., 1996; O'Connor et al., 1991). It was shown that 25% of the subjects with minimal dementia improved at follow-up such that minimal dementia was no longer present, about 25% of the subjects remained minimally demented, and 50% of the subjects had become demented (Cooper et al., 1996; O'Connor et al., 1991). Since the outcome is not the same for all subjects with minimal dementia it would be useful to have predictors of outcome in these subjects. However, these predictors have not yet been investigated. It is important to have predictors of outcome because subjects at high risk for dementia may be candidates for drug therapy that could improve the cognitive impairment or slow down the neurodegenerative process. In addition, the caregivers of these subjects may benefit from counseling on how to handle the cognitive impairment of their partners, relatives, or friends. Because the CAMDEX is a widely used instrument in both clinical and epidemiological settings, information on predictors of outcome in minimally demented subjects may be relevant to many workers in the field of old-age psychiatry and neurology.

In the present longitudinal study of subjects with minimal dementia, we tested a number of variables that, in non-demented elderly, have been associated with an increased risk of dementia or cognitive decline, namely, age (Ott et al., 1998), the apolipoprotein E (apoE) genotype (Coria et al., 1995; Petersen et al., 1995), memory function (Flicker et al., 1991; Visser et al., 2000a), fluency (Devanand et al., 1997; Masur et al., 1994; Nielsen et al., 1999; Visser et al., 2000b), and the score on the Mini-Mental State Examination (MMSE) (Braekhus et al., 1995; Visser et al., 2000a). The presence of depression at baseline was tested as a predictor of reversible minimal dementia because previous studies have indicated that improvement of depression is associated with reversibility of cognitive impairment (Abas et al., 1990; Hill et al., 1992).

METHODS

Subjects

The subjects with minimal dementia were selected from a cohort of 527 subjects of the Amsterdam Study of the Elderly (AMSTEL) who were participating in a 3-year follow-up study. The AMSTEL study is a two-stage population-based study of mental functioning in 4051 non-institutionalized people aged 65-85 years living in Amsterdam, The Netherlands (Launer et al., 1993). The selection procedure and the response rate for the 3-year follow-up study are described in detail elsewhere (Jonker et al., 1998). Minimally demented subjects who had a stroke or Parkinson's disease were excluded at baseline. The study cohort consisted of 63 subjects. All subjects gave their informed consent prior to inclusion in the study.

Baseline assessment and clinical diagnosis

Each subject was assessed for dementia by means of an examination conducted at home by a research nurse and a physician. The assessment included a questionnaire, cognitive tests, and a clinical examination with the validated Dutch version of the CAMDEX protocol (Derix et al., 1992; Roth et al., 1986). An informant interview was administered to the closest relative or caregiver. The diagnosis of minimal dementia was made when, according to the overall clinical impression, there was limited and variable impairment in cognitive and social functioning, such as difficulty with learning and recalling events, a tendency to misplace possessions, and minor errors in orientation, while the DSM-IIIR criteria of dementia were not met (O'Connor et al., 1991; Roth et al., 1986). The diagnoses of dementia and Alzheimer's disease were made according to the DSM-IIIR (APA, 1987), and NINCDS-ADRDA criteria (McKhann et al., 1984), respectively. The diagnosis of depression was made according to the CAMDEX criteria (Roth et al., 1986).

Cognitive measures

The MMSE is a measure of global cognitive impairment and has a maximum score of 30. The CAMCOG is the cognitive section of the CAMDEX. The maximum score is 107. We selected measures of memory function and fluency from the CAMCOG. Memory was tested with the CAMCOG memory subscale (maximum score of 33). The fluency score consisted of the number of animals named in 1 minute. Because age, sex, and education may influence cognitive performance, we performed all analyses with and without correction for these variables. The correction was based on the baseline cognitive scores of the non-demented subjects who were also non--demented at the 3-year follow-up (Visser et al., 1999b). Since the results of both analyses were similar, we only present the uncorrected cognitive scores.

Follow-up

Subjects were reassessed annually for 3 years according to the CAMDEX protocol.

Apolipoprotein E phenotyping

The apoE phenotypes were determined by isoelectric focusing of delipidated plasma samples, followed by immunoblotting (Havekes et al., 1987). Since the apoE phenotypes are the same as the apoE genotypes, we will refer to them as apoE genotypes. Blood samples were not available for four minimally demented subjects. The baseline characteristics of minimally demented subjects with or without blood samples were similar. On the basis of the apoE genotype, we a priori defined a group with an increased risk of dementia (apoE+), which included the genotypes e3e4 (N=16), and e4e4 (N=2), and a group with no increased risk of dementia

(apoE-), which included the genotypes e2e3 (N=2), e2e4 (N=3), and e3e3 (N=36) (Evans et al., 1997; Myers et al., 1996; Slooter et al., 1998).

Statistical analysis

The data were analyzed using SPSS for the Macintosh 4.0 (SPSS Inc., Chigaco, IL, USA). Group comparisons with continuous variables and group size of 10 or larger were carried out with a t-test. Group comparisons with continuous variables and group size smaller than 10 were analyzed with the Mann-Whitney test corrected for ties. Categorical data were analyzed with a Chi square test with continuity correction. When at least one cell had an expected frequency less than 5, the two-tailed Fisher's exact test was applied. All statistical tests were two-tailed. The significance level was set at 0.05. Logistic regression analysis was performed to identify variables that were predictors of outcome. At the first step, age, sex, education, the apoE variable (apoE+/apoE-), the depression variable (present/absent), and the scores on the MMSE, CAMCOG memory subscale, and fluency were entered, and variables were selected that were significantly associated with outcome with backward step selection using the Likelihood Ratio test with p=0.10 as criterion to remove variables. The CAMCOG total score was not entered in the logistic regression analysis because this score included the scores for the MMSE, memory subscale, and fluency and, for this reason, correlated highly with these scores. We also used continuation ratio ordinal regression with backward step selection to select the best predictors if outcome was defined on an ordinal scale (Scott et al., 1997).

RESULTS

Fourteen out of 63 subjects (22%) refused all follow-up assessments and 4 subjects (6%) had died before the first follow-up assessment. The baseline characteristics of the subjects with no follow-up and at least one follow-up were comparable (table 3.1). The average follow-up was 2.3 years (SD 0.77). Forty-five subjects (71%) completed the first follow-up assessment, 41 subjects (65%) completed the second follow-up assessment, and 34 subjects (54%) completed the third follow-up assessment. The reason why cognitive outcome was not available for subjects at the second or third follow-up assessment was refusal to participate (N=3) or death (N=8). We classified the 45 subjects according to the latest available outcome.

Course of minimal dementia

Minimal dementia turned out to be reversible in 11 subjects (24%), persistent in 10 subjects (22%), and progressive in 24 subjects (53%). Of the subjects with dementia

at follow-up, 19 (79%) had Alzheimer type dementia, 1 (4%) had vascular dementia, and 4 (17%) subjects had other types of dementia. Fourteen subjects had become demented at the first follow-up assessment, 4 subjects at the second follow-up assessment, and 6 subjects at the third follow-up assessment. Subjects with dementia after 1 year were older and had lower memory scores at baseline than subjects who had become demented at the second or third follow-up assessment (table 3.2). There were no differences in baseline characteristics between subjects who had become demented at the second or third follow-up assessment. Because age and the memory scores at baseline were different between subjects with dementia after 1 year and subjects who had become demented at the second or third follow-up assessment we considered dementia at 1 year and dementia at 2 or 3 years as separate outcomes.

Table 3.1 Baseline characteristics

	Total sample	At least 1 follow-up	No follow-up
N	63	45	18
Age	79.5 (4.3)	79.4 (4.5)	79.8 (4.0)
Male/Female (% male)	21/42 (33)	14/31 (31)	7/11 (39)
Education	2.9 (1.3)	2.7 (1.3)	3.3 (1.4)
ApoE+/ApoE- (% ApoE+)	18/41 (31)	16/28 (36)	2/13 (13)
Depressed/Not depressed (%depressed)	11/52 (17)	7/38 (16)	4/14 (22)
MMSE score	22.5 (3.6)	22.8 (3.6)	21.6 (3.5)
CAMCOG total score	73.0 (11.2)	73.6 (10.9)	71.4 (12.3)
CAMCOG memory score	14.5 (5.0)	14.6 (4.9)	14.4 (5.5)
Fluency	11.3 (5.3)	11.8 (5.1)	10.1 (5.7)

Predictors of outcome

The baseline characteristics and follow-up cognitive scores according to outcome are shown in table 3.2. Subjects with reversible minimal dementia were younger, had the apoE e3e4 or e4e4 genotype less often, and had better memory performance at baseline than the subjects who were demented at the 1-year follow-up (table 3.2). As expected, the MMSE, CAMCOG total score, and the memory score at follow-up of subjects with reversible minimal dementia were better than the follow-up scores of the subjects from the other groups. The subjects with persistent minimal dementia had better memory scores at baseline than the subjects with dementia at the 1-year follow-up. The follow-up scores on the MMSE, CAMCOG, and memory subscale of subjects with persistent minimal dementia were significantly better than the

Table 3.2 Baseline characteristics and follow-up scores in minimally demented subjects at baseline according to outcome at latest available follow-up assessment

	No dementia	Minimal dementia	Dementia	
			At 2nd or 3th FU assess-ment	At 1st FU assessment
Group	1	2	3	4
N	11	10	10	14
age	77.2 (4.9)[4]	79.0 (4.6)	78.4 (4.9)[4]	82.0 (2.5)[1,3]
Male/Female (% Male)	5/6 (45)	3/7 (30)	3/7 (30)	3/11 (21)
Education	2.7 (1.7)	2.9 (1.3)	2.8 (1.3)	2.5 (1.0)
ApoE+/ApoE- (% ApoE+)	2/9 (18)[4]	3/7 (30)	3/7 (30)	8/5 (62)[1]
Depressed/Not depressed (% depressed)				
-at baseline	1/10 (9)	2/8 (20)	1/9 (10)	3/11 (21)
-at follow-up*	1/10 (9)	2/8 (20)	0/10 (0)	1/13 (7)
MMSE				
-at baseline	23.2 (3.0)	22.1 (4.5)	23.7 (1.9)	22.4 (4.3)
-at follow-up	23.4 (2.2)[2,3,4]	20.6 (3.7)[1,4]	17.0 (3.4)[1]	14.9 (5.7)[1,2]
CAMCOG total score				
-at baseline	74.7 (10.6)	76.2 (11.1)	76.8 (7.9)	68.5 (11.9)
-at follow-up	76.9 (9.0)[3,4]	68.1 (11.5)[4]	64.0 (7.6)[1,4]	53.9 (14)[1,2,3]
CAMCOG memory score				
-at baseline	18.2 (4.3)[4]	15.4 (4.5)[4]	14.9 (3.8)[4]	10.9 (4.2)[1,2,3]
-at follow-up	19.7 (4.2)[2,3,4]	14.6 (3.9)[1,4]	12.3 (3.4)[1,4]	8.1 (3.7)[1,2,3]
Fluency				
-at baseline	12.3 (4.2)	13.0 (7.2)	12.3 (5.2)	10.3 (4.1)
-at follow-up	12.7 (3.2)[4]	10.8 (5.1)	10.1 (4.2)	8.4 (4.4)[1]

The superscript number indicates the group that is significantly different (p-value <0.05).
*Subjects with both depression at baseline and follow-up.

scores of the subjects with dementia after 1 year, but were not statistically significantly different from those of the subjects with dementia after 2 or 3 years. The subjects with dementia after 2 or 3 years were younger and had better memory scores at baseline than the subjects with dementia after 1 year. The educational level, the male:female ratio, the frequency of depression at baseline, and the baseline scores on the MMSE and fluency were not different between the groups.

Predictors for dementia after 1 year in the multivariate analysis were evaluated by comparing group 4 (dementia after 1 year) in table 3.2 with group 1 (reversible minimal dementia), group 2 (persistent minimal dementia), and group 3 (dementia after 2 or 3 years). Age, the apoE variable, and the baseline score on the CAMCOG memory subscale were retained in the model after backward step selection. The sensitivity of the model was 77%, the specificity 94%, the positive predictive value

(PPV) (i.e. the chance that subjects with a predicted probability of dementia after 1 year greater than 0.50 indeed had dementia after 1 year) was 83%, and the negative predictive value (NPV) (the chance that subjects with a predicted probability of dementia after 1 year lower than 0.50 did not have dementia after 1 year) was 91% (table 3.3). Predictors for dementia after 2 or 3 years were evaluated by comparing group 3 (dementia after 2 or 3 years) in table 3.2 with group 1 (reversible minimal dementia) and group 2 (persistent minimal dementia). No variables were retained in the model after backward step selection. Both analyses were repeated after excluding demented subjects who did not have AD-type dementia and these analyses yielded the same results.

Predictors for reversible minimal dementia in the multivariate analysis were evaluated by comparing group 1 (reversible minimal dementia) in table 3.2 with group 2 (persistent minimal dementia), group 3 (dementia after 2 or 3 years), and group 4 (dementia after 1 year). Age, the apoE variable, and the baseline score on the CAMCOG memory subscale were retained in the model after backward step selection (table 3.3). The sensitivity of the model was 55%, the specificity was 91%, the PPV was 67%, and the NPV was 86%.

Continuation ratio ordinal regression was performed with outcome defined on an ordinal scale ranging from reversible minimal dementia, persistent minimal dementia, dementia after 2 or 3 years, to dementia after 1 year. Again, age, the apoE variable, and the baseline score on the CAMCOG memory subscale were retained in the model after backward step selection (table 3.3). This type of analysis does not provide data on sensitivity, specificity, PPV, and NPV.

Table 3.3 Predictors of outcome after logistic regression with backward step selection

Outcome	Selected variables (OR, 95% CI, *p*-value)	Sensitivity	Specificity	PPV	NPV
Dementia after 1 year	Age (1.4, 1.1-1.9, 0.02) apoE (9.4, 1.1-84, 0.04) Memory score (0.8, 0.6-1.0, 0.05)	77	94	83	91
Reversible minimal dementia	Age (0.8, 0.7-1.0, 0.08) apoE (0.15, 0.01-1.7, 0.15) Memory score (1.2, 1.0-1.5, 0.06)	55	91	67	86
Ordinal scale*	Age (1.2, 1.04-1.36, 0.01) apoE (4.6, 1.2-17, 0.02) Memory score (0.86, 0.76-0.97, 0.01)	-	-	-	-

OR=Odds ratio, CI=Confidence interval, PPV=positive predictive value, NPV=negative predictive value. The OR for age and memory score are per unit change. The OR for apoE is the risk of the apoE+ group versus the risk of apoE-group. *Continuation ratio ordinal regression in which outcome was defined on a ordinal scale ranging from reversible minimal dementia, persistent minimal dementia, dementia after 2 or 3 years, to dementia after 1 year. This type of analysis does not provide data on sensitivity, specificity, PPV, and NPV.

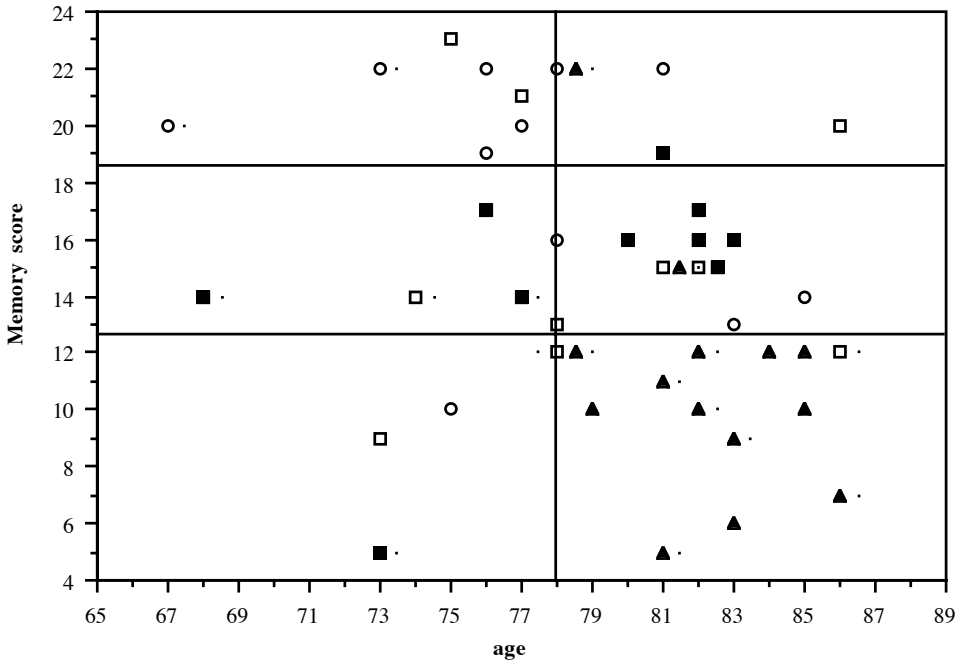

Figure 3.1. Relation between baseline age and score on the CAMCOG memory subscale in subjects with reversible minimal dementia (circle), persistent minimal dementia (open square), dementia after 2 or 3 years (closed square), and dementia after 1 year (triangle). A dot indicates subjects with the apoE-e3e4 or apoE-e4e4 genotype.

The relation between age, baseline score on the CAMCOG memory subscale, the apoE genotype, and outcome is shown in figure 3.1. On the basis of this figure, the following decision rules for predicting outcome could be constructed. Age ≥78 years and a baseline score on the CAMCOG memory subscale ≤12 were the best predictors of dementia after 1 year. The sensitivity of the cut-off scores for detecting subjects with dementia after 1 year was 85%, the specificity 97%, the PPV 85%, and the NPV 94%. Age <78 years and a baseline score on the CAMCOG memory subscale ≥19 were the best predictors of reversible minimal dementia. The sensitivity, specificity, PPV, and NPV of the cut-off scores for reversible minimal dementia were the same as those for the model selected with backward-step selection (table 3.3). Subjects who had intermediate memory scores (greater than 12 but less than 19), or age older than 78 years and high memory scores (≥19), or age younger than 78 years and low memory scores (≤12) had typically persistent minimal demen-

tia or dementia after 2 or 3 years. No decision rules, however, could differentiate between persistent minimal dementia or dementia after 2 or 3 years.

DISCUSSION

This study demonstrated that 24% of the subjects with minimal dementia had reversible minimal dementia at follow-up, 22% had persistent minimal dementia at follow-up, 22% had become demented after 2 or 3 years, and 31% had become demented within one year. Age, the score on the CAMCOG memory subscale at baseline, and the apoE genotype could predict outcome.

The outcome of subjects with minimal dementia is similar to that reported in other population-based prospective studies of minimal dementia (Cooper et al., 1996; O'Connor et al., 1991). O'Conner et al. (1991) showed in a two-year follow--up study of 24 minimally demented subjects that 50% had become demented, 29% had persistent minimal dementia, and 21% had reversible minimal dementia at follow-up. Cooper et al. (1996) reported that 38% of the 53 subjects with minimal dementia at baseline had progressed to dementia after 2 years, while the other subjects remained minimally demented or had improved. We extended these findings by showing that the baseline characteristics and follow-up cognitive scores of subjects with persistent minimal dementia were not statistically significantly different from the baseline characteristics and follow-up cognitive scores of subjects with dementia after 2 or 3 year. It seems therefore likely that subjects with persistent minimal dementia will become demented later.

The finding that memory scores, age, and the apoE genotype could predict outcome in minimally demented subjects is consistent with the findings from other prospective studies of subjects with mild cognitive impairment (Coria et al., 1995; Devanand et al., 1997; Flicker et al., 1991; O'Brien et al., 1992; Petersen et al., 1995; Tierney et al., 1996a; Tierney et al., 1996b; Tröster et al., 1994; Tuokko et al., 1991; Visser et al., 2000a; Visser et al., 2000b; Wolf et al., 1998). In contrast to other studies, we found that neither the baseline score on the MMSE nor the fluency performance was associated with outcome (Braekhus et al., 1995; Devanand et al., 1997; Masur et al., 1994; Nielsen et al., 1999; Visser et al., 2000a; Visser et al., 2000b). One possible explanation is that the inclusion criteria of minimal dementia selected a population that was more homogeneous with respect to these scores than in the other studies.

Depression was not associated with reversible minimal dementia. Four out of seven depressed subjects developed dementia even though the depression improved in three of them. We have made a similar observation in depressed subjects with memory impairment who attended a memory clinic (Visser et al., 2000a). O'Connor

et al. (1991) reported on two minimally demented subjects with depression at baseline in whom the cognitive impairment was thought to be related to their depression. However, the depression improved in these subjects while their cognitive functioning deteriorated. This suggests that if cognitive impairment coexists with depression, the cognitive impairment is not simply secondary to the depression. We have shown before that in non-demented depressed subjects with mild cognitive impairment, the risk of dementia is high if moderate-to-severe memory impairment is present and age is older than 65 years (Visser et al., 2000b).

In order to translate these findings to clinical practice, we tried to formulate some decision rules. Clearly, these rules need cross-validation in our own population and in different settings. The combination of age older than 78 years and low memory scores (≤12) could accurately identify subjects who would become demented within 1 year. Two subjects (15%) fulfilling these criteria had persistent minimal dementia but the cognitive performance of these subjects had declined severely (data not shown). Therefore, minimally demented subjects who are older than 78 years and who have low memory scores may be candidates for drugs that are used in the treatment of dementia. Most subjects (67%) who were younger than 78 years and had high memory scores (≥19) had reversible minimal dementia. However, one-third of the subjects predicted to have reversible minimal dementia did not have it and therefore additional diagnostic tests may be useful to predict outcome in these subjects. We have demonstrated before that the assessment of medial temporal lobe atrophy further increases the predictive accuracy in subjects with minimal dementia who have normal memory scores (Visser et al., 1999b). The remaining subjects had either reversible minimal dementia, persisting minimal dementia, or dementia after 2 or 3 year. Assessment of medial temporal lobe atrophy may also be useful to increase predictive accuracy in these subjects.

Strong points of the study were that we provided follow-up cognitive scores and that we tested a combination of predictor variables. One of the limitations of the study is that about 30% of the subjects had no follow-up assessment. This is not uncommon in population-based prospective studies of elderly subjects (Herlitz et al., 1997; O'Connor et al., 1991). Since the baseline characteristics of the subjects with no follow-up were similar to those who had at least one follow-up, it seems unlikely that selective attrition had occurred. About half of the subjects with reversible minimal dementia or persistent minimal dementia did not complete the 3-year follow-up. Although it is possible that selective attrition had occurred, it seems unlikely because the baseline characteristics and follow-up cognitive scores did not differ between subjects with a 3-year follow-up and subjects with only a 1- or 2-year follow-up (data not shown). Another limitation is that a 3-year follow-up was probably not long enough to establish the definite outcome of subjects with mini-

mal dementia. A fourth limitation is that the small group size limited the power of the study. Finally, it remains to be seen whether the findings from this population-based sample apply in a clinical setting.

In conclusion, the diagnosis of minimal dementia is made in mildly cognitively impaired subjects who form a heterogenous group with respect to clinical outcome. This heterogeneity in outcome can be reduced by looking at age, the apoE genotype, and the score on the CAMCOG memory subscale. Other diagnostic tests, such as assessment of medial temporal lobe atrophy, may further improve predictive accuracy. Subjects who remain minimally demented at follow-up are likely to become demented later because there is continued deterioration, but longer follow-up studies are necessary to establish the definite outcome in these subjects. The fact that depression was not associated with reversible minimal dementia suggests that when cognitive impairment and depression coexist, the cognitive impairment is not necessarily secondary to the depression.

Distinction between preclinical Alzheimer's disease and depression

4

SUMMARY

OBJECTIVE: To assess the prevalence of depression in subjects with preclinical Alzheimer's disease (AD) and to investigate the possibility of differentiating subjects with preclinical AD and depression from subjects with depression-related cognitive impairment.

DESIGN: A prospective observational cohort study.

SETTING: An outpatient memory clinic of an university-affiliated hospital.

PARTICIPANTS: Non-demented subjects with cognitive impairment older than 55 years (N=111) without neurological or somatic causes for the cognitive impairment.

MEASUREMENTS: At baseline data were collected on patient characteristics, the severity of depression, and cognitive functioning. The course of the cognitive impairment and the presence of dementia were assessed after 2 and 5 years.

RESULTS: Twenty-five subjects had preclinical dementia with Alzheimer's type dementia at follow-up. Sixty percent of these subjects (N=15) were depressed at baseline. Subjects with depression and preclinical Alzheimer's disease had at baseline a poorer performance on the cognitive tasks and were older than the subjects with depression-related cognitive impairment. Logistic regression with backward step selection selected age and memory performance as the best predictors for Alzheimer's type dementia in the depressed subjects. The specificity of these predictors for the diagnosis of future Alzheimer's type dementia in depressed subjects was 94%, the sensitivity 90%, the positive predictive value 90%, and the negative predictive value 94%.

CONCLUSIONS: Depression is common in preclinical Alzheimer's disease. Depressed subjects with preclinical Alzheimer's disease can be accurately differentiated from subjects with depression-related cognitive impairment by age and the severity of the memory impairment. Research that aims to investigate preclinical Alzheimer's disease should not exclude a priori subjects with depression since preclinical Alzheimer's disease is often accompanied by depression.

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INTRODUCTION

The differentiation between preclinical Alzheimer's disease (AD) and depression with cognitive impairment is one of the major challenges in psychogeriatric medicine because the symptoms of preclinical AD (cognitive impairment and depressed mood) overlap with those of depression. Preclinical AD refers to the prodromal stage of AD when the cognitive impairment is not yet severe enough to meet the criteria of dementia (Linn et al., 1995). Typically, subjects with preclinical AD demonstrate feelings of anxiety, worry, depression, and psychological vulnerability, but these feelings are less pervasive and less severe than they are in subjects with major depression (Cummings, 1989; Rubin et al., 1989a). Depression in turn can cause cognitive impairment, and this impairment often affects cognitive domains that are also impaired in AD (Christensen et al., 1997a). For this reason, many studies investigating preclinical AD have excluded subjects with depression.

While research has focussed on the differentiation between dementia and depression (desRosiers et al., 1995; Emery et al., 1992), there are no studies on the differences between preclinical AD and depression. One cross-sectional study compared the neuropsychological test performance of subjects with mild cognitive impairment with that of subjects with depression but the cross-sectional design did not allow investigation of the relation between cognitive impairment and subsequent dementia (Rubin et al., 1991). Prospective studies on the relation between mild cognitive impairment and dementia either excluded subjects with depression or did not pay attention to the co-occurrence of depression and cognitive impairment (Devanand et al., 1997; Flicker et al., 1991; Jacobs et al., 1995; Tierney et al., 1996a). The prognosis with regard to subsequent dementia in nondemented patients with depression and mild cognitive disturbances therefore remains unknown. It is also not known how many subjects with preclinical AD have been excluded from prospective studies of non-demented elderly with mild cognitive impairment because depression was an exclusion criterion. The early diagnosis of AD in subjects with mild cognitive impairment is important because these subjects might benefit from treatment with drugs that improve cholinergic transmission (Knapp et al., 1994; Rogers et al., 1998), or drugs that may slow the progression of the disease, such as antioxidants (Pitchumoni et al., 1998; Sano et al., 1997), nonsteroidal anti-inflammatory drugs (Rogers et al., 1993), or estrogens (Felician et al., 1999). In addition, the early recognition and treatment of depression in subjects who are not preclinically demented may improve their prognosis.

The present study investigated prospectively a cohort of non-demented elderly subjects with cognitive impairment who attended a memory clinic. Many of these subjects also had depressive symptoms. The aim of the study was twofold. First, we

established the prevalence of depression in subjects with preclinical AD. Second, we investigated whether subjects with preclinical AD and depression could be differentiated from subjects with depression-related cognitive impairment with respect to age (an important risk factor for AD), depression severity (mild or moderate depression), and cognitive performance. A distinction was made between mild and moderate depression because previous studies indicated that the depression in preclinical AD is mild in most patients (Cummings, 1989; Devanand et al., 1996), and because depression-related cognitive impairment is more severe in moderate depression than in mild depression (Christensen et al., 1997a).

METHODS

Subjects

The patients were selected from the Maastricht Memory Clinic, an outpatient clinic of an university-affiliated hospital for subjects with cognitive impairment (Verhey et al., 1993a). The patients were referred by a general practitioner (53%), a neurologist (28%), or a psychiatrist (19%). Subjects older than 55 years were eligible for inclusion in the study. We excluded subjects with dementia (according to DSM-IV criteria (APA, 1994) and/or a score on the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) below 24 or a score on the Global Deterioration Scale (GDS) (Reisberg et al., 1982) higher than 3), severe sensory impairment, psychosis, panic disorder, post-traumatic stress disorder, bipolar disorder, or cognitive problems in relation to cerebrovascular events, neurodegenerative diseases (e.g., Parkinson's disease), brain neoplasm, head trauma, drug intoxication, alcohol abuse, hypothyroid or hyperthyroid function, or vitamin deficiency. The subjects typically had very mild cognitive decline (GDS stage 2) or mild cognitive decline (GDS 3). The study cohort consisted of 111 subjects. After the study was explained to them, subjects gave their written informed consent.

Baseline assessment and clinical diagnosis

All subjects underwent a standardized baseline assessment that included a detailed history provided by the patient and a significant other, a psychiatric, neurological, and physical examination, appropriate laboratory tests, a neuropsychological assessment (see below), and neuroimaging as described elsewhere (Verhey et al., 1993a). In addition, the MMSE (Folstein et al., 1975), as a measure of global cognitive impairment, the Hamilton Depression Rating Scale-17 items (HDRS) (Hamilton, 1960), the GDS (Reisberg et al., 1982), which is a scale for staging levels of cognitive impairment, and the Blessed Dementia Rating Scale (BDRS) part I (Blessed et al., 1968), as a measure of daily functioning and changes in personality, were ad-

ministered. Depression was diagnosed when the subjects fulfilled the criteria of minor or major depression according to DSM-IV criteria (APA, 1994). This group was subdivided according to the score on the HDRS into a mildly depressed group (HDRS <17) and a moderately depressed group (HDRS ≥ 17) (Hill et al., 1992). None of the subjects were severely depressed (HDRS score higher than 26). All subjects were treated according to standard clinical practice but not according to a specific treatment protocol.

Follow-up procedure

After 2 years and 5 years the subjects were invited for a follow-up assessment. It consisted of a standardized questionnaire about medical history and cognitive complaints, the MMSE, the HDRS, and a neuropsychological test protocol (see below). A neuropsychiatrist and a neuropsychologist, who were unaware of the results of the baseline assessment, diagnosed dementia and AD at follow-up according to the DSM-IV (APA, 1994) and NINCDS-ADRDA criteria (McKhann et al., 1984). If there was disagreement about the clinical diagnosis, a consensus meeting was held and if no agreement was reached the subject was considered not demented. If the subject refused to come for the follow-up assessment, a telephone interview was conducted which included a standardized questionnaire about medical history and cognitive complaints, and the Telephone Interview for Cognitive Status (Brandt et al., 1988) (N=4). If the subject was unable to take part in the telephone interview, a significant other was contacted (N=2).

Neuropsychological assessment

The neuropsychological assessment consisted of a series of standard clinical tests covering the cognitive domains of memory, language, attention, praxis, executive functions, and intelligence, as described elsewhere (Jolles, 1986; Verhey et al., 1993a). In order to reduce the number of variables, we selected three variables that could best differentiate at baseline between subjects with AD at follow-up and nondepressed subjects with no AD at follow-up. The variables that were significantly different between these groups at baseline were entered together with age in a logistic regression model. We then selected, by backward step selection, the three neuropsychological variables that remained in the model for the longest. These variables were delayed recall, time to complete the memory scanning task, and fluency.

Delayed recall from the Auditory Verbal Learning Test (Brand et al., 1985; Lezak, 1995). Fifteen words were presented five times and after each presentation the subject was asked to reproduce as many words as possible. After 20 minutes, the delayed

recall was tested. Three subjects were given a 10-word version of the test. Their results were multiplied by 1.5 to make them comparable to the others.

Time to complete the Memory Scanning Task Letter 1 (MST-L1) (Brand et al., 1987). The subject had to memorize one target letter and cross it out from a sheet containing 24 target letters and 120 nontarget letters. This is a measure of the speed with which information is retrieved from working memory.

Fluency. Fluency was defined here as the ability to name as many professions/trades as possible within 1 minute. It can be regarded as a measure for strategy-driven retrieval of information from semantic memory.

Correction for age, education and sex

Since the MMSE and the neuropsychological test scores correlate with age, sex, and education, we corrected the scores for these variables. The neuropsychological data are expressed as z-scores. The z-score is the number of standard deviations from which the score deviates from the expected score in a normal population of a given age, sex, and education. The z-scores were based on a reference population of 1370 cognitively normal subjects randomly selected from a registry of general practitioners (Jolles et al., 1995; van Boxtel et al., 1998). In this population, multiple linear regression was performed with age, sex, and education entered in the first step, using $P<.05$ as the criterion for remaining in the model. In the next step, nonlinear terms and interaction terms for the significant main effects were entered. The MST-L1 was log transformed to increase the linear relationship with age. On the basis of the resulting model, an expected test score for each subject was calculated. This score was subtracted from the observed score. The residue was divided by the standard deviation of the residue in the reference population to give the z-score. The sign of the z-scores of the MST-L1 was inverted such that a z-score below zero indicated below average performance.

The MMSE was corrected for age, sex, and education in the same way, but the residue was now subtracted from the average expected MMSE score in the study population. Raw data are also given to facilitate comparisons with other studies.

Statistical Analysis

Group comparisons with continuous variables were carried out with a t-test or with the Mann-Whitney test corrected for ties when group size was smaller than 10. The group differences in scores on the BDRS variables were also analyzed with the Mann-Whitney test corrected for ties. Categorical data were analyzed with a Chi square test with continuity correction. When two cells or more had fewer than 5 cases, the two-tailed Fisher's exact test was applied. To identify risk factors for AD in the subjects with depression at baseline, logistic regression with backward step

selection was used with AD at the 2-year follow-up, and, for subjects without AD at the 2-year follow-up, also with AD at the 5-year follow-up, as outcome variable. We allowed different probabilities of AD in both periods, but the relation of the covariates to AD in each period was the same. This technique makes optimal use of the available data where some subjects had only a 2-year follow-up, and is known as continuation ratio ordinal regression (Scott et al., 1997). To evaluate the predictive accuracy of the predictors of AD selected in the continuation ratio ordinal regression analysis, these variables were entered in a logistic regression analysis with only subjects who completed the 5-year follow-up. All statistical tests were two-tailed. The significance level was set at 0.05.

RESULTS

Outcome at follow-up

Of the 111 subjects evaluated at baseline, 98 (88%) were seen after 2 years and 52 of these (53%) were also seen after 5 years. The final available evaluation was taken as the follow-up time point. Two subjects (2%) died before follow-up. Nine subjects (8%) had no follow-up because they were untraceable (N=3) or refused to participate (N=6). Two subjects (2%) were excluded from the study because the diagnosis of Parkinson's disease or cerebral bleeding was made at the 2-year follow-up. Subjects with no follow-up were significantly older at baseline than the subjects who were not demented at follow-up (table 4.1).

Dementia was diagnosed in 19 subjects after 2 years. At the 5-year follow-up, dementia was diagnosed in another 6 of the 41 patients who were not demented at the 2-year follow-up. In 24 subjects the diagnosis probable Alzheimer was made and in one subject the diagnosis of possible Alzheimer was made. We refer to these subjects as the 'preclinical AD group'.

Frequency and severity of depression at baseline

Depression at baseline was diagnosed in 62 out of 111 subjects (56%). Sixty percent of the patients with preclinical AD were depressed at the time of the baseline evaluation, as were 52% of the subjects without dementia at follow-up. Mild depression tended to be more common in the depressed preclinical AD group (87%) than in the depressed no dementia group (61%) (p= 0.13).

Distinction between depression with and without AD at follow-up

The baseline characteristics of the subgroups with mild or moderate depression at baseline and no dementia at follow-up and those of the subgroup with depression at baseline and preclinical AD are given in table 4.2. The baseline characteristics of the

Table 4.1 Baseline characteristics according to outcome at follow-up.

	Outcome at follow-up				No follow-up
Variable	Not demented (N=73)	Demented (N=25)	Died (N=2)	Exclusion (N=2)	(N=9)
Age (SD)	63.1 (6.2)	70.6 (6.6)*	81.5 (3.5)*	74.9 (1.8)	70.8 (6.5)*
Male/Female	43/30	11/14	0/2	2/0	4/5
Education (Years) (SD)	10.0 (1.3)	10.2 (1.3)	11 (5.0)	8.0 (2.0)	9.8 (4.5)
GDS -2	42	6*	0	0	5
-3	31	19	2	2	4
BDRS (SD)	1.4 (1.2)	2.2 (1.5)*	3.5 (1.4)	3.8 (1.8)	1.8 (1.7)
Depression severity					
-No depression	35	10	0	0	4
-Mild depression	23	13	2	1	2
-Moderate depression	15	2	0	1	3
HDRS (SD)	10.2 (6.5)	9.4 (5.0)	10.0 (1.4)	13.5 (7.8)	11.1 (9.3)
MMSE (SD)	28.3 (1.6)	26.8 (1.9)*	26.5 (0.71)	25.5 (2.1)	28.3 (1.4)
MMSE corrected (SD)†	28.1 (1.5)	27.2 (1.9)*	27.1 (0.6)	26.9 (1.6)	28.6 (1.7)
Delayed recall (SD)‡	-0.63 (1.2)	-1.63 (1.3)*	-2.33 (0.04)	-0.89 (1.2)	-0.73 (1.3)
MST-L1 (SD)‡	-0.63 (1.0)	-1.39 (1.5)*	-1.88§	-2.1§	-0.93 (0.91)
Fluency (SD)‡	-0.41 (0.98)	-0.93 (0.83)*	-1.61 (1.1)	-1.8§	-0.61 (0.74)

*P <0.01, compared to the not-demented group. †Corrected for age, sex, and education. ‡Z-scores corrected for age, sex, and education. §Data available for only one subject.

subjects with preclinical AD with mild (N=13) or moderate (N=2) depression at baseline were not significantly different.

The subjects with mild or moderate depression and no dementia at follow-up were significantly younger at baseline than the subjects with depression and preclinical AD. There were no differences in sex or education between the groups. The MMSE and the three cognitive scores at baseline were significantly better in the subjects with mild depression than in the subjects with preclinical AD. The delayed recall score at baseline was in the subjects with moderate depression significantly better than in the subjects with preclinical AD. With the exception of the HDRS score, the baseline scores of the mildly and moderately depressed subjects without dementia at follow-up were similar.

