Different rates of cognitive decline in autosomal dominant and late-onset Alzheimer disease

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ABSTRACT

As prevention trials advance with autosomal dominant Alzheimer disease (ADAD) participants, understanding the similarities and differences between ADAD and "sporadic" late-onset AD (LOAD) is critical to determine generalizability of findings between these cohorts. Cognitive trajectories of ADAD mutation carriers (MCs) and autopsy-confirmed LOAD individuals were compared to address this question. Longitudinal rates of change on cognitive measures were compared in ADAD MCs (n=310) and autopsy-confirmed LOAD participants (n=163) before and after symptom onset (estimated/observed). LOAD participants declined more rapidly in the presymptomatic (preclinical) period and performed more poorly at symptom onset than ADAD participants on a cognitive composite. After symptom onset, however, the younger ADAD MCs declined more rapidly. The similar but not identical cognitive trajectories (declining but at different rates) for ADAD and LOAD suggest common AD pathologies but with some differences.

Keywords: Alzheimer disease, autosomal dominant AD, late-onset AD, cognitive, comorbidities

1 NARRATIVE

1.1 Contextual background

The discovery of rare causative mutations for Alzheimer disease (AD)[1,2] has advanced knowledge about the far more common sporadic form of late-onset AD (LOAD) and led to development of AD mouse models.[3] Pathogenic mutations in the *APP, PSEN1,* and *PSEN2* genes result in relative overproduction/underclearance of the amyloid-beta (Aβ) peptide 1-42 isoform[4] and are ~100% penetrant, providing support for the amyloid hypothesis of AD etiology.[5,6] More recently persons at risk of autosomal dominant AD (ADAD) have enabled secondary prevention trials for AD by serving as participants who are certain to develop AD at a predictable age which permits adequate power to be achieved with fewer participants.[7,8] These therapeutic trials include an assumption that these two pathologies are similar to some extent, i.e., a therapeutic compound found effective in preventing ADAD may also be effective in preventing LOAD. Yet direct comparisons between these cohorts on cognition, an indirect measure of underlying pathology and an important indicator of therapeutic efficacy recommended by Food and Drug Administration guidelines[9] (despite their recent controversial decision on the compound, aducanumab)[10] are rare. The central question addressed in this study is whether rates of cognitive decline in ADAD and LOAD are similar, a difficult comparison due to large age differences in the groups. If underlying pathologies are similar,[11,12] rates of cognitive decline may be similar between ADAD and LOAD.

Previously observed differences between ADAD and LOAD include: prevalence (<1% of all AD is mutation-related), age of symptom onset (typically decades younger in ADAD), [13,14] and frequency of comorbidities at neuropathological examination (lower in

ADAD).[11] Similarities in clinical, cognitive, imaging, cerebrospinal fluid (CSF), and neuropathological measures have been noted between ADAD and LOAD[13] but most studies compared ADAD only indirectly to LOAD rather than including data from both ADAD and LOAD individuals in the same analyses.[15-17]

Literature on age-at-onset (AAO) effects in symptomatic LOAD clinical progression are mixed with some studies finding: no differences,[18] a more aggressive clinical disease course with younger onset (<60 or 65 years),[19,20] a less aggressive clinical course with younger age at symptom onset.[21] Methodological differences may contribute to the mixed findings as AAO is often self-reported, follow-up periods may be only 1-2 years, neuropathological or biomarker AD confirmation is lacking, and arbitrary ages define experimental groups (e.g. <65 years; >65 years).[19,22,23]

Preclinical comparison of cognitive decline between LOAD and ADAD groups is rare, as large studies of LOAD have added biomarker collection (permitting detection of developing pathology prior to symptom onset) only in the last ~ 15-18 years (e.g. Alzheimer's Disease Neuroimaging Initiative, ADNI).[24] AAO effects on preclinical rate of decline are unknown at this time.

Studies comparing cognitive rates of change (albeit indirectly) often find younger onset AD, whether mutation-related or not, progresses more rapidly than late-onset.[19,25,26]

Only one small study directly compared cognitive decline in ADAD and LOAD after symptom onset.[23] Rosselli et al. studied affected members (n=12) of a large *PSEN1* (*E280A*) kindred in Colombia compared to LOAD patients (n=10). As matching on age was not possible, groups were matched on mean Mini Mental State Exam (MMSE) scores and years of education at entry. Administering the Consortium to Establish a

Registry for Alzheimer's Disease (CERAD) neuropsychological battery[27] three times over 18 months, they found that groups were similar at baseline but mutation carriers (MCs) declined faster over time, particularly on the MMSE. Limitations shared by these studies include lack of autopsy/biomarker confirmation of clinical diagnostic accuracy (i.e., confirming all LOAD participants had AD) and no preclinical data.[19,23,25,26]

One aim of the Dominantly Inherited Alzheimer Network[28] (DIAN, an international longitudinal clinical and biomarker study of ADAD) is to compare the clinical, cognitive, and pathological phenotypes of ADAD with LOAD before and after symptom onset.[28] DIAN MCs inherit a causative mutation in one of three genes (*PSEN1, PSEN2, and APP*) with high penetrance (nearly all will develop AD pathology). The appropriate LOAD comparison sample should demonstrate comparable confidence in the presence of AD pathology. Use of the LOAD sample from the National Alzheimer Coordinating Center (NACC) permitted inclusion of participants with autopsy confirmation of AD neuropathology.[29] Other benefits of the NACC sample as a comparison LOAD group to DIAN MCs are abundant longitudinal data and use of identical clinical and cognitive batteries.[30]

1.2 Study design and main results

With no overlap in age distributions between the two cohorts, onset of clinical symptoms was used to align groups on a clinical landmark for comparison of cognitive rates of change prior to and after symptomatic onset. AAO is subtracted from each visit age to obtain the estimated years to onset (EYO) to link data to the clinical course temporally. See Figure 1. However, many MCs have yet to reach symptomatic onset. Fortunately, estimating symptomatic AAO is predictable in MCs based on the family specific

mutations.[31] This approach is commonly used to place ADAD data along a clinical timeline for analyses.[32-34]

Data from DIAN MCs were compared longitudinally to data from NACC autopsy-confirmed LOAD participants on a composite of 10 standard cognitive tests[35] common to both studies. A second composite without speeded tasks (tasks shown to decline with age[36]) was analyzed. To ensure comparison of pathological AD in the LOAD sample, only NACC participants with autopsy results consistent with intermediate to high likelihood AD were included. This sample was further restricted to participants who had no clinical symptoms at baseline (providing data for preclinical comparison) but later developed clinical symptoms prior to death. These two selection criteria yielded an extremely old LOAD cohort with a mean age at baseline = ~85 years compared to ADAD age at baseline = ~38 years. See Table 1 for cohort characteristics.

The LOAD group declined cognitively more rapidly prior to symptom onset; but after symptom onset, the ADAD group declined more rapidly. See Figure 2 and Table 2. Clinical progression as measured by the Clinical Dementia Rating® Sum of Boxes (CDR-SB) indicated faster clinical progression in LOAD prior to and after symptom onset. Removing speeded tasks and adjusting for comorbidities (e.g., hypertension, depression, etc.) did not substantially alter the findings (see Tables 2 and 3).

1.3 Study conclusions and implications

With few previous direct comparisons between ADAD and LOAD (none with preclinical data or with LOAD autopsy confirmation), the present study provides valuable observations regarding the course of cognitive decline in these two cohorts before and after symptom onset. The two groups are similar in that both cohorts had confirmed AD

(neuropathologically confirmed in LOAD participants, genetically determined in ADAD participants) and were assessed longitudinally with the same clinical and cognitive battery. When comparing the longitudinal performance of these groups, aligned temporally at symptom onset, from cognitive normality (preclinical AD) to symptom onset and dementia progression, LOAD individuals declined more rapidly preclinically and performed more poorly at symptom onset than ADAD. After symptom onset, ADAD participants declined more rapidly.

These findings imply that ADAD and LOAD may represent similar AD pathologies with some differences and that generalizability between cohorts could be limited. Cognitive decline seen in LOAD prior to symptom onset may be multifactorial with contributions from co-pathologies, AD and advancing age. However, the more aggressive course of ADAD after symptom onset, despite the group being much younger and having fewer age-associated comorbidities (hypertension and hypercholesteremia), suggests some additional or different pathological process may be active. Age-associated cognitive decline interacting with sporadic AD pathology would not predict these results. The greater amyloid burden in ADAD compared to LOAD[10] may contribute to greater cognitive decline after symptom onset but the mechanism is unknown.

1.4 Limitations and future directions

The main limitation of this study was the substantial confounding of age between the cohorts, as must be the case when comparing ADAD with LOAD. Attributing observed differences to either etiological or age differences is not possible. Other limitations include: few years of follow-up for both cohorts (average ~3-5 years); dependence on estimated EYOs for a portion of the ADAD cohort; wider range of EYO in the ADAD

cohort; and lack of antemortem biomarker data (the NACC database has only recently included amyloid imaging or CSF data). Additionally, both DIAN and NACC are observational studies and unobserved factors could affect or confound the results. The differences observed in this study indicate that molecular biomarkers changes in ADAD and LOAD should be examined for changes that may explain the different cognitive trajectories observed in this study, with particular focus on changes occurring around and after symptom onset. Longitudinal biomarkers studies in LOAD (e.g., ADNI[24]) are progressing to provide adequate samples sizes to address this question. Examining other cohorts such as familial late-onset AD[37] (fLOAD) or early-onset non-familial AD (EOAD) may provide insights regarding whether the more aggressive decline in ADAD is due to younger age (EOAD versus LOAD) or different pathology (fLOAD versus LOAD). Sample sizes and data for these groups are limited in availability but the Longitudinal Early-onset Alzheimer's Disease Study (LEADS)[38] examines EOAD with clinical, cognitive, biomarker, and genetic tools similar to DIAN and may soon be useful in addressing the influence of AAO.

2 CONSOLIDATED RESULTS AND STUDY DESIGN

ADAD and LOAD groups are confounded by age and therefore confounded by age-related conditions and comorbidities, making direct comparisons difficult. In this study, groups were matched on clinical disease course instead of age or biomarkers because of the rich, longitudinal clinical and cognitive data available in both cohorts. Groups were aligned temporally at symptom onset, either observed (LOAD) or estimated/observed (ADAD), allowing cognitive performance to be compared before, after and at symptom onset. See Figure 1.

Because the LOAD sample was chosen to be cognitively normal at baseline and to have developed symptoms later, symptomatic onset was observed (i.e., the first visit in which a CDR>0 was assigned). Onset of symptoms in the ADAD cohort either was observed (similar to LOAD) or estimated using the mutation-specific AAO for their family mutation.[31] The observed/estimated AAO is subtracted from the age at each visit to derive the estimated EYO for that visit, linking visits to the clinical timeline.

Clinical and cognitive data from the DIAN and NACC databases were compared to examine LOAD and ADAD rates of decline. All MCs were included (n=310) except ten carriers of the Dutch *APP* mutation *E693Q* (which exhibits a different phenotype). Inclusion criteria for NACC LOAD participants were: cognitively normality at baseline (CDR=0); cognitive impairment at a later assessment (CDR>0); and neuropathological AD changes sufficient to meet intermediate to high likelihood of AD using NIA Reagan criteria[39] or intermediate to high level of AD change under the NIA-AA criteria (at least A1B2C2).[40] These criteria yielded a sample of 163 NACC LOAD participants.

Ten individual raw cognitive test scores and two composite scores (global and non-speeded cognition) were converted to z-scores (based on combined group data) and analyzed by general linear mixed models with random coefficients[41] to allow estimation of within-person rate of change in cognitive performance and its comparison between ADAD and LOAD participants. Analyses were adjusted for education, sex, body mass index (BMI), and apolipoprotein E (*APOE) ε*4. However, age was not covaried, as there was no overlap between groups on this variable. Additional analyses covaried for comorbidities the groups had in common (depression, hypertension and hypercholesteremia).

LOAD declined faster on the global cognitive composite preclinically and performed more poorly at symptom onset but ADAD declined more rapidly after symptom onset. Removing speeded tasks and adjusting for comorbidities did not change this finding.

3 DETAILED METHODS AND RESULTS

3.1 Methods

3.1.1 Source of data

DIAN is an international, longitudinal, biomarker study of ADAD to determine the sequence and rate of pathologic changes in MCs relative to non-carriers and to compare the clinical, cognitive and pathological phenotypes of ADAD with LOAD.[28] Participants are at 50% risk of inheriting a causative mutation in one of three genes (*PSEN1, PSEN2, and APP*). MCs and noncarriers undergo extensive clinical, cognitive, and biomarker assessments every 1-3 years.

The NIA-funded NACC facilitates collaborative research by managing and sharing data from past and present NIA-funded Alzheimer's Disease Research Centers (ADRCs) across the United States. NACC developed standardized clinical, cognitive and neuropathological data collection from participants, with and without cognitive impairment, enrolled at ADRCs to study the characteristics and course of AD and other neurodegenerative diseases.[30,42] Clinical and cognitive data on over 43,000 participants (mean age ≅ 75 years) collected annually are available as well as neuropathological data from more than 5,500 of these participants (at time of this data transfer). The DIAN clinical assessment and cognitive battery were designed to match those of the NACC Uniform Data Set (UDS)[30] to facilitate direct comparisons between ADAD and LOAD.

3.1.2 Group inclusion/exclusion criteria

For LOAD, longitudinal data were obtained from the NACC UDS version 2 and UDS version 3 for visits conducted between September 2005 and December 2018 (data from both UDS versions were combined using conversion tables developed by the NACC Crosswalk study).[43] To identify a LOAD cohort comparable to ADAD (i.e., high probability of AD), NACC participants with AD neuropathological changes who were clinically normal at baseline (CDR=0) and later received a CDR>0 during longitudinal follow-up were selected. Criteria for inclusion (and sample size related to each criterion) were: availability of autopsy data (n=5,512); cognitively normal (CDR=0) at baseline assessment (n=1018); and cognitive impairment (CDR>0) at a later assessment (n=541); and neuropathological AD changes sufficient to meet intermediate to high likelihood of AD using NIA Reagan criteria[39] or intermediate to high level of AD change under the NIA-AA criteria of at least A1B2C2 (n=163).[40] These criteria yielded a sample of 163 NACC LOAD participants.

For ADAD, longitudinal UDS and clinical data were obtained from DIAN data freeze #13 from MCs (n=310), including asymptomatic and symptomatic individuals. Ten carriers of the Dutch mutation (*APP E693Q*) were excluded due to phenotypic differences.[44] Local institutional review boards (IRBs) or ethics committees of each performance site approved the DIAN study and participants provided written informed consent for data collection and sharing. ADRC participants gave written informed consent for the sharing of their data through the NACC. The Washington University IRB approved this analysis of DIAN and NACC data.

3.1.3 AAO and EYO

As stated previously these two groups are confounded by age and age-related conditions and comorbidities. Instead of matching groups on age, groups were matched on clinical disease course, taking advantage of the rich, longitudinal clinical and cognitive data available in both cohorts. Specifically, groups were aligned temporally at symptom onset, either observed (LOAD) or estimated (ADAD), allowing cognitive performance to be compared before, after and at symptom onset. Considering the age at symptom onset as the origin (EYO=0), AAO was subtracted from participant age at each visit to derive the estimated years to onset of symptoms - negative numbers indicate visits that occurred prior to symptom onset and positive numbers indicate visits that occurred after symptom onset

For LOAD AAO, symptomatic AAO in the LOAD cohort was defined as the participant's age at the visit when the CDR became greater than zero. Infrequently, a CDR>0 may 'bounce' back to CDR=0 on a subsequent visit. To account for this possibility, the AAO was further defined as the age at time of cognitive assessment when either a CDR>0 was first rendered or for the purpose of a sensitivity analysis, a CDR>0 was first rendered and subsequently remained >0.

For ADAD AAO, nearly all ADAD MCs will develop symptomatic AD at a predictable age (within a few years), typically near the age of onset of their affected family members. Ryman[31] and colleagues analyzed hundreds of ADAD pedigrees with individual data on age of symptom onset. Age at onset was strongly correlated with, and most accurately estimated by, the specific mutation type. The DIAN database uses mutation-specific AAO to estimate individual participant AAO when available. In the case of rare mutation types where there was insufficient data to calculate a mutation-specific AAO, parental

AAO (also highly correlated with MC AAO) was used as the symptomatic AAO. When a MC was asymptomatic at baseline and later became symptomatic, the age at the visit when a CDR>0 occurs was used as the observed AAO, similar to the LOAD participants. Of the 310 DIAN MCs in this study, 19 had observed AAO values and 291 were estimated.

For both groups, EYO for each visit was calculated by subtracting AAO (estimated or observed) from participant age at each visit. Data were located on disease course by each visit's respective EYO where EYO=0 represents symptomatic onset. This approach is commonly used in studies of ADAD.[32-34] With ADAD and LOAD groups aligned on symptom onset (EYO=0), analyses focused on three clinical comparisons: rate of longitudinal change prior to symptom onset (preclinical disease), performance at symptom onset (EYO = 0), and rate of longitudinal change after symptom onset (disease progression). See Figure 1.

3.1.4 Cognitive Measures

In addition to the standard clinical information collected in the UDS and genetic risk information conferred by the presence of an *APOE* ε4 allele, the following cognitive measures (as described and cited by Weintraub[35]) were analyzed: Animal Fluency, Boston Naming (30 odd items); WAIS-R Digits Forward and Backward; WMS-R Logical Memory – Immediate and Delayed, Mini Mental Status Examination (MMSE), Trailmaking A, Trailmaking B and WAIS–R Digit Symbol. Substitutions for proprietary measures were made according to the NACC Crosswalk study.[43] A global composite of all 10 measures was created by first orienting all tests in the same direction (i.e., a high score means better cognitive performance for all tests), then computing a z-score for

each test across both groups, and finally averaging these scores across all tests. Cognitive composite scores have been shown to provide greater sensitivity to cognitive changes than individual tests scores and to provide better generalizability of study outcomes.[45] Because age-related slowing has been among the most robust gerontological findings[36] and because of the profound age differences between the two cohorts, a second composite was generated that excluded speed-dependent tasks (Trailmaking A and B, WAIS-R Digit Symbol, and Animal Fluency). A non-speed composite may attenuate potential differences due to age-related slowing.

3.1.5 Comorbidities

Comorbidities increase with age and may affect cognitive status.[46] To include the presence of a comorbid condition in the statistical models used, the condition had to be present in both cohorts with sufficient data for analysis. Four conditions or measures met these criteria. Depression was assessed using the Geriatric Depression Scale(GDS).[47] A score of six or more on the GDS was treated as positive for depressive symptoms. The presence of hypertension and hypercholesteremia were obtained through self-report by participant or their study partner. BMI was included as a measure of general health.

3.2 Statistical analyses

Individual raw cognitive test scores and composite test scores were analyzed by general linear mixed models with random coefficients[41] to allow estimation of within-person rate of change in cognitive performance and its comparison between ADAD and LOAD participants. Specifically, these models incorporated a piecewise linear growth/decline trajectory of longitudinal change linked at the EYO of 0, facilitating three

major clinically significant comparisons between ADAD and LOAD participants as parts of the main fixed effects: the rate of longitudinal change prior to and after symptomatic onset of AD, as well as the cognitive performance at symptomatic onset (EYO=0, i.e., the intercept). Additional analyses were conducted to examine the effects of the most common comorbidities by including them as additional fixed effects, as well as their interactions with participant groups both for the intercept and for the slopes prior and after EYO of 0. Because the two participant groups have essentially no overlap in baseline age, no attempt was made to adjust for age. Interpretation of group differences requires caution as they may be completely due to age differences.

All general linear mixed models in the longitudinal analyses were fitted using the maximum likelihood method. Statistical tests were based on the approximate *F* or *t*-tests with denominator degrees of freedom approximated by the Satterthwaite methods.[48] Both adjusted and unadjusted models included an additional random effect of study sites. All statistical analyses were performed with SAS version 9.4 (SAS Institute Inc.), and statistical significance was defined as $P < 0.05$.

3.3 RESULTS

Table 1 contains the summary statistics of demographic, clinical, and genetic characteristics of the two cohorts at baseline and at follow-up visits as appropriate. The LOAD group was more female and significantly older (mean difference of 47 years) than the ADAD group at baseline and at symptom onset (44.6 years) and had more years of education than the ADAD group. The LOAD group reported higher frequencies of hypercholesterolemia and hypertension than the ADAD group, who reported more seizures and depression than the LOAD group. The ADAD group had higher BMI

scores than the LOAD group. The groups did not differ on *APOE ε*4 allele frequency. The LOAD group had more years of follow-up overall. A post hoc analysis found this difference was larger after symptom onset (5.4 years, SD=2.02 for LOAD versus 2.7 years, SD=1.7; p<0.0001 for ADAD). One additional difference was the ranges of EYOs for the groups (i.e., visit age minus AAO). The range of EYO values for the ADAD group was from -36 years to +18 years compared to the LOAD range of -11.2 years to +8.59 years. This observation is expected as DIAN enrolls participants as young as 18 years of age.

Table 2 presents scores and standard errors (SE) adjusted for education, sex, BMI, and *APOE ε*4 of each individual cognitive test and the composite scores at three clinical stages: the estimated rate of longitudinal annual change prior to symptom onset (preclinical disease); the performance at estimated symptom onset (EYO = 0); and the estimated rate of longitudinal annual change after symptom onset (disease progression). Table 2 presents statistical test results comparing these estimates between the ADAD and LOAD cohorts. Due to their greater sensitivity and generalizability, [45] composite scores will be emphasized in these analyses. Figure 2 displays individual performance (spaghetti plots) and unadjusted group mean rates of change (solid lines) over time for the global cognitive composite. In general, LOAD declined more rapidly during the preclinical phase (LOAD global composite annual rate of decline = -0.11 (0.01) versus ADAD = -0.01 (0.004); p<.0001) and performed more poorly at symptom onset (LOAD global composite = -0.14 (0.06) versus ADAD = 0.59 (0.08); p<.0001). However, this finding was reversed after symptom onset, with ADAD declining more rapidly than LOAD on the global composite score (LOAD global

composite annual rate of change = -0.14 (0.02) versus ADAD = -0.24 (0.02); p=0.0211). The removal of tasks heavily dependent on speed from the global composite did not change this observation. Sex had no effect on rate of change on either composite or CDR-SB between groups.

In addition to cognitive measures, clinical progression was measured with the CDR-sum of boxes (CDR-SB), a measure derived from the box scores assigned to arrive at the global CDR.[49] Although clinical and cognitive measures often are correlated, this measure was included to determine consistency between clinical and cognitive progression. LOAD participants declined more rapidly clinically than ADAD (increasing CDR-SB) both before (0.19 versus 0.008; p=0.006) and after symptom onset (1.53 versus 0.93; p=0.0263; Table 2).

The extent to which age-related comorbidities might affect performance of the older LOAD group was addressed with additional analyses of the global composite scores adjusted for depression, hypertension and hypercholesterolemia. See Table 3. These co-morbidities were chosen because they were most prevalent and reported by both cohorts. The results reflected previous findings unadjusted for these conditions: LOAD declined faster preclinically and performed more poorly at symptom onset; ADAD declined more rapidly after symptom onset.

Sensitivity analyses regarding LOAD participants with ambiguous symptom onsets (received a CDR>0 but then “bounced” back to CDR0 at a later visit) were conducted by excluding individuals who reverted from CDR>0 back to CDR=0. These analyses revealed that main results remained stable. See Table 4.

Legend

Figure 1 Short title: Conceptual model of clinically significant phases

Figure 1 Legend: The conceptual analytic model depicting three clinical time points: preclinical phase when EYO is negative, symptom onset when EYO=0, and disease progression when EYO is positive. EYO = Estimated Years to/from Onset.

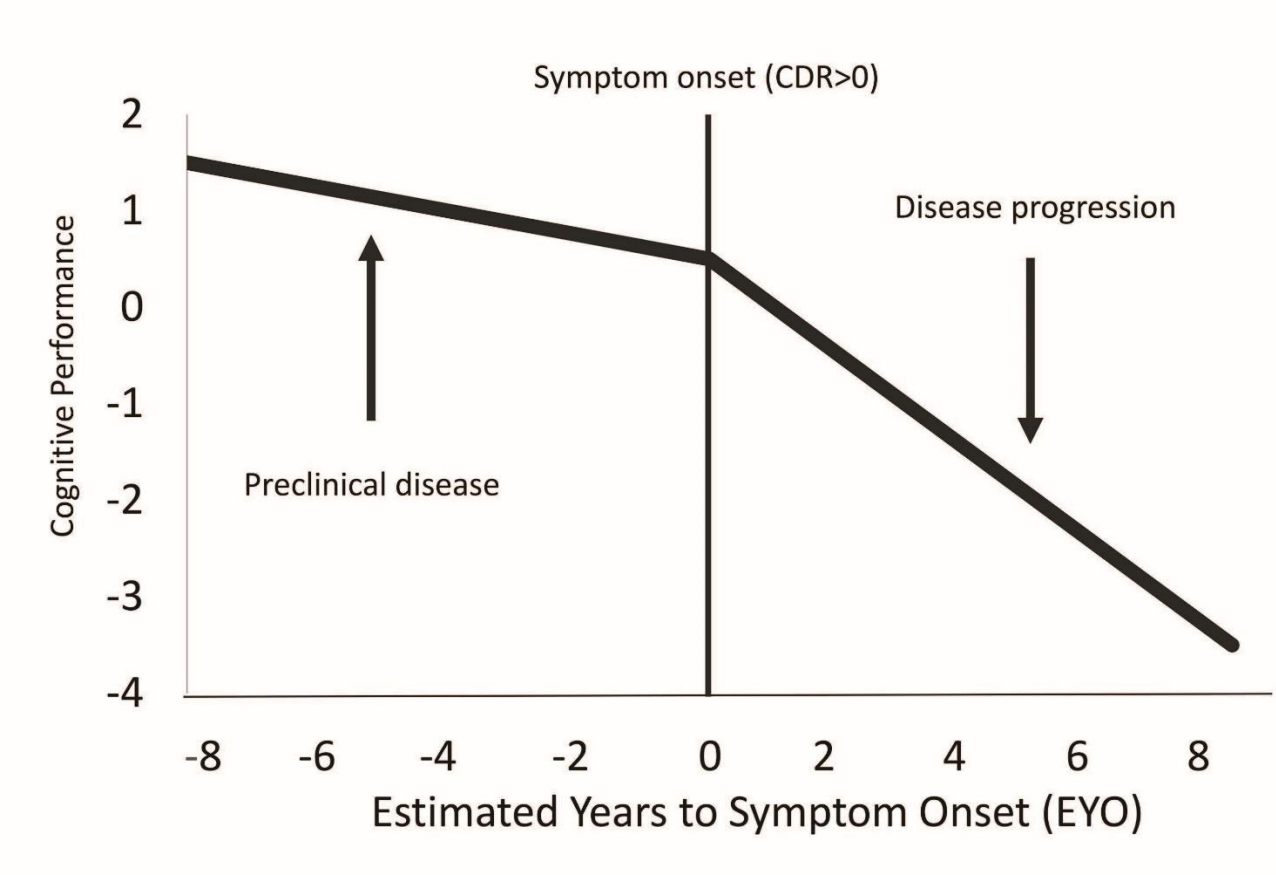
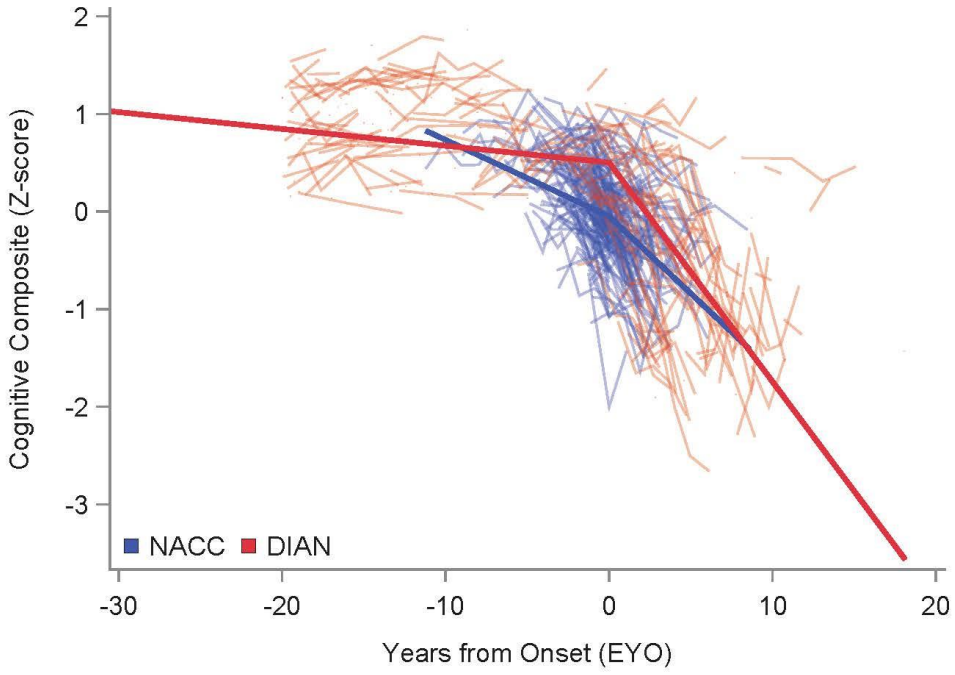


Figure 2.

Figure 2 Short title: Individual and group cognitive performance

Figure 2 legend: Figure displays individual performance (spaghetti plots) and group mean rates of change (solid lines, unadjusted) over time for the global cognitive composite. [Note: The large majority of DIAN participants do not know, nor do they wish to learn, their mutation status. To reduce the possibility of unintended disclosure that a DIAN individual may be a mutation carrier, data points from the few participants who are more than 20 years younger than their estimated age at symptomatic onset are not displayed in Figure 2, although all data were used in the analyses.]



Tables

Table 1 Title Summary statistics of demographic, clinical, and genetic characteristics at baseline visit

Table 1 Legend: NACC = National Alzheimer Coordinating Center; DIAN = Dominantly Inherited Alzheimer Network; CDR = Clinical Dementia Rating® (CDR®); *APOE ε4* = apolipoprotein E gene ε4 allele; BMI = Body Mass Index.

Table 1.	NACC LOAD N=163	DIAN ADAD N=310	p-value
Mean Age in years at Baseline (SD)	84.9 (7.7)	37.9 (8.3)	<.0001
Mean Age at Symptom Onset (SD)	87.2 (8.5)	42.6 (7.8)	<.0001
Mean Years of follow-up (SD)	4.9 (2.3)	3.3 (1.8)	<.0001
Sex n, (% Female)	108 (66.3)	173 (55.6)	0.0278
Mean Years Education (SD)	15.6 (2.6)	14.3 (3.1)	<.0001
Education less than 12 years n (% yes)	5 (3.1)	36 (11.6)	0.0020
Seizures n (% Yes)	1 (0.6)	13(4.2)	0.0298
Hypercholesterolemia† n (% Yes)	61 (37.9)	42 (13.9)	<.0001
Hypertension† n (% Yes)	97 (59.5)	24 (7.8)	<.0001
Depression‡ n (% Yes)	7 (4.6)	39 (12.6)	0.0072
Mean BMI (SD)	24.6 (4.1)	27.3 (5.8)	<.0001
Mutation (*PSEN1:PSEN2:APP*)	N/A	240:24:46	------
CDR at Baseline			<.0001

CDR 0 (n, %)	163 (100)	195 (62.9)	
CDR 0.5 (n, %)	0	75 (24.2)	
CDR 1 (n, %)	0	28 (9.0)	
CDR 2 (n, %)	0	7 (2.3)	
CDR 3 (n, %)	0	5 (1.6)	
% *APOE ε4+*	47 (29.4)	93 (30.0)	0.8883

† either recent/active or remote/inactive as reported by participant or study partner

‡ scores ≥ 6 on the Geriatric Depression Scale

Table 2 Title: Cognitive performance in mean annual rates of change and performance.

Table 2 Legend: Cognitive performance in z-score rates of change (mean annual) before and after symptom onset (EYO=0) and performance at symptom onset for NACC LOAD (n=163) and DIAN ADAD (n=310) participants. Adjusted for sex, education, *APOE ε4,* and BMI. Global composite includes all tests. Non-speed composite excludes Animal Fluency and Trails A and B. MMSE = Mini Mental Status Examination; Trails A and B = Trailmaking A and B; WAIS-R = Wechsler Adult Intelligence Scale-Revised.

Table 2	Preclinical Mean annual change (SE)			EYO=0 Mean performance (SE)			Progression Mean annual change (SE)		
Cognitive Test	**NACC LOAD**	**DIAN ADAD**	**p**	**NACC LOAD**	**DIAN ADAD**	**p**	**NACC LOAD**	**DIAN ADAD**	**p**
Animal Fluency	-0.89 (0.18) (p<.0001)	-0.13 (0.05) (p=0.0148)	<.0001	14.79 (0.76)	20.33 (0.94)	<.0001	-1.32 (0.23) (p<.0001)	-1.29 (0.28) (p<.0001)	0.9358
Boston Naming	-0.47 (0.10) (p<.0001)	0.01 (0.03) (p=0.7410)	<.0001	24.68 (0.51)	26.94 (0.63)	0.0040	-0.88 (0.20) (p<.0001)	-0.59 (0.23) (p=0.0121)	0.3410
Digits Backward	-0.14 (0.07) (p=0.0698)	0.005 (0.02) (p=0.8140)	0.0691	5.64 (0.25)	7.07 (0.33)	0.0008	-0.21 (0.08) (p=0.0166)	-0.52 (0.10) (p<.0001)	0.0200
Digits Forward	-0.17 (0.07)	-0.02 (0.02)	0.0361	7.00 (0.31)	8.59 (0.36)	0.0006	-0.13 (0.09)	-0.38 (0.10)	0.0006

	(p=0.0175)	(p=0.3819)					(p=0.1452)	(p=0.0002)	
Logical Memory – Immediate	-0.60 (0.15) (p<.0001)	-0.16 (0.04) (p=0.0001)	0.0049	9.93 (0.58)	12.15 (0.73)	0.0124	-1.10 (0.23) (p<.0001)	-1.45 (0.25) (p<.0001)	0.3129
Logical Memory – Delayed	-0.74 (0.15) (p<.0001)	-0.17 (0.04) (p<.0001)	0.0002	7.82 (0.61)	10.73 (0.77)	0.0042	-0.96 (0.23) (p<.0001)	-1.69 (0.27) (p<.0001)	0.0434
MMSE	-0.48 (0.11) (p<.0001)	-0.02 (0.02) (p=0.4533)	<.0001	26.89 (0.32)	28.74 (0.46)	0.0008	-1.60 (0.31) (p<.0001)	-1.60 (0.28) (p<.0001)	0.9839
Trails A	3.28 (0.87) (p=0.0002)	0.27 (0.19) (p=0.1714)	0.0008	54.06 (2.50)	26.22 (3.59)	<.0001	9.65 (2.26) (p<.0001)	7.20 (2.16) (p=0.0012)	0.4374
Trails B	14.62 (2.54) (p<.0001)	0.87 (0.54) (p=0.1086)	<.0001	168.36 (7.33)	71.81 (9.96)	<.0001	10.10 (5.33) (p=0.0006)	19.30 (5.09) (p=0.0003)	0.9779
WAIS-R Digit Symbol	-2.34 (0.31) (p<.0001)	-0.46 (0.11) (p<.0001)	<.0001	31.37 (1.73)	54.14 (2.09)	<.0001	-3.60 (0.65) (p<.0001)	-4.83 (0.80) (p<.0001)	0.2419
Global Composite (All above)	-0.11 (0.01) (p<.0001)	-0.01 (0.004) (p=0.0020)	<.0001	-0.14 (0.06)	0.59 (0.08)	<.0001	-0.14 (0.03) (p<.0001)	-0.23 (0.03) (p<.0001)	0.0211
Non-speed Composite	-0.10 (0.01) (p<.0001)	-0.01 (0.004) (p=0.0312)	<.0001	-0.11 (0.06)	0.42 (0.09)	<.0001	-0.15 (0.03) (p<.0001)	-0.24 (0.03) (p<.0001)	0.0348

CDR Sum of Boxes	0.19 (0.07) (p=0.0037)	0.008 (0.01) (p=0.5261)	0.0060	0.59 (0.12)	0.19 (0.22)	0.1074	1.53 (0.20) (p<.0001)	0.93 (0.18) (p<.0001)	0.0263

Table 3. Cognitive rate of change and performance on global cognitive composite adjusted for comorbidities in common.

Table 3. Legend: Global cognitive composite performance in rates of change (mean annual) and performance at symptom onset (EYO=0) for NACC LOAD (n=163) and DIAN ADAD (n=310) participants individually adjusted for comorbidities.

Table 3.	Preclinical Mean annual change (SE)			EYO=0 Mean performance (SE)			Progression Mean annual change (SE)		
Comorbidity	**NACC LOAD**	**DIAN ADAD**	**p**	**NACC LOAD**	**DIAN ADAD**	**p**	**NACC LOAD**	**DIAN ADAD**	**p**
Hypercholesterolemia	-0.08 (0.01)	-0.02 (0.005)	<.0001	-0.05 (0.05)	0.55 (0.06)	<.0001	-0.16 (0.02)	-0.22 (0.02)	0.0255
Hypertension	-0.07 (0.01)	-0.03 (0.01)	<.0001	-0.03 (0.05)	0.36 (0.09)	<.0001	-0.16 (0.02)	-0.22 (0.03)	0.0571
Depression	-0.10 (0.02)	-0.02 (0.004)	<.0001	-0.13 (0.05)	0.41 (0.06)	<.0001	-0.13 (0.02)	-0.20 (0.02)	0.0031

Table 4 Title: Sensitivity analysis excluding NACC participants with ambiguous symptom onset.

Table 4 Legend: Nine NACC LOAD participants who received a CDR>0 and later "bounced" back to CDR 0 were removed from analyses to examine the effect of CDR "bouncers" on composites and clinical decline. Statistical model and variables below are as defined in previous tables. DIAN ADAD n=310; NACC LOAD n=154.

Table 4	Preclinical Mean annual change (SE)			EYO=0 Mean performance (SE)			Progression Mean annual change (SE)		
Cognitive Test	**NACC LOAD**	**DIAN ADAD**	**p**	**NACC LOAD**	**DIAN ADAD**	**p**	**NACC LOAD**	**DIAN ADAD**	**p**
Global Composite (All above)	-0.11 (0.01) (p<.0001)	-0.01 (0.004) (p=0.0020)	<.0001	-0.15 (0.07)	0.59 (0.08)	<.0001	-0.15 (0.03) (p<.0001)	-0.23 (0.03) (p<.0001)	0.0273
Non-speed Composite	-0.10 (0.01) (p<.0001)	-0.01 (0.004) (p=0.0311)	<.0001	-0.12 (0.07)	0.42 (0.09)	<.0001	-0.16 (0.03) (p<.0001)	-0.24 (0.03) (p<.0001)	0.0480
CDR Sum of Boxes	0.19 (0.07) (p=0.0043)	0.008 (0.01) (p=0.5407)	0.0069	0.61 (0.12)	0.19 (0.23)	0.1032	1.63 (0.20) (p<.0001)	0.94 (0.17) (p<.0001)	0.0094

Author Contributions

Virginia D. Buckles, design of the study, analysis and interpretation of the data, drafting and revising the manuscript; Chengjie Xiong, design of the study, analysis and interpretation of the data, revising the manuscript; Randall J. Bateman, design of the study, interpretation of the data, revising the manuscript; Jason Hassenstab, interpretation of the data, revising the manuscript; Ricardo Allegri, Sarah B. Berman, Jasmeer P. Chhatwal, Adrian Danek, Anne M Fagan, Nick C Fox, Bernardino Ghetti, revising the manuscript; Alison Goate, interpretation of the data, revising the manuscript; Neill Graff-Radford, Mathias Jucker, Johannes Levin, Jonathan Vöglein, Daniel S Marcus, Colin L Masters, revising the manuscript; Lena McCue, analysis of the data, revising the manuscript; Eric McDade, Hiroshi Mori, Krista L Moulder, James M Noble, Katrina Paumier, Oliver Preische, John Ringman, Stephen Salloway, Peter Schofield, revising the manuscript; John C Morris, design of the study, interpretation of the data, revising the manuscript.

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Conflicts of Interest

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