Title: Alzheimer's disease first symptoms are age dependent: evidence from the NACC dataset

Authors: Josephine Barnes PhD[1*], Brad Dickerson MD[2], Chris Frost MA DipStat[3], Lize C Jiskoot MSc[4,5], David Wolk MD[6], Wiesje M. van der Flier PhD[4,7]

1 Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Box 16, National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG.

2 Frontotemporal Dementia Unit and Alzheimer's Disease Research Center, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.

3 Department of Medical Statistics, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT.

4 Alzheimer Center, Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, the Netherlands

5 Department of Neurology, Erasmus Medical Center, Rotterdam, the Netherlands

6 Penn Memory Center, Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA

7 Department of Epidemiology & Biostatistics, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, the Netherlands

***Corresponding Author:** Josephine Barnes, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London WC1N 3BG

Tel: +44(0) 203 448 3853

Email: j.barnes@ucl.ac.uk

Author email addresses:

bradd@NMR.Mgh.harvard.edu

Chris.Frost@lshtm.ac.uk

l.c.jiskoot@erasmusmc.nl

david.wolk@uphs.upenn.edu

wm.vdflier@vumc.nl

Abstract

Background: Determining the relationship between age and Alzheimer's disease (AD) presentation is important to improve understanding and provide better patient services.

Methods: We used AD patient data (N=7815) from the National Alzheimer Coordinating Center database and multinomial logistic regression to investigate presentation age and first cognitive / behavioral symptoms.

Results: The odds of having a non-memory first cognitive symptom (including impairment in judgment and problem solving, language and visuospatial function) increased with younger age ($p<0.001$, all tests). Compared with apathy/withdrawal, the odds of having depression, and "other" behavioral symptoms increased with younger age ($p<0.02$, both tests), whereas the odds of having psychosis and no behavioral symptom increased with older age ($p<0.001$, both tests).

Conclusions: There is considerable heterogeneity in the first cognitive / behavioral symptoms experienced by AD patients. Proportions of these symptoms change with age with patients experiencing increasing non-memory cognitive symptoms and more behavioral symptoms at younger ages.

Key words: Alzheimer's disease, clinical neurology history, first symptoms, cognition, behavior, neuropsychology, age

1. Introduction

The prototypical evolution of symptoms in Alzheimer's disease (AD) begins with episodic memory loss followed by impairment in other cognitive and behavioral domains [1, 2]. However, less typical, non-memory presentations of AD have been recognized and include patients with visuospatial dysfunction, visuoperceptual dysfunction, dyspraxia, executive dysfunction, literacy problems and language problems [1-6].

There is evidence from small studies that atypical AD presentations tend to occur at younger ages of onset [4, 7, 8] or are seen in high proportions in younger group studies [9]. Studies assessing the relationship between onset age and first symptoms often dichotomize subjects into early onset (before 65 years) or late onset disease (65 years and above). Such analyses have shown that around one-third of early onset AD subjects present with non-memory symptoms including apraxia and visuospatial dysfunction, aphasia and other language dysfunction, and agnosia [7]. Although the 65 year age cut-off can be useful, it is arbitrary and patterns of predominant first symptoms may vary more gradually with increasing age. An alternative analytical approach is to divide patients into groups based on neuropsychological profiles and assess between-group differences in demographics or other features including onset age [10] or brain atrophy phenotype [11, 12]. Although such studies have revealed differences in AD subgroups and demonstrate the underlying heterogeneity of AD features, many subjects tend to be excluded from such analyses as they fall outside these groups by exhibiting characteristics of neither or both. As such, groups defined in this way may be extremes on a continuum of disease presentations [9, 13, 14].

Since much of the research relating age to AD presentation is single-site or using relatively small sample sizes [4, 7-9], there is a need to demonstrate heterogeneity in larger, less-selected multi-site patient samples to produce more precise estimates of age – AD presentation relationship. Further, those with early onset AD have been shown to have a longer disease duration prior to diagnosis [7, 15], likely in part due to misdiagnosis [16], making the understanding of the different presentations

in AD and how these relate to age extremely important for improving services offered to younger patients.

The aim of this study was to assess the proportions of first predominant reported cognitive and behavioral symptom according to presentation age in a large, multi-site and unselected sample of patients with a clinical diagnosis of AD. We further assessed neuropsychological test performance to test the hypothesis that age influences psychometric impairments in a manner congruent with reported symptoms. Our hypotheses were that: 1) patients presenting at younger ages were more likely to have a first symptom in a non-memory cognitive domain; 2) younger presenting patients were more likely to experience behavioral symptoms.

2. Methods

2.1. Subjects

We included subjects from the National Alzheimer's Coordinating Center (NACC) dataset (http://www.alz.washington.edu/). NACC developed and maintains a database of standardized clinical research data collected from 34 past and present NIA-funded Alzheimer's disease centres (ADC) from across the USA. NACC recruitment and data collection has been described previously [17, 18]. Data included patients seen at ADCs between January 2005 and June 2012. Subjects included in our study had to be demented and have a diagnosis of probable or possible AD according to standard diagnostic criteria at the first visit [19]. We generated subsets of this (total AD) group which excluded those with presence of any other major psychiatric or neurological disorder (AD no other cause) and which additionally excluded AD subjects with possible AD (probable AD no other cause) to investigate the robustness of findings.

The study was approved by an institutional review board at each institution. Written informed consent was obtained from all NACC participants and informants.

2.2. Main outcome measures

The outcome measures assessed were the following: (1) first reported predominant cognitive symptom which included categories: memory; judgment and problem solving; language; visuospatial function; attention/concentration; “other”; fluctuating cognition; no symptom and “unknown”. (2) first reported predominant behavioral symptom which included categories: apathy/withdrawal; depression; psychosis; disinhibition; irritability; agitation; personality change; “other”; REM sleep behaviour disorder; no symptom and “unknown”. Of note, the “no symptom” categories were recorded as “not applicable” by NACC. The symptom nominal variables were recorded by the clinician at the first visit. Specifically, the clinician is asked to indicate which predominant symptom was the first recognized as a decline in the subject’s cognition and behaviour. Only one cognitive and one behavioural symptom category was allowed per patient.

2.3. Neuropsychology

Cognitive functioning was assessed using a standardized neuropsychological battery [20] at the same visit as assessment of first predominant symptoms. Global cognitive functioning was measured using the mini-mental state examination (MMSE) [21]. From this test, copy of the pentagons was used as a measure of visuospatial functioning. For memory, we used logical memory story A, parts 1 and 2 from the Wechsler Memory Scale. Attention and working memory were measured using digit span forward and backward and processing speed by trail making test A and digit symbol from the Wechsler Adult Intelligence Scale (WAIS). Trail making test B was used to measure executive functioning. Fluency (animals and vegetables) and the Boston Naming test were used as measures for language. The number of missing data points varied across tests.

