Development of Screening Guidelines and Clinical Criteria for Predementia Alzheimer’s Disease

The DESCRIPA Study


a Department of Psychiatry and Neuropsychology, University of Maastricht, Maastricht, b Department of Neurology, Alzheimer Centre, VU Medical Centre, Amsterdam, and c Department of Geriatrics, Radboud University Medical Centre, Nijmegen, The Netherlands; d Fundació ACE, Barcelona, Spain; e Kingshill Research Centre, Swindon, f The Research Institute for the Care of Older People, Bath, and g Department of Care of Elderly, University of Bristol, Fishchurch Hospital, Bristol, UK; h Institute Born Bunge, ZNA Middelheim, University of Antwerp, Antwerp, Belgium; i LENITEM, IRCCS Fatebenefratelli, Brescia, and Clinical Neurophysiology Service Unit, Department of Endocrinological and Metabolic Sciences, University of Genoa, Genoa, Italy; k Division of Geriatric Psychiatry, Zentralinstitut für Seelische Gesundheit, University of Heidelberg, Mannheim, and l Alzheimer Memorial Centre and Geriatric Psychiatry Branch, Dementia and Neuroimaging Section Department of Psychiatry, Ludwig-Maximilian University Munich, Munich, Germany; m Discipline of Psychiatry, School of Medicine and Trinity College Institute of Neuroscience, Trinity College Dublin, Trinity Centre for Health Sciences, and n The Adelaide and Meath Hospital Incorporating The National Children’s Hospital, Dublin, Ireland; o Clinical Memory Research Unit, Department of Clinical Sciences Malmö Lund University, Lund, and p NVS Department, Karolinska Institutet, Karolinska University Hospital, Huddinge, Sweden; q Department of Internal Medicine and Clinical Gerontology, Toulouse University Hospital, Toulouse, r Department of Geriatrics, Hospital Broca, Paris, and t Institute National de la Santé et de la Recherche Medicinale INSERM U 888, Montpellier, France; u Department of Neurology, University and University Hospital of Kuopio, Kuopio, Finland; v ‘Carol Davila’ University of Medicine and Pharmacy, Bucharest, Romania; w Aristotle University of Thessaloniki, Memory and Dementia Centre, G. Papanicolaou General Hospital, Thessaloniki, Greece

Key Words
Alzheimer’s disease, diagnosis • Mild cognitive impairment, elderly • Study, longitudinal cohort, observational, multicentre

Abstract
Background: There is an urgent need to identify subjects with Alzheimer’s disease (AD) in the predementia phase, but validated diagnostic approaches are currently lacking. In this paper, we present the background, design and methods of a study, which aims to develop clinical criteria for pre-dementia AD. We also present baseline characteristics of the subjects included. The study was part of the multicentre DESCRIPA project, which is being conducted within the network of the European Alzheimer’s Disease Consortium.

Methods: Clinical criteria will be based on a prospective cohort study of non-demented subjects older than 55 years and referred to a memory clinic. At baseline, a number of markers and risk factors for AD were collected, including demographic variables, measures of performance in activities of daily living, cognitive, neuroimaging and genetic markers,
and serum and cerebrospinal fluid markers. Subjects will be reassessed annually for 2–3 years, and we will evaluate which combination of variables best predicts AD-type dementia at follow-up. **Results:** Between 2003 and 2005, 881 subjects were included from 20 memory clinics. Subjects were on average 70.3 years old, and had 10.4 years of education. The average score on the Mini-Mental State Examination was 27.4.

**Introduction**

Alzheimer’s disease (AD) is one of the most common neurodegenerative disorders, with a prevalence rising from 0.2% in subjects aged between 55 and 65 years to 27% in subjects older than 85 years [1]. According to the current diagnostic criteria for AD, the diagnosis can only be made when a subject is demented [2]. There is an urgent need to diagnose AD in the predementia phase [3]. This will allow physicians to start interventions that may improve cognition, or prevent the progression of the disease at an earlier stage than is currently possible.

There are as yet no evidence-based criteria for predementia AD. A large number of predictors or risk factors for AD in non-demented subjects have been identified, but none of them can individually diagnose predementia AD with sufficiently high sensitivity and specificity [4]. There is evidence that a combination of variables may diagnose predementia AD with good accuracy [5–7]. A recent proposal for research criteria for AD suggested using a combination of variables to diagnose AD in non-demented subjects [3]. However, these approaches need to be validated and could be improved further.