In all subgroups depression was less severe at follow-up than it was at baseline. The depressed subjects with preclinical AD had at follow-up significantly poorer scores on the MMSE, the delayed recall, and fluency than the depressed subjects without preclinical AD (table 4.2). The change in MST-L1 performance of the subjects with preclinical AD was significantly different from that of the subjects

Table 4.2 Baseline characteristics of the subgroups with mild or moderate depression at baseline and no dementia or dementia at follow-up

	Mild depression at baseline	Moderate depression at baseline	Mild or Moderate depression at baseline	Statistics	
	Not Demented at follow-up (Group 1)	Not Demented at follow-up (Group 2)	Demented at follow-up (Group 3)	Group 1 vs group 3	Group 2 vs group 3
	(N=23)	(N=15)	(N=15)	*P* -value	*P* -value
Age (SD)	64.4 (7.1)	62.5 (6.8)	71.5 (5.8)	.002	.001
Male/Female	10/13	8/7	7/8	.85	.72
Education (Years) (SD)	10.3 (3.3)	8.6 (2.5)	10.2 (3.3)	.91	.15
% with 5 year follow-up	57	20	67	.74	.03
Depression severity at follow-up					
-No depression	16	4	8	.30	.16
-Mild depression	4	8	5		
-Moderate depression	1	2	1		
HDRS at baseline (SD)	11.4 (3.4)	19.5 (3.1)	12.3 (4.0)	.47	<.001
Change HDRS	-5.7 (4.7)	-7.5 (4.9)	-3.6 (5.4)	.28	.07
MMSE *	28.3 (1.2)	28.0 (1.7)	27.2 (1.6)	.02	.24
Change MMSE	-0.54 (2.2)	-0.70 (3.0)	-4.2 (4.4)	.01	.03
Delayed recall (SD)†	-0.50 (1.3)	-0.76 (1.2)	-1.78 (1.3)	.005	.03
Change Delayed recall	-0.02 (0.84)	0.30 (1.1)	-0.81 (0.70)	.007	.004
MST-L1 (SD)†	-0.52 (1.1)	-0.79 (1.3)	-1.57 (1.4)	.02	.16
Change MST-L1	-0.01 (0.93)	-0.43 (0.93)	-0.93 (0.77)	.03	.24
Fluency (SD)†	-0.35 (1.0)	-0.71 (0.85)	-1.04 (0.70)	0.004	0.29
Change Fluency	0.18 (0.81)	-0.16 (0.49)	-0.84 (0.64)	0.001	0.01

*Corrected for age, sex, and education. †Z-scores corrected for age, sex, and education.
The change scores only include subjects with scores at both baseline and at follow-up.

with mild depression. Fewer of the subjects with moderate depression attended the 5-year follow-up than did the subjects with preclinical AD (table 4.2).

Logistic regression was performed with AD at follow-up as dependent variable and age at baseline, depression severity (mild or moderate) at baseline and the scores on the delayed recall, the fluency and the MST-L1 at baseline as independent variables. In order to include all subjects in the multivariate analysis, subjects with missing data (MST-L1: N=6; fluency: N=4) were given the average z-score of the study population for that test. Age (OR 1.25 per unit change, 95% CI 1.10-1.43,

P<.001) and the z-score for delayed recall (OR 0.31 per unit change, 95% CI 0.15-0.63, *P*=.001) were selected with backward step selection. The predictive accuracy of age and the z-score for delayed recall for predicting AD in depressed subjects who completed the 5-year follow-up (N=26) was high: the specificity was 94%, the sensitivity 90%, the positive predictive value 90%, and the negative predictive value 94%.

The relation between age and the z-score for delayed recall in depressed subjects with and without AD at follow-up is shown in figure 4.1. Seven subjects with only a 2-year follow-up had questionable dementia at that time. They did not meet all the criteria for dementia and were therefore not diagnosed as being demented. These subjects are marked separately in figure 4.1.

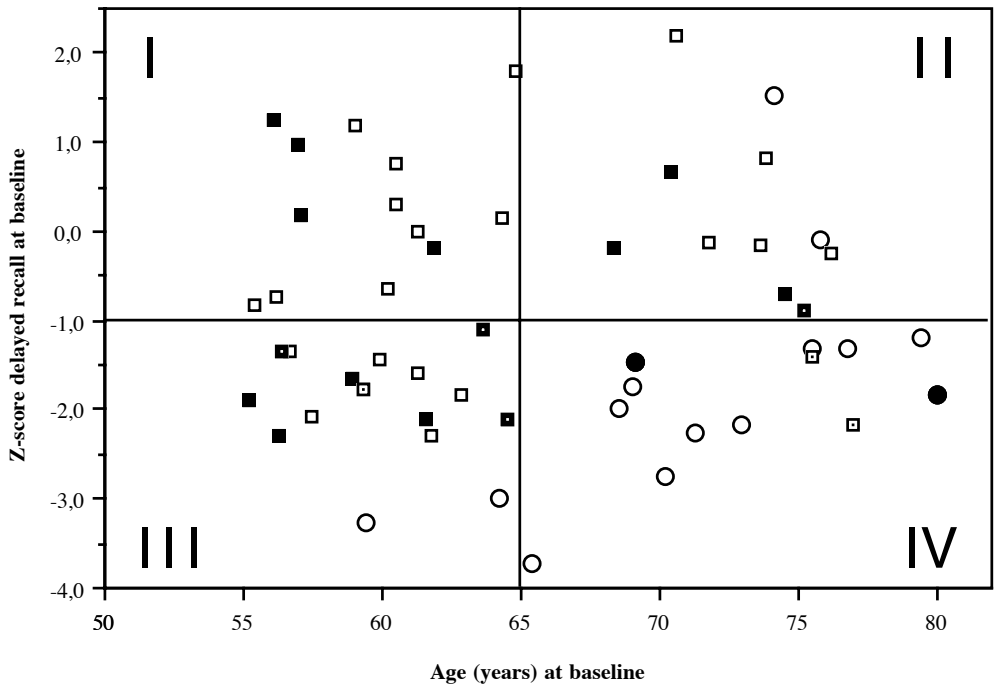

Figure 4.1 The relation between age and the z-score of the delayed recall in depressed subjects with AD at follow-up (circles) and depressed subjects without dementia at follow-up (squares). An open circle/square means that the subject had mild depression at baseline; a filled circle/square means that the subject had moderate depression at baseline. A point in a square indicates that the subject had questionable dementia at the 2-year follow-up.

DISCUSSION

Two main conclusions can be drawn from the results. First, depression is very common in preclinical AD and is often mild in character. Second, it is possible to predict AD in depressed subjects with high accuracy on the basis of their age and memory function. Before we discuss these findings, some limitations of the study should be mentioned.

Not all subjects completed the 5-year follow-up and some of them would have become demented during this time period. This reduces the diagnostic accuracy. We dealt with this problem in two ways. First, we used continuation ratio ordinal regression and, second, we calculated the predictive accuracy on the basis of the subjects who had 5-year follow-up data. Our results may not apply in settings were the prevalence of depression or preclinical AD is different or in settings were subjects are more severely depressed. The strengths of the study were its prospective nature and the length of the follow-up. The clinical setting makes the results relevant to the clinician working in second-line care.

The high prevalence of depression in the subjects with preclinical AD in this study confirms the results of earlier studies (Devanand et al., 1996; La Rue et al., 1993). The mild character of the depression in preclinical AD is in accordance with previous reports (Cummings, 1989; Devanand et al., 1996), and has also been reported in patients with AD (Migliorelli et al., 1995). However, we may have underestimated the prevalence of moderately severe depression in preclinical AD because 80% of the moderately depressed subjects without dementia at follow-up had only a 2-year follow-up.

The best predictors for AD in depressed subjects were their age and the score on the delayed recall task. Figure 4.1 shows that subjects in quadrant I (age below 65, z-score delayed recall > -1) had no risk of AD, while subjects in quadrant IV (age above 65, z-score delayed recall < -1) had a very high risk of AD. Subjects in quadrant II (age above 65, z-score delayed recall > -1) had a 20 to 30% risk of AD, depending on the outcome of the subjects with questionable dementia. About one third of subjects in quadrant III (age below 65, z-score delayed recall < -1) had AD or questionable dementia at follow-up. The likelihood that subjects in this quadrant would have AD at follow-up increased when the z-score of the delayed recall was below -2.5. Fluency and performance of the memory scanning task were not predictors of AD in the depressed subjects, probably because the scores for these tasks overlapped in moderately depressed nondemented subjects and depressed subjects with preclinical AD. This overlap was also recently reported in a meta-analysis of cognitive dysfunction in depression and AD (Christensen et al., 1997a). Since the fluency task and the memory scanning task involve executive functions (Lezak,

1995), which are supposed to be dependent on prefrontal mechanisms (Lezak, 1995), the present data imply that frontal lobe dysfunction would appear to be present in the early stage of AD. The frontal lobe dysfunction in the preclinical AD subjects in our study was not associated with the depression in these subjects because performance of the fluency task and the memory scanning task was similar to that of the subjects with preclinical AD who were not depressed at baseline (data not shown). Thus, the classical distinction between temporoparietal dysfunction in AD and frontal dysfunction in depression can be questioned. The distinction between depressed subjects with and without AD at follow-up can be increased further by using other neuropsychological tests or by biological markers of preclinical AD, such as hippocampal atrophy (Visser et al., 1999b).

The degree of cognitive impairment in the depressed subjects was mild and of the same order of magnitude as that recently reported in a meta-analysis of cognitive dysfunction in depression (Christensen et al., 1997a). Although the severity of depression in the depressed subjects without preclinical AD was diminished at follow-up, this was not accompanied by an improvement of performance of the cognitive tasks, with the exception of the improvement of delayed recall performance in the moderately depressed subjects. This improvement of delayed recall performance was more pronounced when we excluded the subjects with questionable dementia at the 2-year follow-up. Exclusion of these subjects did not result in a greater improvement in the performance of the other tasks (data not shown). The relation between the improvement of depression and the change in cognitive function will be described in detail elsewhere.

The high prevalence of depression in preclinical AD means that research criteria for preclinical AD that exclude subjects with depression, such as the criteria of age-associated memory impairment (AAMI) (Crook et al., 1986), and age-associated cognitive decline (AACD) (Levy, 1994), will also exclude a large number of subjects with preclinical AD. For example, the exclusion criterion of a HDRS score above 12 of the AAMI criteria would have excluded 6 of the 25 subjects (24%) of our sample who had preclinical AD. We therefore suggest that only severely depressed subjects should be excluded, for example those with a HDRS score above 20 which is the highest score on the HDRS of the subjects with preclinical AD.

In conclusion, we demonstrated that depression is common in preclinical AD and is often mild in character. Age and severity of cognitive impairment accurately distinguish between depressed subjects with preclinical AD and depressed subjects without dementia at follow-up. Subjects older than 65 years with mild or moderate depression and a score on the delayed recall task 1 SD below the expected score are likely to have preclinical AD. Research that aims to investigate preclinical AD

should not exclude a priori subjects with depression since preclinical AD is often accompanied by depression.

Medial temporal lobe atrophy and memory dysfunction as predictors for dementia in subjects with mild cognitive impairment

5

SUMMARY

OBJECTIVE: To determine whether the medial temporal lobe is atrophic in subjects with mild cognitive impairment and whether atrophy of this structure is a better predictor of dementia than memory dysfunction is.

METHODS: Forty-five non-institutionalized subjects aged 65-85 years were randomly selected from a population based study to obtain a sample with Alzheimer's disease (AD; n=7), and a clinically non-demented sample (n=38). Twenty of the latter subjects displayed some cognitive impairment and fulfilled CAMDEX criteria for 'minimal dementia'. Coronal T1- weighted MRI was used to visualize the medial temporal lobe. The volume of the parahippocampal gyrus and hippocampus was measured and medial temporal lobe atrophy was assessed qualitatively. The memory subscore from the the CAMCOG was used as a measure of memory functioning. The follow-up period was 3 years.

RESULTS: Nine subjects who were diagnosed as being minimally demented at baseline met the criteria for AD during follow-up. At baseline, the volume of the parahippocampal gyrus of these subjects was smaller than that of the other subjects with minimal dementia. The memory score was the best predictor of clinical outcome. All medial temporal lobe measures increased the accuracy of prediction compared with only the memory score, by reducing the number of false-negative classifications of dementia.

CONCLUSIONS: Severe medial temporal lobe atrophy is already present in some subjects with mild cognitive impairment and is an indicator of subsequent AD. The absence of medial temporal lobe atrophy, however, does not exclude the development of dementia. In the majority of the subjects, memory impairment was a better predictor for dementia than atrophy of the medial temporal lobe. The combination of both could increase predictive accuracy. Non-demented subjects with severe atrophy of the medial temporal lobe could be enrolled in drug trials aimed at slowing the progression of AD.

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INTRODUCTION

Alzheimer's disease (AD) is the most common type of dementia. The diagnosis of AD requires multiple cognitive impairment, including memory dysfunction that is severe enough to interfere with activities of daily living (McKhann et al., 1984). Cognitive symptoms and brain abnormalities, however, are present many years before a clinical diagnosis of AD can be made. This preclinical phase of AD is the subject of intensive investigation because earlier diagnosis of AD may allow drug therapy to be started earlier, which may improve the clinical response.

The earliest neuropathological changes occur in the medial temporal lobe (Braak et al., 1992), which includes the hippocampus and parahippocampal gyrus. Atrophy of these structures can be detected by Magnetic Resonance Imaging (MRI) in an early stage of AD (Convit et al., 1997; Frisoni et al., 1996; Jack et al., 1997; Kesslak et al., 1991; Laakso et al., 1995; Lehéricy et al., 1994; Pantel et al., 1997; Scheltens et al., 1997a; Scheltens et al., 1992). Because the medial temporal lobe plays an important role in the storage of new information (Rombouts et al., 1997; Squire et al., 1991), this atrophy may explain why memory dysfunction is an early symptom of AD (Petersen et al., 1994b; Storandt et al., 1989). Consistent with this, subjects with memory impairment who do not meet the criteria of dementia have an increased risk for subsequent AD (Bowen et al., 1997; Flicker et al., 1991; Linn et al., 1995; Tierney et al., 1996a). In the same way, atrophy of the hippocampus or parahippocampal gyrus increases the risk for subsequent AD in elderly non-demented individuals (de Leon et al., 1993a; Kaye et al., 1997), and in asymptomatic individuals at risk for autosomal dominant AD (Fox et al., 1996).

The aim of the present study was to investigate whether atrophy of the medial temporal lobe is present in mildly impaired subjects who later became demented. In order to get insight into the relation between memory function and medial temporal lobe atrophy, we compared the predictive value for dementia of medial temporal lobe atrophy with that of memory performance alone and the combination of the two. We also investigated the correlation between brain volumes at baseline and cognitive scores at baseline and the decline in cognitive scores at follow-up. In this way we investigated the relation between medial temporal lobe atrophy and cognitive decline as a continuous variable rather than as a dichotomous one.

To exclude the possiblity that medial temporal lobe atrophy is a reflection of generalized atrophy of the brain, we also measured the volume of the remaining part of the temporal lobe. Further, to obtain reference values for cognitive function and brain volumes in AD, we included mildly to moderately demented AD patients. These subjects did not take part in the follow-up study.

METHODS

Subjects

The subjects were participants of the Amsterdam Study of the Elderly (AMSTEL), a two-stage population-based study of mental functioning in non-institutionalized people aged 65-85 years living in Amsterdam, The Netherlands (Launer et al., 1993; Scheltens et al., 1997b). From the 4051 members of the baseline cohort, 787 individuals, randomly selected by age (5-year strata, 65-69 to 80-84 years) and Mini Mental State Examination score (MMSE) (Folstein et al., 1975) (MMSE scores <21, between 22-26 and >27) were asked to participate in a 3-year follow-up study of cognitive function. Of these, 511 individuals (65%) agreed to participate. For the neuroimaging study we randomly selected, from the subjects of the follow-up study, a subsample with a range of cognitive functions to include clinically normal individuals and mildly to moderately demented individuals (Launer et al., 1995). Of the 73 individuals classified as suffering from minimal dementia (see below), 33 were asked to participate and 28 (84%) agreed. As far as possible, a demented individual and a normal individual from the same 5-year age strata and MMSE strata were selected and asked to participate: 19 (70%) of the 27 normal individuals agreed to participate and 16 (76%) of the 21 demented individuals agreed. Thus, the sample overrepresented the group with minimal dementia. Within strata of dementia severity, individuals who did or did not agree to participate did not differ significantly with respect to the CAMCOG score for global cognitive function and its subscale measuring memory function. All subjects gave their informed consent prior to inclusion in the neuroimaging study. Subjects with a diagnosis of depression or dementia due to causes other than AD were excluded (n=9). Of the resulting 54 scans made, 3 could not be used because of movement artefacts and 6 because the scans had not been completely stored on magnetic tape. Of the nine subjects with missing MRI scans, eight had minimal dementia subjects and one had AD. Thus, the scans for 45 subjects were available: 38 non-demented subjects at baseline (20 normal subjects and 18 subjects with minimal dementia) and 7 demented subjects at baseline.

Baseline assessment and clinical diagnosis

Each subject was assessed for dementia by means of an examination conducted at home by a research nurse and a physician. The assessment included a questionnaire, cognitive tests, and a clinical examination with the validated Dutch version of the CAMDEX protocol (Derix et al., 1992; Roth et al., 1986). The cognitive section of the CAMDEX, the CAMCOG, includes sections for testing memory, praxis, calculation, language, attention, concentration, abstract thinking, and orientation, and has a maximum score of 107. An informant interview was administered to the

closest relative or caregiver. The diagnoses of dementia and AD were made according to the DSM-IIIR (APA, 1987), and NINCDS-ADRDA criteria (McKhann et al., 1984), respectively. The diagnosis of minimal dementia was made when the DSM-IIIR criteria of dementia were not met but, based on an overall clinical impression, there was limited and variable impairment in cognitive and social functioning, such as difficulty with learning and recalling events, a tendency to misplace possessions, and minor errors in orientation. Similar entities are 'questionable dementia' or a score of 0.5 on the clinical dementia rating scale (Hughes et al., 1982), and 'mild cognitive impairment' or a score of 3 on the global deterioration scale (Reisberg et al., 1982).

Cognitive measures

We used the CAMCOG total score, the memory subscore of the CAMCOG, and the MMSE. To calculate the change in these scores during follow-up we calculated the net change per year of follow-up. Several subjects who developed AD during the study dropped out before the third follow-up assessment. Therefore, we calculated an adjusted decline score. This score was based on the assumption that once AD was diagnosed at follow-up, the course of cognitive decline would be the same as that in the AD subjects at baseline. For example, in subjects with only a 1-year follow-up we added the average decline of the AD patients at baseline over 2 years, and divided the total decline by three.

Follow-up

Subjects were reassessed annually for 3 years according to the CAMDEX protocol in order to assess the clinical outcome (normal, minimally demented, demented) and the changes in cognitive functioning. The subjects who left the study before the third assessment but after the diagnosis of AD was made were included in the analysis.

MRI acquisition and morphometric analyses

MRI was performed on a Teslacon II (Technicare, Solon, Ohio) operating at 0.6 Tesla, according to a standard protocol reported previously (Scheltens et al., 1992). For this study we used 6 T1-weighted (TR 300 ms, TE 22 ms) coronal slices parallel to the brainstem axis and perpendicular to the hippocampal axis, planned from a midsagittal scout image. Slice thickness was 5 mm with an interslice gap of 1 mm and an in-plane resolution of 0.8 x 1.0 mm.

We selected four consecutive slices such that the first and second slices were made through the head of the hippocampus, and the third and the fourth slices through the body of the hippocampus (figure 5.1). Volumetry was carried out on a SUN workstation with in-house developed software. The hippocampus, the parahip-

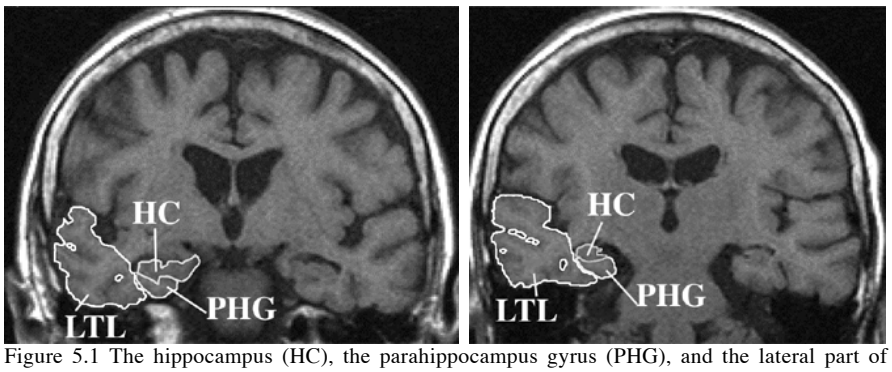

Figure 5.1 The hippocampus (HC), the parahippocampus gyrus (PHG), and the lateral part of the temporal lobe (LTL), at the level of the head of the hippocampus (left image) and the body of the hippocampus (rigth image).

pocampal gyrus, and the intracranial area, as a measure of the intracranial volume, were outlined by hand. A seed function was used for the temporal lobe. The volume of the hippocampus included the hippocampus proper, dentate gyrus, the alveus, and the subicilum. On the first slice, the hippocampus was disconnected from the amygdala with a straight line through the lowest point of the connection between these two structures. The collateral sulcus was taken as the lateral border of the parahippocampal gyrus. The temporal lobe was disconnected from the rest of the brain at the temporal stem: a straight line was drawn from the deepest point of the fissura circularis to the upper-lateral border of the lateral ventricle. For the intracranial area, the outline of the inner table was followed. Below the temporal lobe, either the outer border of the temporal gyri or the tentorium cerebellum was followed and from the medial part of the temporal lobe a straight line was drawn to the bottom of the third ventricle. The volumes of the hippocampus and parahippocampal gyrus were substracted from the volume of the total temporal lobe to give the volume of the lateral temporal lobe. The volumes of the left and right sides were summed because the volumes of the two sides were not statistically significantly different from each other. To correct for individual differences in the volume of the intracranial area, the brain volumes were adjusted (see below) and these adjusted values were used for all analyses. All measurements were done by one rater who was blinded to the subjects' age, diagnosis, and sex. The average difference between the first and second measurement of the brain structures on 10 scans was -0.08 cm^3 (SD 0.29) for the parahippocampal gyrus, -0.07 cm^3 (SD 0.20) for the hippocampus, 0.14 cm^3 (SD 1.1) for the lateral temporal lobe, and -1.9 cm^3 (SD 1.4) for the intracranial area.

Medial temporal lobe atrophy was assessed visually by a neurologist and radiologist in conference, who were blinded to the subjects' age, diagnosis, and sex.

Scores ranged from 0 (no atrophy) to 4 (severe atrophy). The rating scale is based upon a visual estimation of the volume of the medial temporal lobe, including the hippocampus proper, dentate gyrus, subicilum, and parahippocampal gyrus, and the volume of the surrounding CSF spaces, in particular the temporal horn of the lateral ventricle and the choroid fissure, on both sides. In case of severe asymmetry, the score of the most affected side was used. The visual method of scoring correlates well with linear and volumetric measurements and has an high intra-rater reliability (kappa=0.70) (Scheltens et al., 1995; Scheltens et al., 1992; Vermersch et al., 1994).

Statistical analysis

The data were analyzed using SPSS for the Macintosh 4.0 (SPSS Inc., Chigaco, IL, USA). Categorical data were analyzed by a Chi-squared test. The Chi-squared test for trend was used to analyze the medial temporal lobe atrophy scores. Group comparisons of continuous data listed in table 1 were analyzed by using ANOVA and corrected for multiple testing according to Bonferroni. Group comparisons of continuous data listed in table 2 were analyzed by using the Mann-Whitney test. Linear regression was used to correct the brain volumes for differences in intracranial area as described by Jack et al. (1989). Regression coefficients for this correction were derived from the regression analysis of the volume of the brain structures on the intracranial area of the non-demented subjects with completed follow-up and no evidence of cognitive decline. Logistic regression was used to assess the predictive value of memory score, parahippocampal gyrus, hippocampus, medial temporal lobe atrophy score and the combination of memory score and the brain measures for clinical outcome at follow-up (demented or not). This analysis was performed with a combined sample of normal subjects and subjects with minimal dementia at baseline. To assess whether the model improved after addition of one of the brain measures to the memory score, the change in -2Log Likelihood (-2LL) was tested. In the logistic regression analysis, the memory score was corrected for age and education. This correction was based on the linear regression of these variables on the baseline memory score of a sample of 188 subjects from the AMSTEL study without diagnosis of dementia after a 3-year follow-up. The same method was used as for the correction of differences in the volume of the intracranial area (see above). The correlation between brain volumes and cognitive scores at baseline was calculated by linear regression with age and education as covariate, using data for the combined sample of normal subjects and minimally demented subjects. The correlation between brain volumes at baseline and change in cognitive scores during follow-up was calculated by linear regression with age as covariate. Since nine comparisons were made for the correlation between brain volumes and baseline

cognitive scores or rate of cognitive decline, we adjusted for multiple testing according to Bonferroni and considered *p*-values lower than 0.0056 as significantly.

RESULTS

Baseline characteristics

The baseline characteristics of the normal subjects, minimal dementia subjects, and subjects with AD at baseline are listed in table 5.1. Demographic variables were comparable between the groups. As expected, cognitive impairment was severe in the subjects with AD and mild in the subjects with minimal dementia. Brain structures were smaller in the AD group than in the normal group, but this difference was significant for the parahippocampal gyrus only. The volumes of the hippocampus and parahippocampal gyrus in the minimal dementia group were in between those of the normal subjects and the subjects with AD.

Table 5.1 Demographic characteristics, cognitive scores and brain volumes at baseline

	Normal (n=18)	Minimal dementia (n=20)	AD (n=7)
Age in years	76.8 (4.0)	78.8 (4.8)	79.6 (4.9)
Sex, % male	44%	30%	14%
Education in years	8.2 (2.9)	7.7 (2.1)	7.1 (2.0)
Memory score	22 (3.4)	15 (5.2)†	7 (3.8)†‡
CAMCOG score	89.5 (8.4)	74.8 (8.1)†	59 (15.0)†‡
MMSE score	27.1 (2.8)	22.6 (2.0)†	16.6 (6.0)†‡
Range	22-30	19-27	8-25
HC volume	4.73 (0.4)	4.67 (0.5)	4.25 (0.6)
PHG volume	5.77 (0.6)	5.5 (0.7)	5.06 (0.3)†
LTL volume	43.3 (3.6)	42.4 (4.4)	40.0 (2.0)
ICA	261 (22)	253 (17)	256 (17)
MTA score			
-0	8	3	0 †
-1	9	10	3
-2	0	7	3
-3	1	0	1

*AD=Alzheimer's disease; HC=Hippocampus; PHG=Parahippocampal gyrus; LTL=Lateral part temporal lobe; ICA= Intracranial area; MTA= Medial temporal lobe atrophy. Continuous data are means (SD). All volumetric data are in cm^3. † $p < 0.05$ compared to normal group, ‡ $p < 0.05$ compared to the minimal dementia group. All *p*-values are corrected for multiple testing according to Bonferroni.

Outcome at follow-up

Nine subjects left the study before the first follow-up assessment and two subjects between the second and the third follow-up assessments because of refusal (n=7), inability to contact (n=3), and death (n=1). Four of these subjects were from the normal group and had a statistical significantly lower CAMCOG total score and a smaller parahippocampal gyrus volume than the other normal subjects. One of these subjects had severe medial temporal lobe atrophy. This subject was diagnosed as being minimally demented at the first and second follow-up assessments but was lost to follow-up before the third assessment. Seven subjects from the minimal

Table 5.2 Demographic characteristics, cognitive scores, and brain volumes at baseline according to outcome at follow-up

	Normal	Minimal dementia at baseline		AD at baseline	*p*-value	
	No dementia at follow-up Group 1 (n=14)	No dementia at follow-up Group 2a (n=4)	AD at follow-up Group 2b (n=9)	Group 3 (n=7)	Group 2a vs 2b	Group 2b vs 3
Age in years	76.1 (4.8)	77.8 (7)	79.2 (3.7)	79.6 (4.9)	0.88	0.71
Sex, % male	50%	0%	33%	14%	0.21	0.38
Education in years	8.9 (2.8)	8.0 (2.3)	7.1 (2.3)	7.1 (2.0)	0.41	0.95
Memory score	23.1 (1.8)	18.3 (4.4)	15.1 (5.1)	7.0 (3.8)	0.31	0.005
CAMCOG score	92.6 (4.3)	73.5 (7.3)	75.8 (7.6)	59.0 (15.0)	0.64	0.01
MMSE score Range	27.6 (2.3) 22-30	21.0 (1.8) 19-23	23.1 (1.2) 21-27	16.6 (6.0) 8-25	0.05	0.04
HC volume	4.83 (0.4)	5.0 (0.6)	4.45 (0.4)	4.25 (0.6)	0.09	0.27
PHG volume	5.92 (0.5)	5.92 (0.4)	5.2 (0.7)	5.06 (0.3)	0.04	0.67
LTL volume	43.2 (3.3)	43.6 (6.2)	42.3 (4.2)	40.0 (2.0)	0.76	0.49
ICA	264 (21)	244 (8)	250 (20)	256 (17)	0.88	0.56
MTA score					0.24	0.39
-0	6	1	0	0		
-1	8	2	5	3		
-2	0	1	4	3		
-3	0	0	0	1		

AD=Alzheimer's disease; HC=Hippocampus; PHG=Parahippocampal gyrus; LTL=Lateral part temporal lobe; ICA= Intracranial area; MTA= Medial temporal lobe atrophy. Continuous data are means (SD). All volumetric data are in cm^3.

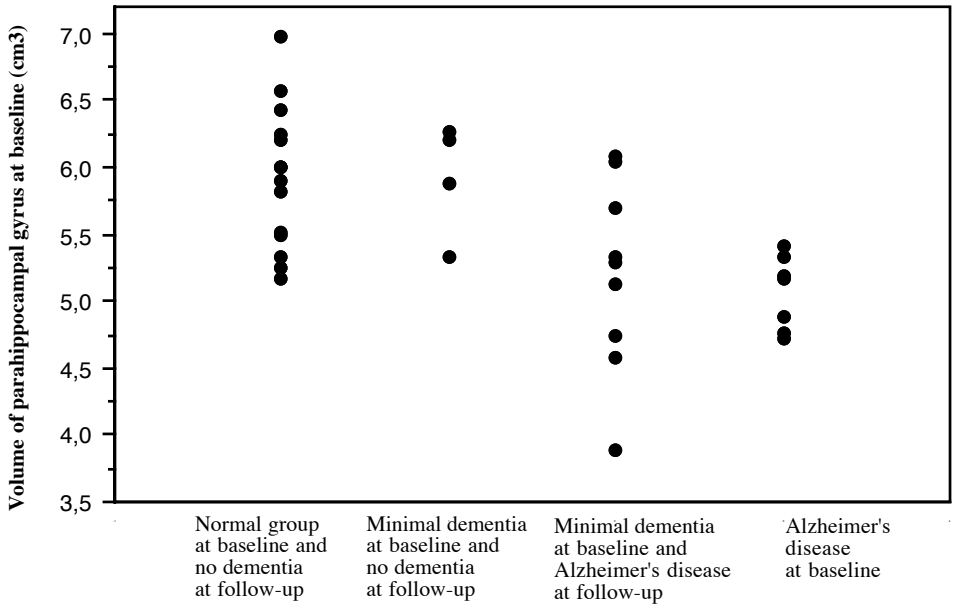

Figure 5.2. Volume of parahippocampal gyrus according to outcome

dementia group who dropped out before the first assessment had baseline characteristics similar to those of the other subjects with minimal dementia.

Nine of the 27 subjects who completed the follow-up study met the criteria for AD. All these subjects were diagnosed at baseline as being minimally demented. When compared with the minimally demented subjects with completed follow-up and no dementia (n=4), the demented subjects had the same or better cognitive scores (MMSE), whereas the parahippocampal gyrus was significantly smaller and the hippocampus tended to be smaller (table 5.2, figure 5.2). Subjects who developed AD during follow-up differed from the subjects with AD at baseline only with respect to the cognitive measures (table 5.2). The minimally demented subjects without dementia at follow-up continued to have cognitive impairment at follow -up.

Correlation between brain volumes and cognitive scores

None of the brain volumes correlated with any of the cognitive scores at baseline in the non-demented group. The volume of the parahippocampal gyrus at baseline

correlated with the change in the memory score (r=0.53, p=0.004). When we corrected for the incomplete follow-up, the volume of the parahippocampal gyrus at baseline correlated with the change in the CAMCOG score (r=0.54, p=0.003) and the change in the memory score (r=0.54, p=0.002).

Prediction of AD

The results of the logistic regression analysis with clinical outcome as dependent variable are summarized in table 5.3. The volume of the hippocampus and the parahippocampal gyrus and the medial temporal lobe atrophy score increased the accuracy of the model relative to that with the memory score only. The increase was

Table 5.3 Logistic regression analyses of clinical outcome

	OR	95% CI	Change in -2LL	*p* Change -2LL	Correctly classified
Model with single variable					
Memory	0.68	0.50-0.91	11.7	<0.001	88%
PHG	0.26	0.08-0.86	7.79	<0.01	77%
HC	0.21	0.05-0.99	5.30	0.02	69%
LTL	0.97	0.85-1.11	0.15	0.70	65%
MTL atrophy score	12.2	1.4-105.6	9.5	<0.01	77%
Model with 2 variables					
Memory + PHG			8.8	<0.001	96%
Memory	0.64	0.44-0.93			
PHG	0.15	0.02-0.98			
Memory + HC			4.2	0.05	92%
Memory	0.67	0.49-0.94			
HC	0.09	0.02-1.29			
Memory + LTL			0.72	0.40	80%
Memory	0.67	0.49-0.92			
LTL	0.92	0.76-1.12			
Memory + MTA Score			4.4	0.04	96%
Memory	0.70	0.51-0.96			
MTA score	8.72	0.76-101.5			

AD=Alzheimer's disease; HC=Hippocampus; PHG=Parahippocampal gyrus; LTL=Lateral part temporal lobe; MTA=medial temporal lobe atrophy; OR=Odds ratio; CI= Confidence Interval; -2LL= -2 Log Likelihood. Change in -2LL is for the models with a single variable the change from maximum -2LL, and for the models with 2 variables the change from the model with only memory. Odds ratios are for one unit change in the independent variable.

due to the correct classification of subjects with dementia at follow-up who had at baseline a small volume of the hippocampus or parahippocampal gyrus or a high medial temporal lobe atrophy score, while the memory score was within normal limits. These subjects were false-negatively misclassified as non-demented in the model with only memory score. The best model, which correctly classified the most subjects, was the combination of memory score with the volume of the parahippocampal gyrus or the medial temporal lobe atrophy score. Only one subject was misclassified as suffering from AD (see figure 5.3).

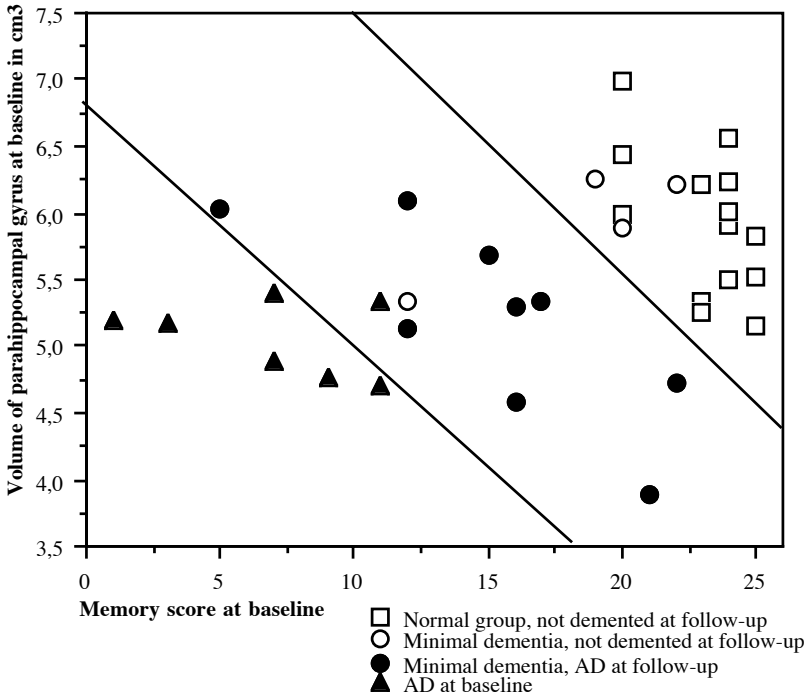

Figure 5.3. Relation between memory score and volume of the parahippocampal gyrus at baseline in subjects with AD at baseline, with AD at follow-up and no AD at follow-up. The lines indicate how the three groups can be differentiated best. The open dot in the middle part is the subject misclassified as demented by logistic regression.

DISCUSSION

We demonstrated that the volume of the parahippocampal gyrus was smaller in subjects with mild cognitive impairment who developed AD within 3 years than it was in subjects with mild cognitive impairment who did not develop AD. Memory dysfunction was a much better predictor of AD than the volumes of the hippocam-

pus or the parahippocampal gyrus or the medial temporal lobe atrophy score were. The combination of memory function and the volumes of the hippocampus or the para-hippocampal gyrus or the medial temporal lobe atrophy score at baseline significantly increased the accuracy of the prediction of the clinical diagnosis of AD compared with that for each measure alone. The increase in accuracy was due to correct classification of subjects who had severe atrophy of the medial temporal lobe but little memory impairment at baseline and who developed AD during follow-up.

The combination of memory function and the volume of the parahippocampal gyrus was slightly superior to the combination of memory function and the volume of the hippocampus but the small study size limits the interpretation of this difference. The memory score plus the medial temporal lobe atrophy score was equal to the combination of memory score plus the volume of the parahippocampus or hippocampus. This makes assessment of the degree of medial temporal atrophy also possible in clinical practice because the medial temporal lobe atrophy score is easy and quick to perform, although the raters should be well trained.

Our finding that memory impairment was associated with a higher risk of AD is consistent with the results of other studies (Bowen et al., 1997; Flicker et al., 1991; Linn et al., 1995; Tierney et al., 1996a), as was the association between atrophy of the medial temporal lobe and preclinical AD (de Leon et al., 1993a; Fox et al., 1996; Kaye et al., 1997). One study compared the combination of psychometrics and a qualitative rating of perihippocampal fluid volume in the prediction of AD in non-demented elderly subjects (de Leon et al., 1993a). The qualitative rating of perihippocampal fluid was found to be superior to the psychometric compound score in predicting AD. The discrepancy between these findings and our findings may be the result of the psychometric compound score used, which included non-memory tests, or the different way of assessing medial temporal lobe atrophy.