2.4. Statistics

All analyses were performed in Stata SE (version 13). We calculated summary demographic statistics. We also calculated the proportions of the total AD group who had other psychiatric and neurological

diagnoses and were excluded from the AD subsets. To investigate memory vs. non-memory complaints we dichotomized the first cognitive symptom as memory or non-memory for those subjects who reported a cognitive symptom (i.e. excluding the no symptom and "unknown" categories). This was used as the dependent variable in binary logistic regression models with age at first presentation as a continuous predictor variable.

We performed separate multinomial logistic regression analyses to assess the relationship of age at first presentation (predictor variable) with i) first predominant cognitive symptom and ii) first predominant behavioral symptom (dependent variables). In our main analyses we considered four age-bands, specifically <60, 60-69, 70-79 and >79 years. We took the oldest age group and the most commonly reported symptom (cognitive or behavioral) as the reference groups. In addition, tests for trend were carried out using models that treated age as a continuous, rather than a categorical, predictor. Symptom groups with fewer than 10 subjects for any age group were excluded from all comparisons. For cognitive symptoms these excluded categories were attention/concentration, "other", fluctuating cognition, no symptom, and "unknown". For behavioral symptoms these were REM sleep disorders and "unknown". All analyses were first performed in the total AD group, and then repeated in the AD subsets.

For graphical representation we created plots showing the proportions of first reported domains/symptoms by age-band. All symptoms, irrespective of group size are represented in these figures.

For each neuropsychological test we performed a linear regression analysis with age at first presentation/10 as a continuous predictor and test score as the outcome variable. Resultant coefficients represent a change in neuropsychological score for a 10 year increase in age of presentation. All analyses included gender and education as covariates and therefore patients without recorded educational attainment were excluded from these analyses. Floor (poorest possible performance) and ceiling (best possible performance) were reported where there were 10

or more subjects exhibiting these effects. Wald tests of the linear effect of the test score were performed. For the copy of the pentagons test, where the result was a binary score, the p value reported is that for this binary predictor. We additionally adjusted for the time between test parts I and II for the logical memory test part II. Semi-partial R^2 values were derived for the relationship between age and test scores.

Analysis of demographic and genetic variables by first predominant cognitive and behavioral symptom is presented in the Supplementary Section and Supplementary table 4.

3. Results

3.1 Demographics

Summary demographic information is shown in table 1. On average, patients were 75 years old when they first presented at the AD Center for their NACC visit but this ranged from 36 to 110 years. More than half of the patients were female. At first presentation, patients were mildly to moderately demented (mean (SD) MMSE 19.3 (6.8)). Demographic results were similar in the total sample and the subsets. The proportions of the total AD group with another psychiatric or neurological diagnosis are displayed in supplementary table 1.

	Total AD	AD no other cause	Probable AD no other cause
N	7815	4644	4350
Age at first presentation	75.5 (9.7) [36-110]	75.7 (9.6) [36-110]	75.7 (9.5) [36-102]
Gender, % women	56.2	56.2	56.6
Probable AD, as % of probable and possible AD	82.6	93.7	100.0
Symptom length, years[a]	5.0 (3.5)	5.0 (3.5)	5.1 (3.5)
Education, years[b]	13.8 (3.9)	14.0 (3.8)	14.0 (3.8)
MMSE at first presentation /30[c]	19.3 (6.8)	19.3 (6.8)	19.3 (6.8)
Global CDR, % scoring 0, 0.5, 1, 2 and 3	0.2, 28.0, 45.1, 17.5, 9.3	0.0, 29.1, 44.9, 17.0, 9.0	0.0, 28.4, 45.5, 17.1, 8.9
CDR Sum of Boxes, /18	7.0 (4.5)	7.0 (4.4)	7.0 (4.4)
APOE e4 % 0,1,2 alleles[d]	42.4, 45.4, 12.3	40.2, 46.9, 12.9	39.4, 47.4, 13.2
Positive for APP, PS1, PS2, n	2, 13, 0	0, 8, 0	0, 8, 0

Table 1 Demographic information for the total AD group and subsets.

Mean (SD) and [minimum, maximum] values are shown unless otherwise stated

Data available in all subjects apart from

a: available in 7674 Total AD, 4559 AD no other cause, and 4272 Probable AD no other cause

b: available in 7750 Total AD, 4605 AD no other cause, and 4316 Probable AD no other cause

c: available in 7328 Total AD, 4353 AD no other cause, and 4091 Probable AD no other cause

d: available in 5218 Total AD, 3200 AD no other cause, and 3003 Probable AD no other cause

3.2. First predominant cognitive and behavioral symptom

The most commonly reported first predominant cognitive symptom was memory (see figure 1). For those who reported a first cognitive symptom the proportion of AD patients with a non-memory first predominant cognitive symptom gradually decreased with increasing age: <60 years 26.1%, 60-69 years 19.8%, 70-79 years 10.5%, >79 years 6.3%. In a logistic regression analysis combining all non-memory cognitive symptom domains the odds of a non-memory first predominant symptom was multiplied by 1.72 (95% CI 1.61, 1.84, $p<0.001$) for each ten year decrease in age. Table 2 shows more detailed results from the multinomial logistic regression analyses that distinguished results for the non-memory symptom domains. Compared with memory, the odds of having judgment and problem solving, language and visuospatial problems as the first predominant cognitive symptom all increased with younger presentation age. These results remained largely unchanged when analyses were restricted to the AD subsets (see supplementary tables 2 and 3).

<Insert Figure 1 here>

		Age-band <60 years compared with >79 years Odds ratio (95% CI)	Age-band 60-69 years compared with >79 years Odds ratio (95% CI)	Age-band 70-79 years compared with >79 years Odds ratio (95% CI)	Age band >79 years	P value from trend test treating age as continuous
First predominant cognitive symptom compared with memory	Memory	1.0	1.0	1.0	1.0	reference
	Judgement and problem solving	**3.8 (2.6, 5.5)**	**2.7 (2.0, 3.7)**	1.1 (0.8, 1.5)	1.0	**<0.001**
	Language	**5.4 (3.5, 8.3)**	**4.9 (3.4, 7.0)**	**2.9 (2.1, 4.1)**	1.0	**<0.001**
	Visuospatial function	**12.1 (7.1, 20.4)**	**7.6 (4.7, 12.4)**	**2.3 (1.4, 3.8)**	1.0	**<0.001**
First predominant behavioral symptom compared with Apathy/ withdrawal	Apathy/ withdrawal	1.0	1.0	1.0	1.0	reference
	Depression	**1.5 (1.2, 1.9)**	**1.5 (1.3, 1.8)**	0.9 (0.8, 1.1)	1.0	**<0.001**
	Psychosis	**0.4 (0.2, 0.6)**	**0.6 (0.4, 0.8)**	**0.7 (0.5, 0.8)**	1.0	**<0.001**