In order to investigate which combination of variables can best identify subjects with predementia AD, the ‘Development of Screening Guidelines and Clinical Criteria for Predementia AD’ (DESCRIPA) study was set up. The study consists of a clinical and population-based part. The objective of the clinical part is to develop criteria for the diagnosis of predementia AD that can be used in clinical practice. The aim of the population-based part is to develop screening guidelines for predementia AD in the general population. In this paper, we will describe the outline of the clinical part of the DESCRIPA study. We will also present baseline characteristics of the subjects included in the study.

**Methods**

**General Outline**

The clinical part of the DESCRIPA study is a prospective cohort study. Non-demented subjects with cognitive complaints are to be followed for 2–3 years. At baseline, variables were collected that could be markers of predementia AD, and we will investigate which combination of variables can best predict conversion to AD-type dementia at follow-up. The design took into account that the study should have sufficient statistical power to test a combination of predictor variables, and that the criteria for predementia AD should allow easy implementation in clinical practice. For the latter reason, the data collection closely followed the routine clinical practice in each centre and we allowed variability between centres in cognitive tests, clinical rating scales and neuroimaging tools, as described below. Centres were selected from the European Alzheimer’s Disease Consortium (EADC), and included 20 outpatient clinics from 11 European countries. Each of these centres held a memory clinic specialized in the diagnosis and treatment of memory disorders. The memory clinics were located in departments of psychiatry (5 centres), neurology (7 centres), and geriatrics (8 centres; see appendix 1 for a list of the participating centres). The European Commission funded the study as a concerted action within the 5th Framework Programme, and provided support for coordination, pooling and data analysis from 1 January 2003 to 1 July 2007, but not for data collection. Subjects were enrolled between 1 March 2003 and 1 March 2005. Each centre collected a minimal dataset, while other parts of the study were optional depending on local clinical practice and local funding possibilities for data collection.

**Subjects**

Inclusion and exclusion criteria were chosen in order to select a population in which criteria for predementia AD would be most useful. Inclusion criteria were new referral to a memory clinic because of a cognitive complaint and an age of 55 years or over. Exclusion criteria were dementia according to DSM-IV criteria at baseline, referral because of a high family risk in otherwise normal subjects, history of schizophrenia, bipolar disorders or recurrent psychotic disorders, and any somatic, psychiatric or neurological disorder that may have caused the cognitive impairment (see appendix 2 for overview of inclusion and exclusion criteria). In cases where doubt existed as to whether the cognitive impairment could be attributed to a specific cause, subjects were included in the study. All centres enrolled consecutive newly referred patients, while 3 centres also retrospectively enrolled subjects that were selected from a database.

**Informed Consent Procedure**

The local Medical Ethical Committee in each centre approved the study. Subjects were asked to provide a written informed consent except in 2 centres, in which the study was considered to be regular patient care and no specific consent was needed.

**Baseline Assessment**

At the baseline assessment, data were collected on variables that were tested as potential markers of predementia AD, variables needed for the characterization of subjects and variables needed for diagnostic purposes. In 13 centres, the baseline assessment followed routine clinical practice. Four centres extended or...
changed part of the routine assessment with additional assessments and tests especially for the DESCRIPA study. In 3 centres, another study on markers of predementia AD was conducted at the same time and the baseline assessment in these centres followed the protocol of those studies. All centres collected data on demographics, cognitive and non-cognitive symptoms, medical history, functional impairment and cognitive performance. In addition, a brief physical examination was undertaken. In a subset of centres, data were collected on social and cognitive activities, neuroimaging, quantitative electroencephalography (Q-EEG), genetic risk factors, markers in serum and plasma, and markers in cerebrospinal fluid (CSF). The baseline assessment included the following variables.

Demographic Variables
Demographic data included age, gender, level of education and level of occupational achievement.

Cognitive and Non-Cognitive Symptoms
Data were collected on the start of the symptoms, course of the symptoms, main complaints and non-cognitive symptoms.

Family History
Data were collected on the number of first-degree and second-degree relatives with dementia and vascular disorders.

Medical History
Data were collected on conditions that may be associated with cognitive impairments such as vascular disorders and vascular risk factors, psychiatric disorders, endocrine disorders and severe somatic disorders. Data were provided by the patient and/or caregiver or extracted from medical files if available.

Medications
All medications taken were recorded and classified in a number of categories.

Smoking and Alcohol Intake
Smoking and alcohol intake measurements were based on the interview with patient and caregiver.

Social and Physical Activities
In all but 2 centres, data were collected on cognitive, physical and social activities. Cognitive activities were assessed using a 7-item scale [8], physical activities with a 5-item scale, hobbies and social activities (e.g. member of a club, volunteer work in church) were assessed using structured questions. For each activity, the frequency and the average number of hours involved per week was rated.