The volume of the lateral temporal lobe in the subjects with a diagnosis of AD at follow-up was less reduced than the volumes of the hippocampus and parahippocampal gyrus, which is in agreement with other studies (Braak et al., 1992; Convit et al., 1997; Kaye et al., 1997). We found that that the volumes of the hippocampus and the parahippocampal gyrus in AD patients was only 10-12% smaller than that of the normal subjects whereas other authors reported differences of 20 to 50% (Convit et al., 1997; Jack et al., 1997; Kesslak et al., 1991; Laakso et al., 1995; Lehéricy et al., 1994; Pantel et al., 1997). One possible explanation for this difference is that a few normal subjects with severe atrophy and some AD patients with normal volumes largely influenced the difference in this small sample. In addition, our scan protocol might not have been sensitive enough in detecting differences in volumes of the hippocampus and parahippocampal gyrus because we measured the volume in only four slices. Another explanation is that our subjects

were older (mean 78 years) than the subjects in the other studies (mean 69 to 76 years) which may have decreased the differences between the groups.

It should be noted that the mildly impaired subjects without dementia continued to have cognitive impairment and may eventually become demented. One may speculate that severe medial temporal lobe atrophy is associated with a faster cognitive decline. This is line with the finding that a smaller volume of the parahippocampal gyrus or hippocampus at baseline was associated with a decrease in cognitive scores during follow-up (this study; Golomb et al., 1996). Also the educational level, which tended to be lower in mildly impaired subjects with dementia at follow-up compared to the mildly impaired subjects without dementia (7.1 years vs 8.0 years), may have influenced the rate of decline.

The limitation of this study is the small group size at baseline and the high drop-out rate. The results should therefore be interpreted with care and should be replicated in larger samples. We cannot exclude the possibility that, at baseline, several of our minimally demented subjects would have been classified as being demented if other dementia criteria had been used (Erkinjuntti et al., 1997). This lack of agreement between dementia criteria, especially in the earliest stages, is a major concern for dementia research and is an incentive to develop new consensus criteria with special interest for very mild dementia. The slice thickness of the MRI scan might have introduced some measurement error, which might explain why we could not find significant differences between minimally demented and normal subjects for all brain measures, and between AD patients and normal subjects for volumes of the hippocampus and lateral part of the temporal lobe volumes despite there being very significant differences in the cognitive scores. The fact that the medial temporal lobe atrophy score was not different between the minimally demented subjects with and without dementia at follow-up might be explained by the small group size and the use of a Chi-square test, which has a low power to detect differences. Nonresponse occurred frequently. In selecting subjects from the general population, nonresponse was found to be associated with greater cognitive impairment and poorer physical and mental health (Launer et al., 1994). Normal subjects who were lost to follow-up had lower CAMCOG scores and a smaller volume of the parahippocampal gyrus at baseline. Thus, it seems likely that refusal to participate was associated with a higher occurrence of cognitive impairment and probably AD.

In conclusion, this preliminary study indicates that severe medial temporal lobe atrophy is present in some subjects who have mild cognitive impairments at baseline but who subsequently develop dementia. These subjects could enrolled in drug trials aimed at slowing the progression of AD. The absence of medial temporal lobe atrophy, however, does not mean that the individual will not develop dementia. In most of the subjects with mild cognitive impairment, memory impairment was a

better predictor of dementia than atrophy of the medial temporal lobe. The combination of both could increase predictive accuracy.

Medial temporal lobe atrophy predicts Alzheimer's disease in subjects with mild cognitive impairments

6

SUMMARY

OBJECTIVE: To investigate whether medial temporal lobe atrophy predicted outcome in non-demented elderly subjects with mild cognitive impairment and whether assessment of the medial temporal lobe could increase the predictive accuracy of age and delayed recall for outcome. We also compared quantitative and qualitative methods of assessing the medial temporal lobe.

METHODS: Non-demented subjects with mild cognitive impairment from a memory clinic older than 50 years (N=31) were followed for on average 1.9 years. The medial temporal lobe was assessed in three different ways: volumetry of the hippocampus, volumetry of the parahippocampal gyrus, and qualitative rating of medial temporal lobe atrophy (MTA). Outcome measures were AD or cognitive decline at follow-up. Delayed recall was tested with a verbal learning test.

RESULTS: Subjects with a small volume of the hippocampus or parahippocampal gyrus or with an high MTA score had AD or cognitive decline at follow-up more often than subjects with a large volume of the hippocampus or parahippocampal gyrus or with a low MTA score. All medial temporal lobe measurements increased the predictive accuracy of age and the delayed recall score for AD or cognitive decline. The highest increase in predictive accuracy for AD or cognitive decline was found for the volume of the hippocampus. The increase in predictive accuracy resulted from an increase in both sensitivity and specificity.

CONCLUSION: The ability to detect subjects at high risk for AD among subjects with mild cognitive impairment will increase when data on age and memory function are combined with measures of medial temporal lobe atrophy. Volumetry of the hippocampus is preferred, but qualitative rating of medial temporal lobe atrophy is a good alternative.

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INTRODUCTION

Many subjects who are investigated for cognitive impairments are not demented at the time of the examination but some of them may develop Alzheimer type dementia (AD) within several years, but it is difficult to identify these subjects. It is important to pick these subjects out because they may benefit from drugs that have been shown to improve cognition in subjects with probable AD, or drugs that may slow the progression of AD (Felician et al., 1999). In addition, the caregivers of these patients may benefit from counselling on how to handle the cognitive impairment of their partners. One of the best predictors of AD in subjects with mild cognitive impairment is memory function (Masur et al., 1994; Sliwinski et al., 1997; Tierney et al., 1996a), but the sensivity of memory functioning for predicting AD was less than 80% in most studies (Masur et al., 1994; Sliwinski et al., 1997; Tierney et al., 1996a). In addition, not all subjects with memory impairment develop AD and the memory impairment may be reversible (Visser et al., 2000a). Several studies have indicated that atrophy of the medial temporal lobe is predictive of AD in nondemented subjects (de Leon et al., 1993a; Fox et al., 1996; Golomb et al., 1996; Jack et al., 1999; Kaye et al., 1997; Visser et al., 1999b) and that measures of medial temporal lobe atrophy can improve the predictive accuracy of memory function for AD (de Leon et al., 1993a; Visser et al., 1999b) or can predict AD independently from memory function (Jack et al., 1999). Because only two of these studies were performed in a clinical setting, it remains uncertain whether the medial temporal lobe should be evaluated as part of the diagnostic work-up of non-demented subjects with mild cognitive impairment. Moreover, as there are different methods to assess the medial temporal lobe, it is unclear which method has the best predictive accuracy: volumetry of the hippocampus (Kaye et al., 1997), volumetry of the parahippocampal gyrus (Visser et al., 1999b), or qualitative assessment of the medial temporal lobe (de Leon et al., 1993a;Visser et al., 1999b).

The aim of the present longitudinal study was to investigate whether medial temporal lobe atrophy predicted outcome in non-demented elderly subjects with mild cognitive impairment and whether assessment of the medial temporal lobe could increase the predictive accuracy of age and delayed recall for clinical outcome. We compared three different methods to assess the medial temporal lobe: volumetry of the hippocampus, volumetry of the parahippocampal gyrus, and qualitative scoring of medial temporal lobe atrophy (MTA score). Outcome was defined as AD at follow-up or cognitive decline at follow-up. The latter outcome measure not only

included subjects with AD at follow-up, but also subjects with severe cognitive decline without dementia at follow-up.

METHODS

Subjects

The patients were selected from the Maastricht Memory Clinic, a university-affiliated outpatient clinic for subjects with cognitive impairment (Verhey et al., 1993a). All subjects were referred by a general practioner, a neurologist, or a psychiatrist because of cognitive impairment. Subjects older than 50 years were eligible for inclusion in the study. Exclusion criteria were dementia, a score on the Global Deterioration Scale (GDS) (Reisberg et al., 1982) higher than 3, sensory impairment, psychosis, panic disorder, bipolar disorder, a score on the Hamilton Depression Rating Scale-17 items (HDRS) (Hamilton, 1960) higher than 22 (Visser et al., 2000b), or cognitive problems in relation to cerebrovascular events, neurodegenerative diseases (eg Parkinson's disease or Huntington's disease), brain neoplasm, head trauma, drug intoxication, alcohol abuse, hypothyroid or hyperthyroid function, or vitamin deficiency. Thirty-one subjects were included in the study. Typically, these subjects had very mild (GDS stage 2) or mild cognitive decline (GDS stage 3). After the study was explained to them, subjects gave their written informed consent.

Baseline assessment and clinical diagnosis

At baseline subjects underwent a standardized assessment which included a detailed history provided by the patient and a significant other, a psychiatric, neurological, and physical examination, appropriate laboratory tests, and a neuropsychological assessment (see below) as described elsewere (Verhey et al., 1993a). In addition, the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), as a measure of global cognitive impairment, the GDS (Reisberg et al., 1982), which is a scale for staging levels of cognitive impairment, and the HDRS (Hamilton, 1960a), were administered. Psychiatric diagnoses were made according to DSM-IV criteria (APA, 1994). The diagnosis of AD was made according to the NINCDS-ADRDA criteria (McKhann et al., 1984). No patient received anti-dementia drugs.

Follow-up assessement

The subjects were invited for a follow-up assessment between 1 and 3 years after the first assessment. The average follow-up period was 1.9 years (SD 0.7). The follow-up assessment consisted of a standardized questionnaire about medical history and cognitive complaints, the MMSE, the GDS, the HDRS, and a neuropsychological assessment (see below). The diagnosis at follow-up was made by an experienced

neuropsychiatrist who was unaware of the results of the baseline assessment including the MRI data. If the subject refused to come for the follow-up assessment, a telephone interview was conducted which included a standardized questionnaire about medical history and cognitive complaints (N=1). No neuropsychological testing was done at follow-up in seven subjects because of refusal (N=5), severe cognitive impairment (N=1), or severe illness (N=1).

The diagnosis of cognitive decline at follow-up was made when subjects had AD or when severe cognitive decline without dementia was present at follow-up. Decline in non-demented subjects was defined as a negative change of 4 points or more on the MMSE (Schmand et al., 1995) or a negative change of more than 1 standard deviation on the delayed recall task such that the second score on the delayed recall task was below the 10th percentile. The latter restriction was taken in order to exclude subjects with regression to the mean. When only the MMSE or the delayed recall score was available at follow-up (N=2), the subject was classified according to that score only.

Neuropsychological assessment

The neuropsychological assessment consisted of a series of standard clinical tests covering the cognitive domains of memory, language, attention, praxis, executive functions, and intelligence, as described elsewhere (Jolles, 1986; Verhey et al., 1993a). Delayed recall perfomance in a verbal learning task was selected as a predictor for AD because several studies have indicated that this is a strong neuropsychological predictor of AD (Masur et al., 1994; Tierney et al., 1996a). Delayed recall performance was assessed with the Auditory Verbal Learning Test (AVLT) (Brand et al., 1985; Lezak, 1995). Fifteen unrelated words were presented five times and after each presentation the subject was asked to reproduce as many words as possible. After 20 minutes, during which non-verbal tests were performed, delayed recall performance was tested. Delayed recall performance was not tested at baseline in two subjects because they refused to do the test. A parallel version of the AVLT was used at follow-up.

Since the MMSE score and delayed recall performance correlate with age, sex, and education, we corrected the scores for these variables. The correction was based on a reference population of 1070 cognitively normal subjects older than 50 years who had been randomly selected from a registry of general practitioners as described in detail elsewere (Jolles et al., 1995; van Boxtel et al., 1998). On the basis of the reference population, an expected score for a given age, sex, and level of education was calculated (Visser et al., 2000a; Visser et al., 2000b). This score was subtracted from the observed score. In the case of the delayed recall task, the residue was divided by the standard deviation of the residue in the reference population to give a z-score

(Visser et al., 2000a). A z-score below zero indicated below average performance. The residue of the MMSE was added to the expected MMSE score of a subject with average age, sex, and level of education in the study population (MMSE=27.7) (Visser et al., 2000b).

MRI Methodology

A 3D volumetric scan (T1-weighted, fast-field echo, TR 24ms, TE 7ms, flipangle 30°, number of averages=2, FOV 230mm, resolution 256x154) and an Inversion Recovery (IR) scan (TR 2107ms, TE 18ms, Turbofactor=3, flipangle 90°, number of averages=2, FOV 230mm, resolution 256x177) were made on a 1.5 Tesla scanner (Gyroscan ACS-II, Philips). The slice thickness of the 3D volumetric scan was 1.5 mm and the scan axis was coronal, perpendicular to the intercommissural line. The slice thickness of IR scan was 3 mm and the scan axis was coronal, perpendicular to the long axis of the hippocampus. The hippocampus, the parahippocampal gyrus, and the intracranial area were measured on the 3D volume scan and the MTA score was determined from the IR scan.

Methodology of brain measurements

Data were transferred to a SUN workstation and the regions of interest were measured with ShowImage (developed at the Department of Clinical Physics and Informatics, VrijeUniversiteit, Amsterdam, The Netherlands). The MRI scan of one subject was not available for volumetry and in this subject only the qualitative rating was performed. The brain structures were manually traced with a mouse-driven cursor. The volumes of the left side and right side were added. The volume of the brain structure was calculated by multiplying the surface area of each region of interest by the slice thickness and summing the volumes of all slices on which the structure was measured. Measurements were done with reference to an anatomical atlas (Duvernoy, 1988). The hippocampus and parahippocampal gyrus were measured by two raters and the intracranial area by one rater. All raters were blinded to all clinical information.

Volumetry of the hippocampus, parahippocampal gyrus, and intracranial area

The hippocampus was measured on the slice on which both the semi-anular sulcus and a notch between the amygdala and the hippocampus in the medial wall of the lateral ventricle were visible (Lehéricy et al., 1994), and then on every second slice. The last slice was the slice before the slice on which the crura of the fornices were visible. On average 10 slices on each side were measured (range 8-13). The volume of the parahippocampal gyrus was measured on the same slices, except for the last slice in order not to include the isthmus of the cingulate gyrus. On average 9 slices

on each side were measured (range 7-12). The intracranial area was measured in rostro-caudal direction on three slices: on the first slice on which the third ventricle appeared, on the slice on which the mamillary bodies had the largest volume, and on the last slice on which the third ventricle was visible. The anatomic boundaries of the hippocampus, parahippocampal gyrus, and intracranial area have been described in detail elsewhere (Visser et al., 1999a). Ten scans were remeasured by both raters in order to assess the intra- and interobserver variability. The Pearson correlation coefficient between the first and second measurement was 0.96 for the hippocampus (rater 1), 0.93 for the parahippocampal gyrus (rater 1), 0.91 for the hippocampus (rater 2), 0.91 for the parahippocampal gyrus (rater 2), and 0.99 for the intracranial area. The Pearson correlation coefficient between the measurement of the hippocampus and parahippocampal gyrus by rater 1 and rater 2 was 0.91 and 0.97 respectively. These correlations indicate a high level of inter- and intrarater agreement for all measurements.

The volumes of the hippocampus and parahippocampal gyrus were corrected for age, sex, intracranial area, and number of slices. We corrected for the number of slices on which the volume of the hippocampus or parahippocampal gyrus were measured in order to reduce the variance because the number of of slices correlated with the total volume of the hippocampus and parahippocampal gyrus but the number of slices did not depend on atrophy of these structures (Visser et al., 1999a). The correction for age, sex, intracranial area, and number of slices was based on a population of 60 healthy subjects aged between 21 and 82 years (average age 56 years, standard deviation 15.9). These subjects were recruited by newspaper advertisements. Regression analysis was performed with the brain structure as dependent variable and intracranial area, age, number of slices, sex, and the interaction term age by sex (because reported differences in aging between male and female) as independent variables (Visser et al., 1999a). Variables and interaction terms that were significant at the p=0.05 level were included in the final model. On the basis of this regression model we calculated z-scores in the same way as we did for the delayed recall. We classified the brain volumes on the basis of the z-score in tertiles. A z-score above 0.44 corresponds with a brain volume in the highest tertile of the reference population, a z-score between 0.44 and -0.44 correponds with a brain volume in the middle tertile of the reference population, a z-score below -0.44 corresponds with a brain volume in the lowest tertile of the reference population.

MTA score

The MTA score is based upon a visual estimation of the volume of the medial temporal lobe, including the hippocampus proper, dentate gyrus, subiculum, and parahippocampal gyrus, and the volume of the surrounding CSF spaces, in particular

the temporal horn of the lateral ventricle and the choroid fissure, on both sides (Barber et al., 1999; Scheltens et al., 1992). The MTA score ranges ranged from 0 (no atrophy) to 4 (severe atrophy). The visual method of scoring correlates well with linear and volumetric measurements and has an substantial intra-rater reliability (kappa=0.70) (Scheltens et al., 1992; Vermersch et al., 1994). MTA was scored by a neurologist who was blinded to all clinical information. In the present study a MTA score of 0 refers to subjects with a rating of 0 on both the left and right side, a MTA score of 1 refers to subjects with a rating of 1 on at least one side, a MTA score of 2 refers to subjects with a rating of 2 or more on at least one side.

Statistics

The data were analyzed using SPSS for the Macintosh 4.0 (SPSS Inc., Chigaco, IL, USA). Group comparisons with continuous variables were carried out with a t-test or with the Mann-Whitney test corrected for ties when the group size was smaller than 10. Categorical data were analyzed with a Chi square test with continuity correction. When at least two cells had an expected frequency of 5 or less, the two-tailed Fisher's exact test was applied. Logistic regression was used to evaluate the predictive value of age (50-60 years, 60-70 years, and >70 years), delayed recall, and the volume of the hippocampus or parahippocampal gyrus or the MTA score for clinical outcome (AD vs no AD, and the absence or presence of cognitive decline at follow-up). Age was used as a predictor because it is a risk factor for AD that is independent of age-corrected brain volumes or age-corrected memory scores (Jack et al., 1999; Visser et al., 2000a). Age and delayed recall were added in the first step and the brain volume or MTA score in the second step. To assess whether the goodness of fit improved after addition of the brain volume or the MTA score, the change in -2Log Likelihood (-2LL) was tested. All tests were 2-tailed, and the significance level was set at 0.05.

RESULTS

Baseline characteristics of the study population are listed in table 6.1. Information on the presence or absence of AD was available in 30 subjects (97%). One subject refused the follow-up assessment and could not be interviewed by telephone. Seven subjects (22% of the baseline sample) had probable AD at follow-up. Of the subjects with no dementia at follow-up (N=23), 3 had cognitive decline at follow-up (two subjects with a decline on the MMSE≥4, and one subject with a decline on the delayed recall >1 SD), 17 subjects had no cognitive decline, and 3 subjects had no cognitive scores at follow-up. The subjects with AD at follow-up and the non--demented subjects with cognitive decline at follow-up will be referred to as the

Table 6.1 Subject characteristics according to outcome

		Outcome#		
		No CD	CD	
	All subjects		No AD	AD
No	31	17	3	7
Age (y)	64.9 (9.5)	61.4 (7.5)	68.6 (12.1)	73.8 (7.8)*
Sex ratio	18M:13F	8M:9F	2M:1F	5M:2F
Education (y)	10.7 (3.2)	11.2 (2.9)	7.0 (1.4)*	10.4 (4.0)
HDRS score	9.8 (6.5)	10.3 (7.5)	11.0 (7.2)	9.1 (5.1)
GDS score				
-2	17	10	2	2
-3	14	7	1	5
MMSE score at baseline	27.7 (1.8)	28.1 (1.7)	27.7 (1.2)	26.4 (2.3)
MMSE score at baseline‡	27.6 (1.3)	27.6 (1.3)	28.4 (0.66)	27.1 (2.2)
MMSE score FU‡	25.9 (3.7)	27.3 (1.6)	25.9 (2.9)	21.1 (5.3)*
Delayed recall Baseline (z score‡)	-0.91 (0.93)	-0.63 (0.9)	-0.97 (0.34)	-1.37 (0.7)
Delayed recall FU (z score‡)	-0.44 (1.3)	0.18 (0.84)	-2.43 (0.34)*	-1.43 (1.3)*
Hippocampus (z score)	-0.24 (1.3)	0.25 (0.99)	-1.47 (0.9)*	-1.1 (0.93)*
Parahippocampal gyrus (z score)	-0.23 (1.1)	0.10 (0.95)	-0.94 (0.53)*	-0.74 (1.1)*
MTA Score				
-0	11	9	1	0*
-1	9	7	0	1
-2	11	1	2	6

Values are means (SD). ‡Corrected for age, sex, and education. #Four subjects had no outcome (three nondemented subjects in whom the presence or absence of cognitive decline could not determined and one subject in whom the presence or absence of dementia could not be established. *Statistically signicifantly different ($p<0.05$) from nondemented subjects without cognitive decline. MMSE=Mini-Mental State Examination; GDS=Global Deterioration Scale; HDRS=Hamilton Depression Rating Scale; MTA=Medial Temporal Lobe Atrophy; FU=follow-up; CD=cognitive decline; AD= Alzheimer's disease.

cognitive decline group (N=10). Subjects with a hippocampal volume in the lowest tertile had a lower MMSE score, and more often had AD or cognitive decline at follow-up than the subjects with a hippocampal volume in the highest tertile (table 6.2a). Subjects with a parahippocampal gyrus volume in the lowest tertile tended to have lower follow-up scores on the MMSE and delayed recall than the subjects with

Legend tables 6.2a-6.2c Values are means (SD). *Tertiles are based on a reference population of healthy subjects. †Corrected for age, sex, and education. [a]One subject with missing data; [b]Two subjects with missing data; [c]Three subjects with missing data; [d]Four subjects with missing data. MMSE=Mini-Mental State Examination; AD=Alzheimer's disease; CD=Cognitive decline: subjects with AD at follow-up or subjects with severe cognitive decline at follow-up without dementia; MTA=Medial Temporal Lobe Atrophy.

Table 6.2a Baseline and follow-up data according to hippocampal volume at baseline

	Hippocampus volume at baseline*			p Value	
	Highest Tertile (I)	Middle Tertile (II)	Lowest Tertile (III)	I vs II	I vs III
No	8	11	11		
age (y)	60.5 (8.7)	65.5 (8.0)	67.0 (11.4)	0.36	0.16
MMSE score†					
-at baseline	27.5 (1.4)	27.3 (1.7)	27.8 (1.4)	0.80	0.51
-at follow-up	28.0 (1.2)[b]	26.7 (1.7)[b]	23.3 (4.8)[b]	0.10	0.03
Delayed recall (z-score)					
-at baseline	-1.1 (0.86)	-0.63 (0.88)[a]	-1.1 (0.84)[a]	0.37	0.60
-at follow-up	0.03 (0.86)[b]	-0.30 (1.2)[a]	-1.2 (1.7)[d]	0.45	0.20
AD/ no AD at follow-up (%AD)	0/8 (0)	2/9 (25)	5/5 (50)[a]	0.49	0.04
CD/ no CD at follow-up (% CD)	0/6 (0)[b]	3/7 (30)[a]	7/3 (70)[a]	0.25	0.01

Table 6.2b Baseline and follow-up data according to parahippocampal gyrus volume at baseline

	Parahippocampal gyrus volume at baseline*			p Value	
	Highest Tertile (I)	Middle Tertile (II)	Lowest Tertile (III)	I vs II	I vs III
No	7	11	12		
age (y)	66.1 (12.0)	61.3 (9.4)	67.0 (8.2)	0.39	0.55
MMSE score†					
-at baseline	27.4 (1.3)	27.8 (1.5)	27.3 (1.6)	0.56	0.93
-at follow-up	27.3 (1.7)[b]	27.5 (1.4)[b]	23.4 (4.5)[b]	0.39	0.07
Delayed recall (z score)					
-at baseline	-0.89 (0.98)[b]	-0.87 (0.93)	-0.97 (0.81)	0.95	0.67
-at follow-up	0.42 (0.72)[b]	-0.52 (1.3)[c]	-0.90 (0.81)[b]	0.14	0.07
AD/ no AD at follow-up (%AD)	1/6 (14)	1/10 (9)	5/6 (45)[a]	1.0	0.32
CD/ no CD at follow-up (% CD)	1/5 (17)[a]	2/7 (22)[b]	7/4 (64)[a]	1.0	0.13

Table 6.2c Baseline and follow-up data according to MTA score at baseline

	MTA score at baseline			p Value	
	0	1	2	0 vs 1	0 vs 2
No	11	9	11		
age (y)	61.4 (8.6)	65.5 (7.6)	67.0 (11.4)	0.36	0.16
MMSE score†					
-at baseline	27.5 (1.0)	28.3 (1.7)	27.1 (1.6)	0.12	0.47
-at follow-up	27.1 (1.4)[a]	26.8 (1.8)[a]	23.1 (5.8)[c]	0.66	0.24
Delayed recall (z score)					
-at baseline	-0.92 (0.7)[a]	-0.38 (1.0)	-1.38 (0.48)[a]	0.07	0.12
-at follow-up	-0.26 (1.0)[b]	0.15 (0.99)[a]	-1.35 (1.6)[d]	0.50	0.15
AD/ no AD at follow-up (% AD)	0/11 (0)	1/8 (11)	6/4 (60)[a]	0.45	0.004
CD/ no CD at follow-up (% CD)	1/9 (10)[a]	1/7 (13)[a]	8/1 (89)[b]	1.0	0.001

a parahippocampal gyrus volume in the highest tertile (table 6.2b). Subjects with a MTA score of 2 more often had AD or cognitive decline at follow-up than the subjects with a MTA score of 0 (table 6.2c). Baseline cognitive scores and age were not statistically significantly different in the groups with different brain volumes or MTA scores. Also sex, education, and HDRS score did not differ between the groups ($p>0.15$).

The first set of logistic regression analyses was performed with AD at follow-up as dependent variable and included data for 6 subjects with AD at follow-up and 22 non-demented subjects. After age and the delayed recall score were entered in the first step, the volumes of the hippocampus and the parahippocampal gyrus volume, and the MTA score all improved the model (table 6.3). The change in -2LL was largest for the hippocampal volume, indicating that this variable increased the predictive accuracy the most. The increase in predictive accuracy resulted from an increase in sensitivity.

In the second set of logistic regression analyses, the dependent variable was cognitive decline at follow-up and included data for 9 subjects with cognitive impairment at follow-up and 15 subjects without cognitive impairment. After age and the delayed recall score were entered in the first

Table 6.3 Logistic regression analyses of clinical outcome

	Change in 2LL*	p Value Change -2LL	Sensitivity	Specificity	PPV	NPV
AD as outcome						
Step 1						
Age and Delayed recall	6.4	0.04	17%	90%	33%	79%
Step 2						
+ HC	4.7	0.03	50%	90%	60%	86%
+ PHG	3.5	0.06	50%	90%	60%	86%
+ MTA score	4.4	0.04	83%	86%	63%	95%
Cognitive decline as outcome						
Step 1						
Age and Delayed recall	7.2	0.03	73%	67%	60%	79%
Step 2						
+ HC	21	<0.001	89%	93%	89%	93%
+ PHG	6.8	0.01	78%	87%	78%	87%
+ MTA score	5.5	0.02	78%	87%	78%	87%

*Change in -2LL is in step 1 the change from maximum -2LL, change in -2LL is in step 2 the change in -2LL from -2LL in step 1. HC=Hippocampus; PHG=Parahippocampal gyrus; -2LL= -2 Log Likelihood; PPV= positive predictive value; NPV=negative predictive value.

step, the volumes of the hippocampus and the parahippocampal gyrus, and the MTA score all improved the model (table 6.3). Again, the change in -2LL was largest for the hippocampal volume, indicating that this variable increased the predictive accuracy the most. The increase in predictive accuracy resulted from an increase in both sensitivity and specificity.

DISCUSSION

The main conclusions of this prospective study of non-demented elderly with mild cognitive impairment from a memory clinic were that measures of medial temporal atrophy predicted outcome at follow-up and improved the predictive accuracy of age and delayed recall performance for outcome. Hippocampal volume increased predictive accuracy for outcome more than the other measures of medial temporal lobe atrophy.

Almost all subjects with a volume of the hippocampus and hippocampal gyrus in the highest tertile or an MTA score of 0 failed to show further cognitive decline (figure 6.1). The memory impairment in these subjects was often reversible. In contrast, subjects with a volume of the hippocampus and hippocampal gyrus in the lowest tertile or an MTA score of 2 had a high risk of further cognitive decline (figure 6.1). The delayed recall score of these subjects often remained the same or decreased and the MMSE score decreased. The subjects with a volume of the hippo-

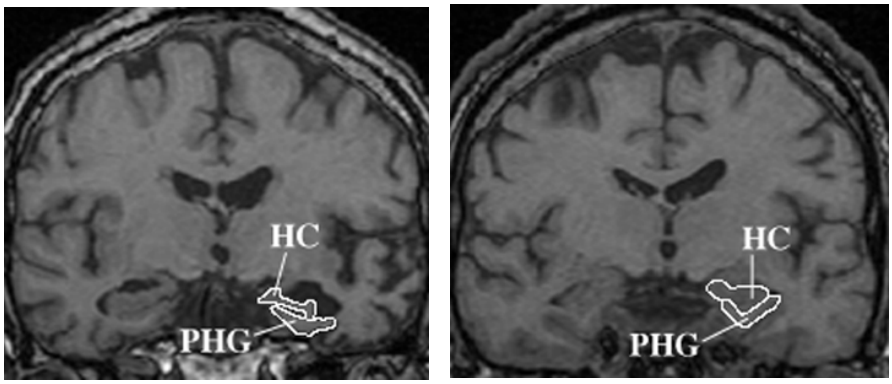

Figure 6.1 The left image shows the MRI scan of a 69 year old subject with AD at follow-up. The delayed recall z-score declined at follow-up from -1.50 to -2.30. The hippocampus (HC) z-score in this subjects was -0.62, the parahippocampal gyrus (PHG) z-score -1.28, and the MTA score 2 at baseline. The right image shows the MRI scan of a 61 year old subject who had at baseline a similar degree of delayed recall impairment (z-score -1.60). His memory impairment, however, improved at follow-up (delayed recall z-score -0.12) The hippocampus z-score at baseline in this subject was -0.29, the parahippocampal gyrus z-score 1.41, and the MTA score 0.

campus or parahippocampal gyrus in the middle tertile or subjects with a MTA score of 1 had a prognosis with respect to cognitive outcome that was in between that of subjects with a large hippocampal volume, large parahippocampal gyrus volume, or an MTA score of 0 and that of subjects with a small hippocampal volume, small parahippocampal gyrus volume, or an MTA score of 2. These observations are consistent with earlier observations of subjects with or without mild cognitive impairment (de Leon et al., 1993a; Golomb et al., 1996; Visser et al., 1999b).

All medial temporal lobe measures were found to improve the predictive accuracy of age and the delayed recall score for AD or cognitive decline at follow-up. The improvement in predictive accuracy, however, was larger when cognitive decline was used as an outcome measure. This can be explained by the small sample size with only six demented subjects, but also by the finding that the medial temporal lobe measurements of the subjects with AD at follow-up and of the subjects with cognitive decline but no dementia at follow-up overlapped. The increase in predictive accuracy for cognitive decline resulted from an increase in sensitivity and specificity. These findings corroborate the observation that assessment of the medial temporal lobe increases predictive accuracy for clinical outcome above that of cognitive dysfunction (de Leon et al., 1993a) and are consistent with the observation that hippocampal volume and memory scores were independent predictors of AD in subjects with mild cognitive impairment (Jack et al., 1999). The increase in specificity for clinical outcome has not been reported before, while the increase in sensitivity has (Visser et al., 1999b).

The volume of the hippocampus was a better predictor of outcome than the volume of the parahippocampal gyrus. This is in contrast with our previous study that showed a better predictive accuracy of the parahippocampal gyrus for AD in non-demented elderly (Visser et al., 1999b), but it corroborates the observation of Kaye et al. who demonstrated that non-demented subjects with AD at follow-up had at baseline smaller hippocampal volumes but not parahippocampal gyrus volumes at baseline than subjects without dementia at follow-up (Kaye et al., 1997). In addition, case-control studies with mildly demented AD patients have indicated that hippocampal volume could better discriminate between control subjects and subjects with AD than the parahippocampal gyrus volume (deToledo-Morrell et al., 1997; Jack et al., 1997; Krasuski et al., 1998). The lower discriminative ability of the parahippocampal gyrus may result from larger interindividual differences in this structure (Jack et al., 1997). The entorhinal cortex, which is a subregion of the parahippocampal gyrus, is probably a better predictor of cognitive decline than the total volume of the parahippocampal gyrus although large interindividual differences also exist in this structure (Bobinski et al., 1999). Alternatively, the discrepancy between studies concerning the predictive accuracy of hippocampal and parahip-

pocampal gyrus volumes may depend on the way mild cognitive impairment is defined. In our previous study, in which we found that the parahippocampal gyrus volume predicted outcome better than the hippocampal volume, subjects were selected according to the criteria of minimal dementia (Visser et al., 1999b) while in the present study subjects with GDS stages 2 or 3 were selected. Subjects with minimal dementia had at baseline more severe cognitive impairment (average MMSE score of 22.6) than the subjects with mild cognitive impairment in the present study (average MMSE score of 27.7). Thus, the predictive accuracy of brain structures may also depend on the severity of cognitive impairment (Killiany et al., 2000). The volume of the hippocampus was a better predictor for clinical outcome than the MTA score. However, the MTA rating can be performed in 1-2 minutes, which is ten times faster than volumetry (Wahlund et al., 1999). In addition, the MTA score can be determined from an hardcopy and there are no reference data of healthy subjects needed to correct for differences in intracranial volume. Since the MTA score has a reasonably good predictive accuracy, it could be used in settings where volumetry is not possible.

One of the limitations of the study was the short follow-up period. We may therefore have missed subjects who would have become demented after the follow-up assessment. For this reason we also used a broader definition of cognitive decline as an outcome measure, but it remains to be investigated whether the subjects with cognitive decline at follow-up who were not demented have since developed AD. The small sample size may have limited the ability to detect significant differences. MMSE and delayed recall scores at both baseline and follow-up were not available for all subjects and this may have influenced the observed differences in baseline and follow-up scores. However, an analysis of the change scores of these variables that included only subjects with cognitive scores at both baseline and follow-up yielded similar results (data not shown). We included in this study subjects that were between 50 and 60 years old because AD is also seen in these subjects. However, the risk of AD is this group is smaller than in subjects older than 60 and this may have influenced the results. We therefore repeated the logistic regression analyses after exluding subjects who were younger than 60 (data not shown). These analyses yielded the same results as the analyses with all subjects. Strong points of the study were the clinical setting which makes the findings relevant for patient samples, the fact that medial temporal lobe measures were combined with the delayed recall score and age in predicting clinical outcome, and the fact that we compared different ways of assessing the medial temporal lobe.

In summary, the ability to detect subjects with mild cognitive impairment subjects who are at high risk for AD will increase substantially when data on age and memory function are combined with measures of medial temporal lobe atrophy.

The increase in diagnostic accuracy results from an increase in both sensitivity and specificity. Volumetry of the hippocampus is preferred, but qualitative scoring of medial temporal lobe atrophy is a good alternative. This study supports the view that assessment of the medial temporal lobe is a useful supplement to the diagnostic work-up of subjects with mild cognitive impairment.

Brain correlates of memory dysfunction in alcoholic Korsakoff's syndrome

7

SUMMARY

OBJECTIVE: To investigate the relation between anterograde amnesia and atrophy of brain structures involved in memory processing in alcoholic Korsakoff's syndrome.
METHODS: The volume of brain structures involved in memory processing was measured with MRI scans from 13 subjects with Korsakoff's syndrome, 13 subjects with chronic alcoholism without Korsakoff's syndrome, and 13 control subjects. The brain structures analyzed were the hippocampus, the parahippocampal gyrus, the mamillary bodies, the third ventricle, and the thalamus. Brain volumes were correlated with the delayed recall of a verbal learning test.
RESULTS: Compared with subjects with chronic alcoholism and control subjects, subjects with Korsakoff's syndrome had a reduced volume of the hippocampus, the mamillary bodies, and the thalamus, and enlargement of the third ventricle. The impairment of delayed recall correlated with the volume of the third ventricle (r=-0.55, p=0.05) in the Korsakoff group.
CONCLUSION: Anterograde amnesia in alcoholic Korsakoff's syndrome is associated with atrophy of the nuclei in the midline of the thalamus, but not with atrophy of the mamillary bodies, the hippocampus, or the parahippocampal gyrus.

INTRODUCTION

Anterograde amnesia is one of the most prominent features of Korsakoff's syndrome (Kopelman, 1995). The brain correlate of the anterograde amnesia in Korsakoff's syndrome is still controversial. Neuroimaging and neuropathological studies have indicated that several structures may be the brain substrate of the anterograde amnesia including the mediodorsal nucleus of the thalamus (Shimamura et al., 1988; Victor et al., 1989), the parataenial nucleus of the thalamus (Mair et al., 1979; Mayes et

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al., 1988), the mamillary bodies (Estruch et al., 1998; Squire et al., 1990), the frontal cortex (Shimamura et al., 1988), the cingulate gyrus (Joyce et al., 1994), the nucleus basalis of Meynert (Arendt et al., 1983), the nucleus coeruleus (Mayes et al., 1988), the hippocampus (Jernigan et al., 1991; Kril et al., 1997), and the amygdala (Jernigan et al., 1991; Kril et al., 1997). It is surprising that none of the neuroimaging studies so far made use of volumetry on Magnetic Resonance Imaging (MRI) scans. The advantage of volumetry is that it can demonstrate correlations between the volume of brain structures and memory impairment (Deweer et al., 1995). Another advantage of this technique is that the volume of brain structures and cognitive function can be measured more-or-less at the same time in contrast to post-mortem studies.

The aim of the present study was to investigate in subjects with alcoholic Korsakoff's syndrome the relation between anterograde amnesia and the volume of brain structures that are known to be involved in memory processing, focussing on structures of the limbic system. We measured on high-resolution MRI scans the volume of the hippocampus, the parahippocampal gyrus, the mamillary bodies, and the thalamus. We also measured the volume of the third ventricle because dilatation of this structure may reflect atrophy of nuclei in the midline of the thalamus, including the mediodorsal nucleus of the thalamus (Jacobson et al., 1990). All the subjects with Korsakoff's syndrome were alcoholics. Because prolonged alcohol intake is neurotoxic, we included a control group of alcoholics without Korsakoff's syndrome in order to identify brain abnormalities that are due to thiamine deficiency and not to prolonged alcohol intake. A second control group consisted of matched healthy volunteers. Care was taken to match the three groups on an individual basis for age, sex, and education. We first determined which brain structures were significantly different between alcoholics with Korsakoff's syndrome and alcoholics without Korsakoff's syndrome. We then correlated the volume of the structures that were significantly different in subjects with Korsakoff's syndrome with the severity of anterograde amnesia in these patients.

