

# Symptom profiles in patients with Alzheimer's disease with and without concomitant cerebrovascular disease: an observational study

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## Research article

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# Abstract

Background: Diagnostic criteria of Alzheimer's disease (AD) and vascular cognitive impairment (VCI) describe different cognitive profiles. AD patients often have concomitant cerebrovascular disease (CVD) and these patients could therefore be expected to display symptoms of both AD and VCI. AD patients with concomitant CVD display symptoms of cognitive impairment with less AD pathology than those without CVD. Medial temporal atrophy (MTA) on magnetic resonance imaging (MRI) is a biomarker of neurodegeneration in AD, and we would expect less MTA in AD patients with CVD. The first aim was to examine whether there were differences in the results of cognitive tests for memory, executive function, and processing speed, or in depressive symptoms, between AD patients with and without CVD. Secondly, to assess whether MTA on MRI is more pronounced among AD patients without CVD. Methods: A total of 192 AD patients with amnesic mild cognitive impairment or mild dementia underwent cognitive assessment and depression screening. Cerebral MRIs were assessed for MTA, white matter hyperintensities, and lacunar and cortical infarcts. CVD was defined as the presence of white matter hyperintensities Fazekas scale  $\geq 2$  or any infarct. To study the effect of CVD, several multiple linear regression analyses were carried out using CVD adjusted for age and sex as the independent variable, and cognitive test scores, depression scores, and MTA as dependent variables. Results: Mean age was 72.2 (SD 8.3) years. The number of AD patients with and without concomitant CVD was 121 and 71, respectively. The group with CVD scored significantly lower on tests of attention, executive function and immediate recall compared with the group without CVD. In analyses controlled for age and sex, concomitant CVD was not associated with significant differences in any cognitive test nor in depressive symptoms. A statistically significant association between AD with concomitant CVD and more pronounced MTA was identified. Conclusions: The results indicate that cognitive test profiles, depressive symptoms, and MTA scores cannot be used to distinguish AD patients with and without CVD.

## Background

Alzheimer's disease (AD) is the most common cause of dementia, followed by cerebrovascular disease (CVD) (1). Autopsy studies suggest that mixed dementia is increasingly common with age and accounts for most dementia cases in the oldest group of patients, the most frequent combination being AD and vascular pathology (2). AD pathology consists of amyloid plaques and neurofibrillary tangles, whereas common cerebrovascular lesions associated with cognitive impairment are macroscopic infarcts, microinfarcts, myelin loss, cerebral amyloid angiopathy, perivascular space dilatation and arteriosclerosis (2).

Although autopsy studies provide valuable insight, the clinician will have to rely on history, clinical findings, cognitive testing and biomarkers to identify the underlying etiology in dementia. For a clinical diagnosis of AD, early and progressive loss of episodic memory is the most characteristic symptom, which is reflected in the diagnostic criteria (3, 4). Recent criteria applied for research recommend the use of biomarkers in addition to clinical symptoms (5, 6). The most commonly available AD biomarker in clinical practice is medial temporal atrophy (MTA) on magnetic resonance imaging (MRI), which is used

as a marker of neurodegeneration (7). Although less specific for AD than amyloid biomarkers in cerebrospinal fluid, MTA correlates well with both neurofibrillary tangle deposition, number of neurons in the area, and cognitive deficits (8-10). As hippocampal atrophy is a hallmark of AD, MTA is used as a biomarker supporting AD as the etiology of cognitive impairment and dementia and has been included in research diagnostic criteria (6, 11).

Vascular cognitive impairment (VCI) is an umbrella term that refers to cognitive dysfunction due to vascular brain injury. Although vascular brain injury may be the sole cause of impaired cognition, a combination of CVD and neurodegenerative diseases is common. Deficits typically associated with VCI are executive dysfunction, slow processing speed, depressive symptoms, impairment of gait and balance, and urinary incontinence (12). According to recent diagnostic criteria for VCI, the presence of these symptoms may indicate a vascular etiology (13) when there is verification on MRI or CT of underlying cerebrovascular lesions presumed to be responsible for the cognitive impairment (13, 14).