Physical Examination
Data were collected on weight, height, blood pressure, primitive reflexes, extrapyramidal symptoms, gait disturbances and other focal neurological signs. Assessments were undertaken according to local practice.

Short Cognitive Screening Tests
The Mini-Mental State examination was administered in all centres [9]. A clock-drawing test was done in all but 1 centre.

Rating Scales for Functional Impairments
The effect of cognitive impairment on global functioning was measured with the Clinical Dementia Rating Scale (CDR, 18 centres), the Global Deterioration Scale (GDS, 7 centres) and the Cognitive Impairment Rating Scale functional part (CIRS-FP, 17 centres). The CDR rating was based on a regular clinical interview in 11 centres, a structured interview in 4 centres, and either a regular or structured interview in 3 centres. The CIRS-FP assesses effect of cognitive impairment on daily functioning in the domains of memory, language, executive function/problem solving, praxis/visuoconstruction and attention/concentration (see http://www-np.unimaas.nl/scales/cirs). In order to pool data from centres that used different scales, a variable of mild functional impairment will be used that reflects a similar degree of impairment on each scale. Mild functional impairment on the CDR was defined as a CDR sum of boxes score of at least 1.5 or a score of 1 in one of the CDR boxes, on the GDS it was defined as a score of at least 3, and on the CIRS-FP as a rating of at least mild impairment in the memory domain. The overlap in the definition of mild functional impairment according to different scales was good [76% for the overlap between CDR and GDS (n = 294, \( \chi^2 = 39, p < 0.001 \)), 67% for the overlap between CDR and CIRS-FP (n = 688, \( \chi^2 = 68, p < 0.001 \)) and 79% for the overlap between GDS and CIRS-FP (n = 290, \( \chi^2 = 56, p < 0.001 \)).]

Scales for Instrumental Activities of Daily Living and Activities of Daily Living
Instrumental activities of daily living (IADL) or activities of daily living (ADL) function was measured with the Blessed Dementia Rating Scale (3 centres) [10], the Lawton IADL scale (9 centres) [11], the Katz ADL scale (8 centres) [12], the Alzheimer’s Disease Cooperative Study ADL scale (1 centre) [13], the Bayer ADL or self-rating Bayer ADL scale (3 centres) [14], the Bristol ADL scale (1 centre) [15] or the Barthel Index (2 centres) [16]. Four centres did not use any IADL or ADL scale. In order to pool data from centres that used different scales, individual items that assessed the same activities will be pooled, and the number of IADL or ADL items impaired will be used as a predictor.

Scales for Non-Cognitive Symptoms
Non-cognitive symptoms were measured with the Neuropsychiatric Inventory (13 centres) [17], or the Behave-AD scale (1 centre) [18]. Depression severity was measured with the Hamilton Depression Rating Scale (HDRS, 5 centres) [19], the Montgomery Åsberg Rating Scale (MADRS, 4 centres) [20], the 15-item Geriatric Depression Scale (GDS-15, 7 centres) [21], the Cornell Scale for Depression in Dementia (Cornell, 4 centres) [22] or the Centre of Epidemiological Studies depression scale (CES-D, 1 centre) [23]. One centre did not use any depression rating scale. In order to pool data from different depression scales, we dichotomized scores for clinically significant depressive symptomatology on each scale. These cut-offs were a score >13 on the HDRS [24], a score >14 on the MADRS [24], a score >7 on the GDS-15 [25], a score >10 on the Cornell [22] and a score >24 on the CES-D [26].

Cognitive Tests
All centres performed cognitive testing but the cognitive tests administered varied. In 18 centres, a standardized protocol was administered by a neuropsychologist in all patients. In 2 centres,
tests were administered by a physician as part of the clinical assessment. We selected for each centre a primary test for verbal memory, language, attention and executive function, and visuoconstruction, which was identical or similar to tests used in other centres. We also selected alternative tests for each primary test in case subjects had missing data for the primary test. The primary tests selected for each domain are listed in appendix 3. Raw scores were converted to age-, education-, and gender-corrected z-scores according to normative data of healthy control subjects, and these z-scores were used for further analysis. If possible, the same normative data set was used in each centre (see appendix 3). Neuropsychologists were also asked to give a global rating of the cognitive impairment in the domains of memory, language, executive function/problem solving, praxis/visuoconstruction, and attention/concentration using the CIRs-cognitive part (see http://www-np.unimaas.nl/scales/cirs).

Neuromaging
MRI was the primary imaging modality in 9 centres, computed tomography (CT) in 9 centres, and single photon emission computed tomography (SPECT) in 2 centres. In addition, SPECT imaging was performed on a regular basis in 4 other centres as well. Neuroimaging markers of predementia AD that were tested include medial temporal lobe atrophy and white matter lesions on MRI or CT using qualitative rating scales [27, 28]. On SPECT scans, perfusion was investigated as a marker of predementia AD.

