Neurological manifestations of autosomal dominant familial Alzheimer's disease: a comparison of the published literature with the Dominantly Inherited Alzheimer Network observational study (DIAN-OBS)

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Summary

Background Autosomal dominant familial Alzheimer's disease (ADAD) is a rare disorder with non-amnestic neurological symptoms in some clinical presentations. We aimed to compile and compare data from symptomatic participants in the Dominantly Inherited Alzheimer Network observational study (DIAN-OBS) with those reported in the literature to estimate the prevalences of non-amnestic neurological symptoms in participants with ADAD.

Methods We prospectively collected data from the DIAN-OBS database, which recruited participants from study centres in the USA, Europe, and Australia, between Feb 29, 2008, and July 1, 2014. We also did a systematic review of publications to extract individual-level clinical data for symptomatic participants with ADAD. We used data for age of onset (from first report of cognitive decline), disease course from onset to death, and the presence of 13 neurological findings that have been reported in association with ADAD. Using multivariable linear regression, we investigated the prevalences of various non-amnestic neurological symptoms and the contributions of age of onset and specific mutation type on symptoms.

Findings The DIAN-OBS dataset included 107 individuals with detailed clinical data (forming the DIAN-OBS cohort). Our systematic review yielded 188 publications reporting on 1228 symptomatic individuals, with detailed neurological examination descriptions available for 753 individuals (forming the published data cohort). The most prevalent non-amnestic cognitive manifestations in participants in the DIAN-OBS cohort were those typical of mild to moderate Alzheimer's disease, including visual agnosia (55·1%, 95% CI 45·7–64·6), aphasia (57·9%, 48·6–67·3), and behavioural changes (61·7%, 51·5–70·0). Non-amnestic cognitive manifestations were less prevalent in the published data cohort (eg, visual agnosia [5·6%, 3·9–7·2], aphasia [23·0%, 20·0–26·0], and behavioural changes [31·7%, 28·4–35·1]). Prevalence of non-cognitive neurological manifestations in the DIAN-OBS cohort was low, including myoclonus and spasticity (9·3%, 95% CI 3·8–15·0), and seizures (2·8%, 0·5–5·9) and moderate for parkinsonism (11·2%, 5·3–17·1). By constrast, prevalence was higher in the published data cohort for myoclonus and spasticity (19·4%, 16·6–22·2 and 15·0%, 12·5–17·6, respectively), parkinsonism (12·5%, 10·1–15·0), and seizures (20·3%, 17·4–23·2). In an analysis of the published data cohort, ischaemic stroke was more prevalent at older ages of onset of symptoms of ADAD (odds ratio 1·09 per 1 year increase in age of onset, 95% CI 1·04–1·14, p=0·0003); and motor symptoms were more common at younger age of onset (myoclonus 0·93, 0·90–0·97, p=0·0007; seizures 0·95, 0·92–0·98, p=0·0018; corticobulbar deficits 0·91, 0·86–0·96, p=0·0012; and cerebellar ataxia 0·82, 0·74–0·91, p=0·0002). In the DIAN-OBS cohort, non-cognitive symptoms were more common at more severe stages of disease.

Interpretation The non-cognitive clinical manifestations of Alzheimer's disease seem to affect a small proportion of participants with mild to moderate ADAD, and are probably influenced by disease severity, environmental, and genetic factors. When evaluating patients with potential ADAD, clinicians should note that cognitive symptoms typical of sporadic Alzheimer's disease are the most consistent finding, with some patients manifesting non-cognitive neurological symptoms. Future work is needed to determine the environmental and genetic factors that cause these neurological symptoms.

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Introduction

Autosomal dominant familial Alzheimer's disease (ADAD) is a rare, completely penetrant form of Alzheimer's disease that typically presents at a much earlier age than do sporadic forms of Alzheimer's disease. Despite its rarity, ADAD has been used as a model to understand pathological processes and develop potential therapies for sporadic Alzheimer's disease because of similarities in clinical course and pathophysiology.[1] Although most carriers of symptomatic mutations in

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For more on **DIAN-OBS** see http://www.dian-info.org/

For **DIAN study centres** see http://www.dian-info.org/institutions_map.htm

Research in context

Evidence before this study

We reviewed publications in the Alzheimer Disease & Frontotemporal Dementia Mutation Database and the Alzheimer Research Forum database and searched PubMed for articles published in English before Jan 27, 2015. We identified 188 peer-reviewed journal articles that reported individual-level data for age of onset, disease course from onset to death, and the presence of 14 neurological findings previously reported to be associated with autosomal dominant familial Alzheimer's disease (ADAD). 169 of these reports were on a small number of subjects or families and across a wide spectrum of clinical severity. These reports suggested a relatively high prevalence of non-cognitive neurological manifestations, including behavioural changes, motor symptoms, and seizures, which might be further influenced by the specific gene mutation. However, we identified only six single-centre and three multicentre studies of cohorts and no compiled individual-level data reviews.

Added value of this study

We compared the prevalences of symptoms between the Dominantly Inherited Alzheimer's Network observational study and published data for participants with ADAD, and determined correlations between clinical features and gene mutation type and position. This study provides one of the largest and most diverse collections of data for prospectively followed, symptomatic, ADAD populations. With the large number of *PSEN1* mutation carriers, we were also able to explore whether atypical clinical features were associated with specific codon position, as has been suggested previously. However, we found no clear associations of clinical features with *PSEN1* codon position.