Among memory clinic patients, microbleeds and lacunar infarcts are common findings and about one third may have white matter hyperintensities (WMH) severe enough to affect cognition (7, 15). At a given level of dementia severity, AD patients with coexisting CVD show a lower burden of AD lesions at autopsy than AD patients without other pathologies (16). Based on the diagnostic criteria for VCI, it would therefore be expected that AD patients with concomitant CVD have more pronounced symptoms of executive dysfunction, slower processing speed, and more depressive symptoms, with a relative sparing of memory, as compared to AD patients without CVD. As MTA is considered a biomarker of AD, we would also expect AD patients with CVD to have less MTA.

The aim of this study was to investigate whether there are differences in cognitive test results and measures of depression in AD patients with amnesic mild cognitive impairment (aMCI) and mild dementia with and without CVD. Further, we wanted to compare visually assessed MTA among AD patients with and without CVD.

## Methods

### Patients

The patients were recruited from the Progression of Alzheimer's Disease and Resource Use (PADR) study. Patient recruitment and assessments have been described in a previous paper (17). The PADR study included 282 patients with AD, of whom 177 had AD dementia and 105 had aMCI (Figure 1). As the cognitive profiles of different etiologies of dementia become less distinct with increasing disease severity, only patients with mild dementia and aMCI were included in these analyses (18). Of the remaining 260 AD patients, those who had had an MRI scan taken within six months prior to or after the baseline assessment were included in the analyses, resulting in 192 patients in the present study. This sample size ensures at least 90% power to detect group differences of 0.5 standard deviations (SD) or larger. If true differences are small, however, the power will be low. Because differences in cognitive profiles could

depend on disease stage, additional subgroup analyses were performed for the aMCI and the mild dementia groups.

## Assessments

At baseline, patients underwent comprehensive neuropsychological and physical examinations (17). Demographic data, medical history, and drug use were recorded. The cognitive test battery included the Mini-Mental State Examination (MMSE, 0-30) as a global test, the Word List Learning (0-30) and Word List Recall (0-10) from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) as tests of memory, the Trail Making Test A as a test of processing speed, and the Trail Making Test B as a test of executive function. (19-21). Global function was rated with the Clinical Dementia Rating Sum of Boxes (CDR-SB, 0-18, higher scores denoting more severe impairment) (22). Depressive symptoms were assessed in interviews with caregivers using the Cornell Scale for Depression in Dementia (data on 180 of 192 patients) (23).

Apolipoprotein E (ApoE) genotyping was conducted using the Illumina Infinium OmniExpress v1.1 chip at deCODE Genetics, Reykjavik, Iceland, and the result was dichotomized based on the presence of at least one ApoE  $\epsilon$ 4 allele into carriers and non-carriers of ApoE  $\epsilon$ 4.

The diagnostic measures of the PADR study have been described previously (17). The National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria were used for the AD dementia diagnosis (3). The Winblad criteria were used to diagnose mild cognitive impairment (MCI) (24). MCI patients with impaired memory as an early symptom and a score equivalent to or below -1.5 SD on at least one memory test were categorized as aMCI. This group included both multi- and single-domain aMCI patients. The aMCI group was considered to have AD (without dementia) when clinical and cognitive symptoms were consistent with those associated with AD, and further testing did not reveal a more likely primary cause of impairment, in accordance with clinical criteria for the diagnosis of MCI due to AD (25).

## MRI scans

Structural brain imaging using MRI was conducted as part of the regular clinical examinations at several centers using different MRI protocols. Afterward, an experienced neuroradiologist with extensive training examined all MRI scans blinded to the clinical data. WMH were evaluated using the Fazekas scale, rating severity of WMH in the periventricular and subcortical regions combined on a scale 0-3 (26). The presence and number of lacunes ( $\leq 10$  mm) and cortical infarcts were recorded. MTA was rated using the Scheltens MTA scale, which includes evaluation of the choroid fissure, the temporal horn of the lateral

ventricle and the height of the hippocampus, yielding a score of 0-4 (higher score denoting more atrophy) (27). MTA was assessed on the left and right side separately, and the mean score was calculated.