	Disinhibition	0.7 (0.4, 1.3)	0.9 (0.6, 1.4)	0.8 (0.6, 1.1)	1.0	0.3
	Irritability	0.9 (0.6, 1.2)	1.0 (0.8, 1.3)	1.2 (1.0, 1.4)	1.0	0.6
	Agitation	**0.5 (0.3, 1.0)**	1.0 (0.7, 1.5)	0.9 (0.7, 1.2)	1.0	0.4
	Personality change	1.4 (0.8, 2.5)	1.3 (0.8, 2.1)	1.1 (0.8, 1.6)	1.0	0.1
	Other	**1.9 (1.2, 3.0)**	1.2 (0.8, 1.8)	0.9 (0.6, 1.3)	1.0	**0.01**
	No symptom	**0.6 (0.5, 0.8)**	**0.8 (0.6, 0.9)**	**0.9 (0.7, 1.0)**	1.0	**<0.001**

Table 2 Relationship between first cognitive/behavioral symptoms with age at first presentation in the total AD group. Odds ratios for first cognitive symptom and first behavioral symptom are for the younger age-bands compared with the oldest age-band. P values relate to models where age is used as a continuous variable. Significant results are shown in bold. Odds ratios are represented to 1 decimal place and p values to 1 significant figure.

The most commonly reported first behavioral symptom was apathy/withdrawal (see table 2 and figure 2). Overall, compared with apathy/withdrawal, the odds of having depression and “other” behavioral symptoms increased with younger presentation age. By contrast, the odds of having psychosis and no reported symptom increased with older presentation age. Notably, the significant behavioral findings were typically smaller in magnitude than those seen between presentation age and cognitive symptoms. These behavioral symptom results remain largely unchanged when analysis was restricted to the two AD subgroups (see supplementary tables 2 and 3).

<insert Figure 2 here>

3.3 Neuropsychological results

Results from linear regression analyses relating age at presentation to performance on neuropsychological tests are shown in Table 3. The table presents the effect of ten year increases in age on test score adjusted for gender and education. Results showed that older age at presentation was associated with poorer scores on logical memory tests, trails making tests A and B, digit symbol, category fluency and Boston Naming Test. For example a ten year increase in age at presentation was associated with a 0.11 (95% CI 0.02, 0.20) lower logical memory test score. By contrast younger ages of presentation were associated with reduced ability to copy pentagons and shorter digit spans.

Domain / skill assessed	Test	N	Floor value (N at floor)	Ceiling value (N at ceiling)	Change in test score (95% CI) for ten year increase in age of presentation	Semi-partial R^2	P value
Global cognitive function	MMSE, /30	7279	0 (144)	30 (62)	-0.03 (-0.19,0.13)	<0.0001	0.7
Visuospatial function	MMSE pentagon (binary)	2780	NA	NA	0.05 (0.03, 0.07)	0.0093	<0.001
Memory	Logical memory part I, /25	6337	0 (1199)	NA	-0.11 (-0.20, -0.02)	0.0009	0.02
	Logical memory part II, /25	6061	0 (3175)	NA	-0.25 (-0.33, -0.17)	0.0063	<0.001
Attention and working memory	Digit span forwards length, /8	6519	0 (107)	8 (573)	0.18 (0.15, 0.22)	0.0146	<0.001
	Digit span backwards length, /7	6467	0 (347)	7 (88)	0.17 (0.14, 0.21)	0.0152	<0.001

Processing speed	Trails A, 0-150 seconds*	5945	150 (962)	NA	1.34 (0.19, 2.48)	0.0008	0.02
	WAIS digit symbol, up to 93	5457	0 (226)	NA	-0.65 (-1.05, -0.25)	0.0017	0.002
Executive functioning	Trails B, 0-300 seconds*	4400	300 (1908)	NA	7.04 (4.27, 9.80)	0.0054	<0.001
Language	Animals, coded up to 77	6569	0 (144)	NA	-0.54 (-0.67, -0.41)	0.0102	<0.001
	Vegetables, coded up to 77	6453	0 (369)	NA	-0.20 (-0.30, -0.10)	0.0024	<0.001
	Boston Naming Test, 30	6371	0 (91)	30 (111)	-1.47 (-1.66, -1.28)	0.0331	<0.001

Table 3 Changes in mean age of presentation with neuropsychological tests. Changes in test scores for a ten year increase in age of presentation are shown together with their 95% CIs. Regression analyses are adjusted for gender and education. Regression analysis for logical memory part II is also adjusted for time between first and second parts. Semi partial R^2 values which represent the amount of variance in test scores explained by presentation age. *Higher score denotes a poorer performance. NA: not applicable.

4. Discussion

This study showed that non-memory first symptoms including judgment and problem solving, language, and visuospatial problems increased gradually with younger presentation of AD. This is evidenced by higher odds ratios of these non-memory symptoms compared with memory symptoms in the younger age bands vs. the oldest age band. In addition, younger patients were more likely than older patients to have a behavioral symptom. Relative to having apathy/withdrawal, depression and "other" behavioral symptoms increased with younger presentation (higher odds ratios in younger age bands compared with oldest), whereas psychosis increased with older presentation (lower odds ratios in younger age bands compared with oldest). Odds ratios were generally higher for the cognitive symptoms than behavioral symptoms and showed clearer increases per lower age band for the non-memory cognitive symptoms.

We show that 74% of AD patients presenting at <60 years had a predominant first symptom of memory problems compared with 92% in those 70 years or over. The proportions of memory vs. non-memory first symptoms are similar to that of previous studies: one study reported that 68% of cases under 65 years at onset age had a memory presentation compared with 94% in cases 65 years and above [7]; another reported that 63% of AD patients with onset <60 years had a memory presentation [22]. In another single-site study where the average onset was around 60 years, 79% of cases had typical AD, mild memory problems or an amnestic syndrome as opposed to other focal AD types [9] which is again in keeping with our findings.

Our data also give weight to smaller neuropsychological studies which have shown that earlier onsets of AD are associated with more fronto-parietal and less temporal lobe dysfunction [23]. Our result of a greater proportion of early visuospatial dysfunction at younger ages (7% under 60 years vs. 1% 70 years and above) replicates other smaller studies which have shown the average age of those presenting with visual AD subtypes was below 65 years [7-9]. In terms of proportions, one study found that combined apraxia/visuospatial dysfunction made up 12% of younger onset cases (<

65 years onset) [7], which is higher than our 7%; unfortunately, apraxia is not recorded by NACC. Much like our analyses, that study also demonstrated higher proportions of language presentations at younger onset (9% [7], similar to our 7%). Our study demonstrates that age cut-offs used in research are arbitrary as non-memory presentations increase with decreasing age.

Our data show that some older AD patients do not have a first symptom of memory dysfunction (8% of 70+ year olds). Heterogeneity in AD presentations has previously been shown in a selected subset of NACC data with a study demonstrating dysexecutive and amnestic syndromes with the average age of these groups being greater than 70 years [10]. Taken together these findings demonstrate AD heterogeneity remains at older ages, a finding further substantiated by phenotype clustering in AD subjects over 60 years [24] as well as in selected cohorts such as the Alzheimer's Disease Neuroimaging Initiative [25].