Implications of available evidence

This study indicates that the prevalence of atypical clinical features in ADAD is low and might have been overestimated. Non-cognitive neurological symptoms of Alzheimer's disease seem to affect a minority of ADAD mutation carriers, suggesting that the mutations are not the predominant factor for non-cognitive neurological manifestations of Alzheimer's disease. The factors that influence the presence of neurological symptoms include unidentified genetic and environmental factors, with some impact from the age of onset, stage of disease, and type of mutation. Non-amnestic cognitive impairment is common in ADAD, as in sporadic Alzheimer's disease. As ADAD has provided a wealth of understanding of Alzheimer's disease pathophysiology, future work comparing ADAD with sporadic Alzheimer's disease should lead to a better understanding of both sporadic and dominantly inherited Alzheimer's disease.

amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), or presenilin 2 (*PSEN2*) genes present with early amnestic symptoms[2] similar to individuals with sporadic Alzheimer's disease, some have additional behavioural and neurological deficits, such as seizures, myoclonus, spastic paraparesis, or visual disturbances, with substantial diversity in age of onset, clinical presentation, and rate of progression.[1,3–5] The location of mutations within genes can also affect pathophysiology and age of onset, as is the case for *PSEN1* mutations before and after codon 200.[6]

As a consequence of the rarity of ADAD and the reported variability in presentation, it has been difficult to estimate the prevalence of neurological manifestations of ADAD mutation carriers as a group. We aimed to better clarify the prevalence of non-amnestic manifestations of ADAD from a prospective, global, observational ADAD study—the Dominantly Inherited Alzheimer's Network observational study (DIAN-OBS)—and individual-level data for symptomatic participants extracted from published reports. Additionally, we aimed to assess relationships of these clinical manifestations with the age of onset and the location of ADAD mutations within affected genes.

Methods

Participants and systematic review

Between Feb 29, 2008, and July 1, 2014, participants in the DIAN observational study (DIAN-OBS) were recruited to study centres in the USA, Europe, and Australia. Participants were members of families of mutation carriers (*APP*, *PSEN1*, or *PSEN2*) known to cause ADAD.[7] Each study participant and someone who knew the participant well underwent semi-structured interviews by qualified study raters to collect detailed demographic information, medical history, and family history. All study staff underwent audiotape recordings of the clinical assessments at the beginning of the study and for every tenth participant to ensure compliance with the protocol and increase inter-rater reliability. Each participant completed a physical and neurological examination by a clinical evaluator who was masked to the participant's mutation status. Individuals were considered to be symptomatic at the time of analysis if they had both a Clinical Dementia Rating scale—sum of boxes score[8] greater than zero, and a known pathogenic ADAD mutation as confirmed by genetic testing using methods previously described.[9,10] Only symptomatic individuals from the DIAN-OBS cohort were included in this study.

The DIAN-OBS study was reviewed and approved by all participating sites institutional or ethics review boards (IRB). Written informed consent was obtained from all participants (or from their legally authorised representatives, if appropriate). Also obtained were signed, IRB-approved DIAN-OBS consent forms that included a statement informing participants that

deidentified data would be shared with authorised investigators for future research following guidelines for preserving confidentiality through coded identifiers.

In an expansion of our previously reported ADAD meta-analysis dataset,[11] we collected clinical data for 1228 carriers of 183 known pathogenic mutations in *APP*, *PSEN1*, and *PSEN2*. We used publications cited in the Alzheimer Disease & Frontotemporal Dementia Mutation Database and AlzGene, and searched PubMed for papers published in English up to Jan 27, 2015 using the terms "dominant Alzheimer", "dominant AD", "ADAD", "presenilin", "PSEN1", "PSEN2", and "APP". We recorded information for genotype information; pedigree information; ages of onset and death; clinical descriptions of the disease course and symptomatology; and pathological findings for each symptomatic individual, when available. MT read through the reports and extracted these data. In this published data group, only symptomatic individuals were included; individuals were designated as symptomatic by the authors of the publication. Length of follow-up in this group was defined as the time from age of onset until the individual either died or was lost to follow-up. Age of onset was determined by clinician judgment as the age at which the individual began to exhibit cognitive decline. Years of follow-up were calculated by subtracting the individual's age of onset from their age at the latest visit. We did not include individuals with *APP* mutations and predominant cerebral amyloid angiopathy in the analysis because this presentation can be associated with less uniform pathology.

Procedures

DIAN-OBS data are required to pass quality control measures before being entered into a time-locked (yearly updates) database (DIAN datafreeze 8). Using data from these individuals, we constructed a database of age, sex, mutated gene, mutation type (including specific aminoacid change of the mutation [eg, PSEN1 E280A]), *APOE* genotype, family history, medical history, list of medications, age of onset evaluation, physical examination findings, neurological examination findings, Clinical Dementia Rating (including supplemental boxes for behaviour and language), Functional Activities Questionnaire (FAQ), Mini-Mental State Examination (MMSE), Geriatric Depression Scale (GDS), Unified Parkinson's disease rating scale (UPDRS), vascular contributions to dementia or history of stroke (Hachinski Ischemic Score [HIS]), Neuropsychiatric Inventory Questionnaire (NPI-Q), clinical judgment of symptoms, clinician diagnosis, and psychometric battery summary. Individuals from the DIAN-OBS cohort were assessed by study investigators at each clinical centre for the presence of non-amnestic cognitive or non-cognitive symptoms with neurological exams during their initial visit and each visit thereafter and sections from the National Alzheimer's Coordinating Center's Uniform Data Set (UDS),[12] paying specific attention to the health history (UDS from A5 and B2), UPDRS (UDS form B3), and clinician judgment of symptoms (UDS form B9). UPDRS scores were calculated based on review of performance in each of 27 motor domains (eg, body bradykinesia, facial expressiveness, and gait), with a maximum possible score of 108. If an individual exhibited a specific symptom during any visit, that symptom was marked as present (appendix).