Quantitative Electroencephalography
Q-EEG was performed in 5 centres. Frequency band analysis was used to identify markers of predementia AD.

Genetic Markers
The apolipoprotein E genotype was determined at baseline in 17 centres. APOE genotype was determined on genomic DNA extracted from EDTA anticoagulated blood using the polymerase chain reaction technique. In a subset of subjects, DNA was stored for future analysis.

Plasma and Serum Markers
Each centre provided data on the routine biochemical and haematological laboratory data. In addition, serum and plasma were collected and stored at −80°C for further analysis in 13 centres. Planned analyses include measurement of β-amyloid 1–42 and 1–40 in plasma.

CSF Markers
CSF was collected in 9 centres. Planned analyses include measurement of β-amyloid 1–42, total τ, and τ phosphorylated at threonine 181.

Follow-Up Assessment
In 19 centres, subjects were reassessed annually for 2–3 years. The follow-up assessment consisted of a standardized questionnaire about cognitive complaints, non-cognitive symptoms, current drug use, medical disorders, physician attendance and hospitalization in the period after the previous assessment. In addition, the MMSE and clock-drawing test were scored, and the same scales for functional impairment and IADL/ADL and cognitive tests used at baseline were administered. In case of possible dementia, further diagnostics were performed, including a physical examination, assessment of depression severity, and laboratory and neuroimaging investigations where appropriate. If a subject refused to attend the follow-up assessment or a follow-up assessment could not be arranged, a telephone interview was conducted that included the same standardized questionnaire as described above, the CDR, and the Telephone Interview for Cognitive Status [29]. In 1 centre, the follow-up was conducted according to routine clinical practice. Subjects from this centre who were not seen at follow-up were contacted 2 years after the baseline assessment by telephone, as described above.

Procedure for Making Diagnoses
Dementia was diagnosed according to the DSM-IV criteria [30], AD was diagnosed according to NINCDS-ADRDA criteria [2], vascular dementia according to NINCDS-ADRE criteria [31], Lewy Body dementia according to the McKeith criteria [32], and fronto-temporal lobe dementia according to the Neary criteria [33]. Clinicians were asked to make the diagnosis at follow-up blinded to data collected at baseline, but in some centres clinicians had access to baseline cognitive and neuroimaging data. Therefore, an endpoint committee, blinded to the baseline assessment data, will review all clinical diagnoses. Each follow-up diagnosis will be reviewed by 2 members of the endpoint committee. If this diagnosis disagrees with the diagnosis provided by the centre, other members of the endpoint committee will review the case. The final diagnosis will be established by consensus. If no consensus can be obtained, the subject is considered not demented.

Outcome Measures
The main outcome measure will be conversion to AD-type dementia according to the NINCDS-ADRDA criteria of probable or possible AD at follow-up. As many subjects with predementia AD will not progress to AD-type dementia during the follow-up period of 2 years [34], a secondary outcome measure will be used which includes subjects with AD and non-demented subjects with amnestic mild cognitive impairment (MCI) at follow-up. These non-demented subjects with amnestic MCI are supposed to be at a higher risk of AD at longer follow-up intervals.

Missing Data
In case of missing data, investigators were asked to specify the reason why data were missing. Prespecified reasons for missing data were patient refusal, technical problems, data not in the centre’s standard protocol, contraindication for assessment and lack of time.

Analysis and Sample Size Considerations
Criteria for predementia AD will be developed in several ways. First, a prediction rule will be constructed using logistic regression models and receiver operating characteristic curves. Variables will be entered stepwise in the order in which they are collected in the diagnostic work-up, so variables that can be easily obtained are entered first (e.g. demographics) while variables that are more difficult to obtain (e.g. CSF measures) are entered later. To reduce the number of variables, only variables will be entered in the analysis that are different between subjects with or without probable or possible AD at follow-up on univariate tests at a p
value of 0.10 or less. After each step, it will be determined which variables in the model can be left out without reducing the overall predictive accuracy. The final model will consist of variables that are retained in the model after each step. This model will be converted to a prediction rule.

Secondly, a non-guided forward stepwise logistic regression model will be applied. In the first step, variables that are different between subjects with or without AD-type dementia at follow-up on univariate tests at a p value of 0.10 or less will be entered. Analysis will be undertaken in different sets of subjects, as not all data are available for all subjects. In this way, the shortest diagnostic algorithm with a good predictive accuracy (AUC > 0.85) will be established. Thirdly, the Predementia Alzheimer’s Disease Scale (PAS) will be scored. The PAS is a scale, which consists of 6 markers of predementia AD. It will be determined which cut-off score can best differentiate between subjects with or without predementia AD. In addition, the PAS will be adjusted or extended with other variables if these variables are predictive on univariate tests. In addition, the dataset will be used to cross-validate other diagnostic algorithms for predementia AD.