## Statistics

Patient characteristics were described by means and SD or percentages as appropriate. Patients with WMH rated as  $\geq 2$  on the Fazekas scale or any lacunar or cortical infarct were categorized as AD with concomitant CVD in the analyses, whereas patients with Fazekas scale  $\leq 1$  and no lacunes or cortical infarcts were classified as AD without CVD. CVD was treated as a dichotomous variable in the analyses. Groups were compared using independent samples t-tests.

Associations between CVD and cognitive test scores, MTA, Apolipoprotein E  $\epsilon 4$  carrier status, CDR-SB, and the Cornell Scale of Depression in Dementia, respectively, were estimated by multiple linear regression, adjusting for age and sex. As the aim of the analyses was to study the effect of CVD on each of the cognitive test results, scores for depressive symptoms and MTA separately, we carried out one multiple regression analysis for each of these dependent variables. For all multiple regression analyses the independent variable was CVD, adjusted for age and sex. We checked whether assumptions for regression were met by visual inspection of residual plots. Subgroup analyses for aMCI and mild AD dementia were performed for all dependent variables.

Data were analyzed using IBM SPSS Statistics for Windows, version 25.0, Armonk, NY, USA. Statistical significance was defined as  $p < 0.05$ . No adjustment for multiple comparisons was applied.

## Results

Clinical characteristics and cognitive performance of the study patients are shown in Table 1 and MRI findings in Table 2. The mean age was 72.7 (SD 8.3) years, 54% were women, the mean length of education was 12.0 (SD 3.6) years and the mean MMSE score 24.0 (SD 4.4) points. Of the 192 patients in the study, 121 (63%) had concomitant CVD.

In unadjusted analyses, patients with concomitant CVD were older (75.4 versus 68.1 years,  $p < 0.001$ ) and more likely to report a history of stroke or transient ischemic attack (24/121 versus 4/71 patients,  $p = 0.007$ ) than patients without CVD. The group with CVD also had higher CDR-SB scores (4.1 versus 3.4 points,  $p = 0.024$ ), poorer results on the Trail Making A ( $p = 0.015$ ) and B tests ( $p = 0.011$ ) and the Word List immediate recall test ( $p = 0.031$ ). There were no differences in depressive symptoms as assessed with the Cornell scale. The group with CVD had more pronounced MTA (2.1 versus 1.5 points,  $p < 0.001$ ). No statistically significant differences in delayed recall, phonemic verbal fluency or MMSE were found.

When adjusting for age and sex, there were no statistically significant associations between CVD and the results of cognitive tests or depressive symptoms (Table 3). The association between CVD and MTA was

also statistically significant in the adjusted analysis; coefficient 0.364 (95% confidence interval, 0.084–0.645),  $p$  0.011.

Adjusting for CDR-SB score in addition to age and sex did not change the results. Subgroup analyses were performed for aMCI and mild dementia. Numerically the effects seemed to be weaker in the dementia group, but no statistically significant difference between the aMCI and the dementia group was observed.

## Discussion

In this exploratory study of AD patients in memory clinics, we had expected to find that AD patients with concomitant CVD also had symptoms typical for VCI, therefore cognitive test results and depression would differ between patients with and without CVD. Differences were shown in univariate analyses, but after adjusting for age and sex we found no difference in cognitive profiles or depressive symptoms between the two groups. Neuropathology studies have shown that AD patients with concomitant CVD get symptoms with less neurodegeneration than AD patients without. Therefore, as MTA is considered a biomarker of AD in diagnostic criteria, we had expected to find more MTA among patients without CVD. Contrary to this, we observed that patients with CVD had more pronounced atrophy of the medial temporal lobes than those without CVD.