See Online for appendix

	DIAN-OBS cohort (n=107)	Published data cohort (n=753)	p value
Sex			..
Male	47 (44%)	260 (35%)	
Female	60 (56%)	277 (38%)	
Data not available	0	216 (27%)	
Gene mutation			..
PSEN1	86 (80%)	547 (73%)	
PSEN2	2 (2%)	35 (5%)	
APP	19 (18%)	171 (23%)	
Age of symptom onset (years)	42·9 (8·17)	46·0 (10·5)	0·0004
Length of follow-up (years)	3·93 (3·18)	8·33 (4·59)	<0·0001
CDR score	1·05 (0·79)	..	..
CDR-SB score	5·39 (5·06)	..	..
MMSE score	20·98 (10·92)	..	..

Data are n (%) or mean (SD). DIAN-OBS=Dominantly Inherited Alzheimer Network observational study. CDR=Clinical Dementia Rating scale. CDR-SB=Clinical Dementia Rating scale—sum of boxes. MMSE=Mini-Mental State Examination.

Table 1: **Baseline demographics and clinical characteristics**

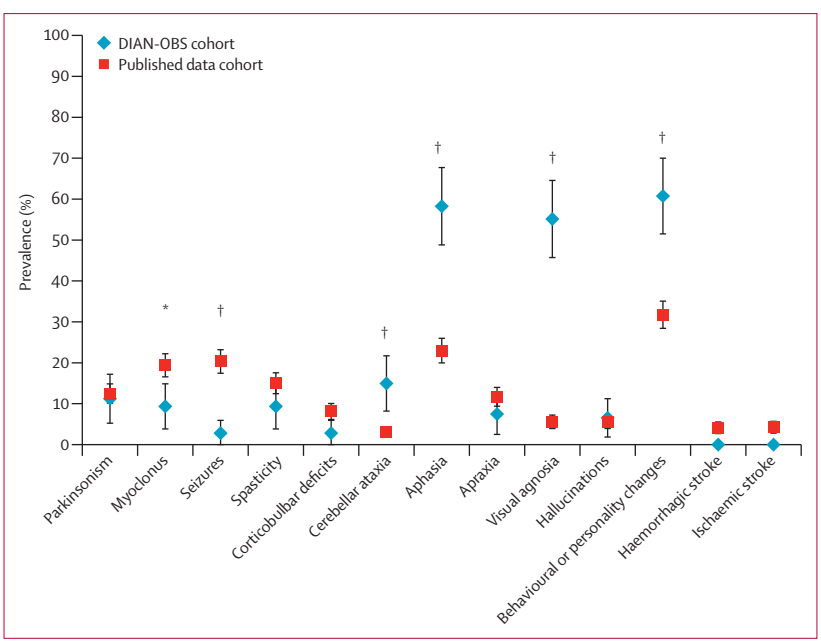

Figure 1: **Cognitive and non-cognitive symptom prevalence in the DIAN-OBS and published data cohorts**
Error bars show 95% CIs. p values shown are for the DIAN-OBS cohort *vs* published data cohort. DIAN-OBS=Dominantly Inherited Alzheimer Network observational study. *p=0·0·0117. †p<0·0001.

	DIAN-OBS cohort (n=107)		Published data cohort (n=753)		p value
	Number diagnosed	Prevalence (95% CI)	Number diagnosed	Prevalence (95% CI)	
Parkinsonism	12	11·2% (5·3–17·2)	94	12·5 % (10·1–14·8)	0·71
Myoclonus	10	9·3% (3·8–14·9)	146	19·4% (16·6–22·2)	0·0117
Seizures	3	2·8% (0·5–5·9)	153	20·3% (17·4–23·2)	<0·0001
Spasticity	10	9·3% (3·8–14·9)	113	15·0% (12·5–17·6)	0·12
Corticobulbar deficits	3	2·8% (0–5·9)	61	8·1% (6·2–10·0)	0·051
Cerebellar ataxia	16	15·0% (8·2–21·7)	23	3·1% (1·8–4·3)	<0·0001
Aphasia	62	57·9% (48·6–67·3)	173	23·0% (20·0–26·0)	<0·0001
Apraxia	8	7·5% (2·5–12·5)	88	11·7% (9·4–14·0)	0·19
Visual agnosia	59	55·1 % (45·7–64·6)	42	5·6% (3·9–7·2)	<0·0001
Hallucinations	7	6·5% (1·9–11·2)	42	5·6% (3·9–7·2)	0·69
Behaviour or personality changes	65	61·7% (51·5–70·0)	239	31·7% (28·4–35·1)	<0·0001
Haemorrhagic stroke	0	0	31	4·1% (2·7–5·5)	..
Ischaemic stroke	0	0	32	4·2% (2·8–5·7)	..

DIAN-OBS=Dominantly Inherited Alzheimer Network observational study.

***Table 2*: Symptom prevalence between cohorts**

Statistical analysis

We calculated and compared the prevalences of a group of non-cognitive and non-amnestic cognitive symptoms in the DIAN-OBS cohort and the published data cohort. We calculated symptom prevalence for individuals with mutations in *APP*, *PSEN1*, and *PSEN2* in the published data cohort by constructing a generalised linear mixed model in SAS version 9.4 with the mutated gene and age of onset as fixed effects and a unique identifier for family pedigree as a random effect to take into account the impact of familial genetics. We did not include the effect of *APOE* ε4 carrier status because of limitations in sample size. The model was only constructed for the published data cohort because the DIAN-OBS cohort was not large enough to simultaneously determine the effect of age of onset, gene mutation, and family pedigree.

