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Profiling baseline performance on the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) cohort near the midpoint of data collection

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All authors have read and provided consent to be associated with this manuscript.

SUPPORTING INFORMATION

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

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Abstract

Objective: The Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) seeks to provide comprehensive understanding of early-onset Alzheimer's disease (EOAD; onset <65 years), with the current study profiling baseline clinical, cognitive, biomarker, and genetic characteristics of the cohort nearing the data-collection mid-point.

Methods: Data from 371 LEADS participants were compared based on diagnostic group classification (cognitively normal [$n = 89$], amyloid-positive EOAD [$n = 212$], and amyloid-negative early-onset non-Alzheimer's disease [EOnonAD; $n = 70$]).

Results: Cognitive performance was worse for EOAD than other groups, and EOAD participants were apolipoprotein E (*APOE*) $\varepsilon 4$ homozygotes at higher rates. An amnestic presentation was common among impaired participants (81%), with several clinical phenotypes present. LEADS participants generally consented at high rates to optional trial procedures.

Conclusions: We present the most comprehensive baseline characterization of sporadic EOAD in the United States to date. EOAD presents with widespread cognitive impairment within and across clinical phenotypes, with differences in *APOE* $\varepsilon 4$ allele carrier status appearing to be relevant.

Keywords

Alzheimer's disease; atypical variant; amnestic; early-onset; memory

1 | INTRODUCTION

Despite increasing research on Alzheimer's disease (AD), limited data exist on individuals diagnosed with AD earlier in life. Less than 5% of patients with AD are diagnosed between the ages of 40- and 64 years of age, making "early-onset AD" (EOAD) an uncommon phenomenon.[1] Such patients experience consequences that differ from "late-onset AD" (LOAD) personally and occupationally, as declines in cognition and functioning occur as they are raising families, caring for aging relatives, and maintaining professional careers.[2] Relatively preserved insight of this early decline also results in elevated rates of depression compared to LOAD.[3] Better understanding of the core clinical, imaging, and genetic features of sporadic EOAD could clarify its onset and trajectory, and promote the development of effective disease-modifying therapies.

The clinical presentation and longitudinal course of EOAD are relatively distinct from LOAD. EOAD manifests in a more aggressive disease course with greater cognitive severity than LOAD, and greater involvement of non-memory cognitive domains.[4–6] Patients with EOAD are also relatively less encumbered by health-related comorbidities such as diabetes, obesity, and circulatory disorders.[7] Relative to LOAD, EOAD more frequently presents with logopenic variant primary progressive aphasia (PPA), posterior cortical atrophy (PCA), or frontal-variant AD.[5,8,9] Magnetic resonance imaging (MRI), fluorodeoxyglucose– positron

emission tomography (FDG-PET), and diffusion tensor imaging (DTI) consistently show less medial temporal/hippocampal involvement in EOAD compared to LOAD—yet greater parietal and overall cortical atrophy,[10] parietal lobe hypometabolism,[11] and posterior cingulate and parietal white-matter degradation.[12]

To date, no uniform criteria for EOAD have been implemented and sample sizes in research have been small. The Longitudinal Early-Onset Alzheimer's Disease Study (LEADS, National Institute on Aging (*NIA*) *R56057195, NIA U016057195*)[13] aims to address these gaps in knowledge with the largest prospectively-evaluated cohort of participants with sporadic EOAD in the United States. LEADS is an observational study seeking to recruit and follow 600 cognitively impaired and 100 cognitively unimpaired individuals 40 to 64 years of age at 18 U.S. sites. LEADS was designed to provide comprehensive understanding of clinical/physiologic manifestations of EOAD, including clinical, cognitive, fluid and imaging biomarker (blood, cerebrospinal fluid, MRI, FDG-PET, amyloid beta [Aβ]-PET, tau-PET), and genetic analyses at 12-month intervals. Goals of LEADS include (1) defining EOAD and its phenotypic variants, (2) understanding disease progression, (3) understanding the impact and unique challenges of EOAD, and (4) identifying resources to assist younger-onset cognitive impairment.[13] In addition, at present no attempts at pharmacological interventions in sporadic EOAD or non-amnestic variants have been undertaken; consequently, a final goal of LEADS includes deriving essential clinical, functional, and biomarker metrics for use in clinical trials and ultimately launching a clinical trial platform.