According to diagnostic criteria, a diagnosis of AD requires evidence of a decline in memory and learning, whereas diagnostic criteria for (VCI) describe deterioration in complex attention and executive function. AD patients with concomitant CVD could thus be expected to show additional symptoms associated with the vascular pathology, but no such difference was demonstrated in our study. The literature shows conflicting results on whether concomitant CVD in AD leads to distinct cognitive deficits (18, 28, 29). Even in comparisons of AD with vascular dementia (VaD), the cognitive dysfunction has been shown to be similar, although VaD patients may have better memory and worse executive functioning (30). The cognitive effects of small vessel disease may be heterogeneous and not particularly distinct, and neuropsychological profiles have only modest ability to distinguish between AD and subcortical VaD (31, 32). Subcortical infarcts have been associated not only with reduced processing speed and impaired executive function but also with reduced episodic memory (33). These discrepancies could be related to individual differences in the distribution of pathology in the brain.

Threshold effects may be another reason why studies on cognition in AD with CVD show mixed results. There are indications that a certain amount of vascular pathology may be required to produce distinct symptoms (34). On the other hand, in the late stages of AD, the effect of AD pathology on symptoms may be so strong that it overwhelms the influence of other pathologies (2). Depending on disease stage in AD and cerebrovascular burden, different studies may thus lead to conflicting results. In our study, the group of AD patients not classified with CVD may also have had some CVD, as many of them had some degree of WMH on MRI (Fazekas score of 1) and most had vascular risk factors (35).

No statistically significant association between CVD and depressive symptoms was found. Studies on neuropsychiatric symptoms in VCI compared to AD have shown conflicting results (36). Some find that depression is more common in VCI than in AD, and WMH have been associated with depression (37, 38).

Interestingly, we found a statistically significant association between CVD and more pronounced MTA. We had anticipated the inverse association, as studies have shown that patients with concomitant CVD show less severity of AD pathology than do other AD patients at the same disease stage (39). Various mechanisms may explain this finding. The outcome may be due to the lack of specificity of MTA as a biomarker of AD and of WMH as a marker of small vessel disease. Studies also show that these biomarkers may be interlinked. WMH in white matter tracts connected with the medial temporal lobe may lead to MTA by inducing axonal loss and subsequent atrophy (40). The hippocampus is vulnerable not only to AD pathology but also to vascular damage, as suggested by its sensitivity to hypertension and to hypoxia (41, 42).

Although strongly associated with small vessel disease, WMH in the elderly may result from inflammation or other non-ischemic damage (43). Some of these mechanisms may simultaneously increase WMH and induce atrophy of the medial temporal lobe. In autosomal dominant AD, increased WMH volumes are found years before symptom onset, suggesting that WMH may be part of the pathogenetic processes in AD (44). The results of the present study align with studies where WMH were independently associated with entorhinal cortex volume in aMCI, an effect also observed in patients without significant CVD (45). Even in normal controls, WMH are associated with increased rates of hippocampal atrophy, also when controlling for CSF biomarkers, vascular risk factors, and concurrent brain atrophy (46).

WMH Fazekas 2 is a frequent finding in elderly people and often considered normal above the age of 70-75 years. However, omitting patients with Fazekas 2 from the CVD group in this study did not change the results.

Diagnostic criteria for AD and VCI describe typical symptoms and cognitive deficits for these conditions. However, as there was no observed difference in symptoms between AD patients with and without concomitant CVD after adjusting for age and sex, our findings do not support the idea that symptoms can be used to discern these groups. The patients in our study were well characterized clinically, with diagnoses assessed by a panel of experienced clinicians, and MRIs were systematically interpreted by a highly skilled neuroradiologist blinded to clinical data. Prospective studies with larger study sizes and assessments of CSF and PET biomarkers should be performed to better understand the relationships between symptom profile and underlying pathology in dementia.

As the cognitive profiles of different etiologies of dementia become less distinct with increasing disease severity, only patients with mild dementia and aMCI were included in these analyses

A strength of this study is that the patients were all in the early stages of AD, when cognitive profiles are more distinct than in later stages of the disease. However, the study has some limitations. Analyses were

done post hoc, and we did not have clinical data on urinary incontinence and gait performance or CSF markers to quantify amyloid burden. MRI scans were done at several centers using different protocols. Multiple analyses have been performed, and the results should be regarded as exploratory. Lack of power in the study may explain the lack of statistically significant associations for some of the analyses.