METHODS

Subjects

Thirteen patients with Alcohol-Induced Persisting Amnestic Disorder (or Korsakoff's Syndrome; DSM-IV 291.1 (APA, 1994)), 13 patients with Alcohol Dependence (DSM-IV 303.90), and 13 healthy control subjects participated in the study. These groups are referred to as the Korsakoff group, alcoholic group, and control group, respectively. Patients were diagnosed by a multidisciplinary team consisting of a neuropsychiatrist, a neuropsychologist, and a neurologist. The patients were recruit-

ed from specialized departments for patients with Korsakoff's syndrome or chronic alcoholism from the Vincent van Gogh Institute for Mental Health in Venray, the Netherlands. All patients were abstinent for at least 1 month. The control subjects were recruited via newspaper advertisements. Exclusion criteria for all subjects were age older than 56 years (because of the interaction between age and alcohol-related brain damage (Pfefferbaum et al., 1992)), an intelligence quotient below 80 (in order to exclude subjects with generalized cognitive impairment), the use of psychotropic medication, the presence of depression, psychotic disorders, anxiety disorders, dementia, diabetes mellitus, liver disease, other central nervous system diseases, and cardiac, pulmonary, or endocrine diseases that could affect cognitive functioning. Exclusion criteria for control subjects also included a history of alcohol dependence or a current intake or a history (longer than 1 month) of alcohol intake of 28 or more units a week. Subjects with Korsakoff's syndrome who were not amnestic on neuropsychological testing were also excluded. Written informed consent was obtained from all subjects.

The three groups were matched for age, sex, and education. Subject characteristics are shown in table 7.1. The duration of alcohol abuse was estimated from the history of the patient and a significant other, and by examining medical charts. No differences existed in the duration of alcohol abuse between the subjects with Korsakoff's syndrome and the subjects with chronic alcoholism (table 7.1).

Table 7.1 Subject characteristics

	Korsakoff	Alcoholic	Control
No.	13	13	13
Age (y)	45.7 (6.3)	45.9 (6.1)	45.9 (5.6)
Sex ratio	11M:2F	11M:2F	11M:2F
Education (y)	10.8 (3.2)	10.9 (3.1)	11.4 (2.7)
Alcohol abuse (y)	17.1 (7.5)	17.7 (8.0)	0
IQ score	104 (14.9)	112 (10.6)	111 (7.4)
Delayed recall (z-score)	-2.82 (0.61)[1]	-0.09 (1.2)	-0.01 (1.1)

Values are means (SD).
[1] $p<0.001$ compared to both alcoholic and control group.

Neuropsychological assessment

The neuropsychological assessment has been described in detail elsewere (Krabbendam et al., 2000). Anterograde amnesia was assessed with the delayed recall of the Auditory Verbal Learning Test (Brand et al., 1985). Fifteen words were presented five times and after each presentation the subject was asked to reproduce as many

words as possible. After 20 minutes, during which non-verbal tests were performed, the delayed recall was tested. The data are expressed as z-scores. The z-score is the number of standard deviations that the score deviates from the expected score in a normal population of a given age, sex, and education. The z-scores were based on a reference population of 1870 normal and healthy subjects randomly selected from a registry of general practitioners (Jolles et al., 1995; van Boxtel et al., 1998). As expected, the Korsakoff group performed significantly worse than the alcoholic group and the control group on the delayed recall task (table 7.1). No differences were found between the alcoholic group and the control group.

The shortened form of the Wechsler Adult Intelligence Scale (Wechsler, 1955) was administered to the patient groups to obtain a measure of general intelligence, and the shortened form of an equivalent Dutch intelligence test, the Groningen Intelligence Test (Luteyn et al., 1983), was administered to the control group for the same purpose. No significant differences existed between the three groups (table 7.1).

MRI Methodology

A 3D volumetric scan (T1-weighted, fast-field echo, TR 24ms, TE 7ms, flip angle 30^{o}, number of averages=2, FOV 230mm, resolution 256x154), and an Inversion Recovery (IR) scan (TR 2107ms, TE 18ms, Turbofactor=3, flip angle 90^{o}, number of averages=2, FOV 230mm, resolution 256x177) were made on a 1.5-Tesla scanner (Gyroscan ACS-II, Philips). The slice thickness of the 3D volumetric scan was 1.5 mm and the scan axis was coronal, perpendicular to the intercommissural line. The slice thickness of the IR scan was 3 mm and the scan axis was coronal, perpendicular to the long axis of the hippocampus. The thalamus was measured on the IR scan and all other structures on the 3D volume scan.

Data were transferred to a SUN workstation and the regions of interest were measured with ShowImage (developed at the Department of Clinical Physics and Informatics, VrijeUniversiteit, Amsterdam, The Netherlands). A seed function was used to measure the third ventricle. The cut-off level between cerebro spinal fluid (CSF) and brain was visually adjusted by the rater on each slice. The other structures were manually traced with a mouse-driven cursor. All measurements were taken in a rostro-caudal direction. The volumes of the left side and right side were added in all analyses since the pathological changes in Korsakoff Syndrome and alcoholism are bilateral (Sullivan et al., 1995; Victor et al., 1989). The volume of the brain structures was calculated by multiplying the surface area of each region of interest by the slice thickness and summing the volumes of all slices on which the structure was measured. Measurements were done with reference to several anatomical atlasses

(Duvernoy, 1988; Duvernoy, 1991; Jackson et al., 1996). Each structure was measured by one rater who was blinded to all clinical information.

Methodology of brain measurements

Hippocampus Measurements started with the slice on which both the semi-anular sulcus and a notch between the amygdala and the hippocampus in the medial wall of the lateral ventricle were visible (Lehéricy et al., 1994). Then every second slice was measured. The last slice was the slice before the slice on which the crura of the fornices were visible. On average 10 slices on each side were measured (range 8-13). The measurements included the hippocampus proper, the dentate gyrus, the alveus, and the portion of the subiculum which lies directly underneath the hippocampus (Lehéricy et al., 1994).

Parahippocampal gyrus The same slices on which the hippocampus was measured were used, except for the last slice in order not to include the isthmus of the cingulate gyrus. The upper boundary was the hippocampus or the transverse fissure and the lateral boundary was the collateral sulcus. If this sulcus was not visible, a straight line was drawn perpendicular to the temporal stem through the center of the first gyrus at the medial site of the temporal stem. The brain tissue medial to this line was considered as the parahippocampal gyrus. The lower and medial boundaries consisted of CSF or the tentorium cerebelli at the posterior slices.

Mamillary bodies The mamillary bodies were measured on four or five consecutive slices. On the first slice the mamillary bodies appeared as a bulge in the floor of the third ventricle. On the next two slices the mamillary bodies had an ovoid shape and on the last slices the they were small thickenings in the floor of the 3th ventricle or the medial wall of the hypothalamus. The left and right mammilary body were in most cases measured together.

Third ventricle Measurements started with the slice on which the optic chiasma was connected to the hypothalamus. The last slice was the slice on which the posterior commissure was visible. On average 17 slices were measured (range 15-20). The upper boundary on the slices on which the fornix was visible consisted of a straight line from the most superior point of the left and right side of the thalamus to the fornix. When the fornix was not present, a horizontal line was drawn between the upper medial border of the left and the right part of the thalamus where the distance between the two parts was shortest. The lateral and inferior boundaries consisted of the the thalamus or hypothalamus.

Thalamus Measurements started one slice after the anterior commissure and stopped when the thalamus could no longer be detected. On average 10 slices on each side were measured (range 8-12). The lateral boundary consisted of the internal capsule, the upper boundary of the lateral ventricles, and the medial boundary of the third ventricle. The columns of the fornix, the mamillary bodies, and the nucleus ruber

were excluded. The medial and lateral geniculate bodies were included only when there was no white matter tract between these structures and the thalamus.

Intracranial area The cranial area was measured on three slices: on the first slice on which the third ventricle was measured, on the second slice on which the mamillary bodies were measured, and on the last slice on which the third ventricle was measured. The volume of each section was derived by tracing the outline of the supratentorial compartment, following the dural and tentorial margins.

Intraobserver variability The structures on 10 scans were remeasured. The Pearson correlation coefficient between the first and second measurements was 0.91 for the hippocampus, 0.91 for the parahippocampal gyrus, 0.98 for the third ventricle, 0.90 for the whole thalamus, 0.86 for the mamillary bodies, and 0.99 for the intracranial area. These correlations indicate a high level of intrarater agreement for all measurements.

Correction for age, sex, intracranial area, number of slices, and years of alcohol abuse The years of alcohol abuse did not correlate with any of the brain volumes in the Korsakoff or alcoholic group and therefore we did not correct for it. The number of slices correlated with the total volume of the hippocampus, the parahippocampal gyrus, the third ventricle, and the thalamus. The number of slices on which the hippocampus and parahippocampal gyrus were measured did not differ between the Korsakoff group, alcoholic group, or control group. In order to reduce the variance of the data we corrected for the number of slices. This correction reduced the standard deviation in the total group by 21% (parahippocampal gyrus) and 33% (hippocampus), but the average volume in both the total group and the subgroups remained the same as that without correction for the number of slices. Because the thalamus and the third ventricle could be measured on significantly fewer slices in the Korsakoff group ($p=0.04$) than in the control group, which possibly resulted from atrophy of the thalamus, we did not correct for the number of slices for these structures. The correction for age, sex, intracranial area, and number of slices was based on a population of 60 healthy people ranging in age from 21 to 82 years (average age 56 years, standard deviation 15.9). These subjects were recruited by newspaper advertisements and included the subjects who were control subjects in the present study. Regression was performed with the brain structure as dependent variable and intracranial area, age, number of slices (only with hippocampus and parahippocampal gyrus), sex, the interaction term age by sex (because of reported differences in aging between men and women (Coffey et al., 1998)), and age square (only with the third ventricle) as independent variables. Variables and interaction terms that were significant at the $p=0.05$ level were included in the final regression model. An expected volume for each individual was calculated on the basis of the constant and the beta coefficients from the final regression equation. The expected volume was subtracted from the

observed volume. The difference (residue) was used for all analyses. The data are presented in the table and figures as follows. We calculated an expected brain volume for a subject with the average study age (46 years), male sex, average number of slices on which the hippocampus and parahippocampus were measured, and average intracranial area. To this expected volume we added the residue of the study subjects.

Statistical analysis

The data were analyzed using SPSS for the Macintosh 4.0 (SPSS Inc., Chigaco, IL, USA). Categorical data were analyzed by a Chi-squared test. Group comparisons of continuous data were analyzed with a t-test. Linear regression analysis was used to analyze the relation between memory score and brain volume. All tests were 2-tailed, and the significance level was set at 0.05.

RESULTS

Brain volumes

Brain volumes are listed in table 7.2. The volume of the following structures was significantly different in the Korsakoff group from that in the alcohol group and the control group: the hippocampus (6% decrease compared to both the control and alcoholic group), the mamillary bodies (29% decrease compared to both the control and alcoholic group, figure 7.1), the third ventricle (72% increase compared to the control group and 38% increase compared to the alcoholic group), and the thalamus (10% decrease compared to both the control and alcoholic group). The parahippocampal gyrus was 5% smaller in both the Korsakoff group and the alcoholic group than in the control group (p=0.07). The third ventricle tended to be 25% larger in the alcoholic group than in the control group (p=0.08). A typical example of brain atrophy in Korsakoff's syndrome is shown in figure 7.2.

Table 7.2 Brain volumes

	Korsakoff (Kors)	Alcoholic (Alc)	Control (Con)	*P*-value Kors vs Alc	Kors vs Con	Alc vs Con
Hippocampus	4.27 (0.28)	4.55 (0.35)	4.52 (0.23)	0.03	0.02	0.81
Parahippocampal gyrus	6.15 (0.44)	6.15 (0.45)	6.46 (0.40)	1.0	0.07	0.07
Mammillary bodies	0.049 (0.011)	0.068 (0.015)	0.069 (0.012)	0.001	<0.001	0.89
3th ventricle	1.79 (0.33)	1.30 (0.44)	1.04 (0.28)	0.004	<0.001	0.08
Thalamus	12.0 (1.2)	13.5 (1.1)	13.3 (1.4)	0.003	0.02	0.69
Intracranial area	33.0 (2.5)	33.1 (2.1)	33.9 (1.5)	0.91	0.24	0.25

Values are means (SD) in cm^3.

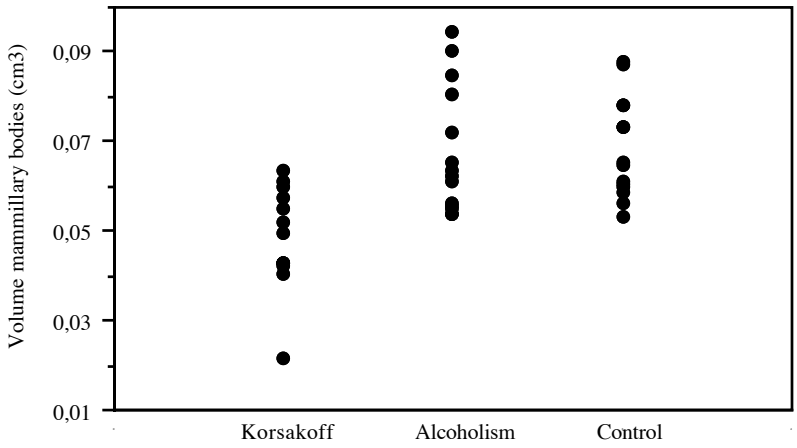

Figure 7.1 Volume of mammillary bodies in subjects with Korsakoff's syndrome, subjects with chronic alcoholism, and control subjects

Correlation between delayed recall and brain volume in the Korsakoff group

The correlation coefficient between delayed recall and brain volume was significant for the third ventricle (r=-0.54, p=0.05). None of the other correlations between delayed recall and brain structures reached significance. These correlations were -0.03 for the hippocampus (p=0.93), 0.09 for the mamillary bodies (p=0.78), and 0.04 for the thalamus (p=0.89).

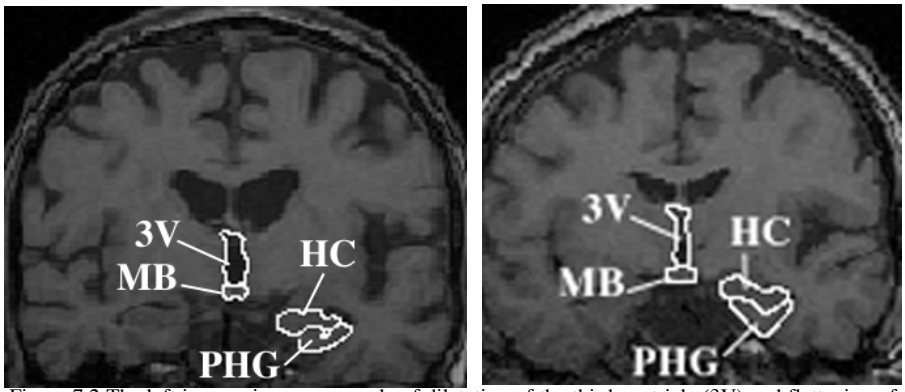

Figure 7.2 The left image gives an example of dilatation of the third ventricle (3V) and flattening of the mammillary bodies (MB) in a subject with Korsakoff syndrome. The hippocampus (HC) and parahippocampal gyrus (PHG) are only slightly atrophic. The right image shows a normal third ventricle, normal mamillary bodies, and the absence of atrophy in the hippocampus and parahippocampal gyrus in an age-matched subject with chronic alcoholism.

DISCUSSION

Volumetry on high-resolution MRI scans demonstrated that the volume of several brain structures that are involved in memory processing was decreased in subjects with Korsakoff's syndrome. The anterograde amnesia of the subjects with Korsakoff's syndrome correlated significantly with the volume of the third ventricle, suggesting that lesions in nuclei in the midline of the thalamus are responsible for the anterograde amnesia of these patients.

The involvement of the nuclei in the midline of the thalamus in the anterograde amnesia has also been reported in other studies of Korsakoff patients (Shimamura et al., 1988; Victor et al., 1989). Of these midline nuclei, the mediodorsal nucleus has often been related to anterograde amnesia (Victor et al., 1989; Zola-Morgan et al., 1985), but there are also studies that contradict the role of this structure in anterograde amnesia (Mair et al., 1979; Markowitsch, 1982; Mayes et al., 1988). Other nuclei in the midline of the thalamus that may be involved in the anterograde amnesia of Korsakoff's syndrome are the parataenial nucleus, the paraventricular nucleus, the intermediodorsal nucleus, the reuniens nucleus, and the rhomboid nucleus (Mair et al., 1979; Mayes et al., 1988; Victor et al., 1989). The severity of the anterograde amnesia may also depend on the number of nuclei that are affected (Aggleton et al., 1983).

Although the volume of the mamillary bodies was reduced in most subjects in the Korsakoff group, it did not correlate with the severity of anterograde amnesia. This is in contrast with earlier studies that showed a positive relation between mamillary body size and memory (Estruch et al., 1998; Squire et al., 1990). The discrepancy might be due to methodological shortcomings in the latter studies because either the number of subjects was small (n=4) (Squire et al., 1990), or the correlation was performed in a sample of alcoholics that included both subjects without cognitive impairment and subjects with severe cognitive impairment (Estruch et al., 1998). Other studies have questioned the role of the mammilary bodies in anterograde amnesia (Shear et al., 1996; Victor et al., 1989). Victor. (1989) reported that some subjects with severe atrophy of the mammilary bodies were not amnesic. Shear et al. (1996) demonstrated that several patients with Korsakoff's syndrome and severe amnesia had no atrophy of the mamillary bodies. Thus, atrophy of the mamillary bodies seems not to be sufficient or necessary to cause severe anterograde amnesia.

The medial temporal lobe appeared not to be involved in the anterograde amnesia. The volume of the hippocampus was modestly reduced in the subjects with Korsakoff's syndrome but it did not correlate with the score on the delayed recall task. A reduced volume of the hippocampus in Korsakoff's syndrome has been

observed in one neuropathological study (Kril et al., 1997). We found that the parahippocampal gyrus tended to be smaller in the alcoholics with or without Korsakoff's syndrome, which suggests that alcohol may have a neurotoxic effect on this structure.

We could not replicate the observation that mamillary body atrophy is common in alcoholics without amnesia (Blansjaar et al., 1992; Shear et al., 1996). However, these studies used qualitative rating scales which are less accurate than volumetry. The alcoholics in our study did not have atrophy of the hippocampus, in contrast to other studies (Sullivan et al., 1995).

One of the strong points of the study was that the brain structures were assessed with volumetry. Earlier neuroimaging studies used linear or qualitative measures, or did not follow anatomical boundaries. The exclusion criteria minimalized the potentially confounding effects of age and concomittant disorders that are often found in subjects with chronic alcoholism. A limitation of the study is that we did not assess all brain structures involved in memory processing such as the frontal lobe, the amygdala, and the cingulate gyrus. These structures may also be associated with the anterograde amnesia. Although our sample was large in comparison to that of other studies, the group size was still small and this has limited the power of the study. Correlational studies in general have the disadvantage that they show correlations and not causal relations. Studies using functional imaging techniques during neuropsychological testing may therefore further increase insight into the brain substrate of anterograde amnesia in alcoholic Korsakoff's syndrome.

In conclusion, this correlational study indicated that anterograde amnesia in alcoholic Korsakoff's syndrome is associated with atrophy of nuclei in the midline of the thalamus, but not with atrophy of the mamillary bodies, the hippocampus, or the parahippocampal gyrus.

APPENDIX

In this appendix we describe a case history of a subject with Korsakoff's syndrome (aged 44.8 years) who was initially selected for the study but who was excluded because he had no impairment on the delayed recall task (z-score= 0.38). Although anterograde amnesia was not present, this subject had many other symptoms of Korsakoff's syndrome, such as a retrograde amnesia of 10 years, confabulation, self-neglect, denial of the disease, inability to handle finances, and a frequent loss of things. These symptoms persisted during his 9-month stay at the hospital. An MRI scan made 7 months after admission revealed severe atrophy of the mamillary bodies (0.033 cm^3), the hippocampus (3.75 cm^3), and the parahippocampal gyrus (5.56 cm^3). However, the volumes of the third ventricle (1.2 cm^3) and thalamus (13.9 cm^3) were normal. This case history gives further evidence for the importance of the midline nuclei of the thalamus in the anterograde amnesia of Korsakoff's syndrome and not the mamillary bodies, the hippocampus, or parahippocampal gyrus.

Characteristics of preclinical Alzheimer's disease

8

SUMMARY

OBJECTIVE: To describe the cognitive and non-cognitive symptoms of subjects in the preclinical phase of Alzheimer's disease (AD) and to give recommendations for criteria of preclinical AD.

METHODS: Subjects with preclinical AD (N=31) were selected from a prospective study of non-demented subjects who visited a memory clinic. Cognitive performance was assessed with neuropsychological tests and the Mini-Mental State Examination (MMSE). The functioning in activities of daily living, and behavioral and affective symptomatology were assessed with clinical rating scales.

RESULTS: The most common impairments were those of memory function (81%), executive function (48%), and language (37%). Sixty per cent of the subjects had an MMSE score in the normal range (≥27). Functioning in activities of daily living was mildly impaired in 74% of the subjects (Global Deterioration Scale (GDS) stage 3), very mildly impaired in 23% (GDS stage 2), and moderately impaired in 3% (GDS stage 4). Symptoms that were most frequently reported were inability to remember a short list (80%), inability to recall recent events (50%), impaired emotional control (43%), psychological anxiety (42%), general somatic complaints (42%), depressed mood (39%), and decreased performance in work and interests (35%). The clinical diagnosis at baseline was cognitive impairment not otherwise specified (77%), amnestic disorder (19%), or no cognitive impairment (3%). A co-diagnosis of mild affective disorder was made in 80% of the subjects.

CONCLUSION: Memory impairment is the predominant finding in the preclinical stage of AD but it is not present in all subjects. Other cognitive domains such as executive functions and language are also frequently affected. The functional impairment in activities of daily living is very mild to mild. Affective symptoms are very common in the preclinical stage of AD. In elderly subjects with depression and mild cognitive impairment, one should consider not only depression -related cognitive impairment but also preclinical AD as possible diagnosis. Criteria for preclinical AD should not focus exclusively on memory dysfunction and they should not exclude subjects with normal MMSE scores, subjects with very mild impairment in activities of daily living, or subjects with mild affective disorders.

This chapter has been submitted as PJ Visser, FRJ Verhey, RWHM Ponds, J Jolles, 'Characteristics of preclinical Alzheimer's disease'.

INTRODUCTION

Before the clinical diagnosis of Alzheimer's disease (AD) (McKhann et al., 1984) can be made, there is a long period in which mild cognitive impairment is present (Almkvist et al., 1998). This period is called the preclinical or prodromal phase of AD (Linn et al., 1995). More knowledge of the characteristics of the preclinical stage of AD is needed to enable better identification of subjects with the disorder. This is important because these subjects may be candidates for anti-AD drug therapy. Indeed, if drug therapy is started in the preclinical phase of AD, it may improve the clinical response and delay the progression of the disease. In addition, the caregivers of these patients may benefit from counselling on how to handle the cognitive impairment of their partners or relatives. Until now, only a few studies have investigated the characteristics of preclinical AD and these studies had several limitations. First, they mainly focused on cognitive symptoms and neglected non-cognitive symptoms or excluded subjects with non-cognitive symptoms (Bondi et al., 1994; Jacobs et al., 1995; Linn et al., 1995; Masur et al., 1994; Small et al., 1997a; Tierney et al., 1996a). However, several reports have indicated that non- cognitive symptoms are also common in the preclinical stage of AD and may even precede the cognitive impairments (Devanand et al., 1996; La Rue et al., 1993; Liston, 1977; Oppenheim, 1994). Second, most studies presented group averages. While the average memory funtion of subjects with preclinical AD is impaired, an unknown number of subjects with preclinical AD may not have any memory impairment. Finally, most of the studies were performed in an epidemiological setting (Bondi et al., 1994; Jacobs et al., 1995; Linn et al., 1995; Masur et al., 1994; Small et al., 1997a). The results from these studies can not be translated to a clinical setting because the presentation of preclinical AD in a clinical setting is different from that in an epidemiological setting. For example, subjects with preclinical AD in a clinical setting may have more severe cognitive impairment than subjects with preclinical AD in a epidemiological setting. Moreover, most subjects with preclinical AD will be seen in a clinical setting, and for this reason clinical studies are needed.

The aim of the present study is to give a detailed description of the cognitive and non-cognitive symptoms of 31 subjects in the preclinical stage of AD in a clinical setting. We describe the performance of these subjects on neuropsychological tests and on the Mini-Mental State examination (MMSE). We report the total score and the score for individual items of clinical rating scales that assess the functioning in activities of daily living, and behavioural and affective symptomatology. We also provide the diagnosis of these subjects at baseline. We conclude with recommendations for identifying subjects with preclinical AD in a clinical setting.

METHODS

Subjects

The subjects with preclinical AD were selected from an ongoing prospective study of subjects with Cognitive Impairment No Dementia (CIND) who attend the Maastricht Memory Clinic. The design of the prospective study is described in detail elsewhere (Verhey et al., 1993a; Visser et al., 2000a; Visser et al., 2000b). In short, subjects were included in the prospective study if they were not demented, were older than 40 years, and had no cognitive impairment due to any neurological disorder, any somatic disorder, or any major psychiatric disorder other than affective disorders. Subjects were reassessed after 2 and 5 years. If necessary, subjects were seen at different time intervals if they experienced cognitive decline. At the time of the present analysis, 199 subjects with CIND had at least one follow-up assessment. Thirty-one of these subjects had AD type dementia at follow-up and could be retrospectively diagnosed as having preclinical AD at baseline: they were not demented at the baseline visit but they met the criteria of probable or possible AD at follow-up (McKhann et al., 1984).

Baseline assessment and clinical diagnosis

All subjects underwent a standardized baseline assessment which included a detailed history provided by the patient and a significant other, a psychiatric, neurological, and physical examination, appropriate laboratory tests, a neuropsychological assessment (see below), and neuroimaging as described elsewhere (Verhey et al., 1993a). The MMSE (Folstein et al., 1975) was used as a measure of global cognitive impairment. The functional impairment on activities of daily living was measured with the Global Deterioration Scale (GDS) (Reisberg et al., 1982) and the first 11 items of the Blessed Dementia Rating Scale part I (BDRS-ADL) (Blessed et al., 1968). Affective symptomatology and changes in personality and drive were measured with the Hamilton Depression Rating Scale-17 items (HDRS) (Hamilton, 1960) and the last 10 items of the Blessed Dementia Rating Scale part I (BDRS-PER) (Blessed et al., 1968). Psychiatric diagnoses were made according to the DSM-IV criteria (APA, 1994). The clinical diagnosis was made by a multidisciplinary team consisting of an experienced neuropsychiatrist, residents in psychiatry and neurology, and neuropsychologists on the basis of all available clinical information and did not depend on specific cut-off scores on cognitive tests or clinical rating scales. Dementia and AD at follow-up according to the DSM-IV (APA, 1994) and NINCDS-ADRDA criteria (McKhann et al., 1984).

Neuropsychological assessment

The neuropsychological assessment consisted of a series of standard clinical tests covering the cognitive domains of memory, language, executive functions and attention, praxis, and intelligence, as described elsewhere (Jolles, 1986; Verhey et al., 1993a). We selected one test for each cognitive domain.

Memory. Memory function was assessed with the Auditory Verbal Learning Test (AVLT) (Brand et al., 1985; Lezak, 1995). Fifteen words were presented five times and after each presentation the subject was asked to reproduce as many words as possible. After 20 minutes, the delayed recall was tested. The variables selected for the study were the number of words memorized after the first presentation as a measure of immediate recall (AVLT-IR), the total number of words reproduced over the five trials as a measure of learning (AVLT-LR), and the number of words recalled after 20 minutes as a measure of delayed recall (AVLT-DR). Data for four subjects who were given a 10-word version of the AVLT were excluded from the analysis of the memory data.

Language. Verbal fluency was taken as a measure of language function (McKhann et al., 1984). Fluency was defined here as the ability to name as many professions/ trades as possible within 1 minute.

Executive functions/attention. The Stroop Color Word Test (Stroop, 1935) was taken as a measure of executive functions and attention. The test involves three cards which display a hundred stimuli each: colour names, coloured patches, and colour names printed in incongruously coloured ink (cards 1-3, respectively). The time needed to read (card 1) or to name colours (card 2 and 3) was recorded. Performance on card 3 is determined for a large part by the time needed to discard irrelevant but very salient information (verbal), in favour of a less obvious aspect (colour naming), which is also known as cognitive interference. We selected the time to complete card 1 (Stroop 1) and the time to complete card 3 (Stroop 3). Subjects who completed card 1 but who could not finish card 3 were given the maximum score of the study population for card 3.

Praxis. The subject had to complete the honeycomb figure (Lezak, 1995). The performance was scored as normal (0), slightly impaired (1),or severely impaired (2).

Intelligence. Intelligence was assessed with the Dutch translation of the WAIS (n=1) (Stinissen et al., 1970), the Groninger Intelligence Test (n=26) (Luteyn et al., 1983), or The Coloured Progressive Matrices (n=3) (Raven, 1965).

The MMSE and all other cognitive scores except for the measure of praxis were corrected for age, sex, and education and expressed as z-scores (Visser et al., 2000a; Visser et al., 2000b). The corrections were based on a reference population of 1400 subjects older than 40 years from the Maastricht Aging Study (Jolles et al., 1995; van Boxtel et al., 1998). This is a prospective study of cognitively normal subjects

randomly selected within age-strata from a registry of general practitioners (Jolles et al., 1995; van Boxtel et al., 1998). The sign of the z-scores of the Stroop 1 and Stroop 3 was inverted such that a z-score below zero indicated below average performance. A z-score below -1.28 is equivalent to a score below the 10th percentile.

RESULTS

Table 8.1 shows the average scores at baseline and table 8.2 the individual scores on an selection of variables.

Table 8.1 Baseline characteristics

Age (years)	70.0 (7.3)
Range	48-81
Sex (M:F)	13:18
Education‡	2.7 (1.2)
Time to AD (years)	2.9 (1.9)
Range	0.6-8.7
GDS	
- 2	7
- 3	23
- 4	1
BDRS-ADL	1.1 (0.7)
BDRS-PER	1.1 (1.1)
HDRS	5.3 (4.8)
MMSE	26.5 (2.3)
AVLT-IR (z-score)	-1.4 (1.2)
AVLT-LR (z-score)	-1.5 (1.3)
AVLT-DR (z-score)	-1.8 (1.3)
Stroop 1 (z-score)	-0.9 (1.2)
Stroop 3 (z-score)	-1.6 (1.7)
Fluency (z-score)	-0.94 (0.86)
IQ (z-score)	-0.54 (1.0)
Honeycomb figure	
- 0	12
- 1	5
- 2	4

GDS=Global Deterioration Scale, BDS-ADL=first 11 items of Blessed Dementia rating Scale, BDS--PER=last 10 items of Blessed Dementia rating Scale, HDRS=Hamilton Depression Rating scale, MMSE= Mini-Mental State Examination, AVLT-IR=immediate recall of Auditory Verbal Learning Test (AVLT), AVLT-LR=learning measure of AVLT, AVLT-DR=delayed recall of AVLT, Stroop 1=time to complete card 1 of the Stroop Color Word Test, Stroop 3=time to complete card 3 of the Stroop Color Word Test. ‡Scored on 5-point scale:1=primary school (equals 6 years of education), 2=technical or vocational training for 12-16 years old or 3 years of secondary school (equals 9 years of education), 3=technical or vocational training for 16-18 years old (equals 10 years of education), 4=technical or vocational training for 18 or more years old or 6 years of secondary school (equals 13 years of education); 5=university degree (equals 16 years of education))

Tabel 8.2. Baseline characteristics of subjects with preclinical AD. Legend see next page.

Demographics			Time to AD (yrs)	Clinical Diagnosis		Clinical rating scales				Cognition z-scores (raw scores[$])				
Age	Sex[§]	Edu[‡]		Diag[¶]	Affec Dis	HDRS	BDRSADL	BDRSPER	GDS	MMSE	Intell	AVLT-DR	Stroop 3	Praxis
48	2	2	6	CI	Yes	..	0.5	0	2	..	0.4	-2.0 (5)	-1.8 (128)	..
56	1	2	2	CI	Yes	10	0	0	2	-1.7 (25)	-3.4	-0.2 (8)	..	(2)
59	2	4	2	CI	Yes	7	1.5	0	3	0.5 (30)	0.7	-3.8 (2)	0.4 (79)	..
60	1	5	2	CI	Yes	16	0.5	0	2	-1.4 (27)	0.2	-1.4 (6)	-2.0 (131)	..
64	2	1	2	CI	Yes	4	0.5	2	3	-1.2 (25)	-1.6	-3.0 (1)	-1.3 (144)	(0)
64	2	1	1	CI	Yes	8	1.5	3	4	-3.4 (21)	-1.4	-3.4 (0)	-2.9 (200)	..
65	2	4	5	CI	Yes	15	0	1	3	-0.4 (28)	-1.4	-3.7 (0)	-0.7 (107)	(0)
66	2	4	3	CI	Yes	12	1.5	1	3	-2.0 (25)	-0.5	-3.7 (0)	-2.2 (147)	(1)
66	1	2	0.5	CI	Yes	2	1.5	4	3	-2.0 (24)	-1.7	-1.4 (4)	-0.8 (129)	..
68	2	1	2	AS	No	4	1.5	0	3	0.1 (27)	0.1	-3.2 (0)	-0.8 (138)	(0)
69	1	5	2	CI	No	1	1	0	3	-1.7 (26)	-1.2	-2.0 (3)	-1.2 (121)	(1)
69	2	3	2	NCI	Yes	10	0.5	0	2	0.6 (29)	-0.2	0.4 (10)	1.8 (72)	(0)
69	1	3	1	CI	Yes	5	1.5	0	3	0.6 (29)	-0.3	-1.7 (3)	-4.0 (250)	(1)
69	1	4	2	CI	Yes	9	2	2	3	-1.3 (26)	-2.8	-1.5 (4)	-0.1 (104)	..
69	1	5	4	AS	No	20	1	0	3	-1.1 (27)	-0.5	-1.2 (5)	-0.4 (105)	(0)
70	2	3	5	CI	Yes	1	0	0	2	1.2 (30)	-0.3	-1.1 (6)	-0.7 (122)	(0)
70	2	1	5	AS	No	6	2	4	3	-1.5 (24)	0.8	-2.7 (1)	0.7 (104)	(0)
71	1	2	9	AS	Yes	6	0.5	0	3	0.5 (28)	-0.4	-2.6 (0)	-0.4 (129)	(0)
71	1	2	2	CI	Yes	2	2	1	3	0.5 (28)	..	-2.3 (1)	-1.3 (155)	..
73	1	2	2.5	CI	Yes	15	..	..	3	0.0 (27)	-1.9	-2.2 (1)	..	..
74	2	2	5.5	CI	Yes	15	1.5	1	3	0.6 (28)	0.1	(8[*)]	-2.4 (238)	(2)
75	2	3	2.5	CI	Yes	10	0	2	..	..	0.4	(4[*)]	-1.0 (144)	(0)
75	2	2	2	AS	No	9	2.5	1	3	-2.6 (22)	-0.2	-2.9 (0)	-2.0 (188)	(0)
76	1	3	2.5	AS	Yes	3	1	1	3	1.0 (29)	0.1	-1.3 (3)	-0.7 (137)	(0)
76	1	2	2	CI	Yes	10	0.5	1	3	-0.9 (25)	-1.3	(4[*)]	-5.3 (380)	(2)
77	2	2	5.5	CI	Yes	16	1	1	3	-0.9 (25)	-0.3	-1.3 (4)	-5.0 (380)	(2)
78	1	3	2	CI	No	11	0.5	1	2	1.1 (29)	0.7	(5[*)]	..	(1)
78	2	2	1	CI	Yes	7	1.5	0	3	0.3 (27)	0.2	-2.4 (1)	-2.3 (210)	(1)
79	2	4	5	CI	Yes	5	1	2	2	-0.2 (27)	-0.5	-1.2 (4)	-2.5 (201)	..
80	2	1	2	CI	Yes	9	2	2	3	-0.9 (24)	0.8	-1.8 (2)	-0.3 (153)	(0)
81	2	3	1.5	CI	Yes	17	1.5	2	3	-0.9 (25)	-1.1	-1.8 (2)	-0.6	..

Legend table 8.2. Edu=educational level; AffecDis= Affective disorder; HDRS=Hamilton Depression Rating Scale; BDRS-ADL=first 11 items of Blessed Dementia Rating Scale; BDRS-PER=last 10 items of Blessed Dementia Rating Scale; GDS=Global Deterioration Scale; MMSE=Mini-Mental State Examination; Intell=Intelligence; .. means missing data..
¶Diag=diagnosis at baseline: CI=cognitive impairment not otherwise specified; AS=amnestic syndrome not otherwise specified; NCI= no cognitive impairment.
§1=Male, 2=female.
‡See tabel 8.1.
*Ten-word version of AVLT.
$Raw scores are for AVLT-DR number of words recalled, for Stroop 3 time in seconds, for Praxis as described in methods.

Baseline characteristics

Half of the subjects (n=15, 48%) were older than 70 years at baseline. One subject was younger than 50 years (3%), two subjects (6%) were between 50 and 60 years, and 13 subjects (42%) were between 60 and 70 years of age. The time between the baseline assessment and the clinical diagnosis of AD varied from 0.6 to 8.7 years (average 2.9 years).

Cognitive performance

Table 8.1 shows the z-scores for the cognitive tests. Delayed recall (z-score -1.8), and the Stroop 3 (z-score -1.6) were the most affected and the IQ (z-score -0.5) was affected the least. Table 8.3 shows the percentage of subjects who scored below the 10th percentile, between the 10th and 50th percentile, and above the 50th percentile. Impairments (a score below the 10th percentile) were most common on delayed recall (81%), learning (59%), and the Stroop 3 (48%), and least common on immediate recall (22%) and IQ (27%). Delayed recall performance was always impaired in subjects with an impaired immediate recall or learning performance, except for one subject. The performance of two subjects (6%) was not impaired on any of the cognitive tests.

Table 8.3 Percentile scores on cognitive tests

	N	≤10th percentile	10th-50th percentile	≥50th percentile
MMSE	29	31%	28%	41%
AVLT-IR	27	22%	37%	41%
AVLT-LR	27	59%	33%	7%
AVLT-DR	27	81%	15%	4%
Stroop 1	29	31%	48%	21%
Stroop 3	29	48%	42%	10%
Fluency	30	37%	53%	10%
IQ	30	27%	37%	37%

Abbreviations see table 8.1

MMSE score
The average MMSE at baseline was 26.5. Seventeen of 29 subjects (59%) had a score of 27 or higher. Ten subjects (34%) had a score between 24 and 27, and two subjects (7%) had a score below 24. Submaximal scores (at least one error) on individual items of the MMSE were seen in more than 20% of the subjects on the following items: delayed recall (item 5) (86%), orientation in time (item 1) (45%), orientation in place (item 2) (31%), attention (item 4) (28%), and the repetition of the sentence (item 7) (28%). None of the subjects had errors on registration (item 3), naming (item 6), or reading (item 9).