As the framework and methodology of LEADS have previously been documented,[13] the aim of this article is to profile baseline clinical, cognitive, biomarker, and genetic characteristics of the sample at approximately the half-way point in data collection. Comparisons between cognitively normal (CN) participants, amyloid-negative cognitively impaired participants (EOnonAD), and amyloid-positive cognitively impaired participants (EOAD) have been undertaken across modalities. Descriptions and documentation of important procedural aspects of the study are also incorporated, including rates of willingness to undergo lumbar puncture (LP) or receive disclosure of genetic test results. It was hypothesized that EOAD participants would present with greater clinical and cognitive severity than CN and EOnonAD subsamples, and it was anticipated that willingness to engage in these more intrusive study procedures would be comparable to other large-scale trials —including the Dominantly Inherited Alzheimer Network (DIAN) and the Alzheimer's Disease Neuroimaging Initiative (ADNI).

2 | METHODS

To date, 212 EOAD, 70 EOnonAD, and 89 CN participants have been enrolled in LEADS and had their data finalized as of 06/01/2022. New participants will be added to LEADS on a rolling basis until final enrollment is reached (400 EOAD, 200 EOnonAD, and 100 CN). All participants were between 40 and 64 years of age at study entry, fluent in English, in good general health and absent other neurological or psychiatric disorder and had a knowledgeable informant. Impaired individuals with genetic mutations in amyloid precursor protein (*APP*), presenilin-1 (*PSEN1*) or Presenilin-2 (*PSEN2*), microtubule-associated

protein tau (*MAPT*), chromosome 9 open reading frame 72 (*C9ORF72*), or granulin precursor aka progranulin (*GRN*) were excluded, consistent with LEADS's focus on sporadic early-onset dementia. Diagnoses within LEADS were assigned via consensus between cognitive neurologists, neuropsychologists, geriatric psychiatrists, and imaging experts during formal review.[13] Both EOAD and EOnonAD participants had a Clinical Dementia Rating (CDR)[14] scale global score of 0.5 to 1.0 at the time of enrollment. CN participants were free of cognitive deficit on neuropsychological testing and had a Mini-Mental State Examination (MMSE)[15] score ≥24 and a CDR global score of 0. Institutional review board (IRB) approval was obtained through a central IRB overseen by Indiana University, and written informed consent was obtained from study participants or their legally authorized representatives.

2.1 | Procedures

Please see Apostolova et al.[13] for a more detailed description of LEADS research methodology. Briefly, all participants underwent a standardized baseline clinical assessment, including medical and family history, concurrent medication review, and medical/neurological examinations. Next, cognitive assessment was undertaken via the National Alzheimer's Coordinating Center's (NACC) Uniform Data Set (UDS) 3.0,[16] NACC Frontotemporal Lobar Degeneration (FTLD) Module,[17] and LEADS-specific measures (MMSE, Rey Auditory Verbal Learning Test [RAVLT],[18] Alzheimer's Disease Assessment Scale – Cognitive Subscale [ADAS-Cog],[19] Digit Symbol Test from Wechsler Adult Intelligence Scale-Revised,[20] and Tablet-Based Cognitive Assessment Tool [TabCAT][21]). Assessment of daily functioning was conducted using the Functional Activities Questionnaire (FAQ).[22] Blood draw was conducted for each participant, along with an optional LP procedure. Finally, brain imaging was undertaken using MRI, PET for Aβ (^{18}F-Florbetaben), tau (^{18}F-Flortaucipir), and glucose hypometabolism (^{18}F-Fluorodeoxyglucose). As was described by Apostolova and colleagues,[13] and will be examined in more detail elsewhere in this Special Issue,[23] for ^{18}F-Florbetaben, a composite neocortical standardized uptake value ratio (SUVR) ≥1.18 (corresponding to 39.2 Centiloids) was used as a quantitative threshold for amyloid PET positivity. Subsequent reports will focus on these brain imaging results.