We planned to enrol 800 subjects, of which it was estimated that 20% would progress to AD-type dementia after 2 years. Taking into account a loss to follow-up of 15%, the number of subjects developing AD-type dementia was estimated to be 136. This number would be sufficient to allow 14 variables in a multivariate analysis, according to the guideline that the number of variables in such an analysis should equal the number of subjects in the smallest outcome group divided by 10.

Results

A total of 893 subjects met inclusion and exclusion criteria. Of these, 881 subjects (99%) agreed to participate in the study. The number of subjects enrolled was higher...
than planned as we allowed participation of centres that joined the EADC after the start of the study. Subjects who refused (n = 12) were younger (65.4 vs. 70.3 years, p = 0.02) and had less years of education (7.7 vs. 10.4 years, p = 0.02) than those who participated. Gender did not differ between the 2 groups. The number of subjects per centre was between 10 and 113 (average 44). The majority of the subjects were prospectively enrolled (n = 835, 95%). The other subjects were retrospectively identified from an existing database. A selection of the baseline characteristics is shown in table 1. Subjects were on average 70.3 years old and had 10.4 years of education. About two thirds had been referred by a physician (mainly the general practitioner), while one third were self-referrals or had been referred otherwise; 76% of the subjects came to the memory clinic with an informant. Overall cognitive impairment as measured with the MMSE was mild, and 93% of the subjects had a CDR overall score of 0.5. Depression at baseline was present in 11% of the subjects.

Data on medical history were available for 871 (99%) of the subjects (table 2). A history of hypertension in 45% of the subjects was the most frequently reported comorbidity, followed by hypercholesterolemia (35%), an atherosclerotic disorder (22%), and depression (21%). A history of hypothyroid or hyperthyroid dysfunction was reported in 109 subjects (12%, 3 subjects reported a history of both hypo- and hyperthyroid dysfunction), of whom 73 (67%) received pharmacological treatment at the time of the baseline assessment. Diabetes mellitus was reported in 93 subjects (11%), of whom 60 (65%) received pharmacological treatment at the time of the baseline assessment.

Cognitive tests had been performed in 862 subjects (98%). The reason for no cognitive data was refusal in 3 subjects, physical limitation in 1 subject, administrative error in 1 subject and was unknown in 14 subjects. The z-scores of the primary cognitive tests are shown in table 1. Delayed recall was the most impaired and visuo-construction the least.

CT scans were performed in 314 subjects at baseline, MRI scans in 435 subjects, SPECT scans in 154 subjects and Q-EEG in 198 subjects. CSF was collected in 193 subjects. The results of these assessments will be reported separately.

We noted marked differences in baseline characteristics between the centres. For example, the average age ranged between centres from 66 to 74 years, the average number of years of education from 7 to 14.1, the average MMSE score from 24.4 to 29.1 and the average z-score of the delayed recall test from –2.63 to –0.05 (table 3).

### Discussion

We described the outline of a study, which aims to develop evidence-based criteria for predementia AD, and we presented baseline characteristics of the subjects included in the study. The main features of the study design
were that we used a combination of variables to develop diagnostic criteria, selected subjects who were representative of the clinical population in which criteria would be used, and followed routine clinical practice.

We selected consecutive newly referred subjects to a memory clinic older than 55 years who were not demented and had no obvious cause of the cognitive impairments. We did not require subjects to have a specific degree of cognitive or functional impairment, because predementia AD can present without cognitive or functional impairments in up to 60% of subjects [38–40].

While broad inclusion criteria will include all subjects with predementia AD, the disadvantage is that the conversion rate to AD-type dementia is lower than if stricter inclusion criteria were used. However, the large number of subjects included will allow multivariate analysis of markers of conversion with sufficient statistical power.

We followed routine clinical practice in order to generate criteria that may have a generalized clinical applicability. We noted a substantial variation in scales and cognitive tests used between the centres. This variation may partly be explained by differences in setting as, for example, psychiatrists may prefer other depression rating scales than neurologists or geriatricians. In addition, the variation may reflect the fact that we included centres from different countries, as in some countries tests and scales are being used that have been validated and for which norms are available in that country. The variation in scales and tests is a challenge for the pooling of data. For cognitive data, we will use age, education and gender-corrected z-scores, as it is assumed that the z-score indicates a similar degree of impairment in a cognitive domain, even if different tests have been used. In a similar way, scores on depression scales and scales for functional impairment will be dichotomized according to equivalent cut-offs on each scale. Not all variables could be collected in all centres as part of regular patient care. This implies that criteria for predementia AD that would require MRI imaging or CSF sampling, for example, may not be applicable in these settings. We will approach this problem by developing a diagnostic algorithm with a stepwise approach, so variables that can be easily collected in clinical practice should be scored first [5].