Functioning in activities of daily living
Seven subjects (23%) had a GDS score of 2 (very mild impairment), 23 subjects (74%) a GDS score of 3 (mild impairment), and one subject (3%) a GDS score of 4 (moderate impairment). The BDRS-ADL score was on average 1.1 (range 0-2). Items that were positive (score ≥0.5) in more than 20% of the subjects were inability to remember a short list (item 3) (80%) and inability to recall recent events (item 7) (50%). The ability to find the way in house (item 4), eating (item 9), dressing (item 10), or sphincter control (item 11) were not impaired in any of the subjects.

Affective symptomatology
The HDRS total score varied from 1 to 20. Thirteen subjects (42%) scored below 7, eleven subjects (35%) scored between 7 and 13, and seven subjects (23%) scored 13 or higher. Only two subjects (6%) had a score of 17 or higher. HDRS items that were positive (score ≥1 on items with a 3-point scale, and ≥2 on items with a 5-point scale) in more than 20% of the subjects were general somatic complaints (item 13) (42%), psychological anxiety (item 10) (42%), depressed mood (item 1) (39%), work and interests (item 7) (35%), somatic anxiety (item 11) (26%), and sleep disturbances early in the morning (item 6) (23%). The BDRS-PER score was on average 1.1 (range 0-4). BDRS-PER items that were positive (score ≥1) in more than 20% of the subjects were impaired emotional control (item 16) (43%), hobbies relinquished (item 20) (23%), and diminished initiative (item 21) (20%). No impairments were reported for diminished emotional responsiveness (item 18), sexual misdemeanor (item 19), and purposeless hyperactivity (item 22).

Initial diagnosis
The baseline diagnosis was cognitive impairment not otherwise specified (N=23, 77%), amnestic disorder (N=6, 19%), or no cognitive impairment (N=1, 3%). A co-diagnosis of mild affective disorder was made in 80% of the subjects. In most of these subjects, the affective disorders were thought to be partially or fully respon-

sible for the cognitive impairment. The affective disorders seen in the subjects with cognitive impairment not otherwise specified were depressed mood (N=13, including three subjects with depression resulting from bereavement) or anxiety (including fear of dementia (N=4), fear of failure (N=3), post-traumatic stress disorder (N=1), or anxiety disorder not otherwise specified (N=2)). The amnestic disorder was thought to be related to depression in one subject and secondary to anxiety disorder not otherwise specified in another subject. The cognitive complaints of the subjects with no cognitive impairment were thought to be due to problems at work (N=1).

DISCUSSION

In this study we described the cognitive and non-cognitive features of 31 subjects with preclinical AD who attended a memory clinic. The cognitive domain that was most often impaired was memory, especially delayed recall. This is in line with the results of other studies (Bondi et al., 1994; Jacobs et al., 1995; Linn et al., 1995; Masur et al., 1994; Small et al., 1997a; Tierney et al., 1996a). However, 5 of 29 subjects (17%) did not have an impaired delayed recall performance. Three of these subjects had impairments of other cognitive measures. Therefore, when selecting subjects with preclinical AD one should not focus exclusively on delayed recall performance (Ritchie et al., 2000). Executive functions and language were also frequently affected in the preclinical stage of AD. Complex executive functions (Stroop Color Word Test card 3) were impaired more often than were simple executive functions (Stroop Color Word Test card 1), which is in accordance with previous studies (Cahn et al., 1995).

Sixty per cent of the subjects had MMSE scores in the normal range (≥27). Thus a normal score on the MMSE does not exclude preclinical AD. Of the two subjects with a MMSE score below 24, one subject had not sufficient functional impairment in the activities of daily living to fulfil the dementia criteria, and the other subject had an amnestic disorder. The MMSE items that were most frequently impaired (orientation in time and delayed recall) were also predictors of dementia in an epidemiological study (Small et al., 1997b). The delayed recall item was also predictive of dementia in a clinical setting (Devanand et al., 1997).

Twenty-five per cent of the subjects had only very mild functional impairment (GDS stage 2). Previous follow-up studies performed in the general population or with volunteers demonstrated that subjects in GDS stage 2 had a very low risk of subsequent dementia (below 5%) (Reisberg et al., 1986; Snowdon et al., 1994). Our study shows, however, that GDS stage 2 in subjects attending a memory clinic with mild cognitive impairment does not exclude subsequent AD. The items of the BDRS-ADL that were most frequently impaired were related to memory impairment.

The most common affective symptoms were depressed mood, loss of interest, anxiety, general somatic complaints, and less emotional control. These symptoms were also reported to be frequently present in subjects with minimal or mild dementia (Ballard et al., 1993). Eighty per cent of the subjects had a co-diagnosis of a mild affective disorder at baseline and in most subjects this affective disorder was thought to be partially or fully the cause of the cognitive impairment. Even fear of dementia or fear of failure was considered to cause the cognitive impairment in some subjects. In retrospect, this seems unlikely because the cognitive impairment was probably the early manifestation of AD. Thus in subjects with depression and mild cognitive impairment one should consider not only depression-related cognitive impairment but also preclinical AD as possible diagnosis. We have previously demonstrated that preclinical AD is a likely diagnosis in subjects with depression and mild cognitive impairment when the subject is older than 65 years and when delayed recall performance is moderately to severely impaired (Visser et al., 2000b). The cause of the affective symptomatology in preclinical AD is not clear. Depression might result from neurodegeneration of brain areas involved in the regulation of mood, such as the nucleus coeruleus as suggested by some studies (Förstl et al., 1992; Zubenko et al., 1988; Zweig et al., 1988) but not all (Hoogendijk et al., 1999) or the subcortical white matter (Alexopoulos et al., 1997). Alternatively, awareness of the cognitive impairment may cause depression (Migliorelli et al., 1995), but this explanation has been refuted in several other studies (Feher et al., 1991; Reed et al., 1993; Verhey et al., 1993b). Another explanation is that a diminished cognitive ability may increase the number of stressful events experienced by subjects with preclinical AD and impair their coping capacity, which in turn may lead to depressed mood or depression. Because of this increased vulnerability to daily stress and to small deviations from the daily routine, we have introduced the term 'emotional vulnerability syndrome' to describe the affective symptomatology of subjects in the preclinical stage of AD (Verhey et al., in press). Finally, the symptoms of preclinical AD may be misunderstood as being those of depression. For example, the decrease in work and interests may be the result not only of depression but also of the cognitive impairment. This explanation is less likely because many subjects with preclinical AD experienced depressed mood and other symptoms of depression. It is possible, however, that the severity of the depression is overestimated because some symptoms of depression and preclinical AD overlap.

The average time between the baseline assessment and the clinical diagnosis of AD was 3 years. This suggests that pharmacological treatment or counselling for AD can be started 3 years earlier if reliable criteria of preclinical AD become available. The time interval, however, may be overestimated because the time between the follow-up assessments was 2 to 3 years. The mental capacities of some subjects

declined rapidly whereas that of others remained stable over a period of 8 years. In order to evaluate variables that could explain this variance, we correlated post-hoc age, education, functional measures, and cognitive measures with the time to AD, but none of these correlations reached statistical significance.

The results of this study are relevant for the development for criteria for preclinical AD. Several such criteria have been proposed, for example, those for questionable dementia (Rubin et al., 1989b), mild cognitive impairment (Petersen et al., 1995; Smith et al., 1996), aging-associated cognitive decline (Levy, 1994), or minimal dementia (Roth et al., 1986). Criteria that require both cognitive impairment and mild interference with activities of daily living, such as those of mild cognitive impairment (Smith et al., 1996), will probably result in a low sensitivity, as suggested by the high prevalence of subjects with only very mild interference with activities of daily living (GDS stage 2) in our study. When screening for preclinical AD, we suggest that the cognitive assessment should not be restricted to memory impairment only but should also include other cognitive domains such as executive functions and language, as has been proposed in the criteria of agingassociated cognitive decline (Levy, 1994) and mild cognitive impairment (Smith et al., 1996). In the present study, we defined cognitive impairment as a score below the 10th percentile (1.28 standard deviation (SD) below the expected mean). Other criteria have used a less severe definition of cognitive impairment (e.g., 1 SD below the expected mean (Levy, 1994)), or a more severe definition (e.g., 1.5 SD below the expected mean (Smith et al., 1996)). In our study, the same subjects would have been classified as having impaired function in at least one cognitive domain if the more severe cut-off of -1.5 SD had been used. With a cut-off of -1 SD, one subject would have been classified as having impaired function in at least one cognitive domain that would not have been considered impaired if the cut-off of -1.28 SD had been used. The cut-off score selected should be based on the specificity of the cut-off scores. In this, the setting will be probably important: in a clinical setting, where the prevalence of preclinical AD is high, a less severe cut-off score can be used, while in a community setting, where the prevalence of preclinical AD is low, a more severe cut-off score is better. Since affective symptomatology is very common, mild-to-moderate depression should not be an exclusion criterion for preclinical AD. As none of the subjects with preclinical AD had a baseline HDRS score higher than 20, subjects with a score higher than 20 can be excluded without a high risk of excluding subjects with preclinical AD. The sensitivity and specificity of criteria of preclinical AD can probably be increased by using biological markers of AD such as hippocampal atrophy (de Leon et al., 1993a; Jack et al., 1999; Visser et al., 1999b).

In conclusion, there is not a simple profile for preclinical AD. Memory impairment is the predominant finding but is not present in all subjects. Affective

symptoms are common in preclinical AD. In elderly subjects with depression and mild cognitive impairment, one should consider not only depression-related cognitive impairment but also preclinical AD as possible diagnosis. Criteria for preclinical AD should not focus exclusively on memory dysfunction and they should not exclude subjects with normal MMSE scores, subjects with very mild impairment in activities of daily living, and subjects with mild affective disorders.

General discussion

9

The aim of the studies described in this thesis was to find a way to identify subjects with preclinical AD from among subjects with mild cognitive impairment. To this end, we have described the characteristics of subjects with preclinical AD, investigated predictors of AD in subjects with mild cognitive impairment using a multidisciplinary approach, and tried to formulate decision rules for detecting subjects with preclinical AD that can be used in clinical practice. We will now discuss the results obtained. In 9.1 we comment on the characteristics of preclinical AD. In 9.2 we discuss the predictors of AD. In 9.3 we propose the Preclinical AD Scale (PAS), a multidisciplinary scale for detecting preclinical AD in subjects with mild cognitive impairment. In 9.4 we discuss some of the methodological limitations of the studies. In 9.5 we conclude with suggestions for future research in preclinical AD and recommendations for clinical practice.

9.1 CHARACTERISTICS OF PRECLINICAL AD

The clinical characteristics of subjects with preclinical AD who visited the Maastricht Memory Clinic were described in chapter 8. The results showed that 80% of the subjects had impaired delayed recall, which means that 20% did not. Seventy-seven per cent of the subjects had mild to moderate impairments of functioning in activities of daily living and 23% only very mild impairments. Eigthy per cent of the subjects had affective symptoms and 20% did not. These results emphasize that there is not a simple profile of symptoms that applies to all subjects with preclinical AD. Criteria for preclinical AD should therefore not focus exclusively on memory dysfunction and they should not exclude subjects with very mild impairment in activities of daily living or subjects with mild affective disorders.

The high prevalence of affective symptoms seen in subjects with preclinical AD confirms the results from earlier studies (La Rue et al., 1993; Liston, 1977; Oppenheim, 1994; Verhey et al., 2000). Depressive disorders were seen in 60% of the subjects with preclinical AD (chapter 4). Most subjects with depression (87%)

Parts of this chapter chapter has been submitted as PJ Visser, FRJ Verhey, RWHM Ponds, J Jolles, 'Preclinical Alzheimer's disease is a clinical entity' (section 9.1), and PJ Visser, FRJ Verhey, J Jolles, 'Predictors of Alzheimer type dementia in subjects with mild cognitive impairment. A review and meta-analysis' (section 9.2).

Table 9.1 Prevalence of depressive disorders in preclinical AD

Subjects	Depression criteria	Prevalence
Memory impairment (chap. 2)	Minor or major depression and HDRS ≥13	26%
Minimal dementia (chap. 3)	CAMDEX depression criteria*	13%
Mild cognitive impairment (chap. 4)	Minor or major depression	60%
Mild cognitive impairment (chap. 4)	Minor or major depression and HDRS <17	52%
Mild cognitive impairment (chap. 4)	Minor or major depression and HDRS ≥17	8%

HDRS= score on the Hamilton Depression Rating Scale
*These criteria are more or less equivalent to the DSM criteria of major depression.

had only mild depression (Hamilton Depression Rating Scale score below 17), which is in line with other studies (Cummings, 1989; Rubin et al., 1989a; Verhey et al., 2000). The difference in the prevalence of depressive disorders reported in chapters 2, 3, and 4 largely depends on the difference in the strictness of the criteria for depressive disorder used. Moderately severe depression had the lowest prevalence (8%) and mildly severe depression the highest (52%) (table 9.1). In chapter 8 we discussed the possible etiology of depression in preclinical AD and concluded that depression could be the result of a diminished cognitive ability so that subjects experience more events as being stressful but at the same time have a diminished capacity to cope with the events. This diminished cognitive ability may also explain why depression is often seen in the preclinical stage of other dementing disorders such as vascular dementia and Parkinson's disease (La Rue et al., 1993; Reding et al., 1985). In addition, cell loss in brain areas involved in mood regulation (Alexopoulos et al., 1997; Förstl et al., 1992; Zubenko et al., 1988; Zweig et al., 1988), subcortical white matter lesions (de Groot, 1999; Hofman, 2000), or awareness of the cognitive impairment (Migliorelli et al., 1995) may contribute to the development of depressive symptoms in preclinical AD.

In order to demonstrate that preclinical AD and AD are indeed separate clinical entities we compared the demographics, scores on clinical rating scales, and scores on cognitive tests of 31 subjects with preclinical AD and 94 subjects with probable or possible AD (MMSE score ≥20) at the time of the first visit to the Maastricht Memory Clinic. The variables examined are listed in table 8.1. Compared to subjects with AD, subjects with preclinical AD had significantly less functional impairment in activities of daily living, as measured with the Global Deterioration Scale ($p<0.001$) and the first 11 items of the Blessed Dementia Rating Scale part I ($p<0.001$). They also had fewer changes in personality and drive, as measured with the last 10 items of the Blessed Dementia Rating Scale part I ($p=0.007$). Cognitive

impairment was less severe on the MMSE, immediate recall, learning, Stroop card 1 and 3, verbal fluency, IQ ($p \leq 0.001$ for all comparisons), and the honeycomb figure ($p=0.01$) in subjects with preclinical AD than it was in subjects with AD. There were no differences in age, score on the Hamilton Depression Rating Scale, and score on the delayed recall measure. Logistic regression analysis with forward step selection selected Stroop card 3, the Global Deterioration Scale score, and IQ as the best discriminators between preclinical AD and AD. Using these variables, 85% of the subjects were correctly classified. Twenty-five percent of the subjects with preclinical AD were misclassified as demented and 12% of the subjects with AD were misclassified as non-demented. These data indicate that preclinical AD and AD are indeed separate clinical entities. Because there was little overlap in scores, the subjects with preclinical AD at baseline were not subjects who were occasionally misclassified as non-demented. The differences between preclinical AD and AD were most pronounced for functional impairment and impairments of cognitive measures other than delayed recall performance. The observation that the delayed recall performance was not significantly different between subjects with preclinical AD and AD corroborates the observation that impairment of delayed recall performance is the first cognitive domain affected by AD in most subjects (Almkvist et al., 1998; Fox et al., 1998; Newman et al., 1994; Nielsen et al., 1999; Small et al., 1997a).

9.2 PREDICTORS OF AD IN SUBJECTS WITH MILD COGNITIVE IMPAIRMENTS

We tested whether age, educational level, impairments on cognitive tests, the MMSE score, the severity of functional impairment, depression, the apoE genotype, and medial temporal lobe atrophy could predict AD in subjects with mild cognitive impairment. In this section we will discuss the findings from the chapters 2-7 and compare them with the findings from other studies. For each predictor variable, we tried to answer the following questions: does the variable predict AD, and if so, how accurately can it predict AD and can it predict AD independently of other variables? In order to see whether a variable predicted AD, we determined in how many studies the variable predicted outcome. The accuracy of the prediction was determined for dichotomous variables by calculating odds ratios and by calculating the sensitivity, specificity, positive predictive value, and negative predictive value. If possible, we pooled the odds ratios of all studies that investigated the variable according to the method described by Mantel and Haenszel (see for example Yusuf et al. (1985)). Clearly, the pooled data need to be interpreted with caution because they were often based on studies that were different in design. The predictive accuracy of continuous

Table 9.2 Predictors of outcome in prospective studies of subjects with mild cognitive impairment

Study	MCI definition‡	N	Setting#	Average age (SD), range	MMSE baseline	Average FU	% with outcome	Demented subjects at FU		
								N	%	%AD
Chapter 2	Amnesia (objectified)	74	C	60 (10), 40-81	27.5	3.8	85	19	30	100
Chapter 3	Minimal dementia	63	E	80 (4), >65	22.5	2.7	71	24	53	79
Chapter 4	Complaints	62	C	66 (7), >55	27.8	3.6	86	25	28	100
Chapter 5	Minimal dementia	20	E	79 (4), >65	22.6	2.7	65	9	69	100
Chapter 6	Complaints	31	C	65 (10), >50	27.6	1.9	100	7	22	100
Hänninen 1995	AAMI	229	E	68, 60-78	26.8	3.6	77	16	9	81
Coria 1995	Amnesia (objectified)	56	C	71 (7), >60	-	3	100	30	54	-
Bowen 1997	Amnesia (objectified)	23	C	74 , 44-89	25.2	4	91	10	48	90
Celsis 1997	ARCD	24	C	62 (9)	27.5	2	100	5	21	100
O'Brien 1992	BSF	68	C	67 (8), >50	28.7	3	94	6	10	83
Rubin 1989b	CDR 0.5	16	R	72 (4), 64-81	-	6	100	11	66	100
Tierney 1996a, b	Complaints	178	C	72 (7)	27.8 (cor)	2	81	29	24	97
Tuokko 1991	Complaints	45	C	69 (8)	-	1.3	100	18	40	100
Tröster 1994	Complaints	35	R	69 (8)	-	5*	86	4	13	100
Devanand 1997	Complaints	127	C	66 (10), >40	-	2.5	60	31	41	87
Flicker 1991	GDS 3	32	C	71	-	2.1	100	21	72	76
De Leon 1993	GDS 3	32	C	71	25	4.1	100	23	72	100
Petersen 1993	MCI (Mayo)	86*	C	81, 73-86	24.6	2.8*	85*	27	37	100
Petersen 1995	MCI (Mayo)	78*	C	81, 73-86	26.2	2.8	85*	25	38	100
Jack 1999	MCI (Mayo)	80	C	78 (7), 60-89	26.4	2.7	100	27	34	100
Wolf 1998	MCI (Zaudig)	60*	C	68 (7), 51-84*	25.7	2.7	68*	8	20	100

‡ MCI=mild cognitive impairment; BSF= Benign senescent forgetfulness; GDS=Global Deterioration Scale, CDR=Clinical Dementia Rating Scale; AAMI= Age Associated Memory Impairment; ARCD= Age Related Cognitive Decline. For a description of the definitions of mild cognitive impairment see Appendix A. # Setting: E=Epidemiological; R=Research (subjects that were recruited by advertisements, spouses or siblings of patients); C=Clinical. * data were not available; the presented data are estimated from descriptions in the text or from the total study population.

Table 9.2 continued

Study	Predictors*								Best Univariate§	Multivariate analysis¶
	Age	Edu	NPA‡	MMSE	Func	ApoE	Dep	MTL atr		
Chapter 2##	Yes	No	MEM (Trend)	Trend	Yes	No	No	-	Age	Selected: Age, MEM, MMSE
Chapter 3‡‡	Yes	No	MEM	No	-	No	No	-	MEM	Best model: MEM
Chapter 4	Yes	No	MEM, LAN,cATT	Yes	Yes	-	-	-	Age	Selected: Age, MEM§§
Chapter 5	No	No	MEM	No	-	-	-	Yes	PHG	Best model: age, MEM, PHG/MTA
Chapter 6	Yes	No	MEM (Trend)	No	Yes	-	-	Yes	MTA	Best model: Age, MEM, HC**
Hänninen 1995	No	No	MEM, LAN, CON	Trend	-	-	-	-	MEM	Best model: MEM, LAN
Coria 1995	No	-	-	-	-	Yes	-	-	-	-
Bowen 1997	-	-	-	No	-	-	-	-	-	-
Celsis 1997	-	-	MEM	No	-	-	-	-	MEM	-
O'Brien 1992	No	-	MEM	No	-	-	-	-	MEM	-
Rubin 1989b	-	No	-	-	-	-	-	-	-	-
Tierney 1996a,b	Trend	Yes	MEM, sATT	Yes	-	Yes	-	-	MEM	Selected: MEM, sATT
Tuokko 1991	No	No	MEM	-	-	-	-	-	MEM	-
Tröster 1994	No	No	MEM	-	-	-	-	-	MEM	-
Devanand 1997	Yes	No	MEM, cATT, CON, LAN, ABS	-	Trend	-	No	-	ABS	Best model: Age,MEM,cATT, CON, LAN, recall MMSE
Flicker 1991	-	-	MEM, LAN	-	-	-	-	-	MEM	-
De Leon 1993	Trend	-	Compound score	-	-	-	-	Yes	HCSF	Best model: HCSF
Petersen 1993	-	-	MEM, CON	Yes	Yes	-	-	-	MEM	-
Petersen 1995	Yes	No	MEM	Yes	Trend	Yes	-	-	MMSE	-
Jack 1999	Yes	-	MEM	Trend	-	No	-	Yes	HC/MEM	Best model: HC, MEM
Wolf 1998	Yes	No	MEM, ORIEN	Yes	-	No	-	Yes	Age/ MEM	-

Edu=education; NPA=neuropsychological assessment; MMSE=Mini-Mental State Examination; Func=functional impairment; ApoE=apolipoprotein E genotype; Dep= Depression; MTL atr=Medial temporal lobe atrophy- Legend continued on next page.

Legend table 9.2 continued.
*Predictors: yes=significant difference on univariate test; no=no significant difference on univariate test; trend=p-value between 0.05 and 0.15; -= not tested.
‡Only tests that were significantly different between subjects with and without dementia at follow-up are listed. MEM=memory tests; LAN=language tests (including fluency); CON=tests involving visuoconstruction; ABS=tests involving abstract reasoning; sATT=tests involved simple attention; cATT=test involving complex attention; ORIEN=tests involving orientation.
#HCSF=rating of perihippocampal cerebrospinal fluid; PHG=volume parahippocampal gyrus; HC= volume hippocampus; MTA=qualitative measure of medial temporal lobe atrophy.
§Best univariate: based on p-value or test-value.
¶Multivariate analyses: Best model: model with a priori selected variables; Selected: variables selected with step backward or step forward procedures.
**Outcome is cognitive decline:subjects with AD (N=7) and subjects with decline on cognitive tests (N=3).
##When subjects with reversible or persistent memory impairment were compared to subjects with AD at follow-up.
‡‡When subjects with reversible or persistent minimal dementia were compared to subjects with dementia at follow-up.
§§Mildly or moderately depressed subjects without dementia at follow-up versus mildly or moderately depressed subjects with dementia at follow-up.

variables could only be determined relative to that of other variables from the same study by comparing the p-value on univariate tests. For data from the Maastricht Memory Clinic[1] and the AMSTEL study (chapter 3) we dichotomized the continuous variables age, memory function, and MMSE score in order to compare the predictive strength of these variables with each other. It was not possible to pool the data for continuous variables across the different studies. In order to see whether the predictor variable was independent of other variables, we compared univariate and multivariate models.

Table 9.2 summarizes the findings from this thesis and those from the other studies that investigated predictors of AD. Some studies listed in table 9.2 were from the same study population. If a subgroup from a larger study was described in a separate chapter or article, we refer only to the results of the larger study if variables are discussed that were tested in both studies.[2] Although the subjects from the studies described in chapters 2 and 4 and the subjects from the studies by Jack et al. (1999) and Petersen et al. (1993) were from the same population, we consider these studies as independent studies because the inclusion criteria were different between the studies.

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[1]The data were from 60 subjects with a completed 5-year follow-up older than 60 years, including 21 subjects who had AD at follow-up, unless specified otherwise.

[2]This applies to chapter 5 in which a subgroup from chapter 3 was investiagted, chapter 6 in which a subgroup from chapter 4 was investiagted, and Petersen 1995 in which a subgroup from Petersen 1993 was investigated.

9.2.1 *Age and education*

Age predicted AD in chapters 2, 3, and 4. The predictor age was tested in 11 other studies. It was a predictor of outcome in four of these (Devanand et al., 1997; Jack et al., 1999; Petersen et al., 1995; Wolf et al., 1998). In two studies, age tended to be a predictor of AD (p-value <0.15) (de Leon et al., 1993a; Tierney et al., 1996b). In five studies, no differences in age existed between subjects with and without preclinical AD (Coria et al., 1995; Hänninen et al., 1995; O'Brien et al., 1992; Tröster et al., 1994; Tuokko et al., 1991). The negative findings can be partly explained by the limited age range (between 68 and 78 years) in one study (Hänninen et al., 1995), a short follow-up period (only 1.3 years) in another study (Tuokko et al., 1991), and a small statistical power due to the small number of demented subjects (≤ 6) in two studies (O'Brien et al., 1992; Tröster et al., 1994). The relation between age and risk of AD after 5 years in non-demented subjects with mild cognitive impairment from the Maastricht Memory Clinic is shown in figure 9.1. The odds ratio (OR) for AD in subjects older than 65 years compared to subjects younger than 65 years was 13.2 (95% confidence interval (CI) 4.4-40) (chapter 2). This indicates that age is a strong risk factor, but it should be noted that the age range was wide (40-80 years) in this study. The OR for AD was lower if the
age range was restricted. The OR for AD after 5 years in subjects older than 75 years compared to subjects aged between 65 and 75 years was 4.2 (95% CI 0.8-23) for subjects with mild cognitive impairment from the Maastricht Memory Clinic and 3.7 (95% CI 1.2-12) for subjects with minimal dementia from the AMSTEL study.

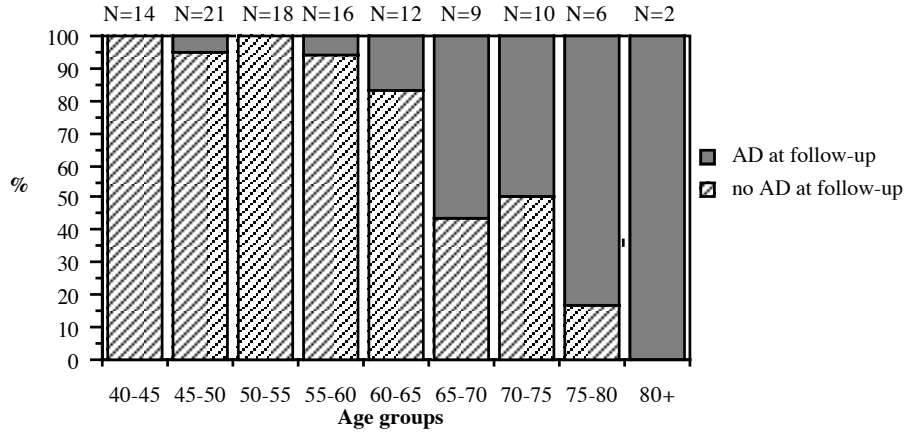

Figure 9.1 Outcome at follow-up of subjects with mild cognitive impairment from the Maastricht Memory Clinic after 5 years according to age at baseline.

The pooled OR for these two studies was 3.9 (95% CI 1.5-10). Except for the studies described in chapters 2 and 4 and in Wolf et al. (1998), in other studies cognitive function or medial temporal lobe atrophy was a stronger predictor of AD than age. Age was a predictor of AD independently of medial temporal lobe atrophy (chapter 6; Jack et al., 1999) and cognitive measures (chapter 2 and 4; Devanand et al., 1997).

Education did not predict AD in any of the studies described in this thesis. Education was tested as predictor of AD in eight other studies. It was found to be a predictor of AD in one study (Tierney et al., 1996b) but not in seven other studies (Devanand et al., 1997; Hänninen et al., 1995; Petersen et al., 1995; Rubin et al., 1989b; Tröster et al., 1994; Tuokko et al., 1991; Wolf et al., 1998). The fact that education was not a predictor of AD in the vast majority of prospective studies involving subjects with mild cognitive impairment is remarkable because many epidemiological studies indicate that a low educational level is a risk factor for AD in the general population (e.g., Launer et al., 1999). It is possible that the inclusion criteria of prospective studies of subjects with mild cognitive impairment lead to the inclusion of subjects with a low educational level without preclinical AD more often than highly educated subjects without preclinical AD in relation to the general population. Thus, the inclusion criterion of mild cognitive impairment is biased toward inclusion of subjects with a low educational level who do not have preclinical AD. This seems plausible because these subjects may experience cognitive impairment more easily than highly educated subjects. Another possibility is that subjects with a low educational level and mild cognitive impairment progress to AD slower than subjects with a high education, and that education may be a predictor in longer follow-up studies. This seems unlikely, however, because there was no relation between educational level and time to AD diagnosis in chapter 8.

In sum, these findings show that age is a predictor of AD in subjects with mild cognitive impairment. The predictive strength of age depends on the age range in the study population. Although age is not a strong predictor compared to other variables, it can predict AD independently of these variables, which suggests that age can increase the predictive accuracy of other variables. In contrast to the results of epidemiological studies, education can not predict AD in subjects with mild cognitive impairment.

9.2.2 *Memory impairment, impairment in other cognitive domains, MMSE score, and functional impairment*

Memory impairment was found to be a predictor of AD in chapters 3 and 4. In chapter 2, the severity of memory impairment significantly predicted reversible memory impairment and it tended to predict AD (p=0.09). Memory impairment was

investigated as predictor in twelve other studies. It predicted AD significantly in all studies but one (Celsis et al., 1997; Devanand et al., 1997; Flicker et al., 1991; Hänninen et al., 1995; Jack et al., 1999; O'Brien et al., 1992; Petersen et al., 1993; Tierney et al., 1996a; Tröster et al., 1994; Tuokko et al., 1991; Wolf et al., 1998). The only study with a negative finding was that of Bowen et al. (1997). The observation that memory impairment only tended to predict AD in chapter 2 and did not predict AD in the study of Bowen et al. is probably because only subjects with moderate-to-severe memory impairment were included in these studies, which limited the range of memory function. The OR for AD after 5 years of memory impairment (delayed recall, with impairment defined as a performance below the 10th percentile) in subjects from the Maastricht Memory Clinic was 10.1 (95% CI 2.8-37). The OR for dementia after 3 years of the memory impairment (CAMCOG subscale, with impairment defined as a performance below the 10th percentile) in subjects from the AMSTEL study was 6.2 (95% CI 1.6-24). The OR for AD after 1.3 years of memory impairment (delayed recall, with impairment defined as a performance <-2 standard deviations below the mean) was 7.4 (95% CI 2.3-24) (Tuokko et al., 1991). The pooled OR of these studies was 7.8 (95% CI 3.7-16) (table 9.3). In most studies, memory impairment was a stronger predictor of AD than the other predictors were (table 9.2), except for age in chapter 2 and 4 and medial temporal lobe atrophy (chapter 5 and 6; de Leon et al., 1993a; Jack et al., 1999; Wolf et al., 1998). In chapter 2 we demonstrated that only 40% of the subjects with memory impairment progressed to AD, and that age and measures of global cognitive functioning and interference with activities of daily living needed to be taken into account in order to predict outcome. In chapter 8 we showed that memory impairment was not present in 20% of the subjects with preclinical AD. In conclusion, although memory impairment is a strong predictor of AD, it is neither sufficient nor necessary for the diagnosis of preclinical AD. Therefore, memory impairment should be combined with other variables to predict AD.

Table 9.3 Predictive accuracy of memory impairment

Study	N	OR (95% CI)	Sens	Spec	PPV	NPV
MMC	37	10.1 (2.8-37)	88	70	71	88
AMSTEL (chap 3)	45	6.2 (1.6-24)	92	43	65	82
Tuokko 1991	45	7.4 (2.3-24)	72	78	68	81
Pooled data	127	7.8 (3.7-16)	85	65	68	83

OR=Odds Ratio; CI=Confidence Interval; Sens=sensitivity; Spec=specificity; PPV=positive predictive value; NPV=negative predictive value. MMC=Maastricht Memory Clinic (see footnote 1).

In chapter 4 we demonstrated that impairmnts in other cognitive domains, namely complex attention and language, were also predictive of AD. This is in line with studies reporting that impairments in other cognitive domains (e.g., language, attention, executive functions and attention, abstract reasoning, and visuoconstruction) predicted AD (Devanand et al., 1997; Flicker et al., 1991; Hänninen et al., 1995; Petersen et al., 1994a; Tierney et al., 1996a). The predictive strength of impairments in other cognitive domains for AD was always less than that of memory impairment (table 9.2), but impairments in other cognitive domains could improve the predictive accuracy of memory impairment for AD (chapter 4; Devanand et al., 1997; Hänninen et al., 1995; Tierney et al., 1996a). Thus, impairments in other cognitive domains are not strong predictors of AD in subjects with mild cognitive impairment but still they can increase the predictive accuracy of memory impairment for AD.

The MMSE score predicted AD in chapter 4, it tended to predict AD in chapter 2, and did not predict AD in chapter 3. Eight other studies also yielded conflicting results. In three studies, the MMSE score was a significant predictor of AD (Petersen et al., 1993; Tierney et al., 1996a; Wolf et al., 1998). In two studies the MMSE score tended to be a predictor of AD (Hänninen et al., 1995; Jack et al., 1999), and in three studies it was not a predictor of AD (Bowen et al., 1997; Celsis et al., 1997; O'Brien et al., 1992). The negative findings of the latter three studies can be explained by the small sample size (Celsis et al., 1997) or by the inclusion criteria that narrowed the range of cognitive impairment: one study included only subjects without objective cognitive impairment (O'Brien et al., 1992) and one study included only subjects with severe memory impairment (Bowen et al., 1997). The finding that the MMSE score was not predictive in the AMSTEL study (chapter 3) was probably because the inclusion criteria limited the range of cognitive impairment. The OR for AD after 5 years of a MMSE score below 27 compared to a score ≥27 was 5.6 (95% CI 1.4-23.5) (data from the Maastricht Memory Clinic). The OR for dementia after 3 years of a MMSE score below 27 compared to a score ≥27 in subjects from the AMSTEL study was 1.55 (95% CI 0.36-6.6). The pooled OR for these two studies was 2.98 (95% CI 1.1-8.3). In chapter 2, the MMSE score predicted outcome independently of the severity of memory impairment, as has also been reported in a population-based study (Small et al., 1997a). This implies that the MMSE score, a global measure of cognitive functioning, can improve the predictive accuracy of specific neuropsychological tests for AD.

Functional impairment predicted AD in chapters 2 and 4. Functional impairment was assessed in chapter 2 with the first 11 items of the Blessed Dementia Rating Scale (BDRS-ADL), and in chapter 4 with both the Global Deterioration Scale (GDS) and the total score on the Blessed Dementia Rating Scale. Only a few

other studies have assessed the predictive value of functional impairment for AD in subjects with mild cognitive impairment. The GDS score was predictive of AD in one study (Reisberg et al., 1994). One study reported that the severity of impairment on performance of instrumental activities of daily living predicted AD in minimally impaired subjects (Petersen et al., 1993). Another study, in which several measures of functional impairment including the BDRS-ADL and the Clinical Dementia Rating scale (CDR) were used, found that the CDR score tended to be a predictor of AD (p=0.15) in subjects with mild cognitive impairment (Devanand et al., 1997). The OR for AD after 5 years of GDS stage 3 versus GDS stage 2 was 4.5 (95% CI 1.2-17) (data Maastricht Memory Clinic) (table 9.4). The OR for dementia after 8 years of GDS stage 3 versus GDS stage 2 was 14.2 (95% CI 4.4-46.1) in the study of Reisberg et al. (1994). The OR for dementia after 2.5 years of CDR 0.5 versus CDR 0 was 1.99 (95% CI 0.8-5.1) (Devanand et al., 1997). The pooled OR of these three studies was 4.3 (95% CI 2.3-8.2). The positive predictive value of a GDS score of 3 or a CDR score of 0.5 was only 56%, indicating that 44% of the subjects with GDS stage 3 or CDR score 0.5 did not develop AD. In chapter 8 we showed that 25% of the subjects with preclinical AD had a GDS score of 2, which indicates that the sensitivity of GDS score 3 for preclinical AD is not high. Measures of functional impairment were always less strong predictors than the other predictors, except for the
MMSE score in chapter 4. In chapter 2, functional impairment was not predictive of AD in a multivariate model together with age, memory performance, or MMSE score. Thus, the severity of functional impairment is a moderately strong predictor of AD in subjects with mild cognitive impairment. The low positive predictive value of the GDS indicates that measures of functional impairment should be combined with other variables for predicting AD.

Table 9.4 Predictive accuracy of functional impairment

Study	N	Functional impairment	OR (95% CI)	Sens	Spec	PPV	NPV
MMC	39	GDS 3 vs GDS 2	4.5 (1.2-17)	84	50	62	77
Reisberg 1994	62	GDS 3 vs GDS 2	14.2 (4.4-46)	81	80	59	93
Devanand 1997	75	CDR 0.5 vs CDR 0	1.99 (0.8-5.1)	52	65	48	68
Pooled data	176		4.3 (2.3-8.2)	69	69	56	79

OR=Odds Ratio; CI=Confidence Interval; Sens=sensitivity; Spec=specificity; PPV=positive predictive value; NPV=negative predictive value, MMC=Maastricht Memory Clinic (see footnote 1). GDS=Global Deterioration Scale; CDR=Clinical Dementia Rating scale.

The conclusion on this section on cognitive predictors of AD is that memory impairment is a strong predictor of AD. However, it is neither sufficient nor necessary for the diagnosis of preclinical AD. Impairments in other cognitive domains, the MMSE score, and functional impairment are less strong predictors of AD. These predictors are not sensitive or specific enough to be used alone, but they can increase the predictive accuracy of memory impairment for AD.

9.2.3 *ApoE genotype*

The apoE genotype was predictive of outcome in subjects with minimal dementia (chapter 3) but not in subjects with memory impairment (chapter 2). In the latter study, however, the apoE-e4 allele frequency in the subjects with preclinical AD (75%) was almost twice as high as that of the subjects who had reversible memory impairment (42%). Moreover, the apoE-e4 allele frequency in the subjects with preclinical AD was similar to that of subjects with AD (average 68%, range 55%--85%) (Nalbantoglu et al., 1994). Thus, the fact that the apoE genotype did not predict outcome in chapter 2 may be due to a lack of statistical power because of the small sample size. The apoE genotype was investigated as predictor in five other studies. Three studies reported that the apoE genotype was predictive of AD (Coria et al., 1995; Petersen et al., 1995; Tierney et al., 1996b). The findings of the latter study, however, could not be replicated in another sample from the same study group (Jack et al., 1999). One study found that the apoE genotype was not predictive of dementia, but this study was hampered by the small sample size (Wolf et al., 1998). The pooled data of all studies included 337 subjects: 122 subjects with AD at follow-up and 217 subjects without AD at follow-up (table 9.5). The pooled OR for AD if the subject was carrier of an apoE-e4 allele was 3.9 (95% CI 2.4-6.2). The sensitivity of the presence of at least one apoE-e4 allele for AD was 63% and the specificity was 69%. The positive predictive value was 54% and the negative predictive value was 77%. The interpretation of these data is that the apoE genotype is a moderately strong risk factor for subsequent AD in subjects with mild cognitive impairment. The absence of the apoE-e4 allele does not exclude AD because the negative predictive value was only 77%. The presence of the apoE-e4 allele is not very specific for AD because the positive predictive value was only 54%. The predictive strength of the apoE genotype for AD was less strong than that of cognitive measures, but stronger than that of age (table 9.2). The apoE genotype predicted outcome independently of age and cognitive function in one study (Petersen et al., 1995) but not in another study (Tierney et al., 1996b).