2.2 | Cognitive composites

Given the numerous cognitive variables assessed in LEADS, performances were combined into the following domain composites: Episodic Memory, Language, Speed/Attention, Visuospatial, and Executive (domain variables listed in Table S1). To compute domain-specific *z*-scores while eliminating the effect of education, residuals were calculated by controlling for education for each clinical score at baseline. Using the residuals of the CN group, each clinical variable was centered by taking the median absolute difference (MAD) (or mean absolute difference [MeanAD] if needed), as follows: $\mathrm{MAD} = \mathrm{median}_i|x_i - \tilde{x}|$. Median was implemented because normality of individual composites was found to be violated using Shapiro-Wilk test. The MAD was subtracted for each variable and standardized using a robust scale estimate suitable for non-normal data to calculate the robust Z-scores: $Z\text{-}score = (X - Median)/(1.486 * MAD)$. Because of this use of the MAD, values for the robust Z-scores in the CN group may be slightly different than 0.0. If MAD

was equal to zero, the MeanAD was used in the scale estimate to calculate the robust Z-scores: $Z\text{-}score = (X - Median)/(1.253314 * MeanAD)$. The robust Z-scores were grouped by cognitive domains, and for each participant the average was taken for each domain for the composite value.

2.3 | Data analysis

Demographic analyses were performed using analysis of variance (ANOVA) tests and *t*-tests for continuous and chi-square analysis for categorical variables. For the primary analyses, analysis of covariance (ANCOVA) tests were used to compare the performance of diagnostic groups on cognitive measures, after controlling for relevant demographic variables. Following significant omnibus testing, *linear regression* analyses were conducted as pairwise comparisons between groups controlling for the effects of age and sex. Supplemental analysis adding MMSE as a covariate in linear regression analyses examined if group differences remained after accounting for cognitive severity. In addition, based on consensus diagnosis, LEADS participants were categorized as CN, amnestic, non-amnestic, PPA, and PCA phenotypes. ANCOVA was conducted to examine the differences in composite domain robust Z-score performances between these clinical variants. Differences in *APOE* genotype and rates of consenting for LP and genetic disclosure were examined using chi-square analyses, ANOVA, and *t*-tests, as appropriate. Measures of effect size were expressed as Cohen's *d* (*t*-tests), partial eta squared (η^2; linear regression analyses), and Cohen's *w* values (chi-square analyses). *p*-values were adjusted using false discovery rate to account for multiple comparisons.

3 | RESULTS

Table 1 displays enrollment statistics and demographic, clinical, and biomarker profiles for participants in LEADS. Age, education, and racial/minority status were similar for the EOAD and EOnonAD groups, with the only difference being a higher proportion of men in the EOnonAD group ($p = 0.009$, Cohen's $w = 0.16$). The CN group members were younger than the EOAD group ($p < 0.001$, $d = 0.57$) and had a higher proportion of women than the EOnonAD group ($p = 0.001$, Cohen's $w = 0.27$). The CN group also demonstrated greater mean years of formal education (p's < 0.001, d's = 0.54–0.55) and a broader representation of racial/ethnic participants than either the EOAD or EOnonAD groups (p's = 0.001–0.02, Cohen's w's = 0.18–0.29). Accordingly, subsequent analyses were adjusted for age and sex. The EOAD group performed worse, on average, on the MMSE (p's < 0.001, d's = 0.74–1.71), had higher CDR global scores ($p = 0.03$, Cohen's $w = 0.13$), and possessed greater Aβ deposition at enrollment (p's < 0.001, d's = 3.49–3.67) than EOnonAD and CN groups.

3.1 | Cognitive profiles

Table 2 reflects the robust Z-score performances for each of the cognitive domain composites assessed in LEADS, adjusted for education, age, and sex. Following significant ANCOVA tests for all domains (p's < 0.001; Table S2), pairwise linear regression comparisons demonstrated that EOAD performed worse than CN for all domains (p's < 0.001, η^2's = 0.05–0.66), and worse than EOnonAD for all domains except Language (p's

< 0.001, η^2's = 0.06–0.29; Table 2). Relative to CN, EOAD showed worse performance on Episodic Memory (z = −2.38), followed by Speed/Attention (z = −1.93) and Executive domains (z = −1.43). The effect size for Episodic Memory was η^2's = 0.66 and 0.29 for CN and EOnonAD comparisons, respectively. EOnonAD performances were worse than CN for all domains except Language (p's < 0.001, η^2's = 0.09–0.25), with Episodic Memory displaying the largest effect magnitude (z = −1.07), followed by Language (z = −0.80) and Visuospatial domains (z = −0.75). After additionally controlling for global cognitive severity using MMSE at baseline (Table 2), the EOAD group continued to perform worse on Episodic Memory and Executive domains relative to CN and EOnonAD groups (p's = 0.001–0.02), as well as on the Speed/Attention domain relative to the EOnonAD group (p = 0.02). The EOnonAD group continued to perform worse on Episodic Memory relative to CN (p = 0.003) after controlling for MMSE (Table 2).