We explored the relationship between clinical severity score at latest visit that Clinical Dementia Rating scale—sum of boxes was available and the frequency of clinical features in the DIAN-OBS cohort. To do this participants were sorted into groups of increasing symptom severity as determined by scores: very mild (0·5–6), mild (6·5–12), moderate (12·5–18), and severe (18·5–24). We were

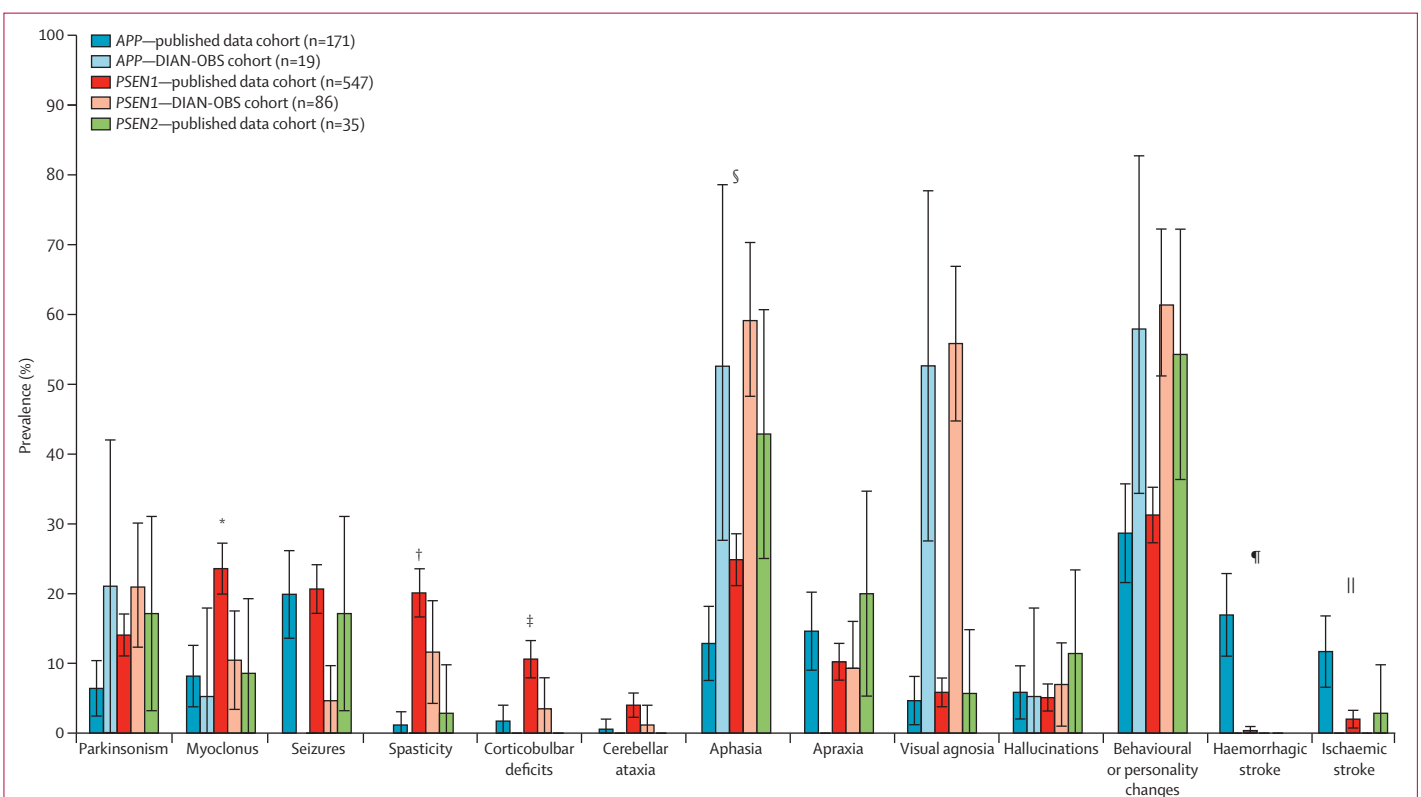

***Figure 2*: Cognitive and non-cognitive symptom prevalence in the DIAN-OBS and published data cohorts by gene mutation**

Prevalence for *PSEN2* mutation carriers in the DIAN-OBS cohort is not shown because there were only two symptomatic individuals. Error bars show 95% CIs. p values shown are for *APP* mutation carriers *vs* *PSEN1* mutation carriers within the published data cohort. DIAN-OBS=Dominantly Inherited Alzheimer Network observational study. *p=0·0125. †p=0·001. ‡p=0·0257. §p=0·0129. ¶p=0·0055. ||p=0·0135.

unable to do a similar exploration in the published data cohort because data were not included in most reports at the time of non-amnestic symptom presentation.

We used the generalised linear mixed model to explore the relationship between age of onset and the prevalences of symptoms in the published data cohort. Additionally, we compared symptom prevalences and age of onset for individuals with *PSEN1* mutations before codon 200 versus those with mutations after codon 200 in both cohorts separately.[6]

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to the data in the study and had final responsibility for the decision to submit for publication.

Results

We included 107 participants with detailed data from the DIAN-OBS database (forming the DIAN-OBS cohort). Our systematic review yielded individual-level data for 1228 individuals; 753 individuals had a detailed description of disease course (forming the published data cohort). Compared with the published data cohort, the DIAN-OBS cohort had a significantly earlier average age of onset (p=0·0004) and shorter average follow up time (p<0·0001; table 1).