In chapter 2 we noted that all apoE-e4 carriers who progressed to AD were older than 65 years which suggested that age may confound the predictive effect of the apoE genotype. Further evidence for an interaction comes from an analysis of

Table 9.5 Predictive accuracy of apolipoprotein E (apoE) genotype

Study	N	MCI definition	OR (95% CI)	Sens	Spec	PPV	NPV
Chapter 2	46	Mem impair	3.6 (0.91-15)	80	53	32	90
Chapter 3	44	Min Dem	2.6 (0.8-8.5)	52	71	67	58
Coria 1995	56	Amnesia	11.0 (3.9-31)	83	77	81	80
Tierney 1996	107	Complaints	2.8 (1.2-6.8)	52	72	41	80
Petersen 1995	62	MCI-M	3.9 (1.4-10.9)	63	71	58	75
Wolf 1998	24	MCI-Z	1.5 (0.2-11.8)	33	75	33	75
Pooled data	337		3.9 (2.4-6.2)	63	69	54	77

The OR indicates the risk for AD of the apoE-e3e4 or e4e4 genotype vs other genotypes. OR=Odds Ratio; CI=Confidence Interval; Sens=sensitivity; Spec=specificity; PPV=positive predictive value; NPV=negative predictive value, Mem impair=memory impairment; Min Dem=Minimal Dementia; MCI-M=Mild Cognitive impairment according to Smith 1996; MCI-Z=Mild Cognitive Impairment according to Zaudig 1992

subjects from the Maastricht Memory Clinic with a 2 or 5 year follow-up (N=87) 45 subjects (0%) without the apoE-e4 allele had AD at follow-up and 2 out of 18 subjects (20%) with the apoE-e4 allele had AD at follow-up (p-value=0.09). In subjects older than 65 years, 2 out of 8 subjects (25%) without the apoE-e4 allele had AD compared to 12 out of 14 subjects (86%) with the apoE-e4 allele (p-v alue=0.008). Although the number of subjects was small, these data indicate that the positive predictive value of the apoE genotype can be increased if age is taken into account.

In conclusion, the apoE genotype is a moderately strong predictor of AD in subjects with mild cognitive impairment. The positive predictive value of the apoE-e4 allele is low. It should preferably be used together with other variables such as age.

9.2.4 *Depression*

Depression did not predict AD in subjects with memory impairment (chapter 2), minimal dementia (chapter 3), or mild cognitive impairment (chapter 4). The small number of depressed subjects in chapter 3, however, may have limited the power to detect significant differences. In one other study depression did not predict AD either (Devanand et al., 1997). The pooled OR of depression for AD (data from chapters 3 and 4) was 1.33 (95% CI 0.6-2.9). These findings are in contrast with the observation that depression predicts dementia in the general population (Buntinx et al., 1996; Devanand et al., 1996; Jorm et al., 1991; Speck et al., 1995; Yaffe et al., 1999). In these studies, however, the pooled OR of depression for dementia was low (OR=1.88, 95% CI 1.46-2.43, N=21914), and the lack of a statistically significant effect of depression on dementia in subjects with mild cognitive impairment might

be due to a lack of statistical power to detect such a small OR. Another explanation for the finding that depression did not predict AD in subjects with mild cognitive impairment is the sample selection. It is possible that the inclusion criteria for prospective studies of subjects with mild cognitive impairment lead to the inclusion of depressed subjects without preclinical AD more often than non-depressed subjects without preclinical AD in relation to the general population. Thus, the inclusion criterion of mild cognitive impairment is biased toward inclusion of depressed subjects without preclinical AD. Evidence for this explanation comes from the observation that many depressed subjects complain about cognitive impairment and often have cognitive impairment on neuropsychological tests and for that reason will meet the criteria of mild cognitive impairment (Kahn et al., 1975; La Rue et al., 1986).

In subjects with mild cognitive impairment, depression was as common in subjects with preclinical AD as it was in subjects without preclinical AD (chapter 2-4). The cognitive impairment in depressed subjects without preclinical AD was often reversible with respect to delayed recall performance but not with respect to performance on tests of language and executive functions (chapter 4). This has been reported before (Abas et al., 1990), and longer follow-up studies are needed to find out whether these subjects will develop dementia later, as has been suggested by one study (Kral et al., 1989). Depressed subjects with preclinical AD could be accurately distinguished from depressed subjects without preclinical AD by age (>65 years) and delayed recall performance (z-score ≤-1) (chapter 4). The high incidence of AD in depressed subjects older than 65 years with moderate-to-severe cognitive impairment corroborates the findings of other studies (Alexopoulos et al., 1993; Copeland et al., 1992; Kral et al., 1989; Reding et al., 1985).

In conclusion, depression cannot predict outcome in subjects with mild cognitive impairment. Depressed subjects with or without preclinical AD could be accurately distinguished from each other by age and the severity of memory impairment. Depressed subjects older than 65 years with mild-to-moderate memory impairment are at a high risk of becoming demented.

9.2.5 *Atrophy of the medial temporal lobe*

Medial temporal lobe atrophy predicted AD in subjects with minimal dementia and mild cognitive impairment (chapter 5 and 6). Similar findings were reported in three other prospective studies of subjects with mild cognitive impairment (de Leon et al., 1993a; Jack et al., 1999; Wolf et al., 1998). The ORs of the presence of the medial temporal lobe atrophy for AD (chapter 5; de Leon et al., 1993a; Jack et al., 1999) or cognitive decline (chapter 6) are listed in table 9.6. The wide confidence intervals reflect the small number of subjects. We pooled these data according to the severity

of medial temporal lobe atrophy. Mild atrophy was defined as a hippocampal z-score < 0 (Jack et al., 1999), a hippocampal z-score < -0.33 (chapter 6), or a medial temporal lobe atrophy score ≥1 (chapters 5 and 6). Moderate-to-severe atrophy was defined as a hippocampal z-score <-2.5 (Jack et al., 1999), a medial temporal lobe atrophy score ≥2 (chapters 5 and 6), or a rating of perihippocampal cerebrospinal fluid ≥2 (de Leon et al., 1993a). Mild medial temporal lobe atrophy was a moderately strong predictor of outcome (OR 4.4, 95% CI 1.7-12). The sensitivity was high (89%) but the positive predictive value was low (46%). Moderate to severe MTL atrophy was a strong predictor of outcome (OR 7.2, 95% CI 3.3-16.1). The positive predictive value was high (80%), but the sensitivity was low (57%). The predictive accuracy of medial temporal lobe atrophy was better than that of age and equal to or better than that of memory impairment (table 9.2). Medial temporal lobe atrophy predicted AD independently of age and memory function (chapters 5 and 6; Jack et al., 1999) and the apoE genotype and MMSE score (Jack et al., 1999).

In order to find out which measure of medial temporal lobe atrophy could predict outcome the best, we compared three different measures: volume of the

Table 9.6 Predictive accuracy of medial temporal lobe atrophy

	Study	MTL atrophy	OR (95% CI)	Sens	Spec	PPV	NPV
Measures of (very) mild atrophy							
I	Chapter 6	MTA score ≥1 vs < 1	27 (0.4-1802)	100	25	75	100
II	Chapter 7	MTA score ≥1 vs < 1	10 (0.9-109)	90	53	53	90
III	Chapter 7	HC z-score <-0.33 vs > -0.33	8.0 (1.6-39)	70	81	70	81
IV	Chapter 7	PHG z-score <-0.33 vs > -0.33	5.9 (1.2-28)	70	75	64	80
V	Jack 1999	HC z-score < 0 vs >0	2.6 (0.8-9.2)	93	21	37	85
Pooled data (studies I, III, V)			4.4 (1.7-12)	89	34	46	83
Measures of moderate to severe atrophy							
VI	Chapter 6	MTA score ≥2 vs < 2	2,1 (0.21-22)	44	75	80	38
VII	Chapter 7	MTA score ≥2 vs < 2	25 (4.9-126)	80	94	89	89
VIII	Jack 1999	HC z-score <-2.5 vs > -2.5	1.9 (0.55-6.7)	22	87	46	69
IX	de Leon 1994	HCSF ≥ 2 vs < 2	37 (7.2-191)	91	89	95	80
Pooled data moderate-severe atrophy (VI-IX)			7.2 (3.3-16.1)	57	88	80	71

MTL=Medial Temporal Lobe; HC= volume hippocampus; PHG= volume parahippocampal gyrus; MTA= qualitative measure of medial temporal lobe atrophy; HCSF= rating of perihippocampal cerebrospinal fluid; OR=Odds Ratio; CI=Confidence Interval; Sens=sensitivity; Spec=specificity; PPV=positive predictive value; NPV=negative predictive value.

hippocampus, volume of the parahippocampal gyrus, and a qualitative score (chapter 5 and 6). All measures were accurate predictors of outcome and increased the predictive accuracy of age and memory function for AD. Volume of the parahippocampal gyrus was the best predictor in chapter 5 and volume of the hippocampus in chapter 6. This discrepancy may due to chance, because the differences were small, to differences in sample selection, or to differences in methods of measurement between the studies in chapter 5 and 6. We recommend volumetry of the hippocampus above volumetry of the parahippocampal gyrus because the hippocampus has less interindividual variation than the parahippocampal gyrus. In addition, the results from case-control studies with mildly demented AD patients indicated that the volume of the hippocampus was better than the volume of the parahippocampal gyrus for distinguishing between control subjects and subjects with AD (deToledo-Morrell et al., 1997; Jack et al., 1997; Krasuski et al., 1998). Qualitative ratings, however, can be a good alternative if volumetry is not possible (chapter 5, 6; de Leon et al., 1993a; Wahlund et al., 1999).

In order to investigate whether medial temporal lobe atrophy is specific for the amnestic syndrome seen in AD, we also measured the volume of the medial temporal lobe in subjects with Korsakoff's syndrome. In Korsakoff's syndrome, the medial temporal lobe was only slightly atrophic and the extent of atrophy did not correlate with the severity of memory impairment (chapter 7). Instead, the extent of atrophy of the midline nuclei of the thalamus correlated with the severity of memory impairment. This implies that, in elderly alcoholic subjects with amnesia, MRI imaging can help to distinguish between Korsakoff's syndrome and AD. It would be of interest to investigate the role of the midline nuclei of the thalamus in the amnestic syndrome of AD because the third ventricle is severely enlarged in AD, and the width of the third ventricle has been found to correlate significantly with the performance of memory tests (de Leon et al., 1980).

Although medial temporal lobe atrophy is a strong predictor for AD-type dementia, it should be noted that medial temporal lobe atrophy is also seen in no-AD type dementia, namely, Lewy body disease (Barber et al., 1999), frontotemporal dementia (Frisoni et al., 1999), vascular dementia (Barber et al., 1999; Laakso et al., 1996; Pantel et al., 1998), and Parkinson's disease (Laakso et al., 1996). Although it can not be excluded that medial temporal lobe atrophy in these dementing disorders is in part due to the co-occurrence of AD pathology, one should always consider the clinical presentation before concluding that medial temporal lobe atrophy is the result of AD. Further, there have been a few reports of subjects with probable AD and medial temporal lobe atrophy in whom no AD pathology was present on pathological examination. These subjects had laminar necrosis (typically seen in subjects with hypoperfusion of the brain) (Ball et al., 1997; Hulette et al., 1997), hippocam-

pal sclerosis (neuronal loss, spongy changes, and gliosis in the hippocampus or subiculum) (Ala et al., 2000; Berg et al., 1998; Corey-Bloom et al., 1993), or herpes encephalopathy (Ball et al., 1997) on pathological examination. However, these are rare causes of dementia and they will not lead to major diagnostic misclassifications.

In conclusion, medial temporal lobe atrophy is a strong predictor of AD in subjects with mild cognitive impairment. It should be used in combination with other predictors of AD. Volumetry of the hippocampus is preferred to volumetry of the parahippocampal gyrus or a qualitative rating. However, qualitative rating of medial temporal lobe atrophy is a good alternative if volumetry is not possible.

9.2.6 *Conclusion*

The findings from section 9.2 are summarized in table 9.7. The ORs, sensitivity, specificity, positive predictive value, and negative predictive value need to be interpreted with some caution because the data on which these variables were based were not the same for all predictor variables. In addition, the studies had a different design. However, ORs provide a rough indication of the strength of the predictor variables. Meta-analyses in general have the limitation of publication bias, that is,

Table 9.7 Predictors of AD in subjects with mild cognitive impairment

	Predictors of outcome*			Predictive accuracy**					
	Sign	Trend	NS	Data§	OR (95%CI)	Sens	Spec	PPV	NPV
Age	7	2	5	9.2.1	3.9 (1.5-10)	56	74	74	56
Education	1	0	10	-	-	-	-	-	-
Memory	13	1	1	9.2.2	7.8 (3.7-16)	85	65	68	83
Other cognitive domains	6	0	0	-	-	-	-	-	-
MMSE	4	3	4	9.2.2	3.0 (1.1-8.3)	67	56	61	62
Functional measures	4	1	0	9.2.2	4.3 (2.3-82)	69	69	56	79
ApoE	4	0	3	9.2.3	3.9 (2.4-6.2)	63	69	54	77
Depression	0	0	3	9.2.4	1.3 (0.6-2.9)	39	56	32	64
MTL atrophy	5	0	0	9.2.5					
-Mild					4.4 (1.7-12)	89	34	46	83
-Moderate					7.2 (3.3-16)	57	88	80	71

OR=Odds Ratio; CI=Confidence Interval; Sens=sensitivity; Spec=specificity; PV=positive predictive value; NPV=negative predictive value. *Number of studies in which predictor was significantly associated with outcome (Sign), tended (p-value between 0.05 and 0.15) to be associated with outcome (Trend), or was not significantly associated with outcome (NS). **All data are pooled data. §Refers to section number in which the separate studies are discussed.

that studies with a positive finding may be published more often than studies with a negative finding which could lead to overestimation of the predictive effect. Publication bias seems unlikely in the case of the variables age, education, MMSE score, functional impairment, and depression because, with the exception of one study, these variables were not the main variable investigated. Most studies investigating the predictive accuracy of cognitive tests included a battery of cognitive tests for different cognitive domains, which makes publication bias for specific cognitive tests or domains unlikely. Publication bias can not be excluded for the variables apoE and medial temporal lobe atrophy.

Predictors of AD in subjects with mild cognitive impairment were age, memory impairment, impairments in other cognitive domains, the MMSE score, the apoE genotype, and medial temporal lobe atrophy. Education and depression did not predict AD. The strongest predictors were memory impairment (OR 7.8) and moderately severe medial temporal lobe atrophy (OR 7.2). This corroborates the observation that these variables were often the strongest predictors on univariate tests (table 9.2). The other predictors had ORs between 3 and 4.5. Mild medial temporal lobe atrophy had the highest sensitivity (89%) but this variable was not very specific (34%) and had a low positive predictive value (50%). Moderate medial temporal lobe atrophy had the highest specificity (88%). This variable had also the highest positive predicting value but the sensitivity of this variable was low (57%). Taken together, these data show that AD can not predicted on the basis of one variable and that several variables should be combined. In chapters 2-6, and in the studies by de Leon et al. (1993), Devanand et al. (199), Hänninen et al. (1995), Jack et al. (1999) it was shown that a combination of variables predicted outcome better than each variable on its own. A proposal to combine variables for predicting AD is given in the next section.

9.3 THE PRECLINICAL AD SCALE (PAS): A MULTIDISCIPLINARY APPROACH TO THE DIAGNOSIS OF PRECLINICAL AD

The main findings of the thesis can be summarized as follows:

- there is not a single profile of preclinical AD (9.1);
- there is not a single predictor that can accurately predict AD in subjects with mild cognitive impairment (9.2);
- a combination of variables can predict AD more accurately than each variable on its own (9.2).

Thus, in order to identify subjects with preclinical AD one should not a priori exclude subjects in whom one of the predictor variables is not present and one should combine several predictor variables. In addition, the assessment should be

Table 9.8 The Preclinical AD scale (PAS)*

		-1	0	1	2	Score	
A. Age		≤59	60-64	65-74	≥75		
B. MMSE							
Age <75 yr	Edu≤ 8 yr	-	≥27	25,26	≤24		
	Edu 8-14 yr	-	≥28	26,27	≤25		
	Edu≥14 yr	-	≥29	27,28	≤26		
Age ≥75 yr	Edu≤ 8 yr	-	≥26	24,25	≤23		
	Edu 8-14 yr	-	≥27	25,26	≤24		
	Edu≥14 yr	-	≥28	26,27	≤25		
C. Functional impairment							
a. GDS		-	GDS 1	GDS 2	GDS 3		Score after step 1 (A-C)
b. CDR[1] - Sum of Boxes		-	0-0.5	1-1.5	≥2		
- Final rating		-	CDR 0	-	CDR 0.5		
c. CAMDEX		-	-	-	Min Dem		
D. Neuropsychological tests[2]		Memory ≥50th perc	Other	1 impaired score	2 impaired scores		Score after step 2 (A-D)
E. MTL atrophy							
a. Qualitative rating[3]	Age<75 yr	-	0	1	2		Score after step 3 (A-E)
	Age ≥75 yr	0	1	2	≥3		
b.Volumetry[4]		≥ 66th perc	33th-66th perc	10th-33th perc	≤10th perc		
F. ApoE genotype		-	Other	e3e4	e4e4		
						TOTAL SCORE	

MMSE=Mini-Mental State Examination; Edu=Education; yr=years; GDS=Global Deterioration Scale; CDR=Clinical Dementia Rating scale; CAMDEX=Cambridge Mental Disorders of the Elderly Examination; Min Dem=minimal dementia; perc=percentile; MTL=Medial Temporal Lobe; ApoE=apolipoprotein E.

1 If the CDR is used, the scoring should be based on the sum of boxes; if this is not possible the final rating can be used.

2 Including 1 test that assesses delayed recall or learning and 1 to 3 tests from other cognitive domains (e.g., language, executive functions, abstract reasoning, visuoconstruction). Impairment is defined as a score below the 10th percentile or above the 90th percentile (speed related tasks). Percentile scores are corrected for age and, if possible, for sex and education as well.

3 Qualitative rating according to the method of (Scheltens et al., 1992) or (de Leon et al., 1993a)

4 Volumetry of hippocampus (preferred) or parahippocampal gyrus; percentiles scores are corrected for age and intracranial volume and, if possible, for sex as well.

*For scoring instructions see also appendix B.3. The PAS and scoring instructions can also be found at www-np.unimaas.nl/pas/

easy to use in clinical practice and therefore simple cut-off points should be used. A proposal for such an approach is the Preclinical AD scale (PAS) (table 9.8 and appendix B.2). In short, it combines the variables that were predictors in section 9.2 (age, MMSE score, functional impairment, cognitive impairment, medial temporal lobe atrophy, and apoE genotype). Each variable is scored on a 3 or 4-point scale and the sum of the individual scores gives the risk for AD. A high score indicates a high risk for AD. None of the items is obligatory, in order to include subjects that have missing data for some variables, but the more items that are scored, the more accurate the prediction will be. Some variables can be assessed in several ways, so as to allow for the variety in diagnostic procedures that are in use.

In order to see whether the PAS is indeed useful to predict AD in subjects with mild cognitive impairment, we validated the PAS in two independent samples from the Maastricht Memory Clinic (total N=96) (see Appendix B.1). We also validated the PAS in a sample from the population-based AMSTEL study (N=237). Most subjects in this sample had no mild cognitive impairments. The validation has the limitation that the PAS was in part based on these populations, but it should be noted that the variables of the PAS were selected on the basis of a metaanalysis of 15 other studies as well (see 9.2). In addition, most of the cut-off points of the PAS items were not based on the populations of the Maastricht Memory Clinic or AMSTEL but were determined a priori or on the basis of the literature (see appendix B.2). The validation study showed that a PAS score ≤4 indicated a low risk for AD, a PAS score of 5 indicated an borderline risk for AD or cognitive decline, and a PAS score ≥6 indicated a high risk for AD. The positive predictive value for AD of a PAS score ≥6 varied from 64% (AMSTEL) to 94% (Maastricht Memory Clinic) and the sensitivity varied from 58% (AMSTEL) to 80% (Maastricht Memory Clinic). The results of the validation study are described in detail in appendix B.1.

In order to see whether it would be possible to reduce the number of subjects requiring elaborate or expensive diagnostic procedures for predicting outcome (e.g., cognitive testing, assessment of medial temporal lobe atrophy, or apoE genotyping), we tested stepwise scoring of the PAS in appendix B.1 (table 9.9). The stepwise scoring of the PAS reflected the decision-making process in clinical practice, in which the patient's history and the results of simple cognitive tests determine which other diagnostic tests would be useful for making a more accurate diagnosis. After each step, subjects with a low, borderline, or high risk for AD were identified and only subjects with a borderline risk proceeded to the next step. The decision rules shown in table 9.9 were as accurate in predicting outcome as the full PAS (see appendix B.1), but using them reduced the number of cognitive assessments by 40%, the number of assessments of medial temporal lobe atrophy by on average 75%, and the number of apoE genotypings by on average 80%.

9.9 Stepwise scoring of the PAS

		Low risk preclinical AD	Borderline risk preclinical AD	High risk preclinical AD
Step1	Age, MMSE, functional impairment	≤1	2-5	≥6
Step 2	Cognitive performance	≤3	4-5	≥6
Step 3	MTL atrophy	≤3	4-5	≥6
Step 4	ApoE genotyping	≤4	5	≥6

Only subjects with an borderline risk proceed to the next step.

In conclusion, a multidisciplinary approach as adopted in the PAS seems to be useful to assess the risk of preclinical AD in subjects with mild cognitive impairment. The PAS will probably result in a higher sensitivity and positive predictive value compared to other diagnostic approaches for preclinical AD, such as Mild Cognitive Impairment (Petersen et al, 1999), because it has no inclusion criteria and combines six variables (see also appendix B.1). The PAS can be used in a stepwise fashion to guide the diagnostic process and to reduce the number of elaborate or expensive diagnostic procedures. The PAS needs to be evaluated in other settings before definite recommendations about cut-off scores can be made. It would be of interest to investigate whether step 1 of the PAS can be used to select subjects in primary health care for referral to secondary health care or to select subjects for a more extensive work-up in epidemiological studies. The PAS can also be used to monitor the course of mild cognitive impairment.

9.4 METHODOLOGICAL CONSIDERATIONS

There are several methodological problems in prospective studies that investigate predictors of AD in subjects with mild cognitive impairment, e.g., sampling bias, loss to follow-up, length of follow-up, problems related to a multidisciplinary approach, missing data, and the clinical diagnosis of AD. We will discuss how we dealt with these problems and how they may have influenced the results of the studies presented in this thesis. Finally, we will discuss some other methodological issues, i.e., equating dementia with AD, the predictive accuracy for AD in subjects with mild cognitive impairment, and whether cognitive data should be corrected for age and education or not.

Sampling bias

The subjects with mild cognitive impairment who were referred to the Maastricht Memory Clinic are a selection of all subjects with mild cognitive impairment. The

findings from studies performed with patients from the Maastricht Memory Clinic may therefore not apply to other subjects with mild cognitive impairment in, for example, the general population, primary health care, or neurological, geriatric, and psychiatric in- or outpatient departments. In order to check whether sampling bias strongly influenced the findings of the studies performed with patients from the Maastricht Memory Clinic, we also investigated the predictors of AD in a less selected sample from the population-based AMSTEL study. The findings regarding the predictive value of memory function, depression, apoE genotype, and medial temporal lobe atrophy in the AMSTEL study were similar to the findings with respect to these variables in the studies from the Maastricht Memory Clinic. Thus the findings from the□□ Maastricht Memory Clinic with respect to these variables seem not to be greatly influenced by sampling bias. The MMSE score and word fluency performance were not predictive of AD in the AMSTEL study while they were in the Maastricht Memory Clinic. This discrepancy could be due to sampling bias; however, there were also other differences in the AMSTEL sample and the Maastricht Memory Clinic sample that may have influenced the results, such as baseline age and criteria of mild cognitive impairment.

Sampling bias also occurred in the AMSTEL study because when subjects were selected from the general population, nonresponders were found to have a greater cognitive impairment and poorer physical and mental health than the responders (Launer et al., 1994). Therefore, the AMSTEL study may have oversampled subjects with mild cognitive impairment who had a relatively good cognitive performance, and thus the findings from the AMSTEL study might not apply in subjects with more severe mild cognitive impairment.

Sampling bias also occurred as a result of the way mild cognitive impairment was operationalized. We defined mild cognitive impairment as objective memory impairment (chapter 2), minimal dementia (chapters 3 and 5), and referral to the Maastricht Memory Clinic (chapters 4 and 6), but there are also other definitions of mild cognitive impairment (appendix A gives a detailed overview of the criteria of mild cognitive impairment).[3] Also the length of follow-up and the baseline age will

[3]Mild cognitive impairment refers to subjective cognitive impairment only in some definitions (O'Brien et al., 1992; Reisberg et al., 1982; Tröster et al., 1994). Other definitions require objective cognitive impairment but the way objective cognitive impairment is defined varies (APA, 1987; Bowen et al., 1997; Celsis et al., 1997; Christensen et al., 1997b; Clarke et al., 1996; Crook et al., 1986; Ebly et al., 1995; Johansson et al., 1992; Levy, 1994; Zaudig, 1992). Other definitions are based on impairment in activities of daily living (Morris, 1993; Reisberg et al., 1982; Ritchie et al., 1997; Roth et al., 1986) or on a combination of impairments on cognitive tests and impairment in activities of daily living (Devanand et al., 1996; Smith et al., 1996). Finally, mild cognitive impairment can also be pragmatically defined as referral to a memory or dementia clinic (chapter 4,6; Devanand et al., 1997; Tierney et al., 1996a; Tuokko et al., 1991). The common denominator of these different criteria of mild cognitive impairment is that cognitive impairment is not severe enough to meet the criteria of dementia. Therefore, mild cognitive impairment is also termed Cognitive Impairment No Dementia (CIND) (Graham et al., 1997).

influence the outcome of subjects with mild cognitive impairment (see table 1.1). The findings from the present thesis may therefore not apply if other definitions of mild cognitive impairment are used or if the study design is different. However, in section 9.2 we noted that there was a strong agreement between most studies with respect to the variables that could predict AD even though the criteria of mild cognitive impairment and the study design varied. There were, however, marked differences in the number of subjects who had preclinical AD and who became demented at follow-up (see table 1.1 and 9.1). This variation in prevalence of preclinical AD will probably determine the predictive accuracy. The positive predictive value is especially dependent on the prevalence of preclinical AD (Fletcher et al., 1988). Therefore, the variables which can predict AD can be generalized to other definitions of mild cognitive impairment and other settings whereas the predictive accuracy can not.

Loss to follow-up

The proportion of subjects in whom there was no information on cognitive functioning was 15% in chapter 2, 28% in chapter 3, 10% in chapter 4, 35% in chapter 5, and 7% in chapter 6. The main reasons why information on cognitive outcome was not available were refusal to participate in follow-up assessments and death before the follow-up assessment. The percentage of subjects without data on cognitive outcome was higher in the AMSTEL study (chapters 3 and 5) than in the Maastricht memoty Clinic studies but it was comparable to that of studies that had a similar design as the AMSTEL study (Herlitz et al., 1997; O'Connor et al., 1991). It can be explained by the old age of the study population at baseline. Another explanation is that the subjects were selected from a population-based study, and that the motivation for participation in follow-up studies may be less in population--based studies than in clinical samples. In order to see whether selective attrition occurred, we compared the baseline characteristics of subjects with and without data on cognitive outcome. In chapter 2 subjects without data on cognitive outcome tended to be older than subjects with such data. In chapter 3 subjects with or without cognitive outcome data had similar baseline characteristics. In chapter 4 subjects without cognitive outcome data were older than subjects with such data. In chapter 5 cognitively normal subjects without cognitive outcome data had lower CAMCOG scores and a smaller volume of the parahippocampal gyrus at baseline than cognitively normal subjects with cognitive outcome data. Subjects who had died before the first follow-up assessment were older and had a poorer cognitive functioning than subjects who refused the follow-up (chapter 3 (data not shown), chapter 4). The cognitive performance of subjects who died before follow-up was similar to or worse than that of subjects with preclinical AD (chapter 3 (data not shown), chapter 4). This may indicate that the subjects who died before the followup would have become

demented if they had not died or that these subjects experienced terminal decline (aspecific cognitive impairment seen in subjects before they die) (Johansson et al., 1997). In sum, there is some evidence for selective attrition. The prevalence of preclinical AD may therefore have been underestimated. On the basis of these data, it is not clear how the selective attrition affected the conclusions with respect to the predictor variables. If selective attrition had an effect, this effect would be small in the Maastricht Memory Clinic studies because the number of subjects without cognitive outcome data was small but would be larger in the AMSTEL study because more subjects had missing data for cognitive outcome. It is possible that some subjects with cognitive impairment that is typical for preclinical AD will in fact had terminal decline.

Length of follow-up

Since the preclinical phase of AD may be longer than 5 years (Almkvist et al., 1998), we probably did not detect all subjects with preclinical AD. The relatively short follow-up period is a problem in all prospective studies of mild cognitive impairment (table 9.2). The average follow-up period of the studies mentioned in table 9.2 is 3.1 years (standard deviation 1.2). A short follow-up period will misclassify some subjects with preclinical AD as not having preclinical AD because some subjects with preclinical AD will become demented after the follow-up period. This can lead to both underestimation and overestimation of the differences between subjects with and without preclinical AD. The differences are underestimated if some subjects who are predicted to become demented develop AD after the follow-up period. These subjects would have moved from B to D in figure 9.2 if the follow-up period had been longer. If this is the case, a short follow-up period will underestimate the positive predictive value and specificity. This problem was noted in chapter 6, in which subjects with severe cognitive decline but no dementia at follow-up had medial temporal lobe atrophy that was similar to the medial temporal lobe atrophy seen in subjects with AD at follow-up. Another example is given in Grober et al. (2000) who demonstrated that the specificity of memory impairment for dementia increases from 70% after 2 years to 90% after 9 years of follow-up. The differences between subjects with and without preclinical AD are overestimated if some subjects who are not predicted to become demented develop AD after the follow-up period. These subjects would have moved from A to C in figure 9.2 if the follow-up period had been longer. If this is the case, a short follow-up period will overestimate the negative predictive value and sensitivity. For example, subjects with mild cognitive impairment who develop dementia after longer time intervals have less severe cognitive impairment at baseline than subjects who develop AD rapidly (see chapter 3). This is also illustrated in the study described by Grober et al.

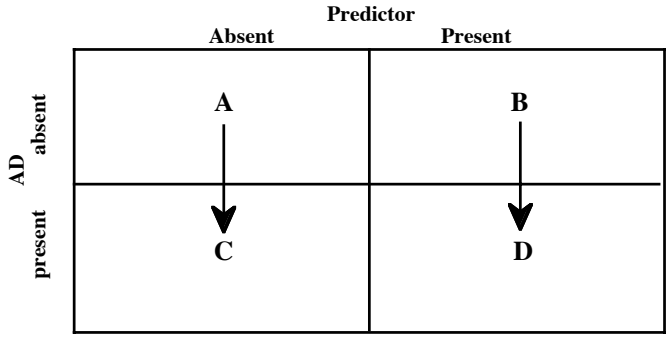

Figure 9.2 Predictive inaccuracy due to a short follow-up period. Some subjects predicted to become demented will become demented after the follow-up period and move from B to D. This underestimates the positive predictive value and specificity. Some subjects predicted not to become demented will become demented after the follow-up period and move from A to C. This overestimates the negative predictive value and sensitivity.

(2000) which showed that the sensitivity of memory impairment for incident dementia decreases from 85% at the 5-year follow-up to 70% after the 5-year followup. Thus, a short follow- up period may underestimate the positive predictive value and specificity and may overestimate the sensitivity and negative predictive value. We dealt with the former problem (underestimation of the positive predictive value and specificity) by formulating secondary endpoints of cognitive decline (chapters 4 and 6). However, these secondary endpoints need to be validated in longer follow-up studies. The latter problem (overestimation of the sensitivity and negative predictive value) can only be solved if markers of AD become available that are sensitive to very early changes.

Another problem related to the follow-up period is the between subject variation in follow-up duration. This variation in follow-up duration is often seen in clinical settings in which subjects are seen annually. We used continuation ratio ordinal regression analysis to overcome this problem (chapter 4). This method is comparable to Cox multiple regression analysis (Jack et al., 1999; Petersen et al., 1995). A disadvantage of these methods is that sensitivity, specificity, and negative and positive predictive values can not be calculated. Another approach was to repeat the analyses with only subjects with 5-year follow-up data (chapters 2 and 4) or 2 or 3-year follow-up data (chapter 3), but this had the disadvantage that there were fewer subjects.

Multidisciplinary approach

We used a multidisciplinary approach to predict AD. Unfortunately, not all variables were available for all subjects. Moreover, the number of subjects with preclinical

AD limited the number of variables that could be tested in one model. In the restricted models we were able to show that most variables were independent predictors of AD, which supports the importance of a multidisciplinary approach. It remains to be investigated, however, whether all variables contribute to the prediction of AD if these variables are used in one model.

Missing data

Missing data are a frequent problem in prospective studies of mild cognitive impairment (Dartigues et al., 1997; Small et al., 1997a). Missing data in these studies are often not randomly distributed among subjects. Subjects with moderately severe impairment often have more missing data than subjects with mild cognitive impairment because subjects with moderately severe impairment refuse cognitive testing or do not complete the cognitive test more often than subjects with mild cognitive impairment. If more than one cognitive test is used in a multivariate analysis, the number of subjects with missing data is high. This problem is often solved by including only subjects with complete data, which causes considerable bias because it oversamples subjects with a relatively good cognitive performance. It is difficult to generalize these data because they only apply to subjects with complete data. In chapter 2, 5% of the subjects had missing data with respect to the cognitive parameters. In chapter 4, 25% of the subjects had at least one missing value for the variables of executive functions or word fluency. Subjects with at least one missing value in that study had lower MMSE and fluency scores and higher depression scores than subjects with complete data. We substituted the missing cognitive data in chapters 2 and 4 in order to include all subjects in the multivariate analysis. Subjects with missing data in these chapters were given the average score of the study population for that test (single imputation approach) (Small et al., 1997a). To investigate how the substitution influenced the outcome, we performed the ordinal regression analysis with and without the subjects with substituted data. The results from these analyses were comparable, which indicates that no major error was introduced by substituting the data. We also added a variable indicating whether a value for a test was substituted or not (Dartigues et al., 1997). This variable was not significant, which again indicates that no major error was introduced by substituting the data. However, the single imputation approach has the disadvantage that the confidence intervals are underestimated, which can lead to false-positive results (Stijnen et al., 1999). An alternative to the single imputation method would have been the recently developed likelihood method or multiple imputation method (Stijnen et al., 1999). In chapters 3 and 6 we left out subjects with missing data. The number of subjects with missing data was, however, small (2% and 6% respectively) and it is not likely that a major error was introduced.

Clinical diagnosis of AD

The diagnosis of AD was made according to the NINCDS-ADRDA criteria of probable or possible AD (McKhann et al., 1984). The clinical diagnosis of probable or possible AD made in the Maastricht Memory Clinic is accurate because 95% of the subjects with the diagnosis of probable or possible AD showed evidence of progressive cognitive decline over the next 3.5 years (Verhey et al., 1993b). Also the dementia diagnosis in the AMSTEL study is accurate because all subjects with probable or possible AD in the AMSTEL study continued to have probable or possible AD at follow-up. However, from the literature it is known that about 10% of the subjects with probable or possible AD will not have AD at pathological examination (Galasko et al., 1994; Klatka et al., 1996). Unfortunately, it was not possible to verify postmortem the diagnosis of probable or possible AD in the Maastricht Memory Clinic and AMSTEL studies. Thus, a small number of subjects who had probable or possible AD in this thesis will have had other causes of dementia. Since this number of subjects is probably smaller than 10% a misdiagnosis will probably not have a large influence on the results.

Equating dementia with AD

In the introduction we noted that most prospective studies used dementia as an endpoint and not AD. We equated dementia with AD because the vast majority of the subjects with mild cognitive impairment who became demented had AD-type dementia. Of the studies listed in table 9.1 (excluding the studies of this thesis), 195 out of the 209 demented subjects (93%) had AD-type dementia at follow-up. Other causes of dementia were vascular dementia or mixed dementia (a combination of AD and vascular dementia) (N=8, 4%) and unspecified or atypical causes of dementia (N=6, 3%). Similar results were obtained in the Maastricht Memory Clinic and AMSTEL studies. Thus, a small number of subjects who are predicted to have AD at follow-up will have non-AD type dementia. Follow-up evaluations are therefore necessary to establish whether indeed AD-type dementia is present in these subjects.

Predictive accuracy for AD in subjects with mild cognitive impairment

In the preceding section we noted that about 7% of the subjects with mild cognitive impairment who are predicted to have AD at follow-up will have non-AD type dementia. In addition, 10% of the subjects with probable or possible AD at followup will have non-AD type dementia on pathological examination (Galasko et al., 1994; Klatka et al., 1996). Furthermore, not all subjects who are predicted to have AD at follow-up will have dementia at follow-up. The positive predictive value of AD in the studies listed in table 9.2 varied from 60% to 95% (data not shown). It seems reasonable to assume that the positive predictive value will not exceed 90% with the

present predictors of AD. Thus, of all subjects predicted to have AD with the predictors that are now available, about 75% (0.90*0.93*0.90) will have pathologically confirmed AD. This percentage may be increased by performing regular follow-up assessments in order to identify subjects with other types of dementia and subjects without dementia at follow-up.

