Non-memory cognitive symptom development in Alzheimer's disease

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Abstract

BACKGROUND: Memory is known to be the most common first symptom in Alzheimer's Disease. Assessing non-memory cognitive symptom development in Alzheimer's Disease is important for understanding disease progression and the potential identification of treatment-responsive subtypes.

METHODS: Data from the National Alzheimer Co-ordinating Center were examined. Logistic regression models were fitted evaluating development of judgement, language, visuospatial and attention symptoms at first and second visits to Alzheimer's Disease Centers. Predictors were age and prior symptoms, adjusting for symptom length and sex. The models were then refitted assessing APOE-ε4 effects.

RESULTS: Each decade reduction in presentation age increased the odds of language, visuospatial and attention symptom development at both visits by 8-18% ($p<0.05$, all tests), and judgement symptoms at second visit by 13% ($p<0.05$). Prior symptoms were not equally predictive of symptom development. For example, having first-predominant language symptoms carried the lowest risk of developing other first-visit symptoms and having memory symptoms was a stronger predictor of developing judgement than other symptoms. The APOE-ε4 gene showed little impact on symptom development when included as a predictor.

CONCLUSIONS: Our findings provide support for the concept that younger-onset AD is associated with the progressive development of more non-memory symptoms beyond the first time point.

Associations between symptoms were evident, which may reflect that pathology can remain isolated in a network for some time. APOE-ε4 status had little influence on cognitive symptom development which may indicate that the effect it has occurs very early in the disease course.

1. Introduction

It is increasingly recognised that memory dysfunction is not always the first or the only cognitive symptom experienced by those with Alzheimer's disease (AD) [1–7]. Many patients experience non-memory cognitive symptoms as their first symptom and those with younger onset (usually onset before 65 years) are more likely to have early non-memory symptoms than older patients [3–7]. There is increased recognition of non-amnestic subtypes of AD including language, visuospatial presentations and executive dysfunction [2]. Less understood is whether there is a pattern of non-memory cognitive symptom development and whether patient variables are important predictors. It has been suggested that the biggest genetic risk factor for sporadic AD (the APOE-ε4 allele [8]) may influence the presentation [9,10]. For example, those with an ε4 allele are more likely to have memory as the first predominant symptom or an isolated amnestic presentation [11].

The presence of cognitive symptoms, as opposed to neuropsychological test scores, is important to investigate as symptoms are easy to evaluate and closely relate to patients' experiences. Further, non-memory symptom data associate with activities of daily living suggesting that patients' lives are affected when symptoms are present [12,13]. However, symptom data can be difficult to analyse due to their categorical nature. A high prevalence of specific symptoms can also be problematic if comparisons are made between individuals with and without a symptom, or in analyses assessing predictors of developing a symptom, so large datasets are required.

In this study we used an AD patient dataset to examine the relationship between age and the development of new non-memory cognitive symptoms, and whether previously-recorded symptoms influenced non-memory symptom development. Finally, the influence of APOE-ε4 was examined. We hypothesised that: younger AD patients would be more likely to develop non-memory cognitive

symptoms; there was likely to be an influence of prior symptoms on symptom development; those without an APOE-ε4 gene were more likely to develop non-memory symptoms.

2. Methods

2.1 Subjects

AD patient data collected by the National Alzheimer's Coordinating Center (NACC) were analysed. NACC maintains a database of standardized clinical research data from individuals with normal cognition, mild cognitive impairment and neurodegenerative diseases, collected from past and present NIA-funded US Alzheimer's Disease Centers (ADCs). Written informed consents were obtained from participants and the study was approved by an Institutional Review Board (IRB) at each ADC. Research using the NACC database was approved by the University of Washington IRB. NACC recruitment and data collection has been described previously [14]. Data included patients seen at 34 ADCs between study inception in 2005 and May 2016. Our study required subjects diagnosed with probable or possible AD according to standard diagnostic criteria [15] at their first NACC visit (n>9000).