## Conclusions

In this study of cognition, depressive symptoms, and MTA in AD patients with and without CVD, no statistically significant differences in cognitive profile or depressive symptoms were identified, and AD patients with concomitant CVD had more pronounced MTA. These results indicate that cognitive test profiles, depressive symptoms, and MTA scores cannot be used to distinguish between AD patients with and without CVD. Our findings highlight limitations of symptom-based diagnostic criteria in identifying the underlying etiology of cognitive impairment and dementia.

## Abbreviations

AD: Alzheimer's disease; aMCI: amnesic mild cognitive impairment; CDR: Clinical Dementia Rating scale; CDR-SB: Clinical Dementia Rating Scale Sum of Boxes; CVD: cerebrovascular disease; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; MRI: Magnetic Resonance Imaging; MTA: medial temporal atrophy; NINCDS-ADRDA: National Institute of Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders; PADR: Progression of Alzheimer's Disease and Resource use; SD: Standard deviation; VCI: vascular cognitive impairment; WMH: white matter hyperintensities.

## Declarations

Ethics approval and consent to participate

The Regional Committee for Medical and Health Research Ethics for South East Norway approved the study (REC number 2011/531). Patients underwent comprehensive cognitive testing at baseline, and only those who were found to have sufficient cognitive capacity to provide their own consent were invited to participate in the study. All patients gave written, informed consent for their participation in the study and for their clinical data to be used for research purposes. Patients who were not able to give informed consent at baseline were not included.

Consent for publication

Not applicable.

Availability of data and materials

The baseline data from patients assessed at Oslo University Hospital and at Innlandet Hospital Trust are available in "The Norwegian Register for persons with cognitive symptoms (NorCog), but restrictions

apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission from the Norwegian National Advisory Unit on Ageing and Health and Norwegian University of Science and Technology.

### Competing interests

The authors declare that they have no competing interests.

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### Authors' Contributions

IS and RE contributed conception and design of the study; RE, MLB and KP assessed the patients, and RE, MLB, KP, IS and KE contributed in diagnosing the patients. RE, IS and ES analyzed the data and RE, IS, ES, KP, MB, KE, AK and GS interpreted the results. RE drafted the manuscript, and all authors participated in writing and revising the manuscript and read and approved the submitted version.

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## Tables

**Table 1. Clinical characteristics and cognitive performance of AD patients with and without cerebrovascular disease (CVD)**

|   | n   | All          |           | With CVD*    |           | Without CVD* |           | p <sup>†</sup> |  |  |
|---|-----|--------------|-----------|--------------|-----------|--------------|-----------|----------------|--|--|
|   |     | n            | mean (SD) | n            | mean (SD) | n            | mean (SD) |                |  |  |
| Age, years, mean (SD)                           | 192 | 72.7 (8.3)   | 121       | 75.4 (6.2)   | 71        | 68.1 (9.4)   | < 0.001   |                |  |  |
| Female, n (%)                                   | 192 | 104 (54.2)   | 121       | 64 (52.9)    | 71        | 40 (56.3)    | 0.646     |                |  |  |
| Education, years, mean (SD)                     | 192 | 12.0 (3.6)   | 121       | 11.7 (3.7)   | 71        | 12.5 (3.5)   | 0.121     |                |  |  |
| Duration of symptoms, years, mean (SD)          | 177 | 3.1 (2.7)    | 115       | 2.9 (2.2)    | 62        | 3.5 (3.4)    | 0.179     |                |  |  |
| Drugs in regular use, mean (SD)                 | 191 | 2.9 (2.6)    | 120       | 3.1 (2.5)    | 71        | 2.5 (2.7)    | 0.018     |                |  |  |
| ApoE ε4 carrier, n (%)                          | 192 | 114 (59.4)   | 114       | 68 (59.6)    | 65        | 46 (70.8)    | 0.138     |                |  |  |
| Stroke/TIA previously, n (%)                    | 192 | 28 (14.6)    | 121       | 24 (19.8)    | 71        | 4 (5.6)      | 0.007     |                |  |  |
| CDR-SB (0-18), mean (SD)                        | 192 | 3.8 (2.1)    | 121       | 4.1 (2.2)    | 71        | 3.4 (2.0)    | 0.024     |                |  |  |
| Cornell scale (0-38), mean (SD)                 | 180 | 4.9 (4.6)    | 115       | 5.1 (4.7)    | 65        | 4.7 (4.5)    | 0.548     |                |  |  |
| <b>Cognitive tests</b>                          |     |              |           |              |           |              |           |                |  |  |
| MMSE (0-30), mean (SD)                          | 191 | 24.0 (4.4)   | 121       | 23.7 (4.1)   | 70        | 24.5 (4.8)   | 0.203     |                |  |  |
| Trail Making Test A, time in seconds, mean (SD) | 187 | 69.4 (31.6)  | 118       | 73.7 (31.5)  | 69        | 62.1 (30.5)  | 0.015     |                |  |  |
| Trail Making Test B, time in seconds, mean (SD) | 174 | 179.3 (66.5) | 108       | 189.5 (60.4) | 66        | 162.5 (72.8) | 0.009     |                |  |  |
| Word List immediate recall (0-30), mean (SD)    | 183 | 12.3 (5.1)   | 114       | 11.7 (5.0)   | 69        | 13.3 (5.3)   | 0.038     |                |  |  |
| Word List delayed recall (0-10), mean (SD)      | 178 | 2.0 (2.1)    | 110       | 1.8 (2.2)    | 68        | 2.4 (2.0)    | 0.074     |                |  |  |