Correction for age and education

There is some debate whether cognitive data should be corrected for age and education because these variables are also predictors of AD (Sliwinski et al., 1997). It is argued that the lower cognitive performance of elderly subjects or subjects with a low educational level is in part due to the fact that these subjects are in the preclinical stage of AD. The correction of the cognitive data for age and education will therefore presumably reduce the sensitivity for detecting subjects with preclinical AD. However, if data are not corrected for age and education, the specificity will decrease because there is ample evidence that even after exclusion of subjects with major neurological, psychiatric, or somatic disorders or preclinical AD, there is an effect of age, education, and sex on cognitive performance (Jolles et al., 1995; Sliwinski et al., 1997). For that reason we chose to correct the cognitive data for age and education. In order to minimize the effects of the cognitive performance of the subjects with preclinical AD on the predictive accuracy of cognitive tests, we adjusted the correction for age and education on a large reference population with a wide age range (the Maastricht Aging Study and the AMSTEL study). Moreover, we excluded subjects with preclinical AD from the reference population in the AMSTEL study. In order to increase the sensitivity for detecting subjects with preclinical AD, we always used age as a predictor together with age-corrected cognitive data.

9.5 CONCLUDING REMARKS

We now conclude with recommendations for future research in preclinical AD, the clinical relevance of the findings, and the general conclusion.

Recommendations for future research in preclinical AD

On the basis of the results described in this thesis, we can make the following recommendations for future research in preclinical AD. Studies that investigate preclinical AD in subjects with mild cognitive impairment should have a follow-up period of at least 5 years (chapter 8) but preferably 10 years (Almkvist et al., 1998). If 5 years is too long to wait for the results for new diagnostic markers, secondary endpoints can be used, such as those proposed in chapter 6. It is also worthwhile considering improvement as an separate outcome because subjects with improve-

ment are less likely to become demented than subjects with persisting mild cognitive impairment. Studies should have a multidisciplinary design and always assess several predictors (including cognition and functional impairment) at the same time. Since some diagnostic markers are expensive (MRI imaging) or invasive (lumbar puncture), a stepwise approach, such as that suggested in 9.3, can be used to select subjects who would benefit the most from the diagnostic procedure. Cognitive performance or functional impairment should not be used as an inclusion or exclusion criterion because both are highly variable in subjects with preclinical AD (chapter 8). Mild depression is often seen in preclinical AD and should therefore not be an exclusion criterion (chapters 2 and 5).

Several markers of AD should be tested as predictors in subjects with mild cognitive impairment. The most promising predictor is the concentration of beta 1-42 amyloid and tau protein in the cerebrospinal fluid (Andreasen et al., 1998; Galasko et al., 1998; Hulstaert et al., 1999; Jensen et al., 1999). Other potential predictors are perfusion of the parieto-temporal cortex as measured with Single Photon Emission Computed Tomography (Black, 1999; Celsis et al., 1997; Johnson et al., 1998), functional MRI findings (Rombouts, 1999; Small et al., 1999), EEG-based methods (Almkvist et al., 1999), spectroscopic imaging of N-acetyl compounds, creatine, and choline (Pfefferbaum et al., 1999), PET imaging of acetylcholine esterase (Iyo et al., 1997; Kuhl et al., 2000), beta amyloid precursor protein isoforms in platelets (Di Luca et al., 1998), dynamic susceptibility contrast MRI findings (Harris et al., 1998), inflammatory markers (Maes et al., 1999), F-4 isoprostanes, blood heme oxygenase-1 levels (Schipper et al., 2000), alpha-2 macroglobulin gene polymorphisms (Blacker et al., 1998), and interleukin-1 gene polymorphisms (Grimaldi et al., 2000; Nicoll et al., 2000). If they turn out to be predictors of AD in subjects with mild cognitive impairment, they can be incorporated in the PAS or a similar multidisciplinary scale.

Clinical relevance

The clinical relevance of the findings is that they can be used to predict outcome in subjects with preclinical AD. Useful variables in this respect were age, the MMSE score, cognitive tests of memory, language, executive functions, visuoconstruction, and abstract reasoning, measures of functional impairment, apoE genotyping, and assessment of medial temporal lobe atrophy. We proposed a way to combine these variables to determine the risk of preclinical AD in subjects with mild cognitive impairment in the Preclinical AD scale (PAS). Moreover, we suggested a stepwise diagnostic assessment for subjects with mild cognitive impairment in order to select subjects who would benefit most from elaborate or expensive diagnostic procedures. The PAS can be used to select subjects who should remain under clinical super-

vision or, after the cut-off scores have been validated in other settings as well, to select subjects for psychological or therapeutic intervention trials. Special attention was paid to the co-occurrence of depression and mild cognitive impairment. We demonstrated that many subjects with preclinical AD had depression. Therefore, in subjects with depression and mild cognitive impairment one should not only consider depression-related cognitive impairment but also preclinical AD as diagnosis. Preclinical AD in depressed subjects is likely if the subject is older than 65 years and has moderately severe memory impairment.

The clinical relevance can be best illustrated by the case history of the 68-year old man with mild cognitive impairment and depressed mood who was described in the prologue of this thesis. The PAS score of this subject after the first step was 4 (borderline score, see table 9.9) which indicated that the subject should have proceed to the next step (cognitive testing). After the cognitive test the PAS score was 5 (borderline score), which suggested that the subject should have been assessed for medial temporal lobe atrophy. However, a regular MRI scan was made and medial temporal lobe atrophy was not assessed. Also apoE genotyping was not done. The final PAS score of 5 indicated an intermediate risk for AD, which implies that the subject should have remained under clinical supervision. A follow-up assessment was done after 12 months and although the PAS score remained the same, no follow--up appointment was made. Three questions arose from this case history: could AD not have been foreseen in this subject; which other diagnostic procedures would have improved the diagnosis at the first visit; was it likely that the cognitive impairment in this subject was related to his depressed mood? These questions can be now answered as follows: future AD was likely in this subject given his PAS score of 5; assessment of medial temporal lobe atrophy and apoE genotyping would have been useful diagnostic procedures; it was not likely that the cognitive impairment was related to depressed mood; instead, the depressed mood was probably a symptom of preclinical AD.

Conclusion

The main conclusions of this thesis are as follows. Age, impairment on cognitive tests, atrophy of the medial temporal lobe, measures of functional impairment, the MMSE score, and the apoE genotype were found to be predictors of AD in subjects with mild cognitive impairment. Furthermore, we found that combinations of these variables were better predictors of outcome than the variables on their own. This suggested that a multidisciplinary approach has advantages over a monodisciplinary approach. A proposal for such a multidisciplinary approach was given in the Preclinical AD scale (PAS).

Summary

Introduction

Before people with Alzheimer's disease (AD) become demented there is a long period in which they experience mild cognitive impairment. This period is called the preclinical phase of AD. It is important to identify subjects with preclinical AD because they may benefit from therapeutic interventions. However, these subjects should be distinguished from other subjects with mild cognitive impairment who do not have preclinical AD. This is difficult because there are no sensitive and specific markers of AD that can be used in subjects with mild cognitive impairment. In addition, the clinical characteristics of subjects with preclinical AD have been poorly described.

The aim of the studies described in this thesis was to investigate which variables predicted AD in subjects with mild cognitive impairment and whether a combination of variables predicted outcome more accurately than each predictor on its own. Furthermore, the clinical characteristics of subjects with preclinical AD were described. Finally, we aimed to provide decision rules that can be easily used in clinical practice to estimate the risk that a patient with mild cognitive impairment will have developed AD-type dementia at follow-up. These decision rules are operationalized in the Preclinical AD Scale (PAS).

Predictors of outcome that were investigated were age, education, impairment on cognitive tests, the MMSE score, the degree of functional impairment, the apolipoprotein E (apoE) genotype, depression, and medial temporal lobe atrophy. The predictors were tested in subjects with mild cognitive impairment from the Maastricht Memory Clinic and the population-based Amsterdam Study of the Elderly (AMSTEL).

Chapter 2

In this chapter we investigated the course of objective memory impairment in non-demented subjects (N=74) from the Maastricht Memory Clinic and we tested predictors of outcome. At the 5-year follow-up, 42% of the subjects had no memory impairment, 19% of the subjects had memory impairment without dementia, and 39% of the subjects had AD-type dementia. Predictors at baseline of outcome in a multivariate analysis were age, scores on the MMSE and delayed recall, and the severity of functional impairment. The apolipoprotein E genotype and the presence of depression at baseline were not predictors of outcome. It was concluded that memory impairmentis often reversible and therefore its presence alone is not sufficient to consider subjects as preclinically demented. Predictive accuracy can be

increased by including simple measures such as age, the scores on the MMSE and delayed recall, and the severity of functional impairment.

Chapter 3
In this chapter we investigated the course of minimal dementia in subjects (N=45) from the AMSTEL study and we tested predictors of outcome. At follow-up, minimal dementia turned out to be reversible in 11 subjects (24%) and persistent in 10 subjects (22%). Twenty-four subjects (54%) had become demented at follow-up. Predictors of outcome in a multivariate analysis were age, score on the CAMCOG memory subscale, and the apoE genotype. Depression at baseline and the baseline MMSE and fluency scores were not predictors of outcome. It was concluded that the outcome of minimal dementia is variable and that predictive accuracy can be improved by including age, the apoE genotype, and the score on the CAMCOG memory subscale.

Chapter 4
The aim of chapter 4 was to assess the prevalence of depression in subjects with preclinical AD in the Maastricht Memory Clinic and to investigate the possibility of distinguishing subjects with preclinical AD and depression from subjects with depression-related cognitive impairment. Sixty percent of the subjects with preclinical AD were depressed at baseline. Subjects with depression and preclinical AD had a poorer performance on the cognitive tasks and were older at baseline than the subjects with depression-related cognitive impairment. Logistic regression with backward step selection selected age and memory performance as the best predictors for AD-type dementia in the depressed subjects. It was concluded that depressed subjects with preclinical AD can be accurately distinguished from subjects with depression-related cognitive impairment because subjects with preclinical AD are older and have more severe memory impairment than subjects with depression-related cognitive impairment.

Chapter 5
The aim of chapter 5 was to determine whether medial temporal lobe atrophy predicted AD in subjects with minimal dementia from the AMSTEL study (N=20) and whether atrophy of this structure is a better predictor of AD than memory dysfunction is. The volume of the parahippocampal gyrus and hippocampus was measured and medial temporal lobe atrophy was assessed qualitatively. At baseline, the volume of the parahippocampal gyrus of minimally demented subjects with AD at follow-up was smaller than that of the other subjects with minimal dementia. The memory score was the best predictor of AD, but all medial temporal lobe measures

increased the accuracy of prediction compared with the accuracy of the memory score only, by reducing the number of false-negative classifications of AD. It was concluded that the ability to detect subjects at high risk for AD among subjects with minimal dementia will increase when data on memory function are combined with measures of medial temporal lobe atrophy.

Chapter 6

In chapter 6 it was investigated whether medial temporal lobe atrophy predicts outcome in non-demented elderly subjects with mild cognitive impairment from the Maastricht Memory Clinic (N=31) and whether assessment of the medial temporal lobe increases the predictive accuracy of age and delayed recall for outcome. We also compared quantitative and qualitative methods for assessing medial temporal lobe atrophy, namely volumetry of the hippocampus, volumetry of the parahippocampal gyrus, and qualitative rating of medial temporal lobe atrophy. Subjects with a small volume of the hippocampus or parahippocampal gyrus or with a high medial temporal lobe score had AD or cognitive decline at follow-up more often than subjects with a large volume of the hippocampus or parahippocampal gyrus or with a low medial temporal lobe score. All medial temporal lobe measurements increased the predictive accuracy of age and the delayed recall score for AD or cognitive decline, by reducing the number of false-negative and false-positive classifications of AD or cognitive decline. Volumetry of the hippocampus increased predictive accuracy the most. It was concluded that the ability to detect subjects at high risk for AD among subjects with mild cognitive impairment is increased when data on age and memory function are combined with measures of medial temporal lobe atrophy. Volumetry of the hippocampus is the preferred method for assessing medial temporal lobe atrophy, but qualitative rating is a good alternative.

Chapter 7

In this chapter we investigated whether medial temporal lobe atrophy is specific for memory problems in subjects with AD or whether it is also seen in subjects with memory problems caused by thiamine deficiency (Korsakoff's syndrome). We therefore investigated the relation between anterograde amnesia and atrophy of brain structures involved in memory processing in 13 subjects with alcoholic Korsakoff's syndrome. It was concluded that anterograde amnesia in alcoholic Korsakoff's syndrome is associated with atrophy of the nuclei in the midline of the thalamus, but not with atrophy of the mammillary bodies, the hippocampus, or the parahippocampal gyrus.

Chapter 8

The aim of chapter 8 was to describe the clinical characteristics of subjects with preclinical AD. Subjects with preclinical AD (N=31) were selected from the Maastricht Memory Clinic study. Memory impairment was the predominant finding in the preclinical stage of AD but it was not present in all subjects. Other cognitive domains were also frequently involved. Functioning in activities of daily living was mildly impaired in 74% of the subjects, very mildly impaired in 23%, and moderately impaired in 3%. Affective symptoms were seen in 80% of the subjects. It was concluded that there was no simple profile of preclinical AD.

General Discussion

Subjects with preclinical AD are generally characterized by memory impairment, mild functional impairment, and affective symptoms. However, not all subjects have memory impairment but may have impairments in other cognitive domains instead. Some subjects may not have impairments on cognitive tests or the functional impairment may be very mild. Thus, there is no simple profile of subjects with preclinical AD. Hence, in order to identify these subjects one should not focus exclusively on memory dysfunction and one should not exclude subjects with very mild functional impairment or subjects with mild affective disorders.

Because depression is common in preclinical AD, one should consider not only depression-related cognitive impairment but also preclinical AD as possible diagnosis in elderly subjects with depression and mild cognitive impairment. Depressed subjects with preclinical AD could be accurately distinghuished from subjects with depression-related cognitive impairment by the age and severity of cognitive impairment.

On the basis of the results of the studies described in this thesis and a meta-analysis of the literature, we concluded that age, memory impairment, impairments in other cognitive domains, the MMSE score, the degree of functional impairment, the apoE genotype, and medial temporal lobe atrophy could predict AD in subjects with mild cognitive impairment. Education and depression were not predictors of AD. A combination of variables predicted outcome better than each variable on its own. We proposed the Preclinical AD Scale (PAS) as a means to detect the risk of AD. The scale consist of six items (age, MMSE score, functional impairment, cognitive test performance, medial temporal lobe atrophy, and apoE genotype) that can be scored on a 3- to 4-point scale. The sum score indicates the risk for subsequent AD. The validation of the PAS in subjects from the Maastricht Memory Clinic and AMSTEL study showed that the PAS can accurately predict outcome in subjects with mild cognitive impairment. The PAS can be used in a stepwise fas-

hion to guide diagnostic work-up and to select subjects who would benefit most from elaborate and expensive diagnostic procedures.

Some methodological issues in prospective studies that investigate predictors of AD in subjects with mild cognitive impairment were discussed, e.g., sampling bias, loss to follow-up, length of follow-up, problems related to a multidisciplinary approach, missing data, the clinical diagnosis of AD, equating dementia with AD, the predictive accuracy for AD in subjects with mild cognitive impairment, and whether cognitive data should be corrected for age and education or not.

We concluded with suggestions for further research and implications for clinical practice.

Appendix A

In appendix A we provided an overview of the different concepts of mild cognitive impairment.

Appendix B

In appendix B.1 we validated the preclinical AD scale in 96 subjects from the Maastricht Memory Clinic and 237 subjects of the AMSTEL study. The PAS seemed to be useful to assess the risk of preclinical AD in subjects with mild cognitive impairment. It was shown that a PAS score indicated a low risk for preclinical AD and a PAS score ≥6 indicated a high risk for preclinical AD. Stepwise scoring with the PAS could reduce the number of cognitive assessments by 40%, the number of assessments of medial temporal lobe atrophy by on average 75%, and the number of apoE genotypings by on average 80%. In appendix B.2 we described how we determined the cut-off points of the PAS items. In appendix B.3 we gave instructions how to score the PAS.

Samenvatting (summary in Dutch)

Introductie

Voordat patiënten met de ziekte van Alzheimer dement worden is er een lange periode aan voorafgegaan waarin zij lichte cognitieve klachten hebben. Deze periode wordt het preklinische stadium van de ziekte van Alzheimer genoemd. Het is belangrijk om patiënten in het preklinische stadium van de ziekte te identificeren omdat ze mogelijk baat hebben bij therapeutische interventies. Om deze patiënten te identificeren moeten zij onderscheiden worden van patiënten die ook lichte cognitieve stoornissen hebben, maar dan om andere redenen, zoals veroudering of depressie. Dit is moeilijk omdat er geen sensitieve of specifieke diagnostische testen voor de ziekte van Alzheimer zijn die gebruikt kunnen worden bij patiënten met lichte cognitieve stoornissen. Verder zijn de klinische kenmerken van patiënten in het preklinische stadium van de ziekte van Alzheimer slecht beschreven.

Het doel van de studie was ten eerste om te onderzoeken welke variabelen Alzheimer type dementie (AD) voorspellen bij patiënten met lichte cognitieve stoornissen en ten tweede of een combinatie variabelen beter AD kon voorspellen dan elke variabele op zichzelf. Ten derde werden de klinische kenmerken van het preklinische stadium van de ziekte van Alzheimer beschreven. Ten vierde wilden we beslisregels voor de klinische praktijk formuleren om het risico in te schatten dat iemand met lichte cognitieve klachten AD zou krijgen. Deze beslisregels werden uitgewerkt in de Preclinical AD Scale (PAS).

De volgende voorspellers werden onderzocht: leeftijd, opleiding, prestatie op cognitieve testen, MMSE score, mate van functionele stoornissen, het apolipoproteine E (apoE) genotype, depressie, en atrofie van de mediale temporaal kwab. Deze voorspellers werden onderzocht in patiënten met lichte cognitieve klachten van de Geheugenpoli Maastricht en in de populatiestudie Amsterdam Study of the Elderly (AMSTEL).

Hoofdstuk 2

In dit hoofdstuk werd gekeken wat het beloop is van geobjectiveerde geheugenstoornissen bij 74 patiënten van de Maastrichtse Geheugenpoli. Verder werd onderzocht welke variabelen het beloop kunnen voorspellen. Na 5 jaar had 42% van de patiënten geen geheugenstoornissen meer, 19% had nog steeds geheugenstoornissen maar was niet dement geworden en 39% van de patiënten had Alzheimer type dementie gekregen. In een multivariate analyse konden leeftijd, de score op de MMSE (een korte cognitieve test), de score op de geheugentaak en de mate van functionele stoornissen

uitkomst voorspellen. Het apolipoproteine E genotype en depressie waren niet voorspellend voor uitkomst. De conclusie van dit hoofdstuk was dat geobjectiveerde geheugenstoornissen vaak reversibel zijn en daarom niet voldoende zijn om iemand als beginnend dement te beschouwen. Het beloop kan beter voorspeld worden als ook rekening wordt gehouden met leeftijd, MMSE score, geheugenscore en mate van functionele beperkingen.

Hoofdstuk 3
In dit hoofdstuk werd het beloop van 'minimal dementia' onderzocht bij 45 proefpersonen uit de AMSTEL studie. Verder werd gekeken welke variabelen uitkomst kunnen voorspellen. Tijdens de follow-up was 24% verbeterd en had geen 'minimal dementia' meer, 22% bleef 'minimal dementia' houden en 54% was dement geworden. Uitkomst kon voorspeld worden door de variabelen leeftijd, score op de geheugenschaal van de CAMCOG en het apolipoproteine E genotype. Depressie, MMSE score en fluency score konden uitkomst niet voorspellen. Geconcludeerd werd dat de uitkomst van 'minimal dementia' variabel is. De uitkomst kan beter voorspeld worden door rekening te houden met leeftijd, apolipoproteine E genotype, en geheugenscore.

Hoofdstuk 4
Depressieve patiënten hebben vaak cognitieve stoornissen die het gevolg zijn van de depressie (de zogenaamde depressie-gerelateerde cognitieve stoornissen). Echter, patiënten in het preklinische stadium van de ziekte van Alzheimer zijn ook vaak depressief en hebben ook cognitieve stoornissen. Het is onduidelijk hoe deze groepen van elkaar onderscheiden kunnen worden. Het doel van dit hoofdstuk was om na te gaan hoe vaak depressie voorkomt bij patiënten die in het preklinische stadium van de ziekte van Alzheimer zijn. Verder werd onderzocht in hoeverre depressieve patiënten in het preklinische stadium van de ziekte van Alzheimer te onderscheiden zijn van patiënten met depressie-gerelateerde cognitieve stoornissen. Zestig procent van de patiënten in het preklinische stadium van de ziekte van Alzheimer was depressief. Meestal was de depressie licht. De depressieve patiënten in het preklinische stadium van de ziekte van Alzheimer waren ouder en hadden meer cognitieve stoornissen dan patiënten met depressie-gerelateerde cognitieve stoornissen. In een multivariate analyse bleken leeftijd en geheugenprestatie het beste onderscheid te kunnen maken tussen de twee groepen. Er werd geconcludeerd dat depressie vaak voorkomt bij patiënten in het preklinische stadium van de ziekte van Alzheimer. Echter, patiënten in het preklinische stadium van de ziekte van Alzheimer kunnen goed onderscheiden worden van patiënten met depressie-gerelateerde cognitieve stoornissen, en wel op basis van leeftijd en geheugenprestatie.

Hoofdstuk 5
In dit hoofdstuk werd onderzocht of de mate van atrofie van de mediale temporaal kwab voorspellend was het krijgen van Alzheimer type dementie bij 20 patiënten met 'minimal dementia'van de AMSTEL studie en of de mate van atrofie beter Alzheimer type dementie voorspelde dan geheugenprestatie. De mate van atrofie van de mediale temporaal kwab werd bepaald door het volume te meten van de hippocampus, het volume te meten van de gyrus parahippocampalis en door een kwalitatieve beoordeling. Proefpersonen die dement werden en de ziekte van Alzheimer kregen hadden aan het begin van de studie al een kleiner volume van de gyrus parahippocampalis dan proefpersonen die niet dement werden. Geheugenprestatie voorspelde uitkomst het beste, maar alle drie de maten van mediale temporaal kwab atrofie verbeterden de nauwkeurigheid waarmee geheugenprestatie uitkomst voorspelde. Dit kwam omdat sommige proefpersonen met Alzheimer type dementie op follow-up nog goede geheugenprestaties hadden, terwijl hun mediale temporaal kwab al wel atrofisch was. De conclusie van dit hoofdstuk was dat proefpersonen met een hoog risico op het krijgen van Alzheimer type dementie beter opgespoord kunnen worden als de informatie over geheugenprestatie gecombineerd wordt met informatie over de mate van mediale temporaal kwab atrofie.

Hoofdstuk 6
In hoofdstuk 6 werd een soortgelijk onderzoek uitgevoerd als in hoofdstuk 5. De proefpersonen (31) waren nu afkomstig van de Maastrichtse Geheugenpoli en hadden lichte cognitieve stoornissen. Ook in dit hoofdstuk werd onderzocht of de mate van mediale temporaal kwab atrofie voorspellend was voor Alzheimer type dementie en of de mate van atrofie beter Alzheimer type dementie voorspelde dan geheugenprestatie en leeftijd. Atrofie van de mediale temporaal kwab werd ook weer bepaald op drie manieren: door het volume te meten van de hippocampus, het volume te meten van de gyrus parahippocampalis en door een qualitatieve beoordeling. Patiënten met een klein volume van de hippocampus of gyrus parahippocampalis of met een hoge kwalitatieve atrofie score hadden vaker de ziekte van Alzheimer of cognitieve achteruitgang bij follow-up dan patiënten met een groot volume van de hippocampus of gyrus parahippocampalis of met een lage kwalitatieve atrofie score. Alle maten van mediale temporaal kwab atrofie verbeterden de nauwkeurigheid waarmee geheugenprestatie en leeftijd uitkomst voorspelden. Dit kwam doordat sommige proefpersonen met Alzheimer type dementie op follow-up aan het begin van de studie nog goede geheugenprestaties hadden, terwijl hun mediale temporaal kwab al wel atrofisch was (net als in hoofdstuk 5), en ook doordat sommige patiënten met ernstige geheugenstoornissen die reversibel bleken, helemaal geen mediale temporaal kwab atrofie hadden. Van de drie maten van mediale temporaal kwab atrofie was het volume van

de hippocampus de beste voorspeller. Geconcludeerd werd, net als in hoofdstuk 5, dat het vermogen om patiënten met beginnende ziekte van Alzheimer op te sporen verbetert als informatie over leeftijd en geheugenprestatie gecombineerd wordt met informatie over de mate van mediale temporaal kwab atrofie. Mediale temporaal kwab atrofie kan het beste bepaald worden met het opmeten van de hippocampus, maar omdat dit tijdrovend is, kan er ook een kwalitatieve maat worden gebruikt.

Hoofdstuk 7
In dit hoofdstuk werd onderzocht of atrofie van de mediale temporaal kwab specifiek is voor de geheugenstoornissen bij de ziekte van Alzheimer of dat deze atrofie ook optreedt bij de geheugenstoornissen bij patiënten met het syndroom van Korsakoff. Bij 13 patiënten met Korsakoff werd het volume van een aantal structuren die een rol bij geheugen spelen gecorreleerd met geheugenprestatie. De conclusie was dat de geheugenstoornissen bij het syndroom van Korsakoff samenhangen met atrofie van de kernen in het midden van de thalamus, maar niet met atrofie van de hippocampus, gyrus parahippocampalis, of corpora mammillaria.

Hoofdstuk 8
Het doel van hoofdstuk 8 was om te beschrijven met welke klachten patiënten in het preklinische stadium van de ziekte van Alzheimer zich presenteerden op de Maastrichtse Geheugenpoli. Hoewel de meeste patiënten (80%) objectiveerbare geheugenproblemen hadden, was er ook een groep zonder objectiveerbare geheugenproblemen. Deze patiënten hadden wel vaak objectiveerbare stoornissen op andere gebieden. De functionele stoornissen waren licht van ernst in 74%, heel licht van ernst in 23%, en behoorlijk ernstig in 3%. Tachtig procent van de patiënten had lichte stemmingsstoornissen zoals depressie of angst. Geconcludeerd werd dat er niet een simpel profiel is voor het preklinische stadium van de ziekte van Alzheimer.

Algemene Discussie
Patiënten in het preklinische stadium van de ziekte van Alzheimer hebben in het typische geval geheugenstoornissen, lichte functionele stoornissen, en lichte affectieve stoornissen. Echter, niet alle patiënten hebben geheugenstoornissen. Ze kunnen ook stoornissen in andere cognitieve domeinen hebben of helemaal geen cognitieve stoornissen. De functionele stoornissen kunnen ook heel licht zijn. Er is dus geen eenvoudig profiel van het preklinische stadium van de ziekte van Alzheimer. Wil men patiënten in het preklinische stadium van de ziekte van Alzheimer opsporen dan moet men niet alleen naar geheugenprestatie kijken en niet bij voorbaat patiënten uitsluiten met hele lichte functionele stoornissen of lichte depressie omdat anders een grote groep niet herkend wordt.

Verder werd gevonden dat depressieve patiënten in het preklinische stadium van de ziekte van Alzheimer goed onderscheiden konden worden van patiënten met depressiegerelateerde cognitieve stoornissen omdat depressieve patiënten in het preklinische stadium van de ziekte van Alzheimer ouder waren en zwaardere geheugenstoornissen hadden.

Op basis van de gegevens van het proefschrift en een meta-analyse van de literatuur werd geconcludeerd dat leeftijd, geheugenstoornissen, stoornissen in andere cognitieve domeinen, de MMSE score, functionele stoornissen, het apoE genotype, en atrofie van de mediale temporaal kwab voorspellers zijn voor AD in patiënten met lichte cognitieve stoornissen. Leeftijd en depressie waren geen voorspellers voor AD. Een combinatie van variabelen voorspelde de ziekte van Alzheimer beter dan elke variabele op zichzelf. We hebben de Preclinical AD Scale (PAS) gemaakt om de variabelen die AD konden voorspellen te combineren. De PAS bestaat uit 6 items: leeftijd, MMSE score, functionele stoornissen, cognitieve test prestatie, atrofie van de mediale temporaal kwab en het apoE genotype. Elk item kan op een 3 of 4 puntsschaal gescoord worden. De totale score geeft het risico op de ziekte van Alzheimer aan. Een validatie van de PAS in patiënten van de Maastrichtse Geheugenpoli en de AMSTEL studie liet zien dat deze schaal nauwkeurig kan voorspellen welke patiënten met lichte cognitieve stoornissen AD zullen krijgen. Een stapsgewijze scoring van de PAS kan het diagnostisch beleid bepalen en patiënten selecteren die het meeste baat hebben bij bewerkelijke of dure diagnostische methoden.

Verder werd een aantal methodologische aspecten van prospectieve studies van patiënten met lichte cognitieve klachten besproken zoals sampling bias, loss to follow-up, duur van de follow-up, problemen met een multidisciplinaire benadering, missing data, de klinische diagnose van AD, het gelijkstellen van dementie met AD, de predictieve nauwkeurigheid en of cognitieve data gecorrigeerd moeten worden voor leeftijd, geslacht en opleiding. We besloten de discussie met suggesties voor verder onderzoek en de klinische relevantie van het onderzoek.

Appendix A

In appendix A wordt een overzicht gegeven van verschillende concepten van lichte cognitieve stoornissen.

Appendix B1-3

In appendix B.1 werd de Preclinical AD Scale (PAS) gevalideerd in patiënten van de Maastrichtse geheugenpoli en proefpersonen van de AMSTEL studie. Daarnaast werd onderzocht of de PAS ook stapsgewijs gescoord kan worden zodat het aantal dure en tijdrovende diagnostische handelingen beperkt kan worden. De PAS had een goede sensitiviteit en specificiteit voor preklische ziekte van Alzheimer. Een score op de

PAS ≥6 gaf een hoge kans op het krijgen van Alzheimer type dementie terwijl een score ≤4 geassocieerd was met een hele lage kans. De stapsgewijze scoring van PAS had dezelfde sensitiviteit en specificiteit als de hele PAS maar het beperkte bovendien het aantal cognitieve testen met ongeveer 40%, het aantal MRI metingen met 70% en het aantal apolipoproteine E genotyperingen met 80%. In appendix B.2 beschrijven hoe de cut-off scores voor de PAS items zijn bepaald. In appendix B.3 geven we instructies hoe de PAS gebruikt dient te worden.

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List of publications

PUBLICATIONS BASED ON THE STUDIES PRESENTED IN THIS THESIS

Chapter 1
Visser, PJ, Verhey, F & Jolles, J (submitted) Course of mild cognitive impairment. A review and meta-analysis.

Chapter 2
Visser, PJ, Verhey, F, Ponds, R, Cruts, M, Van Broeckhoven, C & Jolles, J (2000a) Course of objective memory impairment in non-demented subjects attending a memory clinic and predictors of outcome. *International Journal of Geriatric Psychiatry*, **15** (4), 363-372.

Chapter 3
Visser, PJ, Verhey, F, Jolles, J & Jonker, C (submitted) Course of minimal dementia in a population-based study and predictors of outcome.

Chapter 4
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Chapter 6
Visser, PJ, Verhey, F, Scheltens, P, Hofman, P & Jolles, J (submitted) Medial temporal lobe atrophy predicts Alzheimer's disease in subjects with mild cognitive impairments.

Chapter 7
Visser, PJ, Krabbendam, L, Verhey, F, Hofman, P, Verhoeven, W, Tuinier, S, Wester, A, van den Berg, Y, Goessens, L, Van der Werf, Y & Jolles, J (1999) Brain correlates of memory dysfunction in alcoholic Korsakoff's syndrome. *Journal of Neurology, Neurosurgery and Psychiatry*, **67**, 774-778.

Chapter 8
Visser, PJ, Verhey, F, Ponds, R & Jolles, J (submitted) Characteristics of preclinical Alzheimer's disease.

Chapter 9.1
Visser, PJ, Verhey, F, Ponds, R & Jolles, J (submitted) Preclinical Alzheimer's disease is a clinical entity.

Chapter 9.2
Visser, PJ, Verhey, F & Jolles, J (submitted) Predictors of Alzheimer type dementia in subjects with mild cognitive impairment. A review and meta-analysis.

Appendix B.1
Visser, PJ, Verhey, F, Scheltens, P, Cruts, M, Van Broeckhoven, C & Jolles, J (submitted) Predicting Alzheimer type dementia in subjects with mild cognitive impairments using the Preclinical AD Scale (PAS).

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Curriculum Vitae

Pieter Jelle Visser werd geboren op 18 september 1968 te Amersfoort. Na het behalen van het Gymnasium ß diploma bij de scholengemeenschap De Breul in Zeist begon hij in 1986 aan de studie geneeskunde bij de Universiteit Utrecht. In 1990 behaalde hij het doctoraal examen Geneeskunde (cum laude) en in 1994 het artsexamen. Tussendoor studeerde hij nog een jaar Wijsbegeerte (propedeuse examen 1989). Met het oog op een baan in de Verenigde Staten behaalde hij in 1993 en 1994 de delen 1 en 2 van het Educational Committee for Foreign Medical Graduation (ECFMG)- United States medical licencing examination. Het werd echter geen baan in het buitenland, maar wel een bij de vakgroep Psychiatrie en Neuropsychologie van de Universiteit Maastricht, waar dit promotieonderzoek werd uitgevoerd (1994-1999).
De auteur is getrouwd met Astrid Ferdinand en heeft twee zonen, Simon en Thomas.

Appendix A:
Definitions of mild cognitive impairment

In this appendix we describe various concepts of mild cognitive impairment. These concepts have in common that they apply to subjects without dementia. After each definition we provide the reference of the study that gives the original description (first reference) and references of a selection of cross-sectional and longitudinal studies.

Age-associated memory impairment (AAMI)
- complain of memory impairment
- memory functioning 1SD below the mean performance of young adults
- age >50
- adequate intellectual functioning (scaled score of 9 on the Vocabulary subtests of the WAIS)
- absence of dementia (MMSE ≥24)
- absence of memory-affecting diseases: delirium, confusion, disturbances consciousness; neurologic disorders that could produce cognitive deterioration; infectious or inflammatory brain disease; significant cerebral vascular pathology HIS ≥4; repeated minor head injury or head trauma with period of unconsciousness for 1 hour or more; current psychiatric diagnosis of depression, mania, or any major psychiatric disorder; current diagnosis or history of alcoholism or drug dependence; HDRS ≥13; any medical disorder that could produce cognitive deterioration (including renal, respiratory, cardiac or hepatic disease, uncontrolled diabetes mellitus, malignancy not in remission for more than 2 years, endocrine, metabolic or hematologic disturbances); use of any psychotropic drug or any other drug that may significantly affect cognitive function during the month prior to psychometric testing.
References: Crook et al., 1986; Coria et al., 1995; Dawe et al., 1992; Hänninen et al., 1995; Helkala et al., 1997; Parnetti et al., 1996; Richards et al., 1999; Schröder et al., 1998; Youngjohn et al., 1993.

Age-associated memory impairment (AAMI); Modification Blackford and La Rue
- inclusion and exclusion criteria as AAMI criteria except:
- verbal and performance IQ between 90 and 130.
- exclusion: hypertension, forward span less than 5.
- included: skin cancers, cancer in remission for 12 months, adequately treated hypertension and diabetes mellitus.
References: Blackford et al., 1989; Schröder et al., 1998; Smith et al. , 1991.

Age-consistent memory impairment
- 75% or more of the memory tests within +-1 SD below the age-corrected average
- other inclusion and exclusion criteria as age-associated memory impairment criteria modified by Blackford and La Rue
References: Blackford et al., 1989; Schröder et al., 1998; Smith et al. , 1991.

Age related cognitive decline
- "an objectively identified decline in cognitive functioning consequent to the aging process that is within normal limits given the person's age".
References: DSM-IV 780.9 Z41.8; APA, 1994; Celsis et al., 1997.

Aging-associated cognitive decline
- report by individual or reliable informant that cognitive function has declined
- gradual decline in any one cognitive area that was present for at least 6 months
- difficulties in any one of the following areas: memory and learning, attention and concentration, thinking, language, visuospatial functioning.
- performence on neuropsychological tests or mental state examinations at least 1 SD below age- and education-corrected population mean
- Exclusion criteria: cerebral disease or physical disorder known to cause cerebral dysfunction; depression, anxiety or other significant psychiatric disorders that may contribute to the observed difficulties; delirium; postencephalitic syndrome; post-contussional syndrome; persisting cognitive impairment due to psychoactive substance use or the effect of any centrally acting drug.
References: Levy, 1994 (Working party of International Psychogeriatric Society/ WHO); Hänninen et al., 1996; McKelvey et al., 1999; Richards et al., 1999; Schröder et al., 1998.

Amnestic syndrome
- history of memory loss of a definite onset lasting more than 6 months
- objective evidence for memory loss on neuropsychological testing
- no dementia (DSM-IIIR)
- no specific disease or drug intake capable of memory impairment
References: DSM-IIIR, APA, 1987

Borderline dementia
- score of 8 or 9 on the Information/Orientation subscale from the Clifton Assessment Procedures for the Elderly (CAPE)
References: Clarke et al., 1996

Late Life forgetfulness
- 50% or more of the memory tests between 1 and 2 SD below the age-corrected average
- other inclusion and exclusion criteria as age-associated memory impairment criteria modified by Blackford and La Rue
References: Blackford et al., 1989; Schröder et al., 1998; Smith et al. , 1991.

Limited cognitive disturbance (LCD) (from the CARE (Comprehensive Assessment and Referral Evaluation)
- report a decline in memory
- increased reliance on notes and reminders
- occasionally (less than once a week) forget names of acquaintances, forget appointments or misplace objects
- occasionally (less than once a month) have 'destructive' or 'dangerous' memory lapses
- have one or two errors on cognitive testing
- no intereference with activities of everyday living
References: Gurland et al., 1982

Mild cognitive decline (Global Deterioration Scale stage 3, GDS 3)
At least two of the following:
- getting lost when travelling to unfamiliar location
- decline in work performance apparent to co-workers
- word- and name-finding deficit apparent to intimates
- relatively little retention of material read in passage or book
- decreased facility remembering the names of newly introduced people
- losing or misplacing an object of value
- a concentration deficit apparent upon clinical testing
Memory deficit is demonstrable but not superficially apparent
References: Reisberg et al., 1982; de Leon et al., 1993b; Flicker et al., 1991.

Mild cognitive disorder
- A: objective evidence and/or a history of cerebral dysfunction or systemic physical disorder known to cause cerebral dysfunction
- B: a report of cognitive dysfunction by self or a reliable informant
- C: abnormality on psychological tests
- D: Exclusion criteria (probable) dementia (ICD-10), delirium, amnestic syndrome, alcohol misuse.

References: ICD-10, WHO, 1992, 1993; Christensen et al., 1997b; Ebly et al., 1995.

Mild cognitive impairment (Mayo Clinics)
- memory complaint by patient, family, or physician
- normal activities of daily living
- normal global cognitive functioning
- objective memory impairment or impairment in one other area of cognitive function as evidenced by scores >1.5 SD below age appropriate norms
- CDR score 0.5
- not demented
- age between 60 and 89 years

References: Smith et al., 1996; Jack et al., 1999; Petersen et al., 1995; Petersen et al., 1999; Petersen et al., 1994a.