Since most patients only had early visit data, analyses were restricted to the first two NACC visits. At each visit, patients were assessed by their clinician for the presence or absence of up to seven cognitive symptoms and "other" cognitive symptoms. The clinician's judgement was used to determine symptom presence in consultation with the patient and caregivers. Missing data were typically due to information not being collected or changes in versions of datasheets. The first predominant cognitive symptom was recorded by the clinician, indicating which of the symptom categories was first recognized as a decline in the subject's cognition. The age at which the clinician estimated cognitive decline began was also recorded.

Descriptive summaries of each first predominant cognitive symptom were used to identify symptoms as outcome variables in the analysis. Memory was excluded since its high frequency meant that few patients were at risk of developing this symptom during follow-up. Cognitive symptoms reported in only small numbers of patients were excluded as outcome variables since their rarity would make the statistical power of analyses low.

2.2 Variables

We used first predominant cognitive symptoms reported at first visit, first and second visit cognitive symptoms, symptom duration (between age of decline and age of presentation), interval between the first and second visits, age of presentation, and gender. Mini-mental state examination scores at first visit were also used for group characterisation.

2.3 Statistical analysis

All analyses were conducted in Stata v15. Summary statistics were produced for the variables of interest. Missing responses for symptom presence were explored for both visits.

Logistic regression was the primary method of analysis. The outcome in each model was the development of a symptom never previously reported. Different models were used for symptom development at the first and second NACC visits since only first predominant symptom was available for predicting symptoms at first visit, whereas presence of each of the other symptoms at first visit was also available at the second visit.

Each first visit symptom outcome was modelled separately; modelling the odds of developing the cognitive symptoms of interest at the first NACC visit, conditional on this not being the first predominant cognitive symptom. Therefore, we only explore new symptoms developed between the first predominant symptom and first visit. The predictors of interest were age at first visit, and the first predominant cognitive symptom, adjusting for gender and symptom duration.

The odds of developing symptoms at the second visit were modelled, conditional on the symptom neither being the first predominant cognitive symptom nor reported at visit 1. Predictors of interest were age at first visit, first predominant cognitive symptom, first visit cognitive symptoms, with adjustment for gender, symptom duration prior to first visit and the inter-visit interval. Joint Wald tests assessed whether there was evidence that the first predominant cognitive symptom remained a predictor at visit 2, after adjusting for visit 1 symptoms. Models were fitted omitting the first predominant symptom if found not to improve model fit. Joint Wald tests assessed whether there was evidence that the odds ratios associated with each first visit cognitive symptom predictor were heterogeneous.

To explore APOE-ε4 effects, each of the models described above was re-fitted, adjusting for categorical ε4 allele number.

3. Results

3.1 Demographics

9484 patients attended the first NACC visit, with 87% reporting memory impairment as the first predominant cognitive symptom (see table 1 for summary statistics). Proportions of patients with each reported cognitive symptom at each visit are shown in figure 1. Four non-memory symptoms (impairments of judgement, language, visuospatial function and attention) were deemed sufficiently prevalent to include as outcomes in the symptom development models. See supplementary table S1 for missing baseline variables and supplementary figure S1 for age of presentation distribution.

	Summary statistics
N	9484
Mean age at first visit (SD) [Range]	74.9 (9.9) [35-110]
Mean MMSE at first visit (SD) [Range]	19.3 (6.8) [0-30]

Women (%)		5283 (56)
Symptom duration in years (SD)		4.8 (3.4)
Time between visits 1 and 2, years (SD)		1.2 (0.4)
Attended visit 1 (%)		9484 (100)
Attended visit 2 (%)		5538 (58)
APOE-ε4 alleles (%)*	0	2913 (30.7)
	1	3046 (32.1)
	2	885 (9.3)
First predominant	Memory	8257 (87)
cognitive symptom	Orientation	0 (0)
(%)†	Judgement	413 (4)
	Language	429 (5)
	Visuospatial function	230 (2)
	Attention/concentration	82 (0.8)
	Fluctuating cognition	4 (<0.1)
	Other	38 (0.4)
	Unknown	31 (0.3)

