Received: 16 May 2023 | Revised: 10 August 2023 | Accepted: 13 August 2023

DOI: 10.1002/alz.13460

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Investigation of sex differences in mutation carriers of the Dominantly Inherited Alzheimer Network

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Clinical Trial Registration Information: ClinicalTrials.gov Identifier: NCT00869817

Funding information
National Institute on Aging, Grant/Award Number: U19AG032438; Alzheimer Association, Grant/Award Numbers: AARFD-21-851415, SG-20-690363

Abstract

INTRODUCTION: Studies suggest distinct differences in the development, presentation, progression, and response to treatment of Alzheimer's disease (AD) between females and males. We investigated sex differences in cognition, neuroimaging, and fluid biomarkers in dominantly inherited AD (DIAD).

METHODS: Three hundred twenty-five mutation carriers (55% female) and one hundred eighty-six non-carriers (58% female) of the Dominantly Inherited Alzheimer Network Observational Study were analyzed. Linear mixed models and Spearman's correlation explored cross-sectional sex differences in cognition, cerebrospinal fluid (CSF) biomarkers, Pittsburgh compound B positron emission tomography (^{11}C-PiB PET) and structural magnetic resonance imaging (MRI).

RESULTS: Female carriers performed better than males on delayed recall and processing speed despite similar hippocampal volumes. As the disease progressed, symptomatic females revealed higher increases in MRI markers of neurodegeneration and memory impairment. PiB PET and established CSF AD markers revealed no sex differences.

DISCUSSION: Our findings suggest an initial cognitive reserve in female carriers followed by a pronounced increase in neurodegeneration coupled with worse performance on delayed recall at later stages of DIAD.

KEYWORDS
cognition, dominantly inherited Alzheimer's disease, gender, presymptomatic Alzheimer's disease, sex

1 | BACKGROUND

Alzheimer's disease (AD) is the most common cause of dementia, with prevalence shown to be consistently higher in females in many geographic regions.[1,2] Females have also been reported to have a lifetime risk of AD nearly twice that of males.[3] Hypotheses that have been brought forward in the past have predominantly related to gender, defined as the sociocultural construct characterizing individuals as women or men based on imposed norms, social roles, typical behaviors, as well as access to education and employment, and the longer lifespan of females. However, a growing body of evidence suggests that biological sex differences, including chromosome sets, epigenetics, and hormone levels, might also explain some of these findings.[4,5]

While studies to date have failed to show clear sex differences for amyloid burden in cerebrospinal fluid (CSF) or positron emission tomography (PET) imaging in sporadic AD (sAD),[6–8] several investigations have found a greater burden of tau in CSF and PET in both symptomatic and presymptomatic females[6,9–11] and identified distinct patterns of brain atrophy[12,13] between the sexes, leading some to hypothesize a sex-related modulation downstream of amyloid pathology.[14] Furthermore, a retrospective clinico-pathological study found each additional unit of AD pathology to be associated with a > 20-fold increase in the odds of clinical AD in females but only a 3-fold increase in males.[6] While females have been reported to show higher cognitive reserve despite similar levels of pathology in the early stage of AD,[15,16] this seems to be followed by a greater cognitive decline[17,18] and worse cognitive impairment in the symptomatic stage compared to males.[9,19] Further, a distinct profile of neuropsychiatric symptoms, including a higher prevalence and severity of depression, aberrant motor behavior, and psychotic symptoms, has been reported.[20] A positive carrier status of at least one apolipoprotein E (*APOE*) ε4 allele, known as a major genetic risk factor for the development of sAD,[21] seems to add to this sex-specific vulnerability, with some, but not all,[22] studies finding the interaction of *APOE* ε4 and sex to result in higher levels of tau pathology and neurodegeneration in females,[14,17,23,24] and female carriers to experience higher rates of conversion from mild cognitive impairment (MCI) to AD[25] as well as a greater cognitive decline than their male counterparts.[7,26]

In dominantly inherited AD (DIAD), which is caused by mutations in the presenilin1 (*PSEN1*), presenilin2 (*PSEN2*), or amyloid precursor protein (*APP*) genes,[27] studies investigating sex differences are scarce. In a recent publication on *PSEN1 E280A* mutation carriers, a better performance on verbal memory learning and global cognition in presymptomatic females compared to males was reported, despite similar levels of hippocampal volume, leading the authors to suggest a female reserve on verbal memory function in the presence of AD-related neurodegeneration.[28] An investigation into the effect of *APOE* ε4 carrier status in this cohort, on the other hand, found no interaction

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the current literature using traditional databases (e.g., PubMed, Google Scholar). There were very few publications exploring sex differences in dominantly inherited Alzheimer's disease (DIAD). Most of the studies on sex differences in Alzheimer's disease (AD) cognition and pathology were recovered in the context of sporadic AD; all are cited as appropriate.
2. **Interpretation**: Our findings of distinct sex differences in cognition as well as magnetic resonance imaging are in line with previous reports in sporadic AD and may suggest a greater cognitive reserve despite similar degrees of AD-related pathology in female DIAD carriers.
3. **Future directions**: Longitudinal analyses are needed to corroborate present results and further characterize sex-specific differences in DIAD. Understanding of biological impact of sex on disease presentation and progression are pivotal for the success of future clinical intervention trials.

of *APOE* ε4 and sex on amyloid burden, cerebral hypometabolism, or memory.[29]

The fact that DIAD mutation carriers manifest disease pathology a decade or more before their clinical symptom onset at a young and predictable age[30] allows for investigation across the spectrum of AD progression with diminished risk of age-related co-morbidities, co-pathologies,[31] and survival bias influencing the results. We therefore investigated sex differences in the international cohort of the Dominantly Inherited Alzheimer Network Observational Study (DIAN-OBS),[32] focusing on the cognitive performance as well as established biomarkers of AD pathology and neurodegeneration. A better understanding of the contribution of sex to the clinical-cognitive presentation, pathophysiology, and progression may improve diagnostic accuracy and benefit the design and efficacy of future clinical intervention trials, especially in light of recent results suggesting a lack of impact in clinical and cognitive outcomes for female participants receiving anti-amyloid treatment.[33]

2 | METHODS

2.1 | Participants

All data analyzed was selected from the DIAN data freeze 15.

Participants included in this analysis were recruited through DIAN-OBS (ClinicalTrials.gov Identifier: NCT00869817) and provided written consent or assent with proxy consent prior to enrollment in accordance with the latest Declaration of Helsinki. The study is supervised by the institutional review board (IRB) at Washington University in St. Louis, USA, and all study procedures were approved by the Human Research Protection Office and the IRB at Washington University or the respective participating sites. The DIAN study recruits participants from Asia, Australia, Europe, and the Americas, aiming at enrolling a diverse sample regarding education, sex, gender, race, and ethnicity. Participant enrollment was carried out according to prespecified inclusion and exclusion criteria that have been described previously.[34] As every participant is a member of a family with a known mutation for DIAD, the presence or absence of a DIAD mutation for each of them was determined via polymerase chain reaction–based amplification of the appropriate exon and subsequent Sanger sequencing.

Each participant's estimated years to symptom onset (EYO) was calculated as the difference between age at baseline and, if symptomatic, the actual age of symptom onset according to the patient's history, or, if presymptomatic, the expected age at symptom onset defined according to the mean age of onset of the respective mutation or the parental age of symptom onset (in case the specific variant mean age of onset is unknown).[30] The resulting EYO of each participant therefore serves as a variable of time along the disease stages of DIAD, centered around the individual estimated age of symptom onset (EYO = 0), with EYO < 0 referring to participants prior to, and EYO > 0 referring to participants past, their estimated age of clinical symptom onset.

Carriers of a Dutch or Flemish mutation were excluded from this analysis due to differences in disease presentation and the high burden of cerebral amyloid angiopathy.[35]

According to EYO and baseline score on the global Clinical Dementia Rating (CDR),[36] all mutation carriers (55% female) were further grouped as either presymptomatic (CDR 0, 56% female) or symptomatic (CDR > 0, 53% female). A detailed description of the CDR rating distribution can be found in the supporting information (Table S1). Three mutation carriers initially classified as symptomatic (CDR 0.5) at baseline (EYO ≤ −17) were classified as asymptomatic (CDR = 0) in subsequent follow-up visits. These participants were considered temporarily symptomatic due to a non-degenerative reason and therefore excluded from analysis. Non-carriers (58% female) with a rating of CDR 0 and amyloid PET burden below the cut-off (see section 2.5) were included in the analysis as healthy controls.

Biological sex was self-reported by participants, with options being female or male, and has been confirmed, where available (for 93% of females and 90% of males), via wet lab fingerprinting assay with a 100% concordance. Gender identity was not explicitly assessed. Throughout the article, "female" and "male" as well as "sex" will therefore refer to biological sex and not gender identity. For the sake of consistency, the same terms will also be used when referencing other studies, yet it should be noted that the confirmation of biological sex is not explicitly stated in most investigations and may refer to self-reported sex or self-reported gender.

2.2 | Clinical and neuropsychological assessments

Participants underwent a detailed clinical evaluation that included family history, personal medical history, current medication, and a

thorough neurological examination. Clinicians were blinded to the participant's genetic status and conducted the clinical evaluation of dementia status according to standard protocols and criteria.[37] All participants included in this analysis underwent a neuropsychological examination evaluating delayed recall (Wechsler Memory Scale-Revised Logical Memory), category fluency (Animal Naming Test), and, if available, processing speed (Wechsler Adult Intelligence Scale-Revised Digit Symbol Substitution Test), which are part of a global cognitive composite score.[37] For ease of interpretation, each test was transformed into a *z* score using the mean and standard deviation of non-carriers. Further, the Mini-Mental State Examination (MMSE), the Geriatric Depression Scale (GDS), and the Neuropsychiatric Inventory (NPI) were incorporated into each assessment.

2.3 | Analysis of cerebrospinal fluid

According to the specific guidelines of the DIAN study protocols,[38] CSF was collected under fasting conditions by lumbar puncture, using an atraumatic Sprotte spinal needle, into two 13-ml polypropylene tubes. CSF was then flash-frozen on dry ice and aliquoted into polypropylene tubes before storage at −80°C. Amyloid beta (Aβ)42, Aβ40, total tau (t-tau), and phosphorylated tau-181 (p-tau181) were measured using the validated LUMIPULSE G1200 immunoassay (Fujirebio) according to standardized procedures.

2.4 | Structural magnetic resonance imaging

A T1-weighted accelerated magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequence was performed on 3T scanners according to Alzheimer's Disease Neuroimaging Initiative magnetic resonance imaging (MRI) protocol. Images were processed using FreeSurfer (version 5.3-HCP-patch) for cortical reconstruction and volumetric segmentation. Descriptions detailing the procedures have been published previously.[39,40] Volumetric region of interest (ROI) T1 measures in this analysis were normalized to individual intracranial volumes. In this analysis, we focused on volumetric measures of the hippocampus and amygdala, as well as global cortical atrophy which were calculated using a signature DIAD mask of cortical ROI such as the precuneus, lateral and mesial orbitofrontal, rostral mesial and superior frontal, and superior and mesial temporal region.[41]

2.5 | [^{11}C]PiB PET

Positron emission tomography assessing cortical Aβ deposition was performed using a single bolus injection of approximately 13 mCi of Pittsburgh compound B ([^{11}C]PiB). The regional standardized uptake value ratios (SUVRs) were determined from the 40 to 70 post-injection windows. SUVRs in 34 cortical and 6 subcortical ROIs defined using structural MRIs were retrieved. Cerebellum gray matter was used as the reference region for each SUVR and ROI data were corrected for partial volume effects using a geometric transfer matrix approach. A composite score was subsequently calculated using the average SUVR of the precuneus, the prefrontal cortex (superior frontal and rostral middle frontal), the gyrus rectus (lateral and medial orbitofrontal), and the lateral temporal region (superior temporal and middle temporal gyri).[40,42] Amyloid positivity was defined as a value > 1.42 of the PiB PET composite score.

2.6 | Statistical analysis

Baseline demographics were summarized as mean ± standard deviation for continuous variables and count percentage for categorical variables. Group comparisons between females and males were conducted via Mann–Whitney *U* tests for continuous and Fisher exact tests for categorical variables. For cross-sectional analysis, linear mixed models were used to investigate the main effect of sex as well as the interaction of sex and EYO on cognition and biomarker outcome variables (where available). Analyses were conducted as follows: Model 1.1 investigated sex as a main effect in the whole cohort of mutation carriers. For Model 1.2, an interaction with group (CDR 0 / CDR > 0) was introduced to investigate a sex effect *between* groups and to allow for the retrieval of contrasts assessing the magnitude of a sex effect *within* each group. Similarly, Model 2.1 explored the interaction of sex and EYO in the whole cohort of carriers, while Model 2.2 examined, via a three-way interaction with group, possible differences in sex effects with respect to the corresponding EYO *between* the groups. Subsequent contrast analysis then explored a sex effect with respect to the corresponding EYO *within* each group. Models 1.1 and 2.1 were also run in non-carriers.

Model 1.1: Outcome ~ Sex + EYO
Model 1.2: Outcome ~ Sex x group + EYO
Model 2.1: Outcome ~ Sex x EYO
Model 2.2: Outcome ~ Sex x EYO x group

All models included a random effect for families. If appropriate, years of education and group as well as their interaction with EYO were included as covariates, but only kept when significantly improving the model. Predictors that showed a skewed distribution of their residuals were log-transformed. For cognitive performance, all outcomes of interest were examined separately rather than in a composite because there is evidence for domain-specific sex differences.[43] Finally, in subcohorts in which cognitive assessments and fluid or imaging biomarkers were available, we performed separate Spearman correlations for females and males to investigate the associations between markers of AD(-related) pathology and cognition. Significant differences between the correlation coefficients of female and male presymptomatic or symptomatic carriers were tested based on Fisher *z* transformations for independent correlation coefficients.

All analyses were performed using R (version 4.1.3).[44] Statistical tests were carried out two-sided and *P*-values were considered significant below 0.05. Correction for false discovery rate (FDR) was

performed for all contrast analyses. For ease of interpretation, only the predictors of interest will be discussed and displayed in the main tables; a comprehensive output for each model can be found in the supporting information.

3 | RESULTS

3.1 | Baseline demographics

Baseline characteristics for mutation carriers and non-carriers are presented in Table 1. At baseline, both presymptomatic and symptomatic female carriers tended to be slightly younger and closer to their (estimated) age at symptom onset than the respective male carriers. For non-carriers, no significant sex differences in demographic variables were detected. There were also no significant imbalances between the sexes in any group for DIAD mutation type or *APOE* ε4 status. Average years of education did not differ between females and males of any group and neither did cognitive status as measured by the MMSE score, depressive symptoms (measured via the GDS), and neuropsychiatric symptoms (assessed with the NPI) in any group.

3.2 | Main effect of sex

In all mutation carriers (Table 2, Model 1.1 and Figure 1), we found that females performed significantly better on delayed recall ($\beta = -0.303$, $P = 0.0052$) and processing speed ($\beta = -0.401$, $P = 0.0015$) while male carriers showed a non-significant trend of a better performance on category fluency ($\beta = 0.238$, $P = 0.0528$).

The sex x group interaction (Table 3, Model 2.1) subsequently revealed a significant difference in sex effect between the presymptomatic and symptomatic group for processing speed ($\beta = 0.532$, $P = 0.045$), but no other cognitive tasks. Contrast analysis of the sex x group interaction found a better performance on processing speed ($P = 0.0002$, FDR-corrected $P = 0.0004$) and delayed recall ($P = 0.0081$, FDR-corrected $P = 0.0162$) in female compared to male presymptomatic carriers, but no sex difference for either task within the symptomatic group. However, we found symptomatic male carriers to perform significantly better on category fluency than their female counterparts ($P = 0.0438$), though this finding did not survive FDR correction ($P = 0.0876$).

Investigating CSF markers of AD(-related) pathology, we found no sex effect in Aβ42/40, p-tau181, or t-tau levels in all mutation carriers. The interaction sex x group similarly revealed no difference in sex effect between the presymptomatic and symptomatic group, and contrast analysis showed no sex difference within each group. For PiB PET burden, MRI cortical thickness, and hippocampal volume we found no discernible sex difference in all mutation carriers. However, MRI volume analysis revealed lower amygdala volumes in female mutation carriers ($\beta = 148.723$, $P = 0.0037$). The sex x group interaction found no differences in sex effect between presymptomatic and symptomatic carriers; contrast analysis, however, exhibited significantly lower amygdala volumes in females compared to males within the symptomatic group ($P = 0.0212$, FDR-corrected $P = 0.0424$).

Analysis of sex differences in asymptomatic non-carriers (Table 2, Model 1.1) revealed a significantly better performance in females on delayed recall ($\beta = -0.445$, $P = 0.0017$) and processing speed ($\beta = -0.581$, $P < 0.0001$), as well as lower CSF t-tau levels ($\beta = 0.187$, $P = 0.0012$), while all other measures of cognition as well as imaging and CSF biomarkers demonstrated no differences between the sexes.

3.3 | Interaction of sex and EYO

Investigating the impact of disease stage on sex effects within the DIAD continuum as represented by EYO (Table 2, Model 1.2), the sex x EYO interaction in all carriers found a sex difference for delayed recall, with female carriers performing significantly worse than males ($\beta = 0.021$, $P = 0.0272$; Figure 1) depending on EYO. While the three-way interaction of sex x EYO x group (Table 3, Model 2.2) showed no significant difference for cognitive performance, contrast analysis revealed a significantly pronounced impairment on delayed recall for presymptomatic ($P = 0.0348$, FDR-corrected $P = 0.0696$) and symptomatic ($P = 0.0212$, FDR-corrected $P = 0.0424$) females compared to males of the respective group, though only the latter survived FDR correction.

In CSF, we found no differences for the interaction of sex x EYO and sex x EYO x group. Subsequent contrast analysis within the presymptomatic and symptomatic group also remained without a sex effect.

PiB PET analysis in all carriers revealed no significant sex x EYO interaction and no discernible effect in the sex x EYO x group interaction. However, contrasts showed a significant increase in PiB PET burden in presymptomatic females compared to presymptomatic males, though this finding did not survive FDR correction ($P = 0.038$, FDR-corrected $P = 0.076$). While there was no significant difference for sex x EYO in MRI in all carriers, all measures exhibited a significant interaction for sex x EYO x group, indicating a distinct difference in sex effect between the presymptomatic and the symptomatic group (cortical thickness: $\beta = 0.038$, $P = 0.0002$, hippocampus volume: $\beta = 142.061$, $P = 0.0274$, amygdala volume: $\beta = 83.818$, $P = 0.0068$, Figure 2) depending on EYO. Contrast analysis further revealed significant differences between the sexes within the symptomatic group, with females showing a pronounced atrophy as measured by cortical thickness ($P = 0.0001$, FDR-corrected $P = 0.0004$) and an enhanced volume loss in hippocampus ($P = 0.0147$, FDR-corrected $P = 0.0294$) and amygdala ($P = 0.0036$, FDR-corrected $P = 0.0072$) as disease progresses compared to symptomatic males.

In non-carriers, the sex x EYO interaction (Table 2, Model 1.2) did not reveal any effect on cognition or imaging. However, we found an interaction with EYO for higher levels of p-tau181 ($\beta = -0.009$, $P = 0.0379$) and t-tau ($\beta = -0.012$, $P = .0089$) as well as lower levels in Aβ42/40 ($\beta = 0.004$, $P = 0.0248$) in female compared to male non-carriers.

TABLE 1 Baseline demographics, cognition scores, and parameters of fluid and imaging biomarkers in DIAD mutation carriers and non-carriers.

	All carriers			Carriers (CDR 0)			Carriers (CDR > 0)			Non-carriers (CDR 0)		
Variable	Females ($n = 179$)	Males ($n = 146$)	*P* value	Females ($n = 119$)	Males ($n = 92$)	*P* value	Females ($n = 60$)	Males ($n = 54$)	*P* value	Females ($n = 108$)	Males ($n = 78$)	*P* value
Age at visit (y)	37 ± 11	39 ± 11	0.2	33 ± 9	34 ± 9	0.9	45 ± 10	48 ± 8	0.2	38 ± 12	37 ± 10	0.8
EYO (y)	−9 ± 11	−8 ± 12	0.5	−14 ± 9	−15 ± 9	0.5	2.76 ± 2.60	3.85 ± 3.03	0.032	−10 ± 13	−12 ± 11	0.7
Mutation type			0.2			0.081			>0.9			0.7
APP	28 (16%)	25 (17%)		17 (14%)	14 (15%)		11 (18%)	11 (20%)		16 (15%)	11 (14%)	
PSEN1	141 (79%)	105 (72%)		93 (78%)	62 (67%)		48 (80%)	43 (80%)		78 (72%)	60 (77%)	
PSEN2	10 (5.6%)	16 (11%)		9 (7.6%)	16 (17%)		1 (1.7%)	0 (0%)		14 (13%)	7 (9.0%)	
***APOE ε4* status (≥ 1 allele)**			0.4			0.9			0.3			>0.9
Negative	131 (73%)	100 (68%)		85 (71%)	64 (70%)		46 (77%)	36 (67%)		75 (69%)	54 (69%)	
Positive	48 (27%)	46 (32%)		34 (29%)	28 (30%)		14 (23%)	18 (33%)		33 (31%)	24 (31%)	
Education (y)	14.18 ± 2.85	14.52 ± 3.39	0.6	14.71 ± 2.60	14.86 ± 3.09	>0.9	13.1 ± 3.0	13.9 ± 3.8	0.5	15.01 ± 2.38	15.15 ± 3.03	0.9
First clinical symptom									0.8			
Memory							50 (83%)	45 (83%)				
Other							7 (12%)	8 (15%)				
Missings							3	1				
MMSE	27.2 ± 4.4	26.7 ± 4.9	0.5	29.1 ± 1.09	29 ± 1.4	0.8	23 ± 6	23 ± 6	0.5	29.2 ± 1.2	29 ± 1.3	0.4
Missings	1	0		0	0		1	0		1	0	
GDS	2.45 ± 2.74	2.39 ± 2.66	0.8	1.59 ± 1.81	1.61 ± 2.13	0.6	4.2 ± 3.4	3.7 ± 2.9	0.6	1.48 ± 1.80	1.32 ± 1.81	0.5
Delayed recall (*z* score)	−0.72 ± 1.46	−1.14 ± 1.46	0.008	−0.01 ± 1.01	−0.34 ± 1.05	0.014	−2.12 ± 1.15	−2.51 ± 0.94	0.057	0.14 ± 0.99	−0.20 ± 0.99	0.025

(Continues)

TABLE 1 (Continued)

	All carriers			Carriers (CDR 0)			Carriers (CDR > 0)			Non-carriers (CDR 0)		
Variable	Females ($n = 179$)	Males ($n = 146$)	*P* value	Females ($n = 119$)	Males ($n = 92$)	*P* value	Females ($n = 60$)	Males ($n = 54$)	*P* value	Females ($n = 108$)	Males ($n = 78$)	*P* value
Category fluency (*z* score)	−0.47 ± 1.28	−0.30 ± 1.44	0.3	0.03 ± 1.08	0.22 ± 1.28	0.4	−1.47 ± 1.02	−1.19 ± 1.26	0.2	−0.03 ± 1.06	0.04 ± 0.92	0.4
Processing speed (*z* score)	−0.53 ± 1.64	−1.09 ± 1.62	<0.001	0.23 ± 0.97	−0.36 ± 1.04	<0.001	−2.19 ± 1.57	−2.45 ± 1.63	0.5	0.22 ± 0.98	−0.31 ± 0.95	<0.001
Missings	5	4		0	0		5	4		0	0	
CSF Aβ42/40	0.074 ± 0.034	0.070 ± 0.034	0.4	0.08 ± 0.03	0.08 ± 0.03	0.5	0.052 ± 0.022	0.048 ± 0.018	0.3	0.091 ± 0.010	0.091 ± 0.009	0.8
Missings	27	25		17	11		10	14		18	14	
CSF p-tau181 (pg/mL)	76 ± 65	73 ± 63	0.8	50 ± 41	47 ± 40	0.8	127 ± 75	127 ± 69	>0.9	28 ± 8	31 ± 14	0.4
Missings	27	28		17	12		10	16		26	15	
CSF t-tau (pg/mL)	506 ± 344	504 ± 360	>0.9	374 ± 228	375 ± 258	>0.9	775 ± 384	770 ± 396	0.9	248 ± 76	305 ± 133	0.01
Missings	33	33		21	16		12	17		28	20	
PiB PET (SUVR)	1.93 ± 1.05	1.91 ± 0.97	0.7	1.64 ± 0.82	1.56 ± 0.70	0.9	2.72 ± 1.18	2.69 ± 1.04	>0.9	1.05 ± 0.07	1.03 ± 0.07	0.078
Missings	41	23		19	7		22	16		0	0	
Cortical thickness (mm)	2.25 ± 0.21	2.24 ± 0.21	0.6	2.33 ± 0.12	2.33 ± 0.14	0.9	2.08 ± 0.23	2.05 ± 0.20	0.4	2.35 ± 0.12	2.33 ± 0.11	0.2
Missings	14	13		8	3		6	10		0	1	
Hippocampus volume (mm^3)	8374 ± 1142	8473 ± 1253	0.13	8733 ± 824	9056 ± 686	0.003	7635 ± 1341	7292 ± 1315	0.2	8789 ± 637	8933 ± 767	0.2
Missings	14	13		8	3		6	10		0	1	
Amygdala volume (mm^3)	3342 ± 509	3464 ± 491	0.043	3489 ± 373	3603 ± 405	0.027	3040 ± 612	3182 ± 532	0.4	3470 ± 337	3575 ± 425	0.075
Missings	14	13		8	3		6	10		0	1	

Note: For all groups, continuous variables are presented as mean ± standard deviation and *P*-values were calculated using the Wilcoxon rank sum test. All categorical variables are presented as count (percentage of all measured), Fisher exact test was used to assess significance in differences between females and males. *APOE* ε4 status is considered positive in participants having at least one ε4 allele.

Abbreviations: *APOE*, apolipoprotein E gene; APP, amyloid precursor protein; Aβ, amyloid beta; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; DIAD, dominantly inherited Alzheimer's disease; EYO, estimated years to symptom onset; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; n, total number of respective participants; PET, positron emission tomography; PiB, ^{11}C-Pittsburgh compound B; PSEN1, presenilin 1; PSEN2, presenilin 2; p-tau181, phosphorylated tau protein 181; SUVR, standardized uptake value ratio; t-tau, total tau protein.

TABLE 2 Estimated β coefficients and standard errors for sex as a main effect (Model 1.1) and sex in interaction with EYO (Model 2.1) in female and male DIAD mutation carriers or non-carriers, respectively.

	Carriers		Non-carriers	
Model 1.1 (sex effect)	**$\beta \pm$ SE**	***P* value**	**$\beta \pm$ SE**	***P* value**
Delayed recall (*z* score)	−0.303 ± 0.108	0.0052	−0.445 ± 0.14	0.0017
Category fluency (*z* score)	0.238 ± 0.122	0.0528	0.08 ± 0.144	0.5797
Processing speed (*z* score)	−0.401 ± 0.125	0.0015	−0.581 ± 0.13	<0.0001
CSF Aβ42/40 (log)	−0.012 ± 0.04	0.7532	0.009 ± 0.02	0.6744
CSF p-tau181 (log)	−0.035 ± 0.067	0.6041	0.072 ± 0.056	0.2017
CSF t-tau (log)	0.008 ± 0.06	0.8947	0.187 ± 0.057	0.0012
PiB PET (log)	−0.004 ± 0.041	0.9235	−0.018 ± 0.01	0.0732
Cortical thickness (mm)	0.004 ± 0.017	0.8016	−0.019 ± 0.017	0.2685
Hippocampus volume (mm^3)	134.973 ± 105.287	0.201	35.369 ± 94.852	0.7097
Amygdala volume (mm^3)	148.723 ± 50.732	0.0037	88.06 ± 54.995	0.1111
Model 2.1 (sex x EYO)	**$\beta \pm$ SE**	***P* value**	**$\beta \pm$ SE**	***P* value**
Delayed recall (*z* score)	0.021 ± 0.009	0.0272	0.013 ± 0.012	0.3029
Category fluency (*z* score)	0.014 ± 0.011	0.1907	−0.002 ± 0.013	0.8678
Processing speed (*z* score)	0.014 ± 0.011	0.1955	0.011 ± 0.011	0.3239
CSF Aβ42/40 (log)	0.006 ± 0.003	0.1022	0.004 ± 0.002	0.0248
CSF p-tau181 (log)	−0.007 ± 0.006	0.2554	−0.009 ± 0.005	0.0379
CSF t-tau (log)	−0.007 ± 0.005	0.1832	−0.012 ± 0.005	0.0089
PiB PET (log)	−0.005 ± 0.004	0.2084	−0.001 ± 0.001	0.1059
Cortical thickness (mm)	0.001 ± 0.001	0.4445	−0.001 ± 0.001	0.332
Hippocampus volume (mm^3)	1.032 ± 9.235	0.9111	−0.801 ± 8.37	0.9238
Amygdala volume (mm^3)	6181 ± 444	0.165	6708 ± 4793	0.1633

Note: Full model output can be found in the supporting information (Tables S2 and S3). The reference variable for sex is set to females.
Abbreviations: Aβ, amyloid beta; β, beta-estimate; CSF, cerebrospinal fluid; DIAD, dominantly inherited Alzheimer's disease; EYO, estimated years to symptom onset; PET, positron emission tomography; PiB, ^{11}C-Pittsburgh compound B; p-tau181, phosphorylated tau protein 181; SE, standard error; t-tau, total tau protein.

3.4 | Correlations of biomarkers with cognitive performance

We found lower Aβ42/40 levels significantly correlated with reduced processing speed for presymptomatic females (r = 0.25, *P* = 0.015; Figure 3 and Table S6 in supporting information) and males (r = 0.26, *P* = 0.022), with no other correlations between cognition and CSF biomarkers showing a significant relationship. We further found lower hippocampal volume significantly correlated with worse performance on delayed recall (r = 0.26, *P* = 0.010) and processing speed (r = 0.3, *P* = 0.003), and reductions in cortical thickness significantly correlated with lower scores on delayed recall (r = 0.28, *P* = 0.006) and category fluency (r = 0.21, *P* = 0.032) in presymptomatic female carriers, yet no significant correlations between imaging and cognition in presymptomatic males. With this, we saw a non-significant trend of difference for correlations of cortical thickness and delayed recall (r = 0.28 vs. r = 0.03, Δ *P* = 0.09) and hippocampal volume and processing speed (r = 0.3 vs. r = 0.01, Δ *P* = 0.05) between the sexes.

In the symptomatic stage, correlations were generally stronger than in the presymptomatic stage. Higher CSF Aβ42/40 correlated with higher scores on delayed recall (r = 0.41, *P* = 0.015) in symptomatic males only. Further, higher p-tau181 levels showed a correlation with worse scores on processing speed (females r = −0.37, *P* = 0.013; males r = −0.35, *P* = 0.041) and delayed recall (females r = −0.37, *P* = 0.013; males r = −0.42, *P* = 0.011) in both sexes. Levels of t-tau revealed a significant negative correlation for delayed recall in symptomatic males (r = −0.48, *P* = 0.004) and for processing speed in symptomatic females (r = −0.34, *P* = 0.023) and males (r = −0.37, *P* = 0.030).

A higher amyloid burden in PET correlated with worse performance on processing speed in symptomatic females (r = −0.33, *P* = 0.0498). Lower cortical thickness was correlated with worse scoring on all cognitive measures in both sexes (delayed recall: females r = 0.69, *P* < 0.0001; males r = 0.4, *P* = 0.014, Δ *P* = 0.08; category fluency: females r = 0.56, *P* < 0.001; males r = 0.45, *P* = 0.005; processing speed: females r = 0.64, *P* < 0.0001; males r = 0.61, *P* < 0.0001). Reduced hippocampal volumes significantly correlated in symptomatic females and males with worse performance on delayed recall (females r = 0.58, *P* < 0.001;

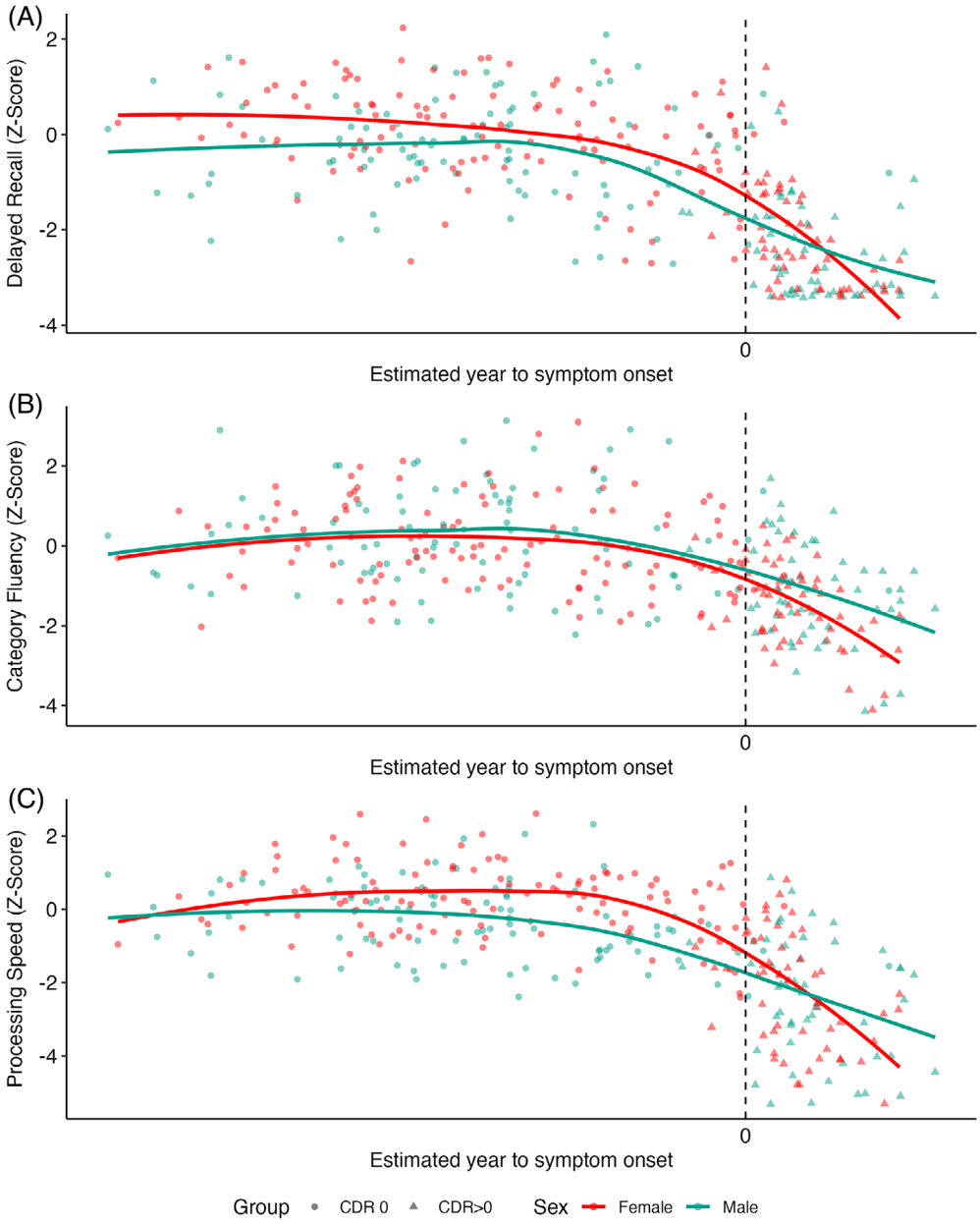

FIGURE 1 Scatter plots for *z*-transformed values of cognitive outcome variables along the years leading up to and past the point of estimated age of symptom onset (dashed line at EYO = 0; to maintain blinding toward mutation status for participants and investigators when reporting individual data points, specific estimated years before onset are not shown) in presymptomatic (dot) and symptomatic (triangle) mutation carriers for delayed recall (A), Animal Naming Test (B) and Digit Symbol Test (C). Females are represented in red, males in green. The curves are locally weighted scatterplot smoothing (LOESS) lines, fitted to raw data values. CDR, Clinical Dementia Rating; EYO, estimated years to symptom onset.

males r = 0.5, $P = 0.002$) and processing speed (females r = 0.51, $P = 0.002$; males r = 0.47, $P = 0.003$), but only in females with category fluency (r = 0.42, $P = 0.011$). Finally, lower amygdala volumes correlated in both sexes with lower scores on delayed recall (females r = 0.54, $P < 0.001$; males r = 0.4, $P = 0.015$) and processing speed (females r = 0.59, $P < 0.001$; males r = 0.41, $P = 0.011$), while category fluency was only significantly correlated in symptomatic females (r = 0.42, $P = 0.013$).

4 | DISCUSSION

We investigated cross-sectional sex differences in DIAD mutation carriers and found females to perform better on delayed recall and processing speed while exhibiting similar degrees of hippocampal volume and cortical thickness and lower amygdala volumes. Meanwhile, there were no sex differences in CSF markers of AD(-related) pathology or PiB PET burden.

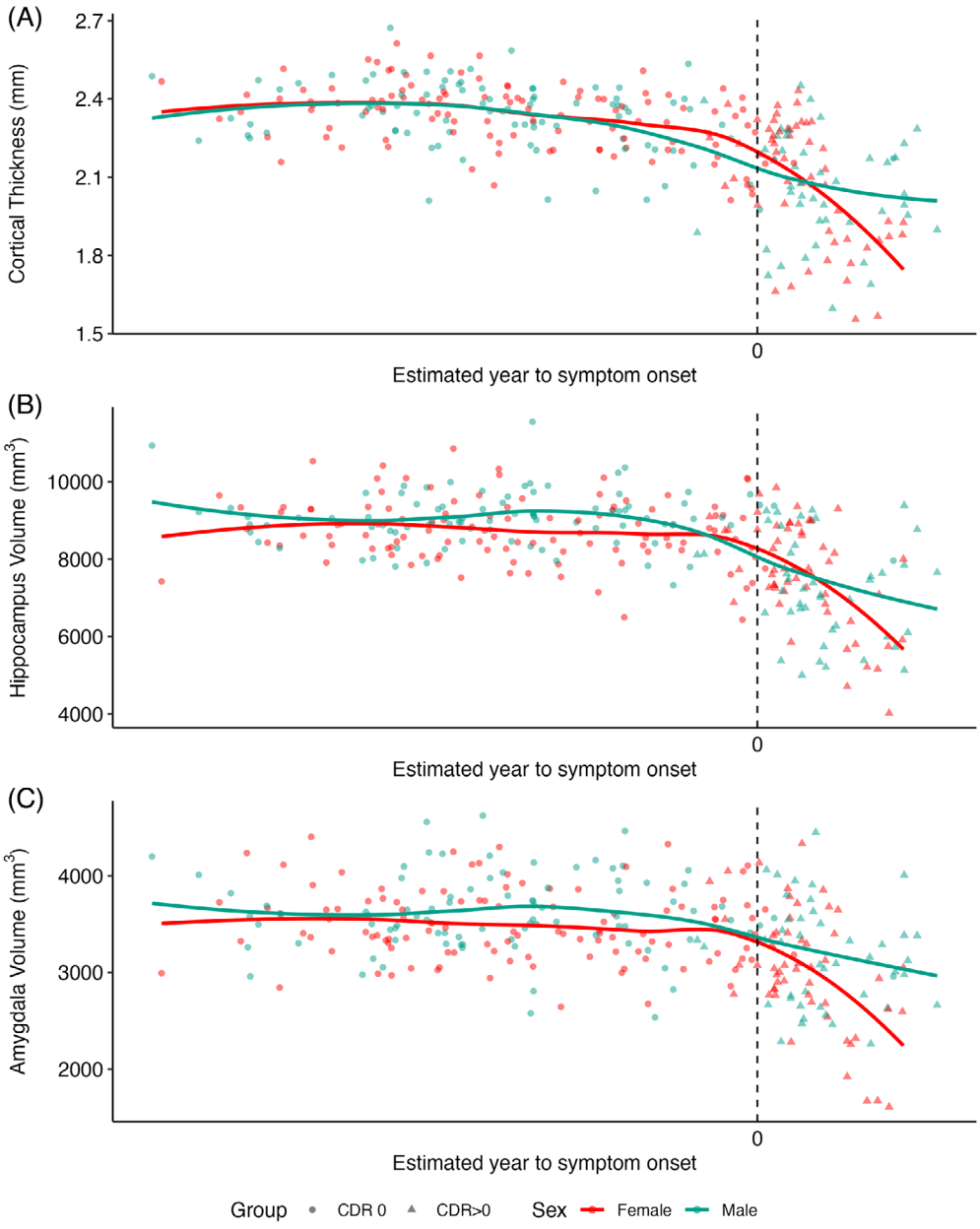

FIGURE 2 Scatter plots for cross-sectional assessments of MRI imaging along the years leading up to and past the point of estimated symptom onset (dashed line at EYO = 0; to maintain blinding toward mutation status for participants and investigators when reporting individual data points, specific estimated years before onset are not shown) in presymptomatic (dot) and symptomatic (triangle) mutation carriers for cortical thickness (A), hippocampus volume (B) and amygdala volume (C). Females are represented in red, males in green. The curves are locally weighted scatterplot smoothing (LOESS) lines, fitted to raw data values. CDR, Clinical Dementia Rating; EYO, estimated years to symptom onset; MRI, magnetic resonance imaging.