\*Fazekas 2 or 3 or lacune or cortical infarction on MRI. † Group differences between those with and those without CVD (Independent samples t-test). CDR-SB, Clinical Dementia Rating scale Sum of Boxes; MMSE, Mini-Mental State Examination; TIA, transient ischemic attack. ✕ Not relevant

**Table 2. MRI findings in AD patients with and without cerebrovascular disease (CVD)**

|  | All |     |        | With CVD* |     |        | Without CVD* |     |       | p <sup>†</sup> |
|--|-----|-----|--------|-----------|-----|--------|--------------|-----|-------|----------------|
|  | n   |     |        | n         |     |        | n            |     |       |                |
| <b>MRI findings</b>                      |     |     |        |           |     |        |              |     |       |                |
| MTA (mean of both sides, 0-4), mean (SD) | 189 | 1.8 | (0.9)  | 119       | 2.1 | (0.9)  | 70           | 1.5 | (0.9) | < 0.001        |
| Cortical infarcts, n (%)                 | 192 | 7   | (3.6)  | 121       | 7   | (5.8)  | 71           | 0   | (0)   | α              |
| Lacunar infarcts, n (%)                  | 192 | 33  | (17.2) | 121       | 33  | (27.3) | 71           | 0   | (0)   | α              |
| Any infarcts on MRI, n (%)               | 192 | 37  | (19.3) | 121       | 37  | (30.6) | 71           | 0   | (0)   | α              |
| <i>White matter hyperintensities:</i>    |     |     |        |           |     |        |              |     |       |                |
| Fazekas 0 or 1, n (%)                    | 192 | 77  | (40.1) | 121       | 6   | (5.0)  | 71           | 71  | (100) | α              |
| Fazekas 2, n (%)                         | 192 | 52  | (27.1) | 121       | 52  | (43.0) | 71           | 0   | (0)   | α              |
| Fazekas 3, n (%)                         | 192 | 63  | (32.8) | 121       | 63  | (52.1) | 71           | 0   | (0)   | α              |