Table 1: Patient characteristics for the whole AD group

* Data missing for 2640 (27.8%) patients

†Fluctuating cognition and orientation were added as categories in revised versions of data collection sheets

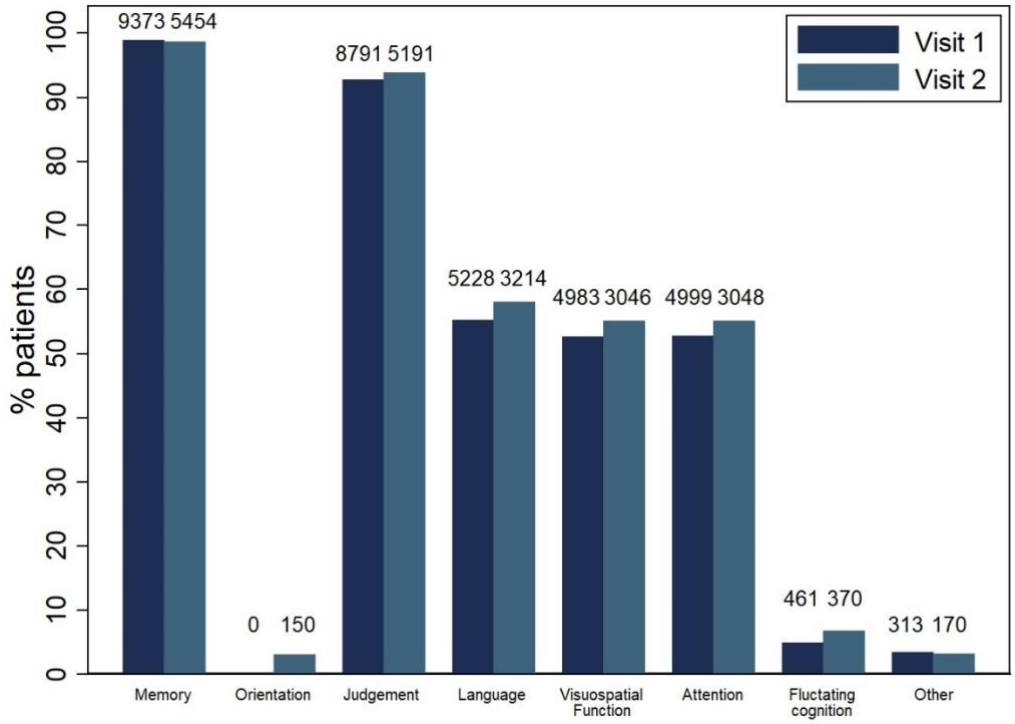

Figure 1: AD patients reporting each cognitive symptom at visits 1 (n=9484) and 2 (n=5538)

58% of patients attended both visits; orientation and "other" were the most frequently missing symptoms, with patients only asked about orientation symptoms at visit 2, so this was missing at visit 1.

3.2 First visit

Results from models relating development of first visit symptoms to age at presentation, symptom duration, gender and first predominant cognitive symptom are shown in figure 2. There was evidence that older patients were less likely to develop language, visuospatial and attention symptoms, with a decade later age of presentation associated with an estimated 8 to 18% decrease in the odds of reporting these. An increase in symptom duration prior to first visit increased the likelihood of developing all non-memory symptoms, with a one-year increase in length of symptoms associated with estimated increases in odds of reporting these symptoms of 12 to 21%. Gender effects differed according to symptom: women were more likely to develop impaired judgement

(19% increase in odds) and attention (11% increase in odds) symptoms while men were more likely to develop language symptoms (11% increase in odds).

Amongst the common first predominant symptoms, memory carried the highest risk for development of impaired judgement. Language and visuospatial function carried the lowest; the odds were lower and statistically significant for both compared with memory. Having language impairment as the first predominant symptom also carried the lowest risk of developing visuospatial symptoms (statistically significantly lower than memory) and the lowest risk of developing attention symptoms, although here differences between first predominant symptoms were less marked, with only judgement carrying a higher risk than the other common first predominant symptoms. For development of language symptoms, having memory or visuospatial function as the first predominant symptom carried the lowest risks, with the risk for memory being statistically significantly lower than those for attention and judgement.