Motivation for behavioral symptom research in dementia has increased recently [26, 27]. The majority of AD patients in our study had a behavioral symptom which is similar, but lower in proportion, to another study which reported around 90% of AD patients having behavioral/psychological symptoms [28]. The highest proportions of symptoms in our study were apathy/withdrawal, depression and irritability which are similar findings to other studies with respect to analogous symptom categories: one study found apathy, depression and agitation to be the most frequently reported in late onset AD [29] and another found apathy, irritability and agitation to be most commonly reported in young onset AD and depression, apathy, irritability and anxiety in late onset AD [30].

In terms of neuropsychology tests we found that older presenting subjects were more impaired with respect to memory scores (logical memory parts I and II), processing speed (trail making A, digit symbol), executive functioning (trail making B) and language (animals and vegetables and Boston naming test). Younger presenting patients had more problems with attention and working memory (digit span forwards and backwards) and visuospatial function (pentagons). Despite the fact that

language problems as a first symptom were associated with younger presentation of AD patients, the neuropsychology revealed that older subjects were more impaired with respect to language at first visit. This may be due to the accrual of more language deficits by first visit in older patients and/or due to the difference in nature between a symptom variable (perception of a problem) and a neuropsychological test score (relatively objective assessment of one aspect of function).

Our findings are in keeping with others who have assessed identical or modified neuropsychological tests and their relationships with onset age. Greater language problems with older onsets have been previously shown (Boston naming test, [32]). Others have demonstrated that those with younger onset have shorter digit spans [33-35] and poorer performance drawing pentagons [36]. Our results differ from that of two studies which found no significant differences between older or younger onset cases in any neuropsychological test performed in their study including language, visuospatial and attention tasks [37, 38]. However, both of these studies were performed using smaller sample sizes, potentially limiting the power to detect differences. Using identical tests to our own, one study has shown that processing speed and executive function was worse in younger subjects (trails A and B [35]) whereas we found older patients performed more poorly in these tests. Studies investigating onset age in AD and neuropsychological features span the past three decades and therefore differences between studies' findings may derive from improved diagnostic criteria [35] as well as differing disease severities of the populations, power to detect differences, and covariates used in analyses. Although we have demonstrated significant relationships between presentation age and neuropsychology, the amount of variance in test scores explained by age was low, with the highest value being for the Boston Naming Test for which age explained 3% of the variance.

The findings of our study are congruent with those investigating the relationship between age and brain morphology and pathology. One autopsy study has demonstrated that hippocampal sparing AD cases (suggestive of a non-memory presentation) were, on average, younger at onset than

typical cases [39] and imaging studies have demonstrated relative preservation of the hippocampus/ medial temporal lobe at younger onsets [40-42]. Although the aging process affects widespread cortical areas including the temporal lobe [43, 44], the areas disproportionately affected by AD and aging processes differ with temporal areas more affected by AD and fusiform, caudal insula and medial frontal regions more affected by aging [45]. Therefore, our finding of a higher proportion of memory (temporal lobe) AD cases with age is partially congruous with the pattern of age-related changes that can occur. Arguably however, aging in addition to AD would potentially lead to more non-memory cases occurring at older ages (such as frontal cases) if age-related differences in AD were driven by a normal aging process applied to a uniform AD process. It is more likely that the differences we observe in terms of symptoms and age relate in part to predominance of e4 in memory cases; e4 is an important risk factor for later onset AD [6] and has been shown to drive atrophy to the medial temporal lobe [46, 47]. Other unknown factors, which cause atrophy outside of the temporal lobe, non-memory deficits and symptoms, and younger onsets, are also likely to influence our findings.

The strengths of this study are the large sample size and systematic data collection which enables more fine-grained analyses of the effects of age on first predominant symptoms. The multi-site nature of the study improves generalizability of results as compared with single-site studies.

One limitation of this study is the likely noise associated with large cohorts of unselected data; our results may be in part caused by misdiagnoses, particularly in the non-memory subtypes, as we did not assess autopsy-confirmed cases. Clinical diagnosis of AD has been shown to be incorrect in 7%-13% of cases investigated at post mortem [48-50]. Notably, a clinical diagnosis of probable AD in the NACC neuropathological cohort was shown to have a sensitivity and specificity of 71% compared with a pathological diagnosis [51]. Biomarker support for AD diagnosis will be an increasingly important tool in the clinical management of young onset disease where diagnostic accuracy may be lower. As biomarkers are increasingly used in practice and their interpretations improve, it may be

that diagnostic accuracy increases with time which will be important to consider in studies where data collection spans many years. In our study, we performed additional analyses in increasingly restrictive subsets to minimize the chances of misdiagnoses influencing results. Results remained largely unaltered, illustrating that symptom heterogeneity is likely to exist in AD. The patients in our study were from the USA and therefore cultural differences may limit the generalizability of our results. These differences may manifest in terms of stigma associated with dementia, when to present to clinic, and the relative importance of specific symptoms. Despite possible differences, we found similar results to that of European studies which have showed an increased predominance of non-memory cognitive symptoms at younger onsets [7, 9]. We chose to investigate presentation age rather than age of cognitive decline which differs from most studies in the literature. This was chosen as it was more likely to be accurately recorded, was available in more subjects than age of decline, and our findings are likely to be more relevant to physicians in clinic. Finally, we cannot exclude the possibility that the first symptoms experienced by AD patients in this study are in part due to normal aging. Adjustment of our results for those found in controls is not possible using NACC data since symptoms are not routinely recorded for controls. Further since a proportion of elderly controls are likely to have underlying AD pathology [52-54], or other neurological conditions, adjustment for a “normal” aging process is difficult.

A further weakness is the recruitment bias that is likely to be present in this data collection: NACC data is derived from academic centers which are more likely to have complex and atypical cases limiting generalizability to community-based patients. Further, subjects had to have a diagnosis of AD according to NINCDS-ADRDA criteria which requires memory impairment. This means that early presenting non-memory AD patients may have been excluded leading to an underestimate in their proportions. Finally, the neuropsychology tests performed do not fully investigate non-memory domains. For example, the pentagon copy test was the only visuospatial neuropsychological examination; this test is not a sophisticated or detailed investigation of such deficits. Similarly, the language tests used may not fully investigate deficits present in younger onset cases. Incorporating

more non-memory tests into neuropsychological batteries is important, especially if younger presenting patients attend clinic.

We conclude that presentation age influences first symptoms experienced by clinically-diagnosed AD patients. Although memory problems are the most common first cognitive symptom experienced at any age, non-memory symptoms including judgment and problem solving, language, and visuospatial problems are more prevalent in younger patients. The largest proportion of AD subjects had apathy/withdrawal as first reported behavioral symptom. Compared with apathy/withdrawal, depression, and "other" behavioral symptoms increased with younger presentation ages whereas older subjects were more likely to have psychosis or no behavioral symptom. Importantly, non-amnestic presentations are acknowledged and behavior is included in the new AD diagnostic criteria [2]. Appreciation that non-memory first symptoms occur in AD, particularly in younger cases, is important so that patients have a less tortuous route to diagnosis. Further, non-memory neuropsychological tests are needed to evaluate the full range of deficits experienced. Better awareness of non-memory symptoms and more comprehensive testing would allow for improved services for patients: for example the development of appropriate information materials for those with visuospatial problems and support services for those who experience behavioural symptoms.

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Figure legends

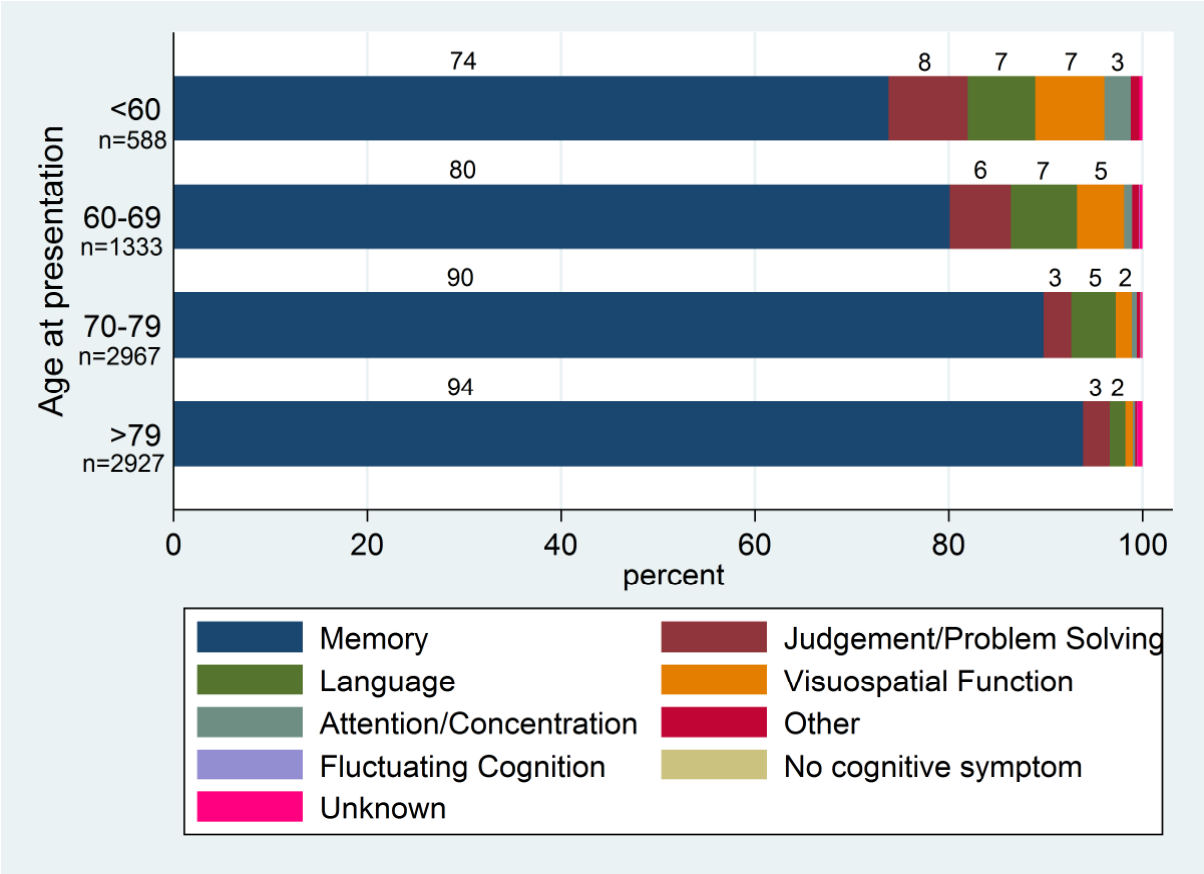

Figure 1 Age at first presentation and first predominant cognitive symptom.

Percentages are given above colored bars for each symptom group where ≥ 2%

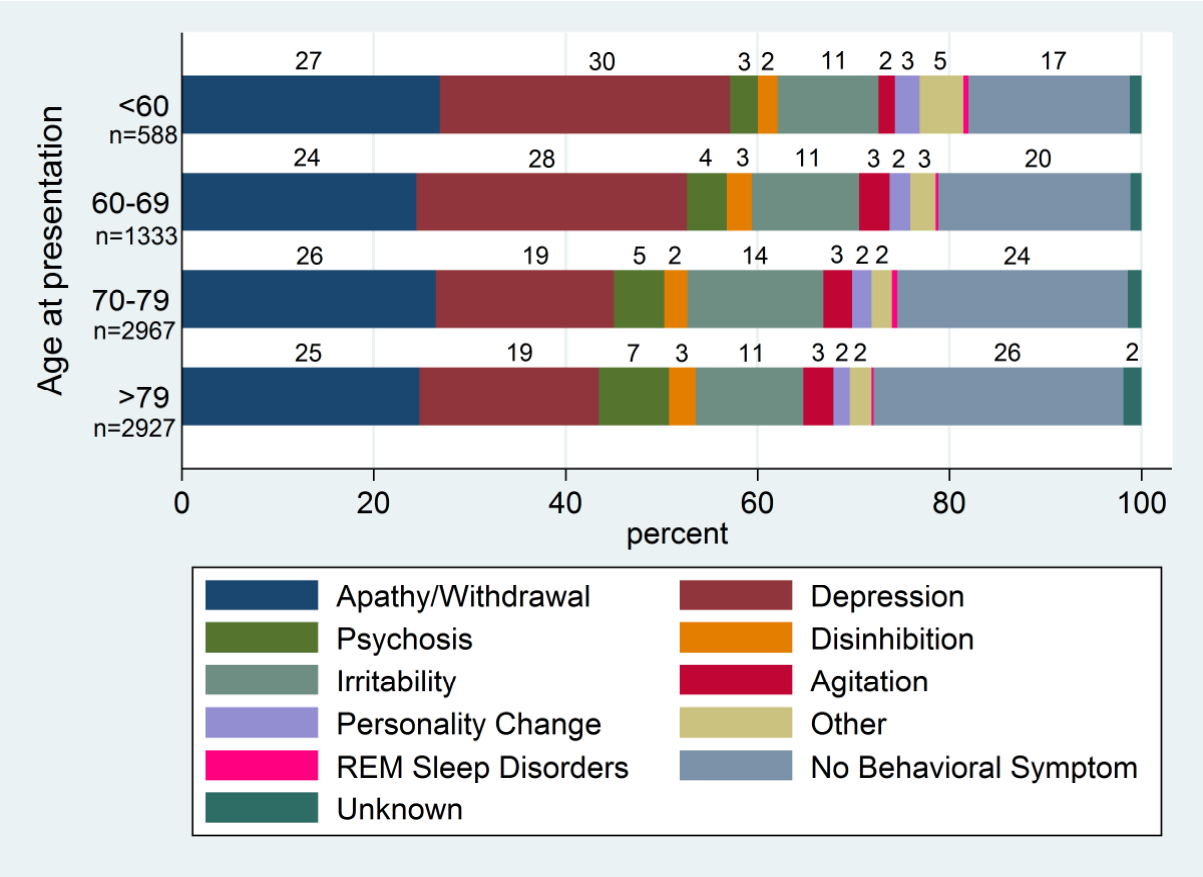

Figure 2 Age at first presentation and first predominant behavioral symptom.