### Table 4. Design characteristics of longitudinal studies of non-demented subjects with cognitive impairments in a clinical setting

<table>
<thead>
<tr>
<th>Observational studies</th>
<th>Trials</th>
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<tbody>
<tr>
<td>DESCRIPTA</td>
<td>PréAL</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td></td>
</tr>
<tr>
<td>Mild functional impairment²</td>
<td>no</td>
</tr>
<tr>
<td>Test impairment</td>
<td>no</td>
</tr>
<tr>
<td>Informant necessary</td>
<td>no</td>
</tr>
<tr>
<td>Age, years</td>
<td>&gt;55</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td></td>
</tr>
<tr>
<td>Disorders causing cognitive impairment</td>
<td>yes</td>
</tr>
<tr>
<td>MMSE cut-off</td>
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</tr>
<tr>
<td>IADL cut-off</td>
<td>no</td>
</tr>
<tr>
<td>Selection</td>
<td>new consecutive patient</td>
</tr>
<tr>
<td>Follow-up length, years</td>
<td>2–3</td>
</tr>
</tbody>
</table>

MMSE = Mini-Mental State Examination; PréAL = Prediction for Alzheimer’s Disease study [41]; ACCORD = Canadian Collaborative Cohort of Related Dementias study [43]; ITINAD = Italian Interdisciplinary Network on Alzheimer’s disease [42]; ADNI = Alzheimer’s Disease Neuroimaging Initiative [44]; ADCS = Alzheimer’s Disease Collaborative Study [72]; InDDEx = Investigation into Delay to Diagnosis of Alzheimer’s Disease with Exelon study [73]; GAL-Int11/18 = Galantamine International Study 11 and 18 [45].

¹ Data from the Competence Net were provided by personal communication; data from the Rofecoxib study were published in [74], data from the Piracetam study in [46].

² Mild functional impairment is an overall Clinical Dementia Rating scale score of 0.5 or an equivalent score on another scale. In all studies, subjects were required to have cognitive complaints.
A number of other large prospective clinical multicentre studies in non-demented subjects with cognitive impairments have been conducted. Some of these studies aimed to investigate markers of predementia AD, such as the Prediction for Alzheimer’s Disease (PréAL) study in France [41], the prospective MCI study of the Italian Interdisciplinary Network on Alzheimer’s disease (ITINAD; [42]), and the Competence Net Dementias study in Germany, while other studies were not designed for this purpose but still could be used for this such as the Canadian Collaborative Cohort of Related Dementias study in Canada [43] and the Alzheimer’s Disease Neuroimaging Initiative (ADNI) in North America [44]. In addition, a number of drug trials in subjects with MCI with a follow-up of at least 1 year have been conducted, and these studies may also be used to test markers of predementia AD [7, 39, 45, 46]. A selection of the design characteristics of these studies is shown in table 4. It can be seen that all studies except the ACCORD study used more restrictive inclusion criteria than the DESCRIPA study. In addition, most studies used additional criteria for excluding subjects with possible dementia at baseline, for example with an MMSE score or a score on a scale for functional impairment. We did not apply such a cut-off as we intended to include subjects who were not demented according to clinical judgment, even though it is possible that the threshold for diagnosing dementia could vary between centres.

The characteristics of the subjects included in the DESCRIPA study indicates that very mild to mildly impaired subjects were included. Vascular, endocrine and psychiatric comorbid disorders were common even though we excluded subjects in which comorbid disorders were considered the main cause of the cognitive impairments. We will investigate whether these comorbid disorders may influence outcome at follow-up. The baseline characteristics are comparable to those from other prospective clinical multicentre studies in non-demented subjects with cognitive impairments, as shown in table 5. We noted substantial differences in baseline characteristics between centres. This may reflect differences in referral patterns and settings between the centres. It is also likely that as a result the conversion rate to AD will vary substantially between centres. We will investigate to what extent this variation in baseline characteristics influences the diagnostic accuracy of criteria of predementia AD in each centre.