The clinical-phenotype representation of our impaired sample included 228 participants (81%) presenting with amnestic syndrome, 23 participants (8%) presenting with non-amnestic syndrome, 16 participants (6%) presenting with PCA, and 15 participants (5%) presenting with PPA. There were no differences in age, education, or racial/ethnic status between amnestic and non-amnestic, PCA, or PPA variants (p's > 0.05). The PCA variant had a greater prevalence of women (81.3%) than the amnestic (61.8%; p = 0.008), non-amnestic (39.1%; p = 0.009), or the PPA variants (40.0%; p = 0.02). Table 3 shows the composite robust Z-scores by phenotype, adjusted for education, age, and sex. Not surprisingly, relative to other cognitive domains, participants with amnestic variant EOAD performed worst on the Episodic Memory domain, whereas participants with PCA variant performed worst on the Visuospatial domain, and those with PPA variant performed worst on the Language domain. The lowest performance for the non-amnestic variant was on the Speed/Attention domain. Following significant ANCOVA results for all domains (p's < 0.001), pairwise linear regression comparisons showed that these clinical variants performed worse relative to the CN group on most cognitive domains—except Language for non-amnestic variant and Executive for PCA variant. Pairwise comparisons between clinical phenotypes showed that the PCA variant performed worse on the Visuospatial and Speed/Attention composites than the amnestic, PPA, and non-amnestic variants (p's = 0.001–0.02, η^2's = 0.08–0.55). No differences were observed between the amnestic, non-amnestic, and PPA phenotypes across domains (p's = 0.12–0.89). See expanded results of *ANCOVA* and linear regression comparisons for syndromic subgroup comparisons in Table S3.

Rates of amyloid positivity across clinical phenotypes were 79.9% for the amnestic variant, 69.6% for the non-amnestic variant, 87.5% for the PCA variant, and 60.0% for the PPA variant. In addition, rates of *APOE ε*4 positivity across clinical phenotypes were 55.7% for the amnestic variant, 26.1% or the non-amnestic variant, 37.5% for the PCA variant, and 26.7% for the PPA variant. No differences were observed across variants for either amyloid positivity or *APOE ε*4 positivity analyses (p's > 0.05), although interpretation of these results is limited given the small sample sizes of the non-amnestic (n = 23), PCA (n = 16), and PPA (n = 15) groups.

3.2 | Genetic and imaging findings

Table 4 shows the *APOE* genotype differences between diagnostic groups. *APOE* ε4 homozygote participants were greater represented in the EOAD versus EOnonAD group ($p = 0.01$, Cohen's $w = 0.15$), although not relative to the CN group ($p = 0.22$, Cohen's $w = 0.07$). In addition, EOAD possessed a trend of greater proportions of ε4 heterozygous participants than both CN and EOnonAD (p's = 0.05–0.07, Cohen's w's = 0.11). Furthermore, EOnonAD possessed a greater proportion of ε2 heterozygous participants than EOAD ($p = 0.046$, Cohen's $w = 0.12$), but not CN ($p = 0.45$, Cohen's $w = 0.06$). Allele counts per group can be observed in Table S4. In addition, a trend was observed whereby age at onset of EOAD was slightly later for *APOE* ε4–positive participants than *APOE* ε4–negative participants ($p = 0.11$, $d = 0.22$). There were no diagnostic group differences (EOAD vs EOnonAD) for age at onset for a given *APOE* ε4 status (*APOE* ε4 positive or *APOE* ε4 negative; p's = 0.49–0.91).

On PET imaging measures, 74.8% of our cognitively impaired subjects were amyloid PET positive (EOAD) and 23.0% were amyloid PET negative (EOnonAD).