Mild cognitive impairment (Zaudig)
- score on the Structured Interview for the Diagnosis of Dementia of the Alzheimer type (SIDAM) between 33 and 51. Most subjects with DSM-IIIR or ICD-10 based definition of mild cognitive impairment fulfilled these criteria.

References: Zaudig, 1992; Wolf et al., 1998.

Mild cognitive impairment (DSM)
- short- and long-term memory impairment with or without impairment in abstract thinking, impaired judgement, disturbance of higher cortical function (aphasia, apraxia, agnosia), or personality change
- no functional impairment

References: DSM-IIIR, APA, 1987; Ebly et al., 1995.

Mild impairment
- mild impairment on at least three out of five cognitive tests (including MMSE)
- no dementia

References: Johansson et al., 1992; Johansson et al., 1997.

Minimal Dementia
- "A limited and variable impairment of recall, minor and variable errors in orientation, a blunted capacity to follow arguments and solve problems and occasional errors in everyday tasks"

References: CAMDEX, Roth et al., 1986; Cooper et al., 1996; O'Connor et al., 1990; O'Connor et al., 1991; Paykel et al., 1994.

Moderate cognitive Impairment
- two neuropsychological tests (out of 16) below cut-off score
- CDR score 0.5
- no functional impairment
References: Stern et al., 1992; Devanand et al., 1996.

Possible dementia prodrome (CERAD)
- equal to questionable dementia
References: Smith et al., 1996.

Questionable dementia (Clinical Dementia Rating Scale 0.5)
- consistent slight forgetfulness; partial recollection of events;'benign' forgetfulness
Three of the following (other combinations also possible see (Morris, 1993):
- fully orientated or slight difficulties with time relationships
- slight impairment in solving problems, similarities, and differences
- slight impairment impairment in 'community affairs'
- life at home, hobbies and intellectual interests are well maintained or only slightly impaired
- fully capable of self-care
References: Berg et al., 1982 (update Morris, 1993); Devanand et al., 1997; Hughes et al., 1982; Morris et al., 1988; Morris et al., 1991; Morris et al., 1996; Morris, 1997.

Subcase 0rganic disorder (Geriatric Mental State Schedule (GMS))
- score of O1 or O2 on the organic disorder section.
References: Gurland et al., 1976ab ; Copeland et al., 1976; Copeland et al., 1992.

Subclinical cognitive decline
- score on the "Détérioration Cognitive Observé" questionnaire (DECO) below 38.
References: Ritchie et al., 1996; Ritchie et al., 1997.

Very mild cognitive decline (Global deterioration scale stage 2, GDS 2)
- report of decline in cognitive capacity in comparison to their abilities 5 or 10 years previously
- no memory impairment evident at clinical interview
References: Reisberg et al., 1982; Flicker et al., 1993.

Appendix B.1: Predicting cognitive outcome using the Preclinical AD Scale (PAS)

SUMMARY

OBJECTIVE: The Preclinical Alzheimer's disease Scale (PAS) is a multidisciplinary scale that aims to predict cognitive outcome in subjects with mild cognitive impairment. Aim of the study was to investigate the predictive accuracy of the PAS for cognitive outcome in subjects with mild cognitive impairment who visited a memory clinic and in subjects from the general population. We also investigated whether stepwise scoring of the PAS can reduce the number of subjects who need to undergo elaborate or expensive diagnostic procedures for predicting outcome.

METHODS: Two independent samples of non-demented subjects with mild cognitive impairments older than 50 years were selected from the Maastricht Memory Clinic (MMC). One sample consisted of subjects with a 2-year follow-up (N=27, MMC 2-year FU sample) and the second sample of subjects with a 5-year follow-up (N=69, MMC 5-year FU sample). Subjects from the general population were participants of the Amsterdam Study of the Elderly (AMSTEL) and were reassessed after 3 years. Outcome measure were Alzheimer's type dementia (AD) for the MMC 5-year FU sample, cognitive decline (AD or severe decline on cognitive tests) for the MMC 2-year FU sample, and dementia for the AMSTEL sample.

RESULTS: A score on the PAS ≥6 was associated with a high risk for AD, cognitive decline or dementia. The positive predictive value at this cut-off varied from 93% (MMC 5-year FU sample) to 64% (AMSTEL sample). The sensitivity at this cut-off varied from 80% (MMC 2-year FU sample) to 58% (AMSTEL sample). Stepwise scoring reduced the number of cognitive assessments by 40%, the number of assessments of medial temporal lobe atrophy by on average 70%, and the number of apoE genotypings by on average 80%.

CONCLUSION: The PAS seems to be useful to assess the risk of preclinical AD in subjects with mild cognitive impairment. Stepwise scoring with the PAS can reduce the number of elaborate or expensive diagnostic procedures.

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INTRODUCTION

Before subjects with Alzheimer's disease (AD) become demented, there is a long period in which they experience mild cognitive impairment. This period is called the preclinical phase of AD (Almkvist et al., 1998; Bondi et al., 1994; Grober et al., 1997; Hock, 1998; Jacobs et al., 1995; Linn et al., 1995). Mild cognitive impairment, however, is not specific for AD and can also result from normal aging or depression. Several criteria have been proposed in order to identify subjects with preclinical AD (Ritchie et al., 2000). The positive predictive value for future AD (or conversion rate) of these criteria is often below 60%, with a few exceptions (see section 1.2 and table 1.1). Moreover, the sensitivity of these criteria is below 50% (Bowen et al., 1997; Devanand et al., 1996; Devanand et al, 1997; Johansson et al., 199), with one exception (80%) (Cooper et al., 1996). The low specificity and sensitivity of these criteria are probably due to fact that only a limited number of variables were used to identify subjects with preclinical AD and because strict cut-off scores were used which excluded a substantial number of subjects with preclinical AD. In order to overcome these limitations we proposed the preclinical AD scale (PAS) (see section 9.3) (table B.1). The PAS combines six predictors of AD (age, MMSE score, functional impairment, cognitive test performance, medial temporal lobe atrophy, and apoE genotype) which were chosen on the basis of a review and meta-analysis of the literature (section 9.2). In this appendix, we validated the PAS in subjects with mild cognitive impairment and in subjects from the general population. We also investigated whether stepwise scoring of the PAS can reduce the number of subjects who need to undergo elaborate or expensive diagnostic procedures for predicting outcome. This stepwise scoring of the PAS reflects the decision-making process in clinical practice: the history and simple cognitive tests determine which other diagnostic tests would be useful for making a more accurate diagnosis. In appendix B.2 we describe how the cut-off points for each predictor variable were defined.

METHODS

Subjects

Subjects with mild cognitive impairment were selected from the follow-up study of the Maastricht Memory Clinic (MMC), a university-affiliated outpatient clinic for subjects with cognitive impairment (Verhey et al., 1993a). The follow-up study is a prospective studies of non-demented subjects older than 40 years who have cognitive impairment that is not due to any neurological disorder, any somatic disorder, or any major psychiatric disorder other than affective disorders (Visser et al, 2000a,b).

Table B.1 The Preclinical AD scale (PAS)*

		-1	0	1	2	Score	
A. Age		≤59	60-64	65-74	≥75		
B. MMSE							
Age <75 yr	Edu≤ 8 yr	-	≥27	25,26	≤24		
	Edu 8-14 yr	-	≥28	26,27	≤25		
	Edu≥14 yr	-	≥29	27,28	≤26		
Age ≥75 yr	Edu≤ 8 yr	-	≥26	24,25	≤23		
	Edu 8-14 yr	-	≥27	25,26	≤24		
	Edu≥14 yr	-	≥28	26,27	≤25		
C. Functional impairment							
a. GDS		-	GDS 1	GDS 2	GDS 3		Score after step 1 (A-C)
b. CDR[1] - Sum of Boxes		-	0-0.5	1-1.5	≥2		
- Final rating		-	CDR 0	-	CDR 0.5		
c. CAMDEX		-	-	-	Min Dem		
D. Neuropsychological tests[2]		Memory ≥50th perc	Other	1 impaired score	2 impaired scores		Score after step 2 (A-D)
E. MTL atrophy							
a. Qualitative rating[3]	Age<75 yr	-	0	1	2		Score after step 3 (A-E)
	Age ≥75 yr	0	1	2	≥3		
b.Volumetry[4]		≥ 66th perc	33th-66th perc	10th-33th perc	≤10th perc		
F. ApoE genotype		-	Other	e3e4	e4e4		
						TOTAL SCORE	

MMSE=Mini-Mental State Examination; Edu=Education; yr=years; GDS=Global Deterioration Scale; CDR=Clinical Dementia Rating scale; CAMDEX=Cambridge Mental Disorders of the Elderly Examination; Min Dem=minimal dementia; perc=percentile; MTL=Medial Temporal Lobe; ApoE=apolipoprotein E. 1 If the CDR is used, the scoring should be based on the sum of boxes; if this is not possible the final rating can be used. 2 Including 1 test that assesses delayed recall or learning and 1 to 3 tests from other cognitive domains (e.g., language, executive functions, abstract reasoning, visuoconstruction). Impairment is defined as a score below the 10th percentile or above the 90th percentile (speed related tasks). Percentile scores are corrected for age and, if possible, for sex and education as well. 3 Qualitative rating according to the method of (Scheltens et al., 1992) or (de Leon et al., 1993a) 4 Volumetry of hippocampus (preferred) or parahippocampal gyrus; percentiles scores are corrected for age and intracranial volume and, if possible, for sex as well.
*For scoring instructions see also appendix B.3. The PAS and scoring instructions can also be found at www-np.unimaas.nl/pas/

From the subjects who participated in the follow-up study we selected for the present study two samples. One sample consisted of all subjects older than 55 years with a

completed 5-year follow-up (N=69). This sample is referred to as the MMC 5-year-follow-up (FU) sample. Another sample consisted of all subjects older than 50 years in whom assessment of medial temporal lobe atrophy was performed (N=27) (see chapter 6). The follow-up in these subjects was on average 2 years (range 1-3 years). This sample is referred to as the MMC 2-year-FU sample. None of the subjects of the MMC 5-year FU sample were included in the MMC 2-year FU sample.

Subjects from the general population were selected from a cohort of 527 subjects of the Amsterdam Study of the Elderly (AMSTEL) who participated in a 3-year follow-up study. The AMSTEL study is a two-stage population-based study of mental functioning in 4051 non-institutionalized people aged 65-85 years living in Amsterdam, The Netherlands (Launer et al., 1993). The selection procedure and the response rate of subjects for the 3-year follow-up study are described in detail elsewhere (Jonker et al., 1998). Subjects with a stroke or Parkinson's disease were excluded. We selected all subjects who completed the 3-year follow-up (N=237).

The baseline characteristics of the subjects are shown in table B.2.

Table B.2 Baseline characteristics

Study	MMC 5-year FU	MMC 2-year FU	AMSTEL
Number of subjects	69	27	237
Follow-up	5 years	2 years	3 years
Age (SD) (range)	64.9 (7.2) (55-81)	65.4 (9.5) (52-87)	73.7 (5.6) (65-84)
Sex (% female)	47%	44%	59%
Education (yr) (SD)	9.9 (3.2)	10.7 (3.2)	7.9 (2.5)
MMSE score (SD)	27.8 (2.0)	27.6 (1.9)	26.5 (3.1)

PAS scoring

Functional impairment was scored in the subjects from the MMC with the GDS and in subjects from the AMSTEL study with the CAMDEX criteria of minimal dementia. The neuropsychological tests in the MMC samples were delayed recall from the Auditory Verbal Learning Test (Brand et al., 1985; Lezak, 1995), time to complete the Memory Scanning Task Letter 1 (Brand et al., 1987), time to complete card 3 of the Stroop Color Word Test (Stroop, 1935), and verbal fluency (the ability to name as many professions/trades as possible within 1 minute). The neuropsychological tests in the AMSTEL study were the CAMCOG memory subscale, the CAMCOG language subscale, and the other items of the CAMCOG including measures of orientation in time and place, attention, visual and tactile perception, praxis, calculation, and verbal abstraction. Medial temporal lobe atrophy was assessed in the MMC

2-year FU sample by volumetry (chapter 6). In the AMSTEL study, medial temporal lobe atrophy was assessed in a subsample of 22 subjects (9.3%) using a qualitative rating method (Scheltens et al., 1992). The subjects from the AMSTEL study in whom medial temporal lobe atrophy was assessed were more often demented at follow-up ($p<0.01$) than the subjects in whom medial temporal lobe atrophy was not assessed. Medial temporal lobe atrophy was not assessed in the MMC 5-year FU sample. Apolipoprotein E (apoE) genotyping was performed in all subjects from the AMSTEL study, in a subsample of 43 subjects (63%) from the MMC 5-year FU sample, and in a subsample of 23 subjects (85%) from the MMC 2-year FU sample. Subjects from the MMC samples with apoE genotyping tended to have AD or cognitive decline (see below) at follow-up ($p=0.13$) less often than subjects without apoE genotyping. All subjects with a missing PAS item were given a score of zero on that item.

Outcome measures

Outcome in the MMC 5-year FU sample was defined as AD according to the DSM-IV (APA, 1994) and NINCDS-ADRDA criteria (McKhann et al., 1984). The main outcome measure in the MMC 2-year FU sample was cognitive decline because the follow-up was only 2 years (chapter 6). The diagnosis of cognitive decline at follow-up was made when subjects had dementia and AD according to the DSM-IV (APA, 1994) and NINCDS-ADRDA criteria (McKhann et al., 1984) or when severe cognitive decline without dementia was present. Cognitive decline in non-demented subjects was defined as a negative change of 4 points or more on the MMSE (Schmand et al., 1995; Tangalos et al., 1996) or a negative change of more than 1 standard deviation on the delayed recall task such that the second score on the delayed recall task was below the 10th percentile. The main outcome measure in the AMSTEL population was dementia according to the DSM-IIIR (APA, 1987) criteria.

RESULTS

Twenty-three of 69 subjects (33%) of the MMC 5-year FU sample had AD at follow-up. Ten of 27 subjects (37%) from the MMC 2-year FU sample had cognitive decline at follow-up (seven subjects had AD at follow-up and three subjects had cognitive decline but were not demented at follow-up). Thirty-one of 237 subjects (13%) from the AMSTEL study had dementia at follow-up. Twenty-five of these subjects (81%) had AD-type dementia.

The total PAS score and the score on the individual PAS items according to outcome are shown in tables B.3 and B.4, respectively. Subjects in the MMC 2-year FU sample with cognitive decline but no dementia at follow-up had PAS

Table B.3 PAS score in MMC, and AMSTEL

	MMC 5-year FU		MMC 2-year FU		AMSTEL	
	No AD at FU	AD at FU	No CD at FU	CD at FU	Not demented at FU	Demented at FU
≤ 0	8	0	2	0	38	1
1	8	1	6	0	60	0
2	10	1	2	0	46	0
3	8	0	3	1	22	1
4	7	2	0	0	17	4
5	4	5	3	1	11	4
6	1	4	1	3	9	2
7	0	6	0	4	0	3
8	0	2	0	1	2	7
9	0	1	0	0	0	4
≥10	0	0	0	0	1	3
Total	46	23	17	10	206	31

AD=Alzheimer's Disease; CD=Cognitive decline (AD or decline MMSE≥4 points or decline delayed recall≥1SD).

Table B.4 PAS score on individual items according to outcome

		MMC 5-year FU		MMC 2-year FU		AMSTEL	
		No AD at FU N=46	AD at FU N=23	No CD at FU N=17	CD at FU N=10	Not demented at FU N=206	Demented at FU N=31
A. Age	-1	19	2	8	1	0	0
	0	16	2	2	0	0	0
	1	10	11	7	4	121	4
	2	1	8	0	5	85	27
B. MMSE	0	37	9	12	7	129	8
	1	8	8	3	1	39	5
	2	1	6	2	2	38	18
C. Functional impairment	0	0	0	0	0	196	8
	1	27	4	10	4	0	0
	2	19	19	7	6	10	23
D. NP tests	-1	13	1	5	0	110	1
	0	9	1	5	2	51	2
	1	13	4	4	4	29	15
	2	11	17	3	4	16	13
E. MTL atrophy	-1	0	0	6	0	4	0
	0	46 (46)	23 (23)	8	3	200 (192)	28 (13)
	1	0	0	2	3	2	2
	2	0	0	1	4	0	1
F. ApoE genotype	0	34 (14)	13 (12)	12 (1)	5 (3)	167	17
	1	11	9	4	5	36	12
	2	1	1	1	0	3	2

In brackets are the number of subjects with a score of 0 who had missing data.

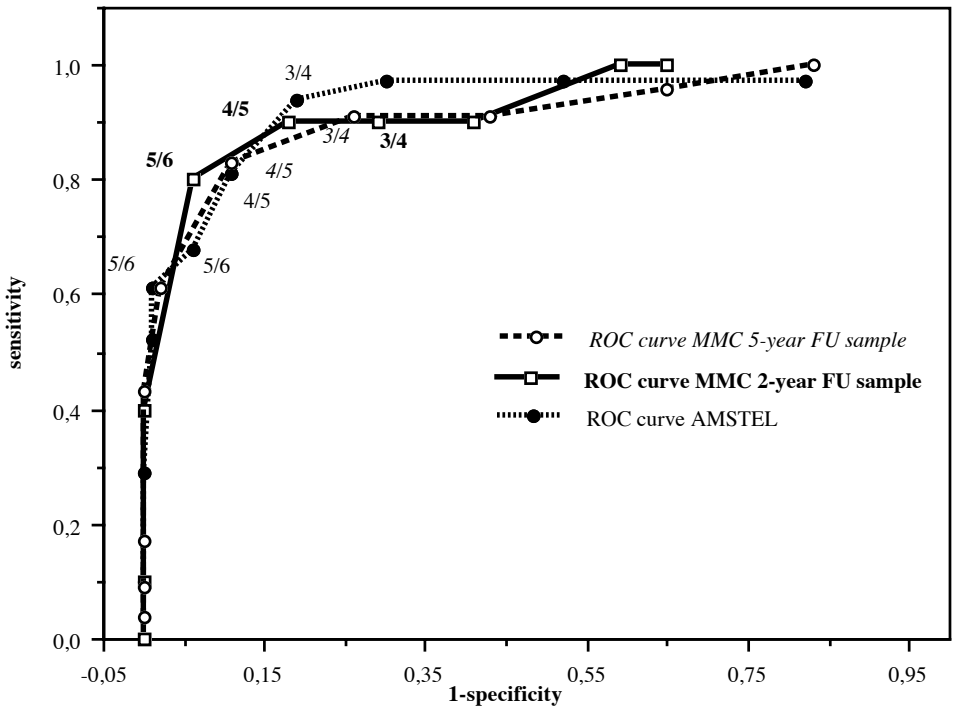

Figure B.1 ROC curve PAS scores in subjects from the Maastricht Memory Clinic (MMC) and AMSTEL study

Table B.5 Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for outcome for different PAS cut-off scores

Study	Cut-off	Outcome	Sensitivity	Specificity	PPV	NPV
MMC 5-year FU	4/5	AD	74%	96%	81%	91%
MMC 5-year FU	5/6	AD	61%	98%	93%	83%
MMC 5-year FU	6/7	AD	43%	100%	100%	78%
MMC 2-year FU	4/5	CD	90%	82%	75%	93%
MMC 2-year FU	5/6	CD	80%	94%	89%	88%
MMC 2-year FU	6/7	CD	40%	100%	100%	74%
AMSTEL	4/5	Dementia	87%	85%	40%	97%
AMSTEL	5/6	Dementia	58%	99%	64%	95%
AMSTEL	6/7	Dementia	42%	99%	86%	94%

AD=Alzheimer's Disease; CD=Cognitive decline (AD or decline MMSE≥4 points or decline on delayed recall≥1SD).

scores of 3, 6, and 7. Subjects with no-AD type dementia in the AMSTEL sample had PAS scores of 5, 6, 7 (N=2), 8, and 9. The ROC curve of the total PAS score is shown in figure B.1. A cut-off between 4 and 5 was best for distinguishing between subjects with and without AD at follow-up in the MMC 5-year FU sample and between subjects with and without dementia at follow-up in the sample of the AMSTEL study. A cut-off between 5 and 6 was best for distinguishing between subjects with and without cognitive decline in the MMC 2-year FU sample.

The sensitivity, specificity, positive predictive value, and negative predictive value of the cut-off values 4/5, 5/6, and 6/7 are shown in table B.5.

The decision rules for the stepwise scoring of the PAS were constructed in order to identify, after each step, subjects with a low risk, a borderline risk, and a high risk of AD. Only subjects with a borderline risk proceeded to the next step. Subjects with a low risk for AD were subjects who had a total PAS score ≤4. Subjects with a high risk for AD were subjects with a total PAS score ≥6. Thus, all subjects who dropped out after step 1, 2, or 3 because of low scores had a total PAS score ≤4. Similarly, all subjects that dropped out after step 1, 2, or 3 because of high scores had a total PAS score ≥6. The first step included items that could be easily scored (e.g., age, MMSE, and functional impairment). The second step consisted of the item cognitive functioning, the third step of the item medial temporal lobe atrophy, and the fourth step of the item apoE genotyping. The decision rules are shown in table B.6 and the results of the stepwise scoring are shown in table B.7 a-c. Stepwise scoring reduced the number of cognitive assessments by 40% (all samples), the number of assessments of medial temporal lobe atrophy by 63% (MMC 2-year FU sample) to 88% (AMSTEL), and the number of apoE genotypings by 72% (MMC 5-year FU sample) to 88% (AMSTEL).

Table B.6 Stepwise scoring of the PAS

		Low risk preclinical AD	Borderline risk preclinical AD	High risk preclinical AD
Step1	Age, MMSE, functional impairment	≤1	2-5	≥6
Step 2	Cognitive performance	≤3	4-5	≥6
Step 3	MTL atrophy	≤3	4-5	≥6
Step 4	ApoE genotyping	≤4	5	≥6

Only subjects with a borderline risk proceed to the next step.

Table B.7.a Stepwise scoring of PAS in MMC 5-year FU sample

	Low-risk score		Borderline-risk score		High-risk score	
	No AD at FU	AD at FU	No AD at FU	AD at FU	No AD at FU	AD at FU
Step 1	24	1	22	20	0	2
Step 2	12 (36)	1 (2)	9	10	1 (1)	9 (11)
Step 3*	-	-	-	-	-	-
Step 4	5 (41)	2 (4)	4	5	0 (1)	3 (14)
Total PAS score	41	4	4	5	1	14

Indicated are number of subjects with a low-, borderline-, or high-risk score after each step. The cumulative number of subjects is given in parentheses. A low-risk score is ≤1 after step 1, ≤3 after step 2, and ≤4 after step 3 and with full score. An borderline-risk score is 2-5 after step 1, 4-5 after step 2, and 5 after step 3 and with full score. A high-risk score is ≥6 after all steps. Dem=Dementia; AD=Alzheimer's Disease; CD=Cognitive decline (AD or decline on MMSE≥4 points or on delayed recall≥1SD); FU= follow-up. *Medial temporal lobe atrophy (step 3) was not determined in this sample.

Table B.7.b Stepwise scoring of PAS in MMC 2-year FU sample

	Low-risk score		Borderline-risk score		High-risk score	
	No CD at FU	CD at FU	No CD at FU	CD at FU	No CD at FU	CD at FU
Step 1	9	1	8	8	0	1
Step 2	3 (12)	0 (1)	4	6	1 (1)	2 (3)
Step 3	1 (13)	0 (1)	3	2	0 (1)	4 (7)
Step 4	0 (13)	0 (1)	3	1	0 (1)	1 (8)
Total PAS score	13	1	3	1	1	8

Legend see table B.7.a

Table B.7.c Stepwise scoring of PAS in AMSTEL population

	Low-risk score		Borderline-risk score		High-risk score	
	No Dem at FU	Dem at FU	No Dem at FU	Dem at FU	No Dem at FU	Dem at FU
Step 1	76	1	124	17	5	13
Step 2	100 (176)	3 (4)	21	7	4 (9)	7 (20)
Step 3*	0 (176)	0 (4)	21	7	0 (9)	0 (20)
Step 4	7 (183)	2 (6)	11	4	3 (12)	1 (21)
Total PAS score	183	6	11	4	12	21

Legend see table B.7.a. *Medial temporal lobe atrophy was assessed in none of the subjects with a borderline-risk score after step 2.

DISCUSSION

The PAS seems to be useful to assess the risk of preclinical AD in subjects with mild cognitive impairment. Stepwise scoring with the PAS can reduce the number of elaborate or expensive diagnostic procedures.

The best cut-off score in the MMC 2-year FU sample was one point higher than in the MMC 5-year FU sample and the AMSTEL sample. This is probably because medial temporal lobe atrophy was scored in the MMC 2-year FU sample but not in the MMC 5-year FU sample and only in 10% of the AMSTEL sample. The scoring of medial temporal lobe atrophy probably also explained why the sensitivity at the cut-off 5/6 was higher in the MMC 2-year FU sample than in the MMC 5-year FU sample and the AMSTEL sample. We have shown before that scoring of medial temporal lobe atrophy increases the sensitivity to detect subjects with preclinical AD (chapters 5 and 6). The positive predictive value was lower in the AMSTEL sample than it was in the samples from the MMC. Since the ROC curve of the PAS score in the AMSTEL study was similar to that of the MMC 5-year FU sample, it seems likely that the lower positive predictive value resulted from the lower incidence of dementia in the AMSTEL study (13% versus 33% in the MMC 5-year FU sample). Alternatively, non-demented subjects with high PAS scores in the AMSTEL sample may have had these high scores for reasons that were not related to preclinical AD, such as sensory impairments or medical conditions causing cognitive impairment, that were not excluded at baseline. Subjects with a high PAS score may also develop non-AD type dementia, as was shown in the AMSTEL sample. It should be noted that the AMSTEL study had only a few exclusion criteria at baseline. The chance of non-AD type dementia will probably be lower if strict somatic and neurological exclusion criteria are applied.

Limitations of this validation study were that the items and the cut-off scores of the items were partly based on the studies in which we validated the PAS. However, the variables of the PAS were also selected on the basis of a meta-analysis that included 15 other studies (see 9.2). In addition, as is shown in appendix B.2, most cut-off scores were based on a review of the literature or defined a priori. Nevertheless, the PAS should also be validated in other settings. Another limitation is that not all PAS items were scored in all subjects. The cut-off point that can best distinguish between subjects with and without AD may be different if all items are scored. In addition, the fact that not all PAS items were scored in all subjects may have underestimated the predictive accuracy because demented subjects with missing item scores had lower PAS scores than demented subjects without missing item scores, but this difference in PAS scores was not seen in non-demented subjects with or without missing item scores (data not shown).

The PAS has several advantages compared to other approaches that aim to identify subjects with preclinical AD. First, the PAS has no strict inclusion criteria. This is important because there is a large heterogeneity in the presentation of preclinical AD. Previous studies have shown that a substantial number of subjects with preclinical AD have no memory impairments (Grober et al., 2000; Tuokko et al., 1991), have only very mild functional impairments (Visser et al., 2000b), or have only very mild medial temporal lobe atrophy (Jack et al., 1999; Visser et al., 1999b). The PAS will therefore have a higher sensitivity for identifying subjects with preclinical AD than criteria that require a certain degree of cognitive and/or functional impairment (Levy, 1994; Petersen et al., 1995; Reisberg et al., 1982; Roth et al., 1986; Rubin et al., 1989b; Smith et al., 1996). Second, the PAS combines six predictor variables. This will result in a higher sensitivity and specificity than criteria that use only one or two variables (Cooper et al., 1996; de Leon et al., 1993a; Devanand et al., 1997; Johnson et al., 1998; O'Connor et al., 1991; Rubin et al., 1989b; Visser et al., 2000b). Third, it can be used in a stepwise fashion which may reduce the number of subjects requiring elaborate or expensive diagnostic procedures. Finally, the PAS can be easily implemented in clinical practice and some variables can be assessed in several ways, so as to allow for the variety in diagnostic procedures that are in use.

One approach to identify subjects with preclinical AD which has recently received much attention is the concept of Mild Cognitive Impairment (MCI) according to the Mayo group (Jack et al., 1999; Petersen et al., 1995; Petersen et al., 1999; Smith et al., 1996). The criteria for MCI include memory complaints, normal general cognitive function, normal activities of daily living, absence of dementia, objective memory impairment or impairment in one other area of cognitive function as evidenced by scores >1.5 SD below age appropriate norms, age 60 through 89 years, and a score on the Clinical Dementia Rating scale of 0.5. Some of the variables that are used to make the diagnosis of MCI are also included in the first two steps of the PAS (namely age, MMSE score, degree of functional impairment, and performance on cognitive tests). The PAS scores after step 2 of subjects meeting the criteria of MCI can vary from 3 (age between 60 and 65 years, high MMSE score, CDR=0.5, one impairment in cognitive functioning), which indicates a low risk for AD, to 8 (age ≥75 years, low MMSE score, CDR=0.5, two impairments in cognitive functioning), which indicates a high risk for AD (table B.6). This means that the PAS can be used to increase the predictive accuracy of subjects fulfilling the criteria of MCI.

The clinical relevance of the PAS is that it can be used to select subjects with mild cognitive impairment who should remain under medical supervision, for example, if subjects have a PAS score ≥5. The stepwise scoring system proposed in

table B.6 can be used to guide the diagnostic process and to select subjects who would benefit most from expensive or elaborate diagnostic procedures. The PAS can also be used to select subjects for pharmaceutical or psychosocial intervention studies, for example, if subjects have a PAS score ≥6. However, before including subjects in trials, this cut-off point should be first validated in other samples. It would be of interest to investigate whether the PAS can be used to monitor the course of mild cognitive impairment even though it was not designed for this purpose. Finally, it should be investigated whether step 1 of the PAS can be used to select subjects in primary health care for referral to secondary health care or to select subjects for a more extensive work-up in epidemiological studies. Issues that need to be investigated further are the cut-off scores in relation to the number of items scored and the setting in which the PAS is applied. In addition, the correlation between the items should be investigated and whether items are scored in equivalent ways (e.g., volumetry versus qualitative rating). The PAS may be extended if other predictors of AD become available.

Appendix B.2: Construction of the Preclinical AD Scale (PAS)

In section 9.3 we proposed the Preclinical AD Scale (PAS) as instrument to assess the risk of AD in subjects with mild cognitive impairment. The items of the PAS were selected on the basis of a review and meta-analysis of the literature (see section 9.2). We will now explain how we arrived at the cut-off score for each item.

A. Age
The incidence of AD in the general population increases with age (Ott et al., 1998). The incidence of AD in subjects younger than 60 years is very low in both epidemiological settings (Ott et al., 1998; Rocca et al., 1986) and in clinical settings (figure 9.1), and therefore subjects younger than 60 are given a score of -1. The risk for AD increases steeply after age 75 in both epidemiological settings (Geerlings et al., 1999; Ott et al., 1998; Rocca et al., 1986) and in clinical settings (figure 9.1), and for this reason subjects older than 75 years are given a score of 2. Epidemiological data show an increase in incidence of AD after age 70 (Ott et al., 1998) but data from the Maastricht Memory Clinic show an increase in incidence of AD already after age 65 (figure 9.1). Because the data of the Maastricht Memory Clinic are based on subjects with mild cognitive impairment, we chose to give subjects between 65 and 75 years a score of 1.

B. MMSE
A MMSE score ≥28 is generally considered a normal score (e.g., Golomb et al. (1993)) and for this reason a MMSE score ≥28 is given a score of 0. A MMSE score ≤25 is associated with a high risk for dementia in the general population and for this reason these scores are given a score of 2 (Braekhus et al., 1995). The remaining scores (26 and 27) are given a score of 1. Since the MMSE score correlates with age and education, it should be corrected for these variables (Crum et al., 1993; Tombaugh et al., 1992). For simplicity of scoring, we dichotomized the effect of age and made the cut-off scores 1 point lower in subjects older than 75 years (Crum et al., 1993). The effect of education was trichotomized (Crum et al., 1993; Maastricht Aging Study, unpublished data). The cut-off score for subjects with a high level of education (≥14 years) was made 1 point higher and the cut-off scores for subjects with a low level of education (≤8 years) was made 1 point lower than the proposed cut-off scores after correction for age.

C. Functional impairment
Global Deterioration Scale (GDS) (Reisberg et al., 1982) stage 3, the Clinical Dementia Rating scale (CDR) (Hughes et al., 1982) score of 0.5, and the diagnosis of minimal dementia (Roth et al., 1986) are given a score of 2 because they are

associated with a high risk of AD (Cooper et al., 1996; de Leon et al., 1993a; Devanand et al., 1997; O'Connor et al., 1991; Reisberg et al., 1986; Rubin et al., 1989b). Memory complaints (which is equivalent to GDS stage 2) are less strongly but still significantly associated with AD and is therefore given a score of 1 (Geerlings et al., 1999; Schmand et al., 1996; Schofield et al., 1997). The cut-off scores for CDR Sum of Boxes are based on Daly et al. (2000) and Rubin et al. (1989).

D. Neuropsychological tests

Impairment is defined as a score below the 10th percentile (or above the 90th percentile for speed related tests) according to age-, sex-, and education-corrected norms. If performance is impaired in one test a score of 1 is given, if performance is impaired in two tests a score of 2 is given, and if performance is not impaired in any test a score of 0 is given. Because memory impairment is the most common symptom in the early stage of AD (Almkvist et al., 1998; Fox et al., 1998; Newman et al., 1994; Nielsen et al., 1999; Small et al., 1997a), a score of -1 is given if memory performance is above average regardless of the score on other tests.

E. Medial temporal lobe atrophy

Medial temporal lobe atrophy can be assessed by either volumetry of the hippocampus (both left and right side) or qualitatively. The PAS rating of volume is based on percentile scores. Atrophy is defined as a volume below the 10th percentile (z-score ≤-1.28) and is given a score of 2. If the volume is in the highest tertile (z-score >0.44), a score of -1 is given, if the volume is in the middle tertile (z-score 0.44-0.44) a score of 0 is given, and if the volume is in the lowest tertile but above the 10th percentile (-1.28< z-score ≤-0.44) a score of 1 is given. Qualitative rating should be performed according to the method described by Scheltens et al. (1992) or de Leon et al. (1993a). Both sides should be rated and the highest rating should be used for the PAS scoring. Both authors take a qualitative rating ≥2 as an indicator of atrophy and therefore a rating ≥2 is given a score of 2. A rating of 0 is given a score of 0 and a rating of 1 a score of 1. Since the qualitative rating correlates with age (de Leon et al., 1997; Scheltens et al., 1992) the cut-off scores for subjects older than 75 years are 1 point lower. Thus, in subjects older than 75 years a rating of 0 is given a score of -1, a rating of 1 a score of 0, a score of 2 a rating of 1, and a rating of 3 or higher a score of 2.

F. Apolipoprotein E genotype

Carriers of the apolipoprotein (apoE) e3e4 genotype are given a score of 1. Carriers of the apoE e4e4 genotype are given a score of 2 because the risk of AD is much higher in homozygotes than in heterozygotes (Slooter et al., 1998). Data on whether subjects with the apoE-e2e4 genotype have an increased risk of AD are inconclusive and therefore this genotype is given a score of 0.

Appendix B.3: Instructions how to score the Preclinical AD Scale (PAS)

General

The PAS should not be used in subjects who have mild cognitive impairments in relation to cerebro-vascular events, neurodegenerative diseases (e.g., Parkinson's disease), brain neoplasm, head trauma, drug intoxication, alcohol abuse, unregulated endocrine disorders (e.g., hypothyroid or hyperthyroid function, diabetes mellitus), vitamin deficiency, or major psychiatric disorders (except mild to moderate depressive disorders)

If a item can not be scored, the score on that item should be 0.

A. Age

No comments.

B. MMSE

If the level of education is not available score if the subject had 8 to 14 years of education.

C. Functional impairment

For scoring instructions of the Clinical Dementia Rating scale (CDR) see Hughes et al. (1982) and Morris et al. (1993), the Global Deterioration Scale (GDS) see Reisberg et al. (1982), and Minimal Dementia see Roth et al. (1986). The CDR item should preferably be scored on the basis of the Sum of Boxes score. If this sum score is not available, the overall rating can be used. If the CDR, GDS, or criteria of 'minimal dementia' can not be scored, subjects with referral to a memory or dementia clinic should be given a score of 1.

D. Neuropsychological tests

Impairment is defined as a score below the 10th percentile (or above the 90th percentile for speed related tests) according to age-, sex-, and education-corrected norms. If the subject can not complete the test due to cognitive problems, the performance should be considered as impaired. If performance is impaired in one test a score of 1 is given, if performance is impaired in two tests a score of 2 is given, and if performance is not impaired in any test a score of 0 is given. A score of -1 is given if memory performance is above average regardless of the score on other tests. The neuropsychological assessment should include two to four tests (preferably three or four). One test should assess memory function and the other tests should assess

other cognitive domains. If two tests are used for the same cognitive domains, the scores for these tests should not correlate more than 0.50 with each other. Preferred memory tests are the delayed recall or learning measure of the Auditory Verbal Learning Test (Brand et al., 1985; Lezak, 1995), Buschke Selective Reminding Task (Buschke, 1984; Buschke et al., 1974), or California Verbal Learning Task (Bondi et al., 1994), or the memory subscale of the CAMCOG (Roth et al., 1986). Recommended other cognitive domains are executive functions (preferred tests: Stroop Color Word Test card 3 (Stroop, 1935), Digit Symbol Substitution test (Wechsler, 1955), Trail Making Test B (Reitan, 1958), and Memory Scanning Task (Brand et al., 1987)), language (preferred tests: Boston Naming Test, category word fluency (Lezak, 1995), and the language subscale of the CAMCOG (Roth et al., 1986)), abstract reasoning (preferred test: WAIS similarities (Wechsler, 1955)), and visuoconstruction (preferred tests: Rosen Drawing Test, Rey-Osterrieth figure, and honeycomb figure (Lezak, 1995))

E. Medial temporal lobe atrophy

Medial temporal lobe atrophy can be assessed by either volumetry of the hippocampus (both left and right side) or qualitatively. The PAS rating of volume is based on percentile scores. These percentile scores should be based on data for a reference population of healthy subjects in order to correct for intracranial volume, age, and sex. Qualitative rating should be performed according to the method described by Scheltens et al. (1992) or de Leon et al. (1993a). Both sides should be rated and the highest rating should be used for the PAS scoring. In the method of Scheltens et al., atrophy of the medial temporal lobe is rated on a coronal MRI scan that is made perpendicular to the longitudinal axis of the hippocampus or parallel to the brain stem (Scheltens et al., 1992). In the method of de Leon et al., the presence of perihippocampal cerebrospinal fluid is rated on a oblique axonal scan (de Leon et al., 1993a). This method has the advantage that it can be used on both MRI and CT scans.

F. Apolipoprotein E genotype

The apoE genotype can be either determined by genotyping (e.g., Slooter et al., 1998); Wenham et al., 1991) or phenotyping (e.g., Havekes et al., 1987).

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