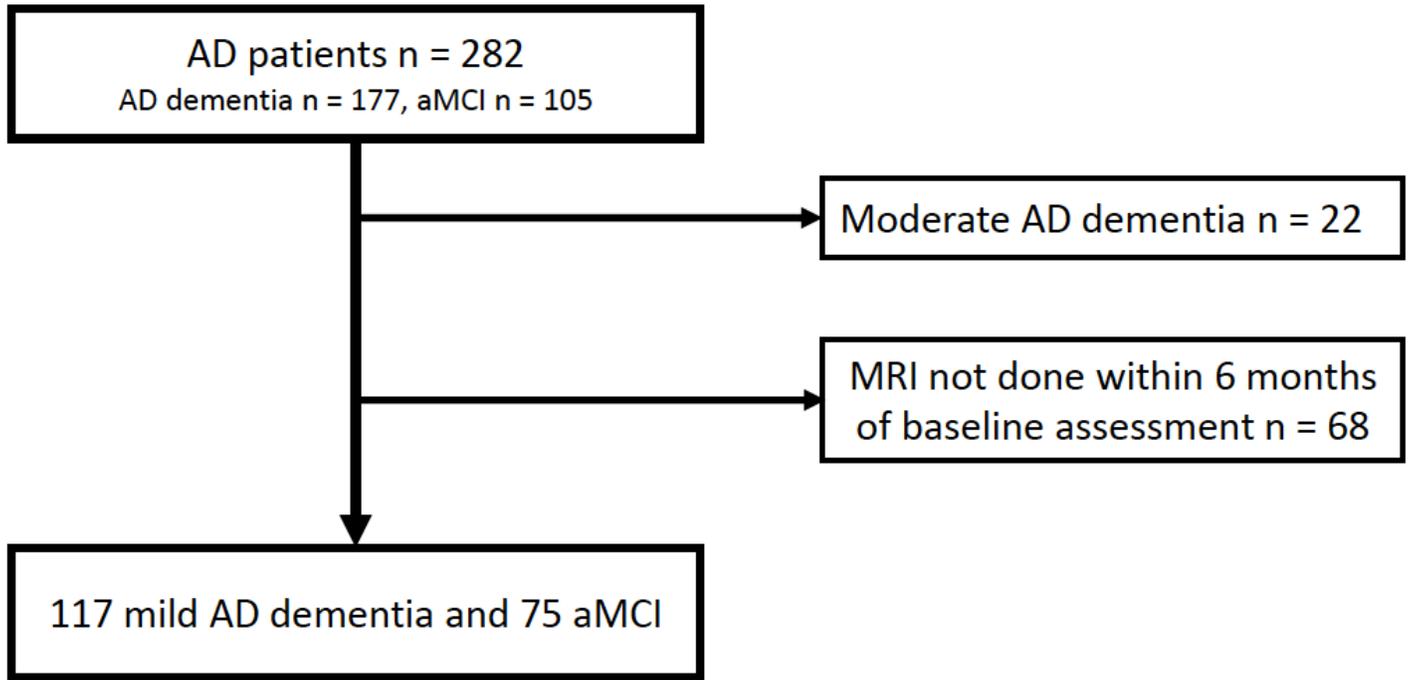
\*Fazekas 2 or 3 or lacune or cortical infarction on MRI. † Group differences between those with and those without CVD (Independent samples t-test). MRI, magnetic resonance imaging; MTA, medial temporal lobe atrophy. α Not relevant

**Table 3 Associations between cerebrovascular disease\* and cognitive test results and depressive symptoms, adjusted for age and sex**

| Dependent variables           | Coefficient | 95% CI            | p     |
|-------------------------------|-------------|-------------------|-------|
| <i>Cognitive tests</i>        |             |                   |       |
| MMSE sum                      | -0.047      | (-1.429, 1.334)   | 0.946 |
| Trail Making Test A           | 2.679       | (-7.464, 12.822)  | 0.603 |
| Trail Making Test B           | 9.487       | (-12.869, 31.842) | 0.403 |
| Word List immediate recall    | -0.701      | (-2.376, 0.975)   | 0.410 |
| Word List delayed recall      | -0.135      | (-0.838, 0.567)   | 0.704 |
| <i>Other variables</i>        |             |                   |       |
| ApoE ε4 carrier (1=yes, 0=no) | -0.100      | (-0.263, 0.064)   | 0.232 |
| Cornell sum                   | 1.066       | (-0.484, 2.615)   | 0.176 |
| CDR-SB                        | 0.231       | (-0.443, 0.904)   | 0.500 |

\* White matter hyperintensities Fazekas scale 2 or 3 or lacune or cortical infarction (1= present, 0 = absent). CDR-SB, Clinical Dementia Rating scale Sum of Boxes; MMSE, Mini-Mental State Examination

## Figures



**Figure 1**

Study flowchart.