34 (32%) participants in the DIAN-OBS cohort exhibited one or more of the non-cognitive symptoms that we specifically examined in our analysis at any point during follow-up (figure 1). Significantly higher prevalences of cognitive symptoms were noted in the DIAN-OBS cohort than in the published data cohort, including for aphasia, visual agnosia, and behavioural or personality changes (table 2). Motor symptoms such as myoclonus and recent or active seizures of any type were less common in the DIAN-OBS cohort. The prevalence of cerebellar ataxia was higher in the DIAN-OBS cohort than in the published data cohort (table 2), but prevalence of parkinsonism was similar between groups (table 2). Of the 12 individuals in the DIAN-OBS cohort who displayed parkinsonian symptoms, 11 were mildly symptomatic (UPDRS total score <36), and one was moderately symptomatic with a UPDRS score of 58. The prevalences of spasticity and corticobulbar deficits did not differ significantly between cohorts (table 2). The prevalence of behavioural and personality changes was greater in the DIAN-OBS cohort, but prevalence of hallucinations was low and similar between cohorts (table 2). No individuals in the DIAN-OBS cohort reported recent or active haemorrhagic stroke or ischaemic stroke, whereas there were a few reports of stroke in the reported data cohort (table 2).

We also examined the prevalences of behavioural and neurological symptoms by mutated gene (figure 2). In the published data cohort, *PSEN1* mutation carriers were significantly more likely than *APP* mutation carriers to have myoclonus (129 [24%] of 547 participants *vs* 14 [8%] of 171 participants; odds ratio [OR] 4·25, 95% CI 1·37–13·2; p=0·0125), corticobulbar deficits (58 [11%] *vs* three [2%]; 9·78, 1·32–72·4; p=0·0257), aphasia (136 [25%] *vs* 22 [13%]; 3·76, 1·33–10·7; p=0·0129), and spasticity (110 [20%] *vs* two [1%]; OR 149·25, 95% CI 7·58–2938·49; p<0·001) than were *APP* mutation carriers. *APP* mutation carriers were significantly more likely than *PSEN1* mutation carriers to have ischaemic stroke (20 [12%] of 171 participants *vs* 11 [4%] of 547 participants; OR 3·92, 95% CI 1·33–11·6; p=0·0135) and haemorrhagic stroke (29 [17%] *vs* two [<1%]; 622·28, 95% CI 6·68–58823·53; p=0·0055). There were no significant differences in the prevalences of parkinsonism, seizures, apraxia, visual agnosia, behavioural or personality changes, or hallucinations between *APP*, *PSEN1*, and *PSEN2* mutation carriers in the published data cohort (table 2).

For the DIAN-OBS cohort, prevalences were calculated only for individuals with *PSEN1* or *APP* mutations because there were too few symptomatic individuals with *PSEN2* mutations. Several symptoms were notably absent from *APP* mutation carriers in the DIAN-OBS cohort: new-onset seizures, stroke, and corticobulbar deficits (figure 2). By contrast with results from the published data cohort, prevalences of any symptoms, including those for

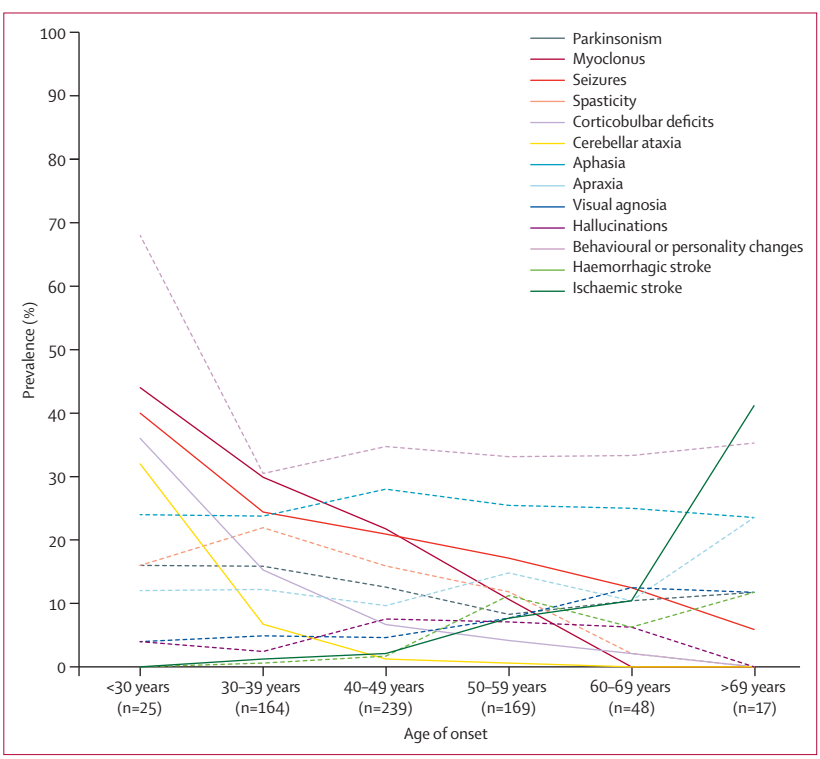

***Figure 3*: Comparison of cognitive and non-cognitive symptom prevalence by age of onset in the published data cohort**

Solid lines show symptoms for which a 1 year increase in age of onset was associated with a statistically significant change in risk of the symptom; symptoms with dashed lines did not show an association between age of onset and risk. DIAN-OBS=Dominantly Inherited Alzheimer Network observational study.

myoclonus, aphasia, or stroke, did not differ between *PSEN1* and *APP* mutation carriers in the DIAN-OBS cohort.