Percentages are given above colored bars for each symptom group where ≥ 2%

Supplementary Section: Analysis of demographic and genetic variables across first predominant symptom groups

Methods

Outcome measures

For analysis of demographic and genetic variables across symptom groups we used the following outcomes: age at presentation, gender, symptom length (the difference between the reported age of decline in the patient and the age at presentation), educational attainment, mini-mental state examination (MMSE), clinical dementia rating scale (CDR), CDR sum of boxes, and number of APOE e4 alleles. We also reported whether there was evidence of familial AD genes (APP, PS1 or PS2). The number of missing data points varied across measures.

Statistics

For assessment of demographic and genetic variables across the different cognitive and behavioral symptom groups analyzed in table 2, we performed different analyses depending on the nature of the outcome variable. For the continuous dependent variables of age at presentation, symptom length, education, MMSE and CDR sum of boxes we used linear regression analyses with either cognitive or behavioral symptom groups as the predictor variables. For symptom length we used a mixed model in order to incorporate Alzheimer's Disease Center (ADC) as a random effect. For education we adjusted for gender; for analyses of MMSE and CDR sum of boxes we adjusted for symptom length, gender and education. All these models, apart from those with age as the outcome variable, were re-fitted additionally adjusting for age at presentation to assess whether any differences were independent of age. Where age was the outcome variable, we refitted the models additionally adjusting for symptom length, where this was recorded, to assess whether differences in age at presentation, according to symptom groups were due to those with specific symptoms potentially waiting longer to present to clinic. Where joint Wald tests of differences in these

continuous outcomes between symptom groups were statistically significant we compared each symptom group with the memory group (for cognitive symptoms) and the apathy/withdrawal group (for behavioral symptoms) using the age-adjusted models, or symptom length-adjusted models where age was the outcome variable.

For CDR and APOE e4 dose we used separate multinomial logistic regression models with CDR score and number of e4 alleles as outcome variables and either first cognitive or first behavioral symptom as predictor variables. For CDR we used gender, education and symptom length as covariates. For gender we used logistic regression with this binary variable as the outcome and either first cognitive or behavioral symptom as the predictor variable. For these categorical variables of interest (sex, CDR and number of e4 alleles) we refitted the models additionally using age as a covariate to investigate whether any differences across groups were independent of age. Likelihood ratio tests were used to test for differences between groups. Differences in distribution of sex, CDR global score and number of e4 alleles were assessed using the age-adjusted models with either memory or apathy/withdrawal as a reference group.

Results

Supplementary table 4 shows basic demographic and genetic summary statistics for cognitive and behavioral symptom groups. The memory symptom group were older at presentation ($p<0.001$, all tests), had a higher proportion of women compared with other groups ($p<0.05$, all tests) and a lower proportion of APOE e4 non-carriers ($p<0.002$, all tests). Those with judgment and problem solving were more impaired on CDR sum of boxes ($p<0.001$) and had higher proportions of subjects scoring 2 or 3 on CDR global scores ($p<0.03$, both tests) compared with memory patients. Compared with memory patients, the language group had a shorter symptom duration ($p=0.01$), higher educational attainment ($p<0.001$) but were more impaired on MMSE, less impaired on CDR sum of boxes ($p<0.001$, both tests), and had a higher proportion of patients scoring 0.5 on global CDR ($p<0.001$).

Visuospatial patients had higher educational attainment compared with the memory symptom group ($p<0.001$).

For behavioral symptom groups, gender distributions differed with higher proportions of women seen in the depression, psychosis, agitation, "other" and no symptom groups as compared to apathy /withdrawal ($p<0.05$, all tests). Compared with the apathy/withdrawal group those with depression were younger at presentation, had shorter symptom lengths, were less well educated, less impaired on the MMSE and CDR sum of boxes ($p<0.001$, all tests). Further, patients with depression were less impaired on global CDR: higher proportions scoring 0.5 and lower proportions scoring 2 compared with apathy and withdrawal ($p<0.002$, both tests). Those with psychosis were older at presentation, had lower levels of education, and were more impaired on the MMSE and CDR sum of boxes ($p<0.001$, all tests) and had a higher proportion of patients scoring 2 or 3 on global CDR compared with apathy/withdrawal ($p<0.03$, both tests). Patients in the disinhibition group had longer symptom lengths ($p=0.02$) and were less impaired on the MMSE ($p=0.003$). Compared with apathy/withdrawal the irritability group had lower education levels and were less impaired on the MMSE and CDR sum of boxes and had a higher proportion of patients scoring 0.5 on global CDR ($p<0.002$, all tests). Patients with agitation had longer symptom lengths ($p=0.03$) and were more impaired on the MMSE and CDR sum of boxes ($p<0.001$, both tests) and had higher proportions of subjects scoring 2 or 3 on global CDR ($p<0.02$, both tests). The "other" group was younger at presentation ($p=0.02$) whereas those without behavioral symptoms were older ($p<0.001$) compared with the apathy/withdrawal group. However, those with "other" and those with no behavioral symptom had shorter symptom lengths ($p<0.03$, both tests) and were less impaired on MMSE and CDR sum of boxes ($p<0.003$, all tests). The no symptom group had a larger proportion of patients scoring 0.5 as well as a smaller proportion of patients scoring 2 and 3 on global CDR ($p<0.001$, all tests) whereas the "other" group

had a smaller proportion of patients with a global CDR score 2 only (p=0.05). There was no evidence of a difference in APOE e4 distribution according to first behavioral symptom.

Discussion

Differences in demographic and genetic variables were seen across the symptom groups. The greater proportion of females with memory as first symptom is in line with the overall estimates for AD as a whole [1] as well as with the typical AD group in a separate study [2]. In our current study the male:female ratio was roughly equal for language much like another study [2] but we reported an equal male female ratio for the visuospatial group which differed from 70% women reported in that study [2]. One other smaller study reported no significant difference in gender ratios between atypical and typical AD cases [3]. We found differences in symptom duration over cognitive symptom groups which was largely driven by those with language symptoms having shorter durations (compared to memory) whilst judgment and visuospatial groups were not significantly different from memory cases. Findings with respect to symptom length / disease durations are mixed in the literature with some studies showing no difference across AD subtypes [2, 3], one showing a shorter duration in younger onset AD compared with later onset AD [4], whilst others show younger onset AD and dementia cases to have longer durations [5, 6] potentially reflecting convoluted or difficult routes to diagnosis in some settings. The nature of the impairment experienced by language patients in particular, combined with the increased likelihood of these cases occurring at a younger age, may indicate rapid referral to ADCs resulting in a shorter symptom length in these cases. Notably, the language cases are the most impaired (on MMSE) at first visit. The apparent discrepancy of language symptom cases appearing to be more impaired on MMSE but less on CDR may be explained by difference in nature of the tests, with MMSE requiring reasonable language skills and, perhaps, overestimating global impairment in those with prominent language deficits.

The lower educational attainment of memory cases is line with what would be expected in older generations, however we found that this difference remained following adjustment of age at assessment. A recent study has shown that about half of AD cases are potentially explained by modifiable risk factors of which low educational attainment was arguably the largest risk factor worldwide [7] and remained important even within the USA population. It may be that this factor is important in the largest proportion of AD patients (memory cases) but less important for the less typical presentations where other factors drive symptoms and age of onset. Genetic factors such as APOE e4 dose are known to be higher in typical / memory AD cases [8-10] and we found highest proportions of APOE e4 carriers in the memory group. The lower proportion of e4 carriers in the visual group is in line findings of others [2, 11] whereas language cases had 57% non-e4 in this study compared with about 50% in another study [2] and 55% in a smaller language group of mild AD subjects from NACC defined using neuropsychology tests [12].

Our findings with respect to those with behavioral symptoms being more cognitively impaired are broadly in line with two studies that found that more severe behavioral symptoms were associated with more impairment [28, 29]. Our finding that patients with psychosis had greater cognitive impairment is similar to two previous reports [29, 31]. The lack of evidence we found of a difference in APOE e4 distribution according to behavioral symptom has been shown previously [29].

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Condition		**Percentage**
Dementia with Lewy bodies		4.0 %
Vascular dementia (NINDS/AIREN Probable)		3.1 %
Vascular dementia (NINDS/AIREN Possible)		1.9 %*
Alcohol-related dementia		0.7 %
Dementia of undetermined etiology		0.6 %
Frontotemporal dementia (behavioral/executive dementia)		1.9 %
Primary progressive aphasia (aphasic dementia)		1.6 %
Primary progressive aphasia subtype	Progressive nonfluent aphasia	0.6 % ^
	Semantic dementia – anomia plus word comprehension	0.4 % ^
	Semantic dementia – agnosic variant	<0.1 % ^
	Other primary progressive aphasia (e.g. logopenic, anomic, transcortical, word deafness, syntactic comprehension, motor speech disorder)	0.7 % ^

Progressive supranuclear palsy	0.1 %
Corticobasal degeneration	0.6 %
Cognitive dysfunction from medications	0.8 %
Cognitive dysfunction from medical illnesses	1.6 %
Parkinson's disease	1.3 %
Central nervous system neoplasm	0.3 %
Down's syndrome	0.1 %
Stroke	5.2 %
Hydrocephalus	0.9 %
Depression	21.0 %
Traumatic brain injury	1.4 %
Other major psychiatric illness	1.3 %
Other cognitive/neurologic condition	6.5 %

Supplementary table 1. Proportion of Total AD group with a diagnosis of another neurological or psychiatric condition in addition to that of possible or probable AD.

*variable not recorded in all subjects. The percentage represents patients with a positive diagnosis in this category as a proportion of all subjects (n=7815)

^variable recorded in primary progressive aphasia subjects. The percentage represents subjects with a positive subtype diagnosis as a proportion of all subjects (n=7815).

		Age-band <60 years compared with >79 years Odds ratio (95% CI)	Age-band 60-69 years compared with >79 years Odds ratio (95% CI)	Age-band 70-79 years compared with >79 years Odds ratio (95% CI)	Age band >79 years	P value from trend test treating age as continuous
First predominant cognitive symptom compared with memory	Memory	1.0	1.0	1.0	1.0	reference
	Judgement and problem solving	**4.7 (2.8, 8.0)**	**2.4 (1.5, 4.0)**	1.1 (0.7, 1.7)	1.0	**<0.001**
	Language	**3.8 (1.9, 7.7)**	**3.8 (2.2, 6.7)**	**3.6 (2.2, 5.8)**	1.0	**<0.001**
	Visuospatial function	**13.6 (6.4, 28.9)**	**8.6 (4.2, 17.6)**	**2.3 (1.1, 4.8)**	1.0	**<0.001**
First predominant behavioral	Apathy/ withdrawal	1.0	1.0	1.0	1.0	reference
	Depression	**2.1 (1.4, 3.0)**	**1.6 (1.2, 2.2)**	1.0 (0.8, 1.3)	1.0	**<0.001**

symptom compared with Apathy/ withdrawal	Psychosis	**0.5 (0.2, 0.9)**	**0.5 (0.3, 0.7)**	**0.6 (0.5, 0.8)**	1.0	**<0.001**
	Disinhibition	0.7 (0.3, 1.5)	0.8 (0.5, 1.4)	0.8 (0.5, 1.1)	1.0	0.3
	Irritability	0.9 (0.6, 1.4)	1.1 (0.8, 1.5)	1.2 (1.0, 1.5)	1.0	0.7
	Agitation	**0.3 (0.1, 0.9)**	1.1 (0.7, 1.8)	1.0 (0.7, 1.4)	1.0	0.4
	Personality change	1.7 (0.8, 3.7)	1.5 (0.8, 2.9)	1.2 (0.7, 2.0)	1.0	**0.03**
	Other	**2.2 (1.2, 4.1)**	1.6 (1.0, 2.7)	0.7 (0.4, 1.2)	1.0	**0.002**
	No symptom	0.7 (0.5, 1.0)	0.9 (0.7, 1.1)	0.9 (0.8, 1.1)	1.0	**0.02**

Supplementary table 2. Relationship between first cognitive/behavior symptoms with age at first presentation in the AD no other cause group. Odds ratios for first cognitive symptom and first behavioral symptom for younger age-bands compared with the oldest age-band. P values relate to models where age is used as a continuous variable. Significant results are shown in bold. Odds ratios are represented to 1 decimal place and p values to 1 significant figure.

		Age-band <60 years compared with >79 years Odds ratio (95% CI)	Age-band 60-69 years compared with >79 years Odds ratio (95% CI)	Age-band 70-79 years compared with >79 years Odds ratio (95% CI)	Age band >79 years	P value from trend test treating age as continuous
First predominant cognitive symptom compared with memory	Memory	1.0	1.0	1.0	1.0	reference
	Judgement and problem solving	**4.9 (2.8, 8.5)**	**2.7 (1.6, 4.5)**	1.1 (0.6, 1.8)	1.0	**<0.001**
	Language	**3.4 (1.6, 7.5)**	**4.0 (2.2, 7.4)**	**3.4 (2.0, 5.7)**	1.0	**<0.001**
	Visuospatial function	**9.8 (4.4, 21.8)**	**7.0 (3.3, 14.6)**	**2.1 (1.0, 4.5)**	1.0	**<0.001**
First predominant behavioral symptom	Apathy/ withdrawal	1.0	1.0	1.0	1.0	reference
	Depression	**2.0 (1.4, 2.9)**	**1.6 (1.2, 2.2)**	1.0 (0.8, 1.3)	1.0	**<0.001**

compared with Apathy/ withdrawal	Psychosis	0.5 (0.3, 1.0)	**0.5 (0.3, 0.8)**	**0.6 (0.5, 0.9)**	1.0	**0.001**
	Disinhibition	0.8 (0.3, 1.8)	0.7 (0.4, 1.3)	0.8 (0.5, 1.2)	1.0	0.3
	Irritability	1.0 (0.6, 1.5)	1.2 (0.9, 1.6)	1.3 (1.0, 1.6)	1.0	0.6
	Agitation	**0.2 (0.0, 0.8)**	0.8 (0.5, 1.4)	0.9 (0.6, 1.4)	1.0	0.1
	Personality change	1.2 (0.5, 3.1)	1.6 (0.9, 3.1)	1.1 (0.7, 1.9)	1.0	0.1
	Other	**2.0 (1.0, 3.9)**	1.5 (0.8, 2.6)	0.7 (0.4, 1.1)	1.0	**0.01**
	No symptom	0.8 (0.5, 1.1)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)	1.0	**0.03**

Supplementary table 3. Relationship between first cognitive/behavior symptoms with age at first presentation in the probable AD no other cause group. Odds ratios for first cognitive symptom and first behavioral symptom for younger age-bands compared with the oldest age-band. P values relate to models where age is used as a continuous variable. Significant results are shown in bold. Odds ratios are represented to 1 decimal place and p values to 1 significant figure.

		N (N APOE)	Age at first presentation, years	Gender, % women	Symptom length, years	Education, years	MMSE at first presentation	Global CDR, % scoring 0, 0.5, 1, 2 and 3	CDR Sum of Boxes / 18	APOE e4 allele % 0,1,2	n APP, PS1, PS2
First predominant cognitive symptom	Memory	6914 (4593)	76.2 (9.4)	57.5	5.0 (3.5)	13.7 (4.0)	19.3 (6.7)	0.0, 27.4, 45.7, 17.7, 9,2	7.1 (4.4)	40.8, 46.7, 12.5	2, 13, 0
	Judgment and problem solving	297 (201)	71.6 (11.2)	42.4	5.2 (3.7)	14.3 (3.8)	19.6 (7.0)	0.0, 23.6, 42.4, 22.2, 11.8	7.9 (4.6)	49.8, 35.8, 14.4	0, 0, 0
	Language	317 (219)	70.5 (8.8)	46.7	4.3 (3.0)	15.2 (3.2)	18.9 (7.4)	2.8, 43.5, 37.9, 7.6, 8.2	5.5 (4.4)	57.1, 35.2, 7.8	0, 0, 0
	Visuospatial function	178 (134)	67.6 (9.7)	48.3	4.8 (3.0)	15.5 (3.2)	19.7 (7.1)	1.1, 28.1, 45.5, 18.0, 7.3	6.8 (4.3)	56.7, 31.3, 11.9	0, 0, 0
	P value for test across symptom groups	NA	<0.001 <0.001#	<0.001 <0.001*	0.001~ 0.02~~	<0.001^ <0.001^^	0.001** 0.005***	<0.001** <0.001***	<0.001** <0.001***	<0.001 <0.001*	NT
First predominant behavioral	Apathy/ withdrawal	1994 (1339)	75.4 (9.7)	48.1	5.3 (3.6)	14.2 (3.8)	18.6 (6.9)	0.0, 19.1, 48.5, 21.6, 10.9	7.8 (4.4)	41.8, 45.3, 12.9	1, 2, 0

symptom	Depression	1652 (1117)	73.8 (10.6)	65.2	4.8 (3.4)	13.5 (4.1)	19.8 (6.6)	0.2, 29.9, 45.9, 15.6, 8.4	6.7 (4.4)	41.1, 46.6,12.4	1, 6, 0
	Psychosis	442 (254)	77.9 (8.9)	63.4	5.1 (3.6)	12.5 (4.1)	16.0 (7.3)	0.0, 12.7, 42.3, 26.9, 18.1	9.1 (4.9)	47.2, 42.9, 9.8	0, 1, 0
	Disinhibition	200 (138)	76.1 (9.3)	49.5	5.9 (3.5)	14.2 (4.0)	19.5 (7.2)	0.0, 21.0, 42.0, 26.5,10.5	8.0 (4.5)	40.6, 45.6, 13.8	0, 0, 0
	Irritability	960 (622)	75.6 (9.1)	52.0	5.0 (3.6)	13.7 (3.8)	19.5 (6.9)	0.2, 28.9, 44.8, 17.0, 9.2	7.0 (4.4)	43.1, 44.9, 12.1	0, 0, 0
	Agitation	233 (162)	75.9 (8.6)	55.4	5.9 (3.3)	13.6 (3.7)	16.0 (8.3)	0.0, 12.9, 35.2, 26.6, 25.3	10.2 (5.3)	40.7, 45.7, 13.6	0, 0, 0
	Personality change	154 (96)	74.0 (10.2)	51.3	5.3 (3.5)	14.0 (3.8)	19.2 (7.6)	0.0, 16.9, 42.2, 26.0, 14.9	8.4 (4.6)	46.9, 41.7, 11.5	0, 0, 0
	Other	191 (126)	73.5 (10.6)	67.0	4.6 (3.3)	14.2 (3.7)	20.0 (6.5)	0.0, 28.3, 50.8, 14.1, 6.8	6.5 (4.2)	42.1, 41.3, 16.7	0, 1, 0
	No symptom	1841 (1267)	76.7 (9.2)	57.7	4.5 (3.3)	14.1 (3.8)	20.7 (5.9)	0.4, 42.9, 42.9, 10.3, 3.5	5.4 (3.6)	42.8, 46.3, 11.0	0, 3, 0

	P value for test across symptom groups	NA	<0.001 <0.001#	<0.001 <0.001*	<0.001~ <0.001~~	<0.001^ <0.001^^	<0.001** <0.001***	<0.001** <0.001***	<0.001** <0.001***	0.9 >0.9*	NT

Supplementary table 4. Demographic and genetic information for cognitive and behavioral symptom groups

N relates to the maximum number of subjects in each group. Numbers of subjects varies across tests.

adjusted for symptom length

* adjusted for age

~ adjusted for Alzheimer's Disease Center

~~ adjusted for Alzheimer's Disease Center and age

^ adjusted for sex

^^ adjusted for age and sex

** adjusted for sex, symptom length and education level

*** adjusted for age, sex, symptom length and education level