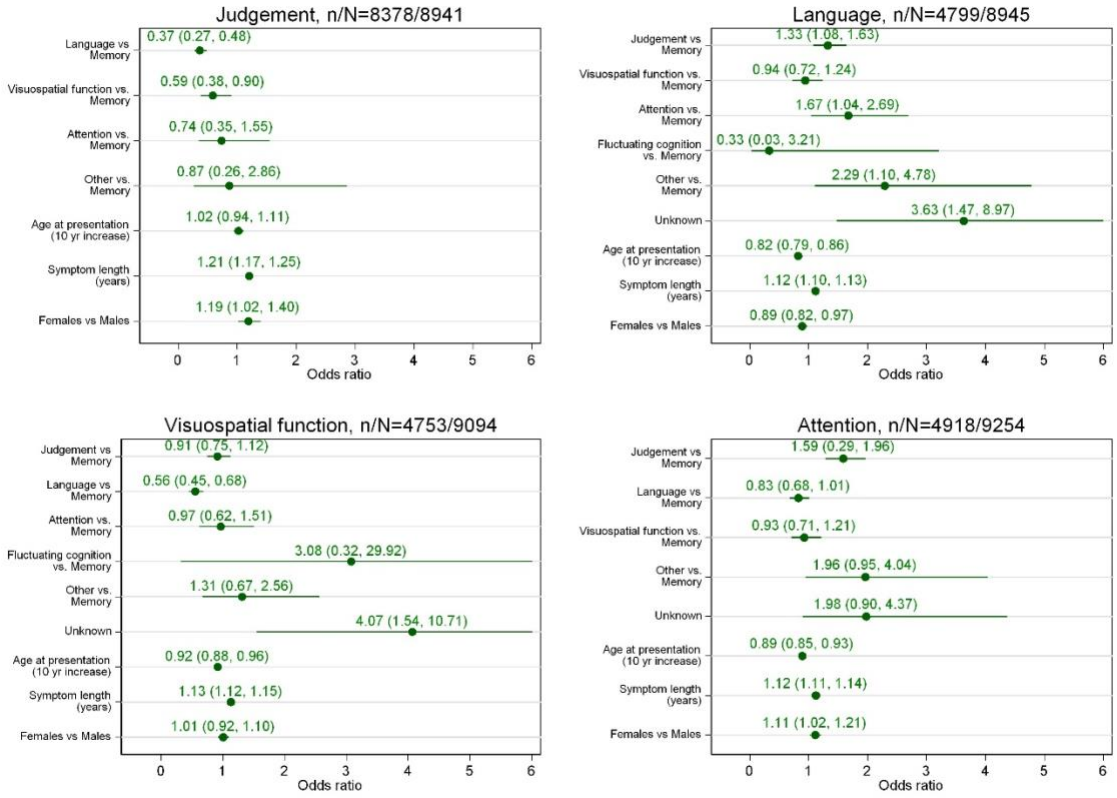

Figure 2: Comparative odds ratios (95% CI) for the development of each of four cognitive symptoms at visit 1 (n/N=number of patients who developed symptom/number at risk). Some 95% CI extend beyond the shown range.

3.3 Second visit

The estimated associations between development of second visit symptoms and age at presentation, symptom length, time between visits, gender and first visit symptoms are shown in figure 3. Wald tests indicated that after adjusting for the symptoms reported at visit 1, there was no evidence of a residual predictive effect of first predominant cognitive symptom ($p>0.1$, all tests, see supplementary table S2).

There was strong evidence that younger subjects were more likely to develop all non-memory cognitive symptoms, with increases in the odds of reporting these symptoms at visit 2 varying from 11 to 23% for a decade later presentation age. Women had 34% lower odds than men of developing judgement symptoms at visit 2. Time between visits was strongly positively predictive of the development of all non-memory cognitive symptoms.

Where there was evidence that first visit symptoms were predictive of second visit symptoms, the relationship was positive. The Wald tests suggested that visit 1 symptoms were not equally predictive of development of judgement and visuospatial function symptoms. Memory problems at visit 1 more than tripled the odds of developing judgement symptoms at visit 2. For visuospatial symptoms at visit 2, memory and judgement symptoms were the strongest predictors, each approximately doubling the odds of development. For development of visit 2 language and attention symptoms, there was no evidence that symptoms were unequally predictive.

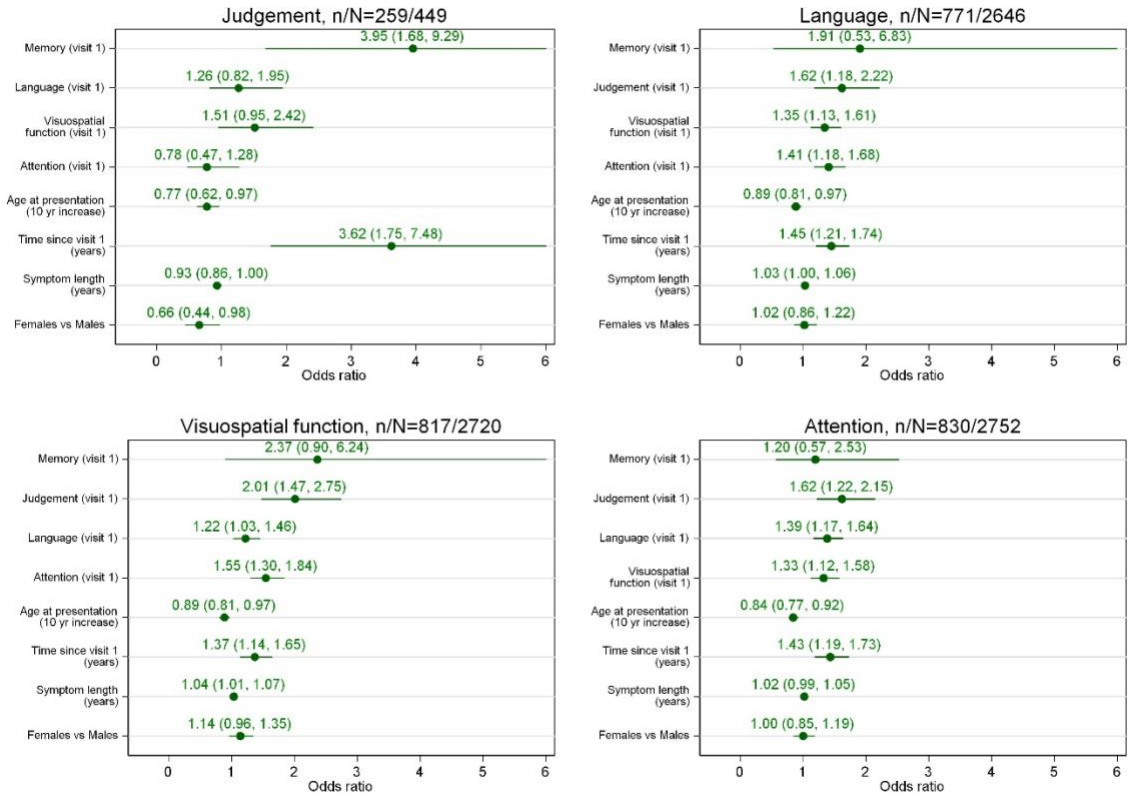

Figure 3: Comparative odds ratios (95% CI) for the development of each of four cognitive symptoms at visit 2 (n/N=number of patients who developed symptom/number at risk). Some 95% CI extend beyond the shown range.

3.4 The effect of APOE-ε4

The effect of APOE-ε4 was typically small, with no consistent pattern in the direction of estimated effects (see supplementary table S3). There was one statistically significant result; notably with sixteen analyses the danger of a false-positive is high.

4. Discussion

Our study found that each decade reduction in presentation age was associated with development of non-memory cognitive symptoms over time, and first visit symptom development differed according to first predominant cognitive symptom. Memory carried the highest risk and language the lowest of developing impaired judgement. Having language as the first predominant symptom

also carried the lowest risk of developing visuospatial and attention symptoms. For development of language symptoms, memory or visuospatial functioning as first predominant cognitive symptom carried the lowest risks. Considering non-memory cognitive symptoms at visit 2, only symptoms developed by visit 1 were predictive of symptom development. Having memory symptoms was a markedly stronger predictor than the others for developing judgement symptoms. Gender had some influence over first visit symptom development (women were more likely to develop attention and judgement symptoms, but less likely to develop language symptoms). At the second visit, men were more likely to develop judgement symptoms. There was no convincing evidence that APOE-ε4 was predictive of non-memory cognitive symptoms.

Finding that younger patients were more likely to develop three of the four non-memory cognitive symptoms between the first predominant symptom occurring and first visit is consistent with the view that younger patients are more likely to have a more non-memory presentation. Further, these results show that more non-memory cognitive domains are affected faster in younger patients. The evidence for patterns of prediction of symptom development may support the theory that pathology can be isolated within specific brain networks before spreading.

The effects of age on presentation observed are consistent with other studies indicating that younger patients have more non-memory cognitive symptoms [3–7]. One similar study assessing development of cognitive problems demonstrated that younger patients were more likely to develop language and concentration problems over time [16].

Finding that language impairment carried the lowest risk for developing other non-memory cognitive symptoms at first visit is possibly attributable to isolated and focal damage at early disease stages [17].

We found some influence of gender on symptom development, particularly at first visit. Results in the literature are mixed. Two studies have shown no significant differences in gender between

typical and atypical AD groups [5,18]. Other studies have shown differences: one showed the visual variant of AD were slightly more likely to be female [11]; another that women were more likely to have first predominant memory symptoms than non-memory symptoms [3].

Our lack of significant predictive results for APOE-ε4 seems at odds with the literature [3,11,19]. However, results are mixed: recent work has shown the ε4 allele to be associated with increased risk of posterior cortical atrophy (PCA) [20]. Other work has shown that visuospatial, executive functioning and attention problems differ in early vs. late AD and this age effect is unchanged by adjusting for APOE-ε4 [21]. Our current work differs from previous analyses as it assesses non-memory cognitive symptom development, including those with memory as a first symptom, adjusting for whether an individual had the symptom previously. Therefore, many non-carriers will have memory as the first symptom. Our data may thus imply that the APOE-ε4 effect on presentation occurs early in the disease and little effect remains once prior symptoms are accounted for.

The main strength of our study is that it is a large multi-site study with systematic data collection. However, we did not examine autopsy-confirmed AD cases; our findings may be influenced by misdiagnoses which may be more prevalent in younger-onset cases [5]. Missing data was present in our analyses due to rolling recruitment and subject withdrawal and not all subjects had APOE testing. Collection of first predominant symptom and age of decline carries risks of recall bias; more objective measures of cognitive function, such as neuropsychological test results, were not investigated. The NACC dataset represents a convenience dataset; the patients are not necessarily representative of the wider AD population. We cannot make conclusions regarding the weight of specific symptoms beyond the first predominant symptom. The initial symptom may still predominate patients' experiences throughout the disease [11].

Younger-onset patients develop more non-memory symptoms, allowing for already-acquired symptoms, suggesting a different course of AD in these patients. APOE-ε4 genotype does not explain

these findings, suggesting that other genes may have a role in non-memory symptom development.

Non-memory cognitive symptoms are important to assess, especially in younger-onset cases.

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Conflicts of interest

None

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Data Availability

The data that support the findings of this study are available from the National Alzheimer's Coordinating Center (NACC). Restrictions apply to the availability of these data, which were used under license for this study. Data are available at https://www.alz.washington.edu/ with the permission of NACC.

References

1. Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: A new lexicon. Lancet Neurol. 2010;9(11):1118–27.

2. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement. 2011;7(3):263–9.

3. Barnes J, Dickerson BC, Frost C, et al. Alzheimer's disease first symptoms are age dependent:

Evidence from the NACC dataset. Alzheimer's Dement. 2015;11(11):1349–57.

4. Koedam ELGE, Lauffer V, Van Der Vlies AE, et al. Early-versus late-onset Alzheimer's disease: More than age alone. J Alzheimer's Dis. 2010;19(4):1401–8.

5. Balasa M, Gelpi E, Antonell A, et al. Clinical features and APOE genotype of pathologically proven early-onset Alzheimer disease. Neurology. 2011;76(20):1720–5.

6. Mendez MF. The accurate diagnosis of early-onset dementia. Int J Psychiatry Med. 2006;36(4):401–12.

7. Jacobs D, Sano M, Marder K, et al. Age at onset of Alzheimer's disease: Relation to pattern of cognitive dysfunction and rate of decline. Neurology. 1994;44:1215–20.

8. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science (80). 1993;261(5123):921–3.

9. van der Flier WM, Pijnenburg YAL, Fox NC, Scheltens P. Early-onset versus late-onset Alzheimer's disease: The case of the missing APOE ε4 allele. Lancet Neurol. 2011;10(3):280–8.

10. Wolk DA, Dickerson BC, Alzheimer's Disease Neuroimaging Initiative. Apolipoprotein E (APOE) genotype has dissociable effects on memory and attentional-executive network function in Alzheimer's disease. Proc Natl Acad Sci U S A. 2010;107(22):10256–61.

11. Snowden JS, Stopford CL, Julien CL, et al. Cognitive phenotypes in Alzheimer's disease and genetic risk. Cortex. 2007;43(7):835–45.

12. Jefferson AL, Barakat LP, Giovannetti T, et al. Object Perception Impairments Predict Instrumental Activities of Daily Living Dependence in Alzheimer's Disease Instrumental Activities of Daily Living Dependence in Alzheimer's Disease. J Clin Exp Neuropsychol. 2006;28:884–97.

13. Martyr A, Clare L. Executive function and activities of daily living in Alzheimer's disease: A correlational meta-analysis. Dement Geriatr Cogn Disord. 2012;33(2–3):189–203.

14. Morris JC, Weintraub S, Chui HC, et al. The Uniform Data Set (UDS): Clinical and Cognitive Variables and Descriptive Data From Alzheimer Disease Centers. Alzheimer Dis Assoc Disord. 2006 Oct;20(4):210–6.

15. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984 Jul;34(7):939–939.

16. Koss E, Edland S, Fillenbaum G, et al. Clinical and neuropsychological differences between patients with earlier and later onset of Alzheimer's disease: A CERAD analysis, part XII. Neurology. 1996;46(1):136–41.

17. Galton CJ, Patterson K, Xuereb JH, Hodges JR. Atypical and typical presentations of Alzheimer's disease: a clinical, neuropsychological, neuroimaging and pathological study of 13 cases. Brain. 2000;123 Pt 3:484–98.

18. Mez J, Cosentino S, Brickman AM, et al. Dysexecutive versus amnestic alzheimer disease subgroups: Analysis of demographic, genetic, and vascular factors. Alzheimer Dis Assoc Disord. 2013;27(3):218–25.

19. Dickerson BC, Wolk DA. Dysexecutive versus amnesic phenotypes of very mild Alzheimer's

disease are associated with distinct clinical, genetic and cortical thinning characteristics. J Neurol Neurosurg Psychiatry. 2011;82(1):45–51.

20. Schott JM, Crutch SJ, Carrasquillo MM, et al. Genetic risk factors for the posterior cortical atrophy variant of Alzheimer's disease. Alzheimer's Dement. 2016;12(8):862–71.

21. Smits LL, Pijnenburg YAL, Koedam ELGE, et al. Early onset alzheimer's disease is associated with a distinct neuropsychological profile. J Alzheimer's Dis. 2012;30(1):101–8.