The study had some limitations. The follow-up period of 2–3 years is relatively short as it may take up to 10 years before subjects with predementia AD convert into AD-type dementia [34, 47, 48]. Using the diagnosis of AD-type dementia at the 2- or 3-year follow-up as the out-
come measure may therefore lead to a false-negative diagnosis of predementia AD in a number of subjects. Therefore, we will also use a composite outcome measure including subjects with AD-type dementia and non-demented subjects with amnestic MCI, who are at a high risk of progressing to AD-type dementia at longer follow-up intervals. We also plan to extend the follow-up period to 5 years.

In subjects who refuse to come for the follow-up, a telephone interview instead of a personal examination will be conducted, and this may yield inaccurate information on current cognitive status. We will therefore repeat analysis after exclusion of subjects in which the diagnosis was based on a telephone interview. Another limitation is that not all variables will have been collected in all centres, which limits the power of some of the multivariate analysis. In addition, the different scales and tests used may not be equivalent. However, this variability reflects clinical practice, and by allowing this the results may be easier to implement.

In conclusion, there is an urgent need to diagnose AD before subjects reach a diagnosis of dementia, and the DESCRIPA study has been designed to contribute to the development of evidence-based criteria for predementia AD.

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Appendix 1

List of Participating Centres

Department of Psychiatry and Neuropsychology, University of Maastricht, The Netherlands [F.R.J. Verhey (PI), P.J. Visser (co-PI), I. Ramakers].
LENITEM – Laboratory of Epidemiology and Neuroimaging & Telemedicine, IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy [G.B. Frisoni (site PI), C. Geroldi, M. Bezzu].
Department of Neurology, Alzheimer Centre, VU Medical Centre, Amsterdam, The Netherlands [P. Scheltens (site PI), P.J. Visser, L. van de Pol].
NVS Department, Karolinska Institutet, Karolinska University Hospital, Huddinge, Sweden [L.-O. Wahlund, B. Winblad (site PI)], Y. Freund-Levi, V. Jelic, A.-C. Tysen].
Institute National de la Santé et de la Recherche Medicinale INSERM U 888, Montpellier, France [J. Touchon (site PI), F. Portet, M. Messaoudi].
Aristotle University of Thessaloniki, Memory and Dementia Centre, 3rd Department of Neurology, G. Papanicolaou General Hospital, Thessaloniki, Greece [M. Tsolaki (site PI), C. Pornari, F. Fotiadou].
Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Lund University, Sweden [L. Minthon (site PI)], A. Wallin, J. Mauritzson].
Department of Internal Medicine and Clinical Gerontology, Toulouse University Hospital, Toulouse, France [B. Vellas (site PI), P.-J. Ousset].
Fundación ACE, Barcelona, Spain [M. Boada (site PI), M. Bueno].
Clinical Neurophysiology Unit, Department of Endocrinological and Metabolic Sciences, University of Genoa, Genoa, Italy [G. Rodriguez (site PI), F. Nobili, N. Girtiler, C. De Leo, A. Brugnolo, B. Dessi].
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Department of Geriatrics, Hospital Broca, Paris, France [A.-S. Rigaud (site PI), H. Lenoir].
‘Carol Davila’ University of Medicine and Pharmacy, Bucharest, Romania [L. Spiru (site PI), I. Ioancio].
Department of Neurology, Kuopio University Hospital, Kuopio, Finland [H. Soininen (site PI), T. Pirttilä, co-investigator, M. Hallikainen], and Department of Radiology (R. Vanninen).
Department of Geriatrics, Radboud University Medical Centre, Nijmegen, The Netherlands [M. Olde-Rikkert (site PI), M. Verbeek, R. Esselink, R. Kessels, J. Claassen, R. Melis, M. Verhoeff-Dassen].
The Research Institute for the Care of Older People (RICE), Bath, UK [R. Jones (site PI), J. Mann, J. Gifford].
Department of Care of The Elderly, University of Bristol, Frenchay Hospital, Bristol, UK (G. Willcock, J. Haworth, P. Kehoe). Alzheimer Memorial Centre and Geriatric Psychiatry Branch, Dementia and Neuroimaging Section Department of Psychiatry, Ludwig-Maximilian University, Munich, Germany [H. Hampel (site PI), S. Teipel, M. Ewers, K. Bürger, M. Omerovic].
Institute Born-Bunge, ZNA Middelheim, University of Antwerp, Belgium [P.P. de Deyn (site PI), S. Engelborghs, J. Saerens, N. Le Bastard, M. Van Buggenhout].
### Appendix 2