Age of onset in the published data cohort was significantly associated with likelihood of experiencing several symptoms (figure 3). Older age of onset was associated with increased odds of ischaemic stroke (OR 1·09 per 1 year increase in age of onset, 95% CI 1·04–1·14; p=0·0003) and decreased rates of myoclonus (0·93, 0·90–0·97; p=0·0007), seizures (0·95, 0·92–0·98; p=0·0018), corticobulbar deficits (0·91, 0·86–0·96; p=0·0012), and cerebellar ataxia (0·82, 0·74–0·91; p=0·0002). More severe clinical stage of disease in individuals in the DIAN-OBS cohort was associated with an increased frequency of most clinical features (with the exception of corticobulbar deficits; figure 4).

In the published data cohort, *PSEN1* mutations after codon 200 were more likely to be associated with spasticity than were those before codon 200 (21 of 215 individuals with mutations before codon 200 had spasticity [prevalence 9·8%; 95% CI 5·6–14·0%] *vs* 89 [27%] of 332 with mutations after codon 200 [26·8%; 21·9–31·7%]; p<0·0001; figure 5). However, in the DIAN-OBS cohort, the prevalences of symptoms did not significantly differ by codon position. Mirroring previous findings,[5] the pre-codon-200 population in the DIAN-OBS cohort had a significantly earlier age of onset than the post-codon 200 population (mean age 37·3 years [SD 6·9] for individuals with mutations before codon 200 *vs* 45·0 years [8·1] for those with mutations after codon 200; p<0·0001), a difference that was not seen in the published data cohort (42·8 years [10·4] *vs* 43·7 years [8·3]; p=0·319).

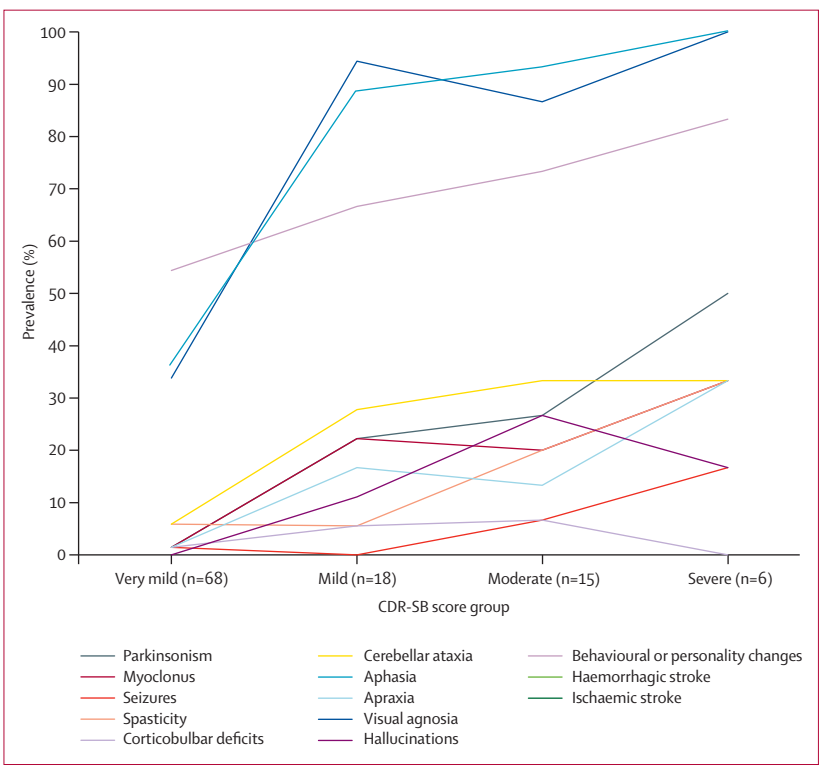

***Figure 4*: Comparison of cognitive and non-cognitive symptom prevalence by disease severity score in the DIAN-OBS cohort**

Total CDR-SB score groups were classified as follows: very mild (0·5–6), mild (6·5–12), moderate (12·5–18), and severe (18·5–24). CDR-SB=Clinical Dementia Rating—sum of boxes plus supplemental sum of boxes. DIAN-OBS=Dominantly Inherited Alzheimer Network observational study.

Discussion

In the DIAN-OBS cohort, the most frequently reported non-amnestic manifestations were cognitive, including visual agnosia, aphasia, and behavioural changes. However, in published data of individuals with ADAD, we found a lower prevalence of non-amnestic cognitive symptoms and a moderate prevalence of motor symptoms and seizures. Younger age of onset and more advanced stages of disease were related to a higher frequency of non-cognitive clinical features. Adding to potential disparity, in *The Lancet Neurology*, Natalie Ryan and colleagues report results from a large European case series in which 16% of participants with ADAD had non-amnestic cognitive phenotypes and about 25% had atypical neurological symptoms in addition to an amnestic phenotype,[13] suggesting that in patients with unusual neurological manifestations, genetic counselling and testing might be warranted. One potential interpretation of the diversity of results is that compared with clinical data collected prospectively in the DIAN-OBS, case reports might overestimate the prevalence of non-cognitive neurological manifestations (eg, myoclonus and seizures), while underestimating cognitive neurological manifestations (eg, visual agnosia, aphasia, and behavioural or personality changes). Two sources of bias that could contribute include measurement bias and ascertainment bias. The DIAN-OBS study complements the published reports to help account for these biases. Likewise, the literature reports provide a broader understanding, with longer follow-up and more advanced disease than that reported in the DIAN-OBS.

With regards to measurement bias, our study demonstrates the effect of using systematic protocols in observational cohort studies (appendix). By using uniform study procedures, symptoms such as non-amnestic cognitive symptoms can be consistently identified. Prospective and uniform neurological assessments might have led to early identification of symptom onset and account for the earlier age of onset reported in the DIAN-OBS cohort. However, the shorter follow-up period in DIAN-OBS probably resulted in a lower prevalence of certain symptoms such as seizures and myoclonus, which were higher in the published data cohort because of higher symptom prevalence at later stages of the disease (figure 4). With further follow-up, DIAN-OBS will be positioned to accurately and prospectively measure symptoms with more advanced disease.

Non-amnestic cognitive phenotypes are more commonly reported in sporadic Alzheimer's disease and include

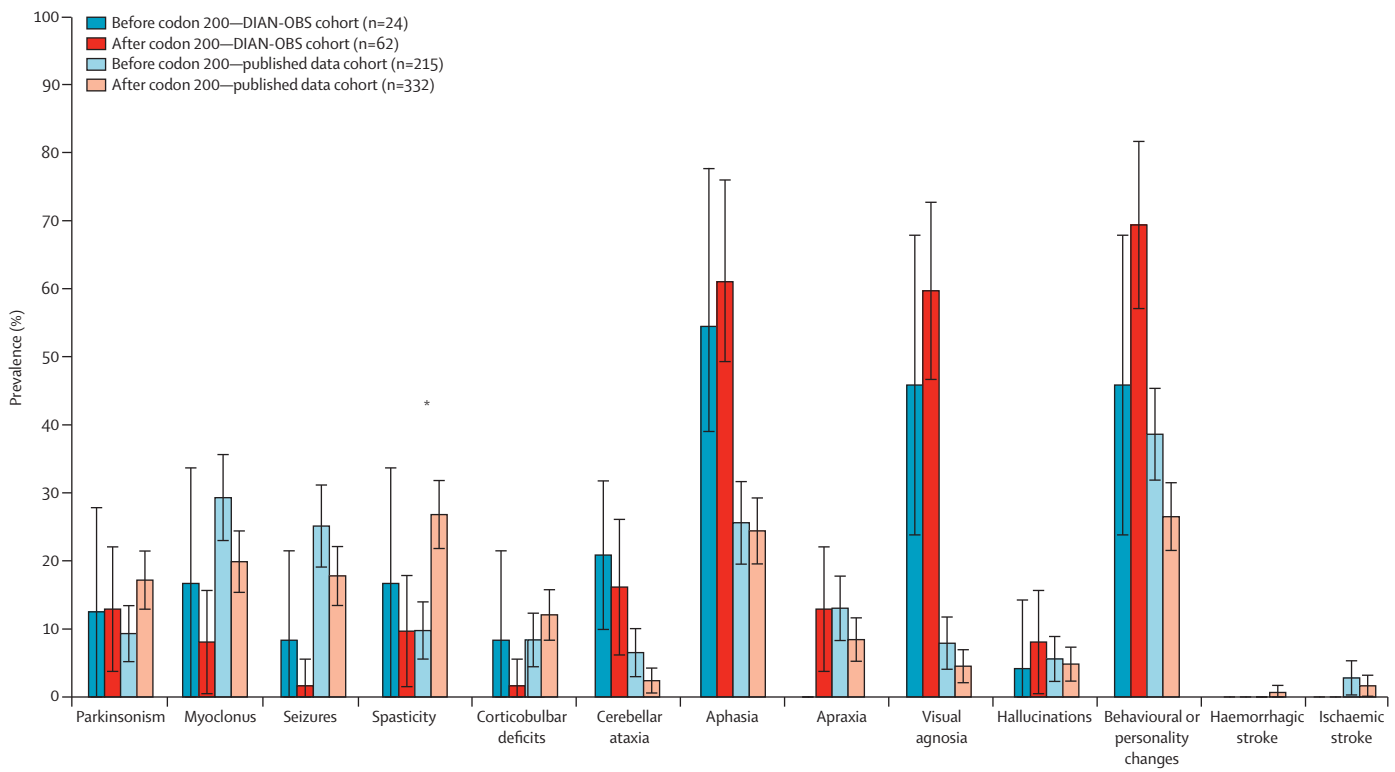

***Figure 5*: Comparison of symptom prevalence for *PSEN1* mutations before and after codon 200 in the DIAN-OBS and published data cohorts**
Error bars show 95% CIs. p value shown is for pre-codon 200 mutation versua post-codon mutation carriers in the published data cohort. DIAN-OBS=Dominantly Inherited Alzheimer Network observational study.*p<0·0001.

language variants, executive-frontal variants, and a visuoperceptual variant (posterior cortical atrophy).[14] In general, these focal variants have been reported less frequently in ADAD.[15,16] In sporadic Alzheimer's disease these variants seem to occur more frequently at younger ages of onset—eg, a study found an odds ratio of greater than 5–12 for non-amnestic cognitive impairment in those with Alzheimer's disease in the sixth decade versus those in the ninth decade.[17] Similar to the common sporadic Alzheimer's disease presentation, in the DIAN-OBS cohort most participants had amnestic impairments as the first presenting symptom.[2] When non-amnestic variants are present, studies suggest that the symptoms are related to neurofibrillary tangles rather than amyloid β plaques.[18] Thus, in both sporadic Alzheimer's disease and ADAD, cognitive symptoms seem to be related to tau pathology.[19]

We sought to determine the effect of age, disease stage, mutation, and other genetic factors on the manifestation of symptoms. Age of onset seems to greatly affect the risk of neurological manifestations. In the published data cohort, individuals who began to decline at a younger age were more likely to develop myoclonus and seizures than were those with an older age at onset. By contrast, ischaemic stroke was associated with older ages of onset. Individuals in the DIAN-OBS cohort had lower overall incidences of myoclonus and seizures than the published data cohorts, possibly due to milder stages of disease (figure 4). In the DIAN-OBS cohort, increased frequency of myoclonus, seizures, and cerebellar ataxia were associated with increased disease severity. Several previous studies suggest that for individuals with ADAD, seizures are correlated with earlier age of onset and more severe disease.[20–24] Our work supports the importance of the age of onset as it relates to myoclonus and seizures, and adds to the association between disease severity and symptom frequency from the DIAN-OBS study. In participants with sporadic Alzheimer's disease, there is also evidence to support that an earlier age of onset is associated with an increased risk of seizures.[25,26]