3.3 | Consent for optional procedures

Approximately 60% of the LEADS sample (54% CN, 60% EOAD, and 64% EOnonAD) consented to receive LP (Table 5). Willingness to undergo LP did not differ by demographics, diagnosis, or cognitive performance at baseline. However, a trend toward more men than women consenting to LP was evident ($p = 0.052$). In addition, cognitively impaired LEADS participants who were approached for disclosure of genetic results have been overwhelmingly agreeable to date (Table 6), with 89% consenting. There were no differences between demographics and cognitive performance at baseline for those who did and did not provide consent. Genetic disclosure consent did not appear to differ between EOAD and EOnonAD ($p = 0.28$). By study design, CN participants were not tested at screening for genetic mutations.

4 | DISCUSSION

The current data represent clinical, cognitive, biomarker, and genetic profiles of patients in LEADS, which is the largest and most comprehensive characterization of EOAD in the United States to date.[13] Despite this, only 8% of the EOAD sample to date, and 14% of the EOnonAD sample, represent individuals of minority status. These results are lower than previous reports suggesting higher rates of EOAD prevalence among African Americans, Native Americans, and Alaska Natives relative to non-Hispanic White participants.[24] It is thus likely that the lower rates currently observed might reflect factors impacting minority enrollment, rather than lower prevalence of EOAD/EOnonAD diagnosis in minority populations. As has been suggested elsewhere,[25] referral bias or differences in diagnostic thresholds applied by specialty providers may account for these low rates of minority enrollment in LEADS. In addition, due to historic injustices, non-Hispanic White participants tend to volunteer for research at consistently greater levels than minority groups.[26] To overcome this limitation, current and future emphasis in LEADS will be the recruitment of more representative samples into the study, with recent receipt of an

Alzheimer's Association Diversity Supplement (*LDRFP-21–818464*) aimed at improving minority representation.

Among cognitively impaired participants, to date 81% presented with amnestic syndrome, 8% presented with non-amnestic syndrome, 6% presented with PCA, and 5% presented with PPA. We observed the characteristic patterns of amnestic, PCA, and PPA syndrome variants possessing disproportionately worse episodic memory, visuospatial, and language skills, respectively.[8,9] The non-amnestic syndrome participants possessed a prominent deficit in Attention/Processing Speed, which suggests generalized dysfunction characterized by difficulty with basic information processing. These rates of non-memory variants in early-onset dementia are lower than anticipated, and also lower than those reported previously. For example, Koedam and colleagues observed rates of non-memory variants of EOAD at 30%, with apraxia/visuospatial dysfunction being the most common non-memory presenting problem (12%).[27] In addition, 64% of Mendez and colleagues' smaller EOAD sample presented with non-memory variants, with language and visuospatial dysfunction comprising 28% and 26% of the sample, respectively. However, our rate of 19% for all atypical variants is still higher than the atypical (i.e., non-amnestic) rate observed in LOAD populations, which is reported to range from 6% to 12.5%.[27,28] The lower rates of non-memory variants in the LEADS cohort may be explained by our focus on sporadic early-onset dementia, and thus the exclusion of participants with genetic mutations like *GRN*, *C9ORF72*, and *MAPT*. As these mutations are associated with frontotemporal dementia or non-AD tauopathies, we may have unintentionally suppressed rates of non-amnestic variants. Our lower rates may additionally reflect syndromic classification tendencies at recruitment sites; specifically, as memory deficits in EOAD are suggested to be less reliant on hippocampal dysfunction,[10] it is possible that participants are being classified as amnestic when systems related to executive functioning and processing speed may actually be driving their poor memory performance.

Relatedly, the presence of AD pathology in cognitively impaired participants (detected via PET) was associated with greater cognitive severity. This was measured by worse global performance on the MMSE and the CDR, as well as by worse performance across cognitive domains assessed in EOAD relative to EOnonAD. This has been reported previously in late-onset dementias.[29] After controlling for global cognitive severity (as measured by the MMSE), Episodic Memory, Executive, and Speed/Attention were still worse in EOAD participants than in those with EOnonAD. Difficulty with Episodic Memory reflects the hallmark cognitive marker of probable AD, with strong relationships between reduced episodic memory performance and smaller hippocampal volumes.[30–33] Research has also shown that following initial memory declines in LOAD, attention, and executive skills are the first non-memory domains to be affected.[34] It has been suggested that declines in these non-memory domains in AD may in part be mediated by temporo-parietal structures.[35]