With disease progression, we saw pronounced impairment of delayed recall in female carriers, predominantly in the symptomatic group, as well as increased cortical thinning and decreased hippocampus and amygdala volumes in symptomatic female carriers. We further found weak to moderate correlations between biomarkers in both subgroups. Specifically, cognition and CSF markers tended to be more highly correlated in male carriers, while cognition and imaging seemed more tightly coupled in female carriers, yet there were no significant differences in these correlations between the sexes in either group.

In cognitively healthy adults, studies report a superior performance of females in verbal memory and processing speed but not category fluency,[15,43,45] mirroring our results in non-carriers.

Female carriers also performed better on processing speed and delayed recall but simultaneously displayed similar levels of hippocampal atrophy and cortical thickness as well as lower volumes of the

TABLE 3 Estimates for the sex x group interaction (Model 1.2) and for the sex x EYO group interaction (Model 2.2) between and within presymptomatic and symptomatic DIAD mutation carriers.

			Carriers (CDR 0)				Carriers (CDR > 0)			
	Carriers		Females	Males			Females	Males		
Model 1.2 (sex x group)	**$\beta \pm$ SE**	***P* value***	**means ± SE**	**means ± SE**	***P* value***	***P* value†**	**means ± SE**	**means ± SE**	***P* value***	***P* value†**
Delayed recall (*z* score)	0.155 ± 0.226	0.495	−0.174 ± 0.104	−0.53 ± 0.118	0.0081	0.0162	−0.16 ± 0.389	−0.361 ± 0.421	0.2674	
Category fluency (*z* score)	0.279 ± 0.257	0.279	−0.0388 ± 0.117	0.1009 ± 0.134	0.3588		0.5061 ± 0.441	0.9244 ± 0.478	0.0438	0.0876
Processing speed (*z* score)	0.532 ± 0.264	0.045	0.0213 ± 0.12	−0.5576 ± 0.136	0.0002	0.0004	0.3367 ± 0.472	0.2902 ± 0.509	0.8294	
CSF Aβ42/40 (log)	0.052 ± 0.084	0.5372	−2.69 ± 0.0386	−2.72 ± 0.0444	0.5618		−2.76 ± 0.0576	−2.74 ± 0.0622	0.7314	
CSF p-tau181 (log)	−0.021 ± 0.142	0.8834	3.9 ± 0.0627	3.87 ± 0.0727	0.7378		4.2 ± 0.0958	4.15 ± 0.1055	0.6742	
CSF t-tau (log)	−0.083 ± 0.127	0.5127	5.91 ± 0.0544	5.95 ± 0.0642	0.625		6.22 ± 0.0842	6.17 ± 0.093	0.6479	
PiB PET (log)	0.036 ± 0.091	0.6904	0.544 ± 0.039	0.529 ± 0.0424	0.7659		0.839 ± 0.1602	0.861 ± 0.168	0.7754	
Cortical thickness (mm)	0.006 ± 0.035	0.8707	2.3 ± 0.017	2.3 ± 0.0186	0.9123		2.35 ± 0.0621	2.36 ± 0.0677	0.7825	
Hippocampus volume (mm^3)	−303.491 ± 225.219	0.1789	8648 ± 104	8884 ± 115	0.0681		9604 ± 392	9537 ± 428	0.7145	
Amygdala volume (mm^3)	84.949 ± 108.42	0.434	3458 ± 49.4	3579 ± 54.5	0.0523		3772 ± 188.4	3977 ± 205.7	0.0212	0.0424
Model 2.2 (sex x EYO x group)	**$\beta \pm$ SE**	***P* value***	**trends ± SE**	**trends ± SE**	***P* value***	***P* value†**	**trends ± SE**	**trends ± SE**	***P* value***	***P* value†**
Delayed recall (*z* score)	0.116 ± 0.066	0.0797	−0.03767 ± 0.00999	−0.00546 ± 0.01159	0.0348	0.0696	−0.25128 ± 0.04779	−0.10349 ± 0.04281	0.0212	0.0424
Category fluency (*z* score)	0.023 ± 0.076	0.7588	−0.01516 ± 0.0115	−0.00377 ± 0.0133	0.5159		−0.18634 ± 0.0552	−0.15163 ± 0.0494	0.638	
Processing speed (*z* score)	0.128 ± 0.079	0.1058	−0.0196 ± 0.0116	−0.0325 ± 0.0135	0.4665		−0.2777 ± 0.0582	−0.1623 ± 0.0509	0.1344	
CSF Aβ42/40 (log)	−0.006 ± 0.024	0.7911	−0.0305 ± 0.00372	−0.0209 ± 0.00416	0.0826		−0.0231 ± 0.0179	−0.0199 ± 0.01591	0.8958	
CSF p-tau181 (log)	0.046 ± 0.041	0.2666	0.0486 ± 0.0062	0.0319 ± 0.00709	0.0758		0.0263 ± 0.03036	0.0557 ± 0.02674	0.4641	
CSF t-tau (log)	0.035 ± 0.037	0.3343	0.0334 ± 0.00558	0.0211 ± 0.00629	0.1432		0.0197 ± 0.0267	0.0429 ± 0.02375	0.5156	
PiB PET (log)	0.007 ± 0.025	0.7687	0.03465 ± 0.00368	0.02314 ± 0.00412	0.038	0.076	0.00568 ± 0.0177	0.00148 ± 0.01635	0.8622	
Cortical thickness (mm)	0.038 ± 0.01	0.0002	−0.00581 ± 0.0015	−0.00565 ± 0.00175	0.9441		−0.04507 ± 0.00704	−0.00691 ± 0.00669	0.0001	0.0004
Hippocampus volume (mm^3)	142.061 ± 64.044	0.0274	−17.11 ± 9.66	−2.45 ± 11.16	0.3177		−255.52 ± 45.32	−103.92 ± 42.48	0.0147	0.0294
Amygdala volume (mm^3)	83.818 ± 30.732	0.0068	−6.45 ± 4.6	−2.52 ± 5.36	0.5775		−110.98 ± 21.92	−23.24 ± 20.52	0.0036	0.0072

Note: Full model output can be found in the supporting information (Tables S4 and S5). The reference variable of sex is set to females and of group is set to symptomatic carriers. Results from CDR subgroups (presymptomatic/symptomatic) were retrieved by post hoc contrast analysis of either the main sex effect by group (Model 1.2) displayed as the estimated means or the sex x EYO interaction by group (Model 2.2) displayed as the estimated trends along EYO, each with confidential intervals.

Abbreviations: Aβ4, amyloid beta; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; DIAD, dominantly inherited Alzheimer's disease; EYO, estimated years to symptom onset; FDR, false discovery rate; PET, positron emission tomography; PiB, ^{11}C-Pittsburgh compound B; p-tau181, phosphorylated tau protein 181; SE, standard error; t-tau, total tau protein.

*Uncorrected *P* value from contrast analysis.

†FDR-corrected *P* value from contrasts analysis.