#### Inclusion and Exclusion Criteria

**Inclusion criteria**
- New referral to a memory clinic because of cognitive complaints
- Age >55 years

**Exclusion criteria**
- Dementia according to DSM-IV criteria at baseline
- Referral because of a high family risk in otherwise normal subjects
- History of schizophrenia, bipolar disorders or recurrent psychotic disorders
- Any somatic, psychiatric or neurological disorder that may have caused the cognitive impairment:
  - Cerebrovascular accident or strategic infarction with an acute onset of the cognitive impairment
  - Neurodegenerative diseases such as Parkinson’s disease and Huntington’s disease
  - Severe head trauma
  - Brain tumour
  - Well-documented professional intoxication (i.e. long-term solvent or heavy-metal exposure)

- Epilepsy
- Brain infections (acute or a sequel of infection)
- Psychotic disorder or delirium
- Severe depression (score on HDRS >20, MADRS >34, GDS-15 >11, Cornell >20, CES-D >40 or hospitalization for depression at the time of assessment)
- Severe vitamin B6, B12 or thiamine deficiency
- Current severe and prolonged alcohol abuse (on average more than 35 units per week for more than 1 year) or history of alcohol abuse for at least 1 year in the past 5 years
- Use of drugs that invariably cause cognitive impairment (e.g. high-dose benzodiazepines)
- Any severe somatic comorbidity that might interfere with study participation (e.g. terminal cancer)

HDRS = Hamilton Depression rating scale; MADRS = Montgomery Åsberg Rating Scale; GDS-15 = 15-item Geriatric Depression Scale; Cornell = Cornell Scale for Depression in Dementia; CES-D = Center for Epidemiologic Studies Depression Scale.

### Appendix 3

#### Primary Tests for Cognitive Domains

<table>
<thead>
<tr>
<th>Test</th>
<th>Number of centres</th>
<th>Reference for normative data used¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVLT [49]</td>
<td>9</td>
<td>6 centres [50], 1 centre [51], 1 centre [52], 1 centre locally collected norms</td>
</tr>
<tr>
<td>Word list of CERAD neuropsychological battery [53]</td>
<td>3</td>
<td>2 centres [54], 1 centre [55]</td>
</tr>
<tr>
<td>Hopkins Verbal Learning Test [56, 57]</td>
<td>3</td>
<td>2 centres [54], 1 centre locally collected norms [59]</td>
</tr>
<tr>
<td>Grober-Buschke Test [58]</td>
<td>2</td>
<td>[59]</td>
</tr>
<tr>
<td>ADAS-Cog 10-word list [60]</td>
<td>1</td>
<td>[54]¹</td>
</tr>
<tr>
<td>Selective Reminding Test [61]</td>
<td>1</td>
<td>Locally collected norms</td>
</tr>
<tr>
<td>Logical Memory Test [62]</td>
<td>1</td>
<td>[62]</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-min verbal fluency for animals [63]</td>
<td>17</td>
<td>[63]</td>
</tr>
<tr>
<td>2-min verbal fluency for animals [64]</td>
<td>1</td>
<td>[64]</td>
</tr>
<tr>
<td>1-min verbal fluency for fruits, animals or car types [65]</td>
<td>1</td>
<td>[65]</td>
</tr>
<tr>
<td>1-min fluency for words starting with ‘F’, ‘A’ and ‘S’ [66]</td>
<td>1</td>
<td>Locally collected norms</td>
</tr>
<tr>
<td><strong>Attention and executive function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to complete Trail Making Test parts A and B [67]</td>
<td>19</td>
<td>18 centres [54], 1 centre [55]</td>
</tr>
<tr>
<td><strong>Visuconstruction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copy of the Rey-Osterrieth complex figure [68]</td>
<td>13</td>
<td>[69]</td>
</tr>
<tr>
<td>Copy CERAD figures [53]</td>
<td>3</td>
<td>2 centres [54], 1 centre [55]</td>
</tr>
<tr>
<td>Copy figures from the AMIPB [70]</td>
<td>1</td>
<td>Locally collected norms</td>
</tr>
<tr>
<td>Copy figures subset from the MDB [52]</td>
<td>1</td>
<td>[52]</td>
</tr>
<tr>
<td>Cube analysis test of the VOSP [71]</td>
<td>1</td>
<td>Locally collected norms</td>
</tr>
</tbody>
</table>

RAVLT = Rey Auditory Verbal Learning Test; CERAD = Consortium to Establish a Registry for AD; AMIPB = Adult Memory and Information Processing Battery; MDB = Mental Deterioration Battery; VOSP = Visual Object and Space Perception battery. ¹Normative data were used to correct test scores for age, gender or education. The same normative data were used in centres that used the same tests if the versions of the test were equivalent. Information on normative data that were collected locally is available on request. ²From the memory tests the learning measure (sum of the words remembered after each learning trial) and free delayed recall measure will be used. ³Because no separate norms for the ADAS-Cog word list with 3 learning trials were available, norms of the CERAD word list were used.
References