To account for other genetic or environmental factors that can affect disease presentation within a pedigree, we included family membership as a covariate in our analysis of symptom prevalence in *PSEN1, PSEN2,* and *APP* mutation carriers. We showed some differences between *APP*, *PSEN1*, and *PSEN2* mutations in the prevalence of certain symptoms (eg, in myoclonus and spasticity for *PSEN1* in the published data cohort). Further, we found a propensity for *APP* mutation carriers to have ischaemic or haemorrhagic stroke. It has been previously reported that *PSEN1* mutations before codon 200 are pathologically different from those after codon 200, probably because of

differences in the severity of cerebral amyloid angiopathy and rates of amyloid deposition.[27] However, aside from spasticity, there were no apparent differences in symptom prevalence between *PSEN1* pre-codon 200 mutations and post-codon 200 mutations. Substantial heterogeneity exists within earlier and later *PSEN1* mutation groups. Additionally, within *PSEN1*, there is a notable paucity of pathogenic mutations between codon 290 and codon 350 (appendix), which gives rise to three possibilities: mutations in this region are asymptomatic, mutations in this region are lethal, or these regions have intrinsically lower rates of mutation.

Although *APOE* ε4 is a major risk factor for sporadic Alzheimer's disease,[28] evidence of its effect on ADAD presentation is less clear.[11,29–31] Our analysis of symptomatic mutation carriers was too small to construct a model that included *APOE* status as a covariate in addition to age of onset, pedigree membership, and mutated gene.

Limitations of the DIAN-OBS include the relatively few symptomatic participants, with 107 individuals in various stages of dementia. Consequently, we could not construct a model that simultaneously takes into account factors that could influence disease course such as the specific gene mutation, duration of follow-up, and *APOE* genotype. Further, the DIAN-OBS dataset includes few severe stages of disease with the average stage at moderate dementia (mean MMSE 20·98 [10·92]).

Accurately determining the prevalences of specific clinical and neurological signs and symptoms is important to define a clinical disease, understand its prognosis and impact on patients, and inform the conduct of clinical research. A more complete understanding of cognitive and other neurological manifestations of ADAD will allow for improvements in diagnosis, prognosis, and management, as well as the design of research studies in this unique population. Future studies will be able to compare the clinical presentation of ADAD patients with that of sporadic Alzheimer's disease in greater detail, leading the field towards a deeper understanding of their shared clinical manifestations, which will be crucial to accurately interpret the findings of treatment trials in each disorder.

For the **participating sites of the DIAN study** see http://www.dian-info.org/institutions_map.htm

For the **DIAN Expanded Registry** see http://dianxr.org

Contributors

MT and DCR did the literature search and prepared the figures. MT, DCR, MSJ, EM, VDB, JCM, and RJB designed the study. EM, NJC, AMF, AG, DSM, RFA, AD, MRF, BG, NRG-R, CL, RNM, CLM, RPM, JMR, SPS, PRS, JCM and RJB, with the Dominantly Inherited Alzheimer Network (DIAN), collected the data. MT, DCR, MSJ, VDB, NJC, AMF, AG, DSM, CX, and RJB did the data analysis. MT, DCR, MSJ, and CX did the statistical analyses. MT, DCR, EM, and RJB interpreted the data and wrote the report. All other authors and investigators from DIAN critically reviewed the report.

Declaration of interests

AMF served on a scientific advisory board for IBL International and serves as a consultant for DiamiR. AG serves on the scientific advisory board for Denali Therapeutics and Cognition Therapeutics and has a patent for tau mutations with royalties paid to Taconics (patent 6,475,723 for pathogenic tau mutations). NCF reports that University College London received fees from Janssen Alzheimer's Immunotherapy for analyses conducted at the Dementia Research Centre. NCF serves as a consultant for Eli Lilly, Novartis, Sanofi, Roche/Genentech, and GlaxoSmithKline, and is a member of the data monitoring committee for the drug aducanumab (Biogen). NRG-R received research support from Eli Lilly, Biogen, and TauRx, and serves as a consultant for Cytox. CLM serves as a consultant for Prana Biotechnology, Eli Lilly, and Actinogen. MNR serves on the data monitoring committee for Servier for the drug CL2-47445-011. RJB reports that he, the Chair of Neurology, and Washington University in St Louis have equity ownership interest in C2N Diagnostics and may receive royalty income based on technology licensed by Washington University to C2N Diagnostics. RJB receives research support from Biogen, Abbvie, Eli Lilly, and Pharma Consortium (Biogen Idec, Elan Pharmaceuticals, Eli Lilly, Hoffman La-Roche, Genentech, Janssen Alzheimer Immunotherapy, Mithridion, Novartis Pharma AG, Pfizer Biotherapeutics R and D, Sanofi-Aventi, and Eisai) and non-financial support from Avid Pharmaceuticals. RJB is also principal investigator of the A4 clinical trial and serves as a consultant for IMI, Sanofi, Global Alzheimer's Platform, Boehringer Ingelheim, and Merck and on the scientific advisory board for Forum. RJB was an invited speaker for Roche and the Organisation for Economic Co-operation and Development. All other authors declare no competing interests.

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