Preliminary examination of *APOE* genotype distributions in LEADS indicated that greater proportions of participants with EOAD were *APOE* ε4 homozygous relative to EOnonAD, with trends also being observed for more frequent *APOE* ε4 heterozygous status relative to both EOnonAD and CN participants. The higher rate of *APOE* ε2 carriers in the EOnonAD group is not surprising, given that the ε2 allele is protective against the development of

AD.[36] The current study's *APOE ε*4 heterozygous rate of 54% (see Table 4) is comparable to some reports,[37] but not others.[38,39] Our rate of *APOE ε*4 homozygosity of 14% was much lower than reported previously (e.g., 22% in [40] and 57% in [37]). Our results correspond to meta-analytic findings of 60.4% *ε*4 heterozygosity and 14.5% *ε*4 homozygosity across all studies of LOAD in the literature.[41] Given suggestions that the *APOE ε*4 status may have a differential impact depending on the age at onset,[37] future aims of LEADS include investigating differences in the frequency and impact of *ε*4 hetero- and homozygosity among EOAD participants in LEADS and LOAD participants in ADNI.

The majority of LEADS participants were agreeable to receiving an LP (60%), which was consistent across age, education, and ethnicity. A trend suggested that men agreed to LP slightly more than women (53% vs 47%). These LP results coincide with the limited data on consent rates for LP participation in AD research. Blazel and colleagues[42] observed that 59% of participants at the Wisconsin AD Research Center—who were comparably young (mean 64.2 years old) and educated (15.6 years)—agreed to participate in an LP as part of an observational longitudinal trial and data collection. Unlike in the current study, they observed that non-Hispanic White individuals were more likely to participate in LP relative to African Americans, and that higher levels of education were associated with greater participation in LP.[42] Differences between studies on education and ethnicity may be associated with the greater cognitive severity of our sample (57% cognitively impaired vs 30% in Blazel)—which may have also resulted in greater overall concern and increased motivation for LP across the demographic spectrum. In addition, unpublished data indicate that of the 1933 participants in ADNI, 71.5% consented to LP.[43] This cohort is contemporaneous with the LEADS cohort, and these generally similar rates further support our findings. Finally, although other research observed higher LP-consent rates (92%) for memory clinic patients across 23 sites predominantly in Europe,[44] the common use of LP in European dementia workups likely explains the difference in findings with our observational research in the United States.

Finally, to date we have observed that most LEADS participants (89%) were willing to receive information about their genetic status. This finding is notably higher than rates observed in recent research from DIAN. Specifically, the rate of willingness to receive disclosure of genetic status in DIAN was found to be 37.3%.[45] These differential results likely reflect variation in a key feature of these respective cohorts. Although DIAN focuses on familial AD, thereby all participants have relatives with known genetic mutations, LEADS is focused on sporadic/non-familial AD. In addition, the majority of DIAN participants are clinically asymptomatic (and genetic testing is, therefore, predictive of future disease status), whereas we did not offer genetic disclosure to asymptomatic (i.e., CN) LEADS participants. Consequently, genetic disclosure likely represents an opportunity for medical/genetic discovery in LEADS patients, whereas in DIAN it likely both seems less beneficial and frequently more fear-inducive, since all DIAN participants are at risk of having a mutation.

The current study has some limitations. First, these results are being presented when only ≈50% of recruitment goals have been met. Although it is possible that continued data collection may alter some findings, the general convergence of our results with previous

literature—combined with the importance of the cohort— support our initial findings. Second, these results reflect only baseline data from LEADS given limited longitudinal data obtained thus far, consequently future work will focus on characterizing change over time in the variables reported herein. Relatedly, the current procedure for calculating cognitive composites—by adjusting for residuals for education only—was undertaken to permit consistency with composite values in future longitudinal analysis (where age-at-assessment will change over time). In response, Tables 2 and 3 listed the composite values after additionally removing the residuals for age and sex to permit the most accurate interpretation possible. Third, the LEADS cohort aimed to focus on sporadic forms of EOAD; therefore, this study is not applicable to participants with autosomal dominant forms of the condition. Fourth, the current sample is predominantly non-Hispanic White and highly educated—consistent with long-standing trends in research both broadly[26,46] and specifically with large-scale AD studies.[47,48] Given that this can limit generalizability of results toward more heterogenous samples of the population, attempts are underway to enrich ethnic, racial, and educational diversity within the LEADS cohort. Finally, as the cognitive test batteries administered during LEADS reflect convergence with the NACC UDS 3.0 data set, the number of measures contributing to the LEADS cognitive composites were more heavily weighted toward memory, language, and executive than speeded processing or visuospatial skills.[16]