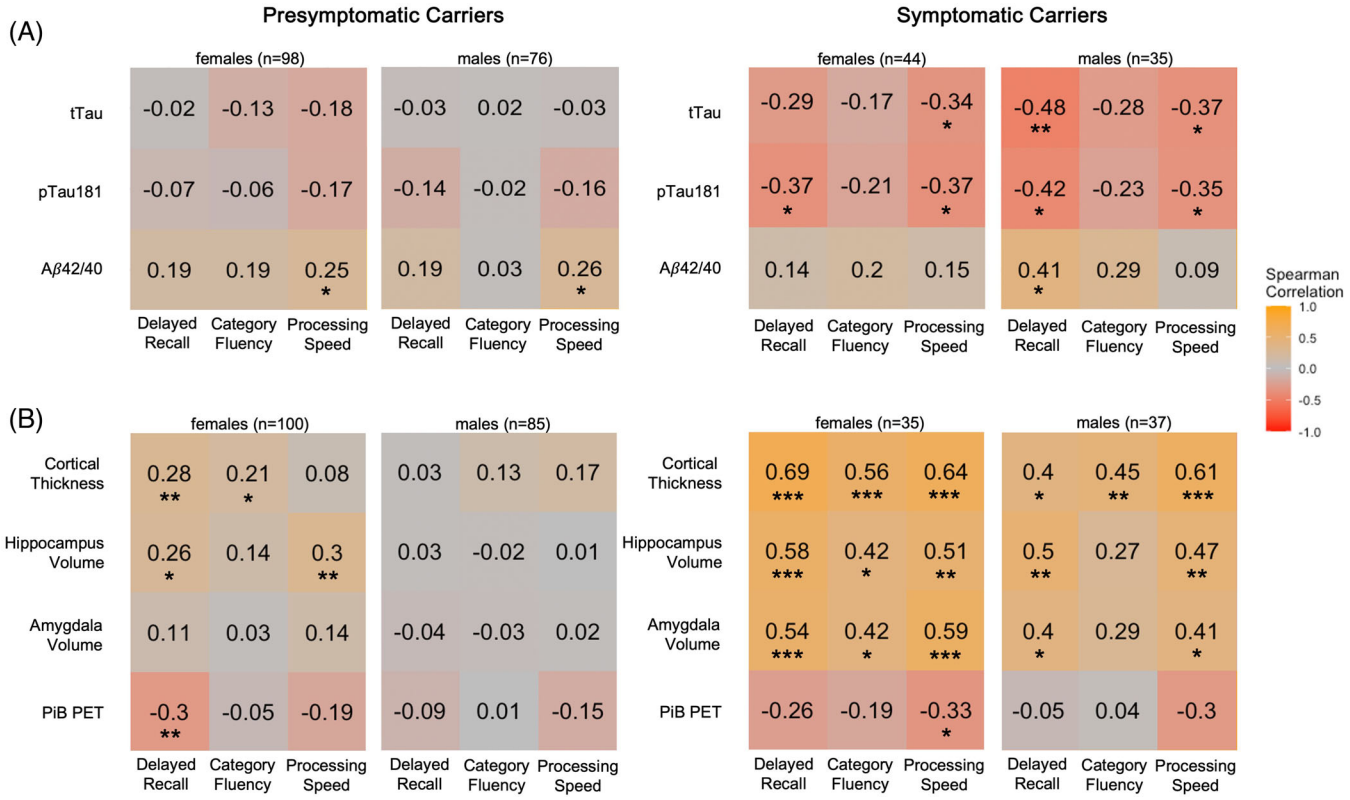

FIGURE 3 Correlation heatmaps for cognitive performance and CSF (top) as well as imaging (bottom) biomarkers, separately analyzed in female and male presymptomatic (A) and symptomatic (B) mutation carriers. For the individual correlations, "*" signifies a *P* value of < 0.05, "**" of < 0.01 and "***" of < 0.001. Aβ, amyloid beta; CSF, cerebrospinal fluid; PET, positron emission tomography; PiB, Pittsburgh compound B.

amygdala compared to males. This could suggest a domain-specific reserve of cognitive functioning in female carriers, allowing them to perform better than their male counterparts despite similar levels of hippocampal atrophy and overall higher levels of neurodegeneration. This supports the hypothesis of a female cognitive reserve previously proposed in sAD, arguing that due to their compensatory abilities, females initially outperform males before succumbing to their higher disease burden.[15,16,46] Our results also extend findings in female presymptomatic *PSEN1-E280A* mutation carriers that reportedly showed better performance on global cognition while exhibiting similar levels of hippocampal volume.[28] Further, a study in adults with Down syndrome (DS), a condition generally acknowledged as a genetic form of AD due to the triplication of the *APP* gene located on chromosome 21,[47] found females to outperform males on episodic memory from age 45 onward while showing no differences in AD(-related) biomarkers.[48]

In our subgroup analysis, presymptomatic females performed significantly better on processing speed and delayed recall, while symptomatic females displayed a trend of worse performance on category fluency and no difference from symptomatic males in the remaining tasks. Considering the worse impairment on delayed recall with disease progression in symptomatic females, these findings suggest the loss of their initial cognitive superiority as they move along the clinical stages of DIAD. This could be triggered by the presence of a higher degree of disease pathology in female carriers because higher amounts of pathology have been associated with a greater cognitive impairment in females with MCI[6,9,11,18] and studies along the spectrum of sAD have found females to gradually perform worse on verbal memory, verbal fluency, and domains relating to non-semantic and visuospatial abilities,[19,49–51] and to show an overall steeper decline in cognition and functional abilities with disease progression[17,43,52] compared to males. Supportive of this hypothesis is our finding of a significantly higher decrease in cortical thickness and volume loss in hippocampus and amygdala with disease progression in symptomatic but not presymptomatic females, possibly contributing to the comparably pronounced memory impairment in females of the symptomatic group. In the spectrum of sAD, sex differences in amygdala atrophy have not been reported consistently,[12] yet several studies have found greater hippocampal and temporal lobe atrophy in females over time.[13,18,53] However, in adults with DS, hippocampal volumes reportedly decreased in a similar manner between females and males.[48]

One reason for the sex-specific increase in neurodegeneration in the symptomatic stage could involve differences in the initial occurrence of amyloid pathology or its downstream pathways. While we only found a trend of increased PiB PET burden with disease progression in presymptomatic females, and so far, little to no sex differences in amyloid burden have been found in CSF,[25] PET,[8,10,54] or *post mortem* brain tissue[6] in sAD or DIAD,[29] a study investigating the impact of

parental history of sAD on their children found female descendants to have a pronounced decrease in Aβ42 levels and an increase in amyloid PET burden while approaching their parental age of onset.[55] Moreover, females have been proposed to be more affected by the presence of amyloid pathology in clinical status and downstream pathology, highlighted by findings of the interaction of sex and reduced Aβ42 levels or elevated amyloid PET burden resulting in steeper cognitive decline, greater hippocampal atrophy, and elevated regional tau PET burden in females compared to males.[7,11,18] Females might develop amyloid pathology earlier and subsequently experience a higher amount of downstream AD(-related) pathology,[56] where processes such as the elevation and spread of tau or increased neuroinflammation might lead to a greater degree of neurodegeneration, resulting in a disproportional worsening of clinical and cognitive status.

However, we did not see any sex differences in CSF markers of AD(-related) pathology when assessing Aβ42/40, p-tau181, and t-tau levels, which mirrors findings in a cross-sectional sample of adults with DS.[48] Investigations of CSF measures in sAD so far have resulted in some,[14,57] but not all,[56] finding higher levels of t-tau and p-tau181 in females, mainly in the context of *APOE* ε4 carrier status or amyloid positivity.[14,56,57] Yet, the interaction of sex and *APOE* ε4 status does not seem to influence tau tangle burden in *post mortem* brain tissue,[14] which has been found to be increased in females.[6] Here, the analysis of tau PET burden in DIAD is of high interest, especially considering that symptomatic females in our analyses tended to show higher correlations of cognition with imaging measures. In sAD, sex differences have been reported in cerebral tau PET burden, with female *APOE* ε4 carriers[23,58] as well as Aβ-positive females[10,11] exhibiting higher levels of tau PET burden compared to males, thereby mirroring prior findings in CSF.[14,25]

Finally, we found no significant sex differences when correlating cognition and biomarkers within the subgroups. However, trends of higher correlation coefficients between imaging and cognitive outcomes were seen in female carriers, resulting in subthreshold significant sex differences for the correlation of hippocampal volume and processing speed in the presymptomatic stage, and of cortical thickness and delayed recall in both clinical stages of DIAD. This could, too, hint at a pronounced vulnerability toward downstream AD(-related) pathology on cognitive ability in female carriers, adding to the hypothesized loss of a superior cognitive performance and findings of a steeper cognitive decline in females as the disease progresses.

Our cohort comprises young individuals with a known DIAD mutation, resulting in a considerable advantage for the investigation of sex differences without age-related confounders modulating the observed effects. In sAD on the other hand, age is the strongest known risk factor and females have been argued to have a higher lifetime risk for AD due to a longer lifespan, rather than underlying pathophysiological differences.[4,5] Similarly, neuropathological studies have shown that increasing age is associated with the development of several degenerative co-pathologies.[31] Differences in prevalence between females and males for those pathologies might therefore result in additive clinical burden in a sex-dependent manner.[59,60] For example, cardiovascular risk factors are increased in older age in females, while cardiovascular mortality in males has been shown to rise earlier, between the ages of 45 and 65, selecting males with lowest risk to live on to older age.[61]

Because females in this analysis are relatively young, the risk of confounding by age-related changes in estrogen levels is also comparatively small. However, we want to acknowledge that we were not able to control for events of altered estrogen levels such as menopause, surgery, antiestrogen therapy, hormone replacement therapy, or hormonal contraception. Reductions in estrogen levels have been hypothesized to increase the risk for cognitive decline and AD pathology by causing a rise in amyloid and tau burden as well as changes in cell metabolism in females,[4] but more studies are needed to understand the complex impact of estrogen and other sex hormones on susceptibility and progression of cognitive impairment and AD pathology. Further, tau PET imaging and plasma measures were not available for this analysis. We consider both biomarker entities highly relevant for a better understanding of sex differences in DIAD and aim to conduct these analyses as soon as possible. We also acknowledge that, as EYO is an estimate, some error might occur around the actual year of symptom onset for presymptomatic carriers. However, because this risk applies to both females and males equally, we do not expect this to have a substantial impact on our analysis of sex differences. Last, the observed cross-sectional sex differences allow only limited interpretation for the disease trajectory; further analysis of longitudinal data in DIAD is needed to corroborate the present findings.

In summary, this study provides the first investigation into cross-sectional sex differences in the DIAN-OBS cohort, examining measures of cognition, AD pathology, and neurodegeneration. These results have important implications for the understanding of disease presentation and progression in DIAD and direct relevance to the study of sex differences in sAD, as well as considerations regarding study design in future anti-amyloid and anti-tau intervention trials.

ACKNOWLEDGMENTS

We acknowledge the altruism of the participants and their families and contributions of the DIAN research and support staff at each of the participating sites for their contributions to this study. This manuscript has been reviewed by DIAN Study investigators for scientific content and consistency of data interpretation with previous DIAN Study publications. Data collection and sharing for this project was supported by The Dominantly Inherited Alzheimer Network (DIAN, U19AG032438) funded by the National Institute on Aging (NIA), the Alzheimer's Association (SG-20-690363-DIAN), the German Center for Neurodegenerative Diseases (DZNE), Raul Carrea Institute for Neurological Research (FLENI); partial support by the Research and Development Grants for Dementia from Japan Agency for Medical Research and Development, AMED JP22dk0207049; and the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), Spanish Institute of Health Carlos III (ISCIII), Canadian Institutes of Health Research (CIHR), Canadian Consortium of Neurodegeneration and Aging, Brain Canada Foundation, and Fonds de Recherche du Québec – Santé.

CONFLICT OF INTEREST STATEMENT

AA has served as a consultant for Biogen Inc., and H. Lundbeck HS. RJB is the Director of the DIAN-TU and Principal Investigator of the DIAN-TU-001. He receives research support from the National Institute on Aging of the National Institutes of Health, DIAN-TU Trial Pharmaceutical Partners (Eli Lilly and Company, F. Hoffman-La Roche, Ltd., and Avid Radiopharmaceuticals), Alzheimer's Association, GHR Foundation, Anonymous Organization, DIAN-TU Pharma Consortium (active: Biogen, Eisai, Eli Lilly, and Company, Janssen, F. Hoffmann-La Roche, Ltd./Genentech, United Neuroscience; previous: AbbVie, Amgen, AstraZeneca, Forum, Mithridion, Novartis, Pfizer, Sanofi). He has been an invited speaker and consultant for AC Immune, F. Hoffman La Roche, Ltd., and Janssen and a consultant for Amgen and Eisai. TLSB has received funding from the National Institutes of Health and Siemens; has a licensing agreement from Sora Neuroscience but receives no financial compensation; has received honoraria for lectures, presentations, speakers bureaus, or educational events from Biogen and Eisai Genetech; has served on a scientific advisory board for Biogen; holds a leadership role in other board, society, committee, or advocacy groups for the American Society for Neuroradiology (unpaid) and Quantitative Imaging Biomarkers Alliance (unpaid); and has participated in radiopharmaceuticals and technology transfers with Avid Radiopharmaceuticals, Cerveau, and LMI. JPC has served as the chair of the American Neurological Association Dementia and Aging Special Interest Group and is on the medical advisory boards for Humana Healthcare and ExpertConnect and is supported by National Institute on Aging grants R01AG071865, R01AG062667, RF1AG079569, and P01AG036694. CC receives research support from: Biogen, EISAI, Alector, and Parabon. The funders of the study had no role in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. Dr. Cruchaga is a member of the advisory board of Vivid genetics, Halia Therapeutics, and Adx Healthcare. GSD is supported by NIH (K23AG064029, U01AG057195, U19AG032438), the Alzheimer's Association, and Chan Zuckerberg Initiative. He serves as a consultant for Parabon Nanolabs Inc, as a Topic Editor (Dementia) for DynaMed (EBSCO), and as the Clinical Director of the Anti-NMDA Receptor Encephalitis Foundation (Inc., Canada; uncompensated). He is the co-Project PI for a clinical trial in anti-NMDAR encephalitis, which receives support from Horizon Pharmaceuticals. He has developed educational materials for PeerView Media, Inc., and Continuing Education Inc. He owns stock in ANI pharmaceuticals.

JH is a paid consultant for F. Hoffmann-La Roche, Ltd., Prothena, and Parabon Nanolabs, and is on a Data Safety and Monitoring Board for Eisai. JL reports speaker fees from Bayer Vital, Biogen, EISAI, TEVA and Roche; consulting fees from Axon Neuroscience and Biogen; author fees from Thieme medical publishers and W. Kohlhammer GmbH medical publishers. In addition, he reports compensation for serving as chief medical officer for MODAG GmbH, is beneficiary of the phantom share program of MODAG GmbH, and is inventor in a patent "Pharmaceutical Composition and Methods of Use" (EP 22 159 408.8) filed by MODAG GmbH, all activities outside of the submitted work.

JJLG is supported by NIH-NIA (K01AG073526), the Alzheimer's Association (AARFD-21-851415, SG-20-690363), the Michael J. Fox Foundation (MJFF-020770), the Foundation for Barnes-Jewish Hospital, and the McDonnell Academy. FL receives research funding from the National Institutes of Health, Roche, Banner Institute, Biogen, Tau Consortium, and from CHDI Foundation. EMD received support from the National Institute on Aging, an anonymous organization, the GHR Foundation, the DIAN-TU Pharma Consortium, Eli Lilly, and F Hoffmann La-Roche; has received speaking fees from Eisai and Eli Lilly; and is on the data safety and monitoring board and advisory boards of Eli Lilly, Alector, and Alzamend. JCM is the Friedman Distinguished Professor of Neurology, Director, Knight ADRC; Associate Director of DIAN and Founding Principal Investigator of DIAN. He is funded by NIH grants # P30 AG066444; P01AG003991; P01AG026276; U19 AG032438; and U19 AG024904. RJP receives research funding from the National Institutes of Health and the National Institute on Aging. RSV is funded by the Spanish Institute of Health Carlos III (ISCIII, grant 20/00448). CX is supported by National Institute on Aging (grants R01 AG067505 and R01 AG053550. All other authors have no competing interests to disclose. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Participants included in this analysis were recruited through DIAN-OBS (ClinicalTrials.gov Identifier: NCT00869817) and provided written consent or assent with proxy consent prior to enrollment in accordance with the latest Declaration of Helsinki. The study is supervised by the institutional review board (IRB) at Washington University in St Louis, USA and all study procedures were approved by the Human Research Protection Office and the IRB at Washington University or the respective participating sites.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wagemann O, Li Y, Hassenstab J, et al. Investigation of sex differences in mutation carriers of the Dominantly Inherited Alzheimer Network. *Alzheimer's Dement*. 2024;20:47–62. https://doi.org/10.1002/alz.13460

APPENDIX

Collaborators of the Dominantly Inherited Alzheimer Network

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