5 | CONCLUSIONS

These limitations, however, do not overshadow the considerable strengths of the current study, which include a substantive characterization of baseline clinical, cognitive, biomarker, and genetic characteristics of sporadic EOAD in the United States. Our findings have supported previous smaller studies, suggesting that EOAD presents with widespread cognitive impairment, characterized by several known clinical phenotypes. The presence of amyloid positivity portends further cognitive impairments in several domains, with differences in *APOE ε*4 allele carrier status appearing to be relevant. Finally, as this work represents an introduction to the multifaceted data collected in LEADS, future investigation will explore more rich associations between EOAD and cognition, neuropsychiatric symptoms, genetics, and imaging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Findings represent the most comprehensive baseline characterization of sporadic early-onset Alzheimer's disease (EOAD) to date. Cognitive impairment was widespread for EOAD participants and more severe than other groups.
- EOAD participants were homozygous apolipoprotein E (*APOE*) ε4 carriers at higher rates than the EOnonAD group.
- Amnestic presentation predominated in EOAD and EOnonAD participants, but other clinical phenotypes were present.

RESEARCH IN CONTEXT

Systematic Review:

Traditional literature searches (e.g., PubMed) and the collective expertise of the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) Consortium were utilized to review known information about early-onset Alzheimer's disease (EOAD). Although knowledge is present about familial EOAD, less is known of sporadic EOAD, no uniform criteria for EOAD have been implemented, and sample sizes in previous research have been small.

Interpretation:

In a sample of 371 participants ages 40 to 64 years across a range of diagnostic groups (cognitively normal, EOAD, and early-onset non-Alzheimer's disease), results showed that cognitive impairment is widespread in EOAD, and multiple clinical phenotypes are present within the condition. These findings are consistent with previous smaller studies.

Future Direction:

This work represents an introduction to the multifaceted data collected in LEADS. Future investigations will explore the potential associations between EOAD and cognition, neuropsychiatric symptoms, genetics, and imaging.

TABLE 1

Demographic characteristics of the cognitively normal, early-onset Alzheimer's disease, and early-onset non-Alzheimer's disease groups.

					Post Hoc Comparisons (*p* value)		
	CN	**EOAD**	**EOnonAD**	**Omnibus Test (*p* value)**	**EOAD versus CN**	**EOnonAD versus CN**	**EOAD versus EOnonAD**
N	89	212	70				
Age, years	56.13(6.0)	58.78 (3.9)	57.99 (6.0)	9.04 (<0.001)	<0.0001	0.06	0.30
Sex, % female	61.8%	52.4%	34.3%		0.13	<0.001	0.009
Minority, %	29.2%	7.5%	14.3%		<0.001	0.02	0.09
Education, years	16.67 (2.2)	15.42 (2.4)	15.37 (2.6)	9.76 (<0.001)	<0.001	<0.001	0.88
Mini-Mental State Examination	29.19(1.0)	21.95 (5.0)	25.51 (4.3)	94.41 (<0.001)	<0.001	<0.001	<0.001
Amyloid SUVR	1.03 (0.1)	1.57(0.2)	1.00 (0.1)	542.12 (<0.001)	<0.001	0.07	<0.001
CDR Global (0.5 [%]/1.0 [%])	0%/0%	66.5%/33.5%	80.0%/20.0%		-	-	0.03

Note: Values represent mean and SD unless otherwise noted. Omnibus Test represents test statistic value (and *p* value) from the omnibus analysis of variance (ANOVA). EOAD versus CN, EOnonAD versus CN, and EOAD versus EOnonAD represent *p* values from the post hoc *t-tests* comparing the respective groups following significant ANOVA.

Abbreviations: ANOVA, analysis of variance; Amyloid SUVR, standardized uptake value ratio from amyloid-PET (positron emission tomography); CDR Global, Clinical Dementia Rating scale - global score (range of 0, 0.5, 1.0, 2.0, 3.0); CN, cognitively normal; EOAD, early-onset Alzheimer's disease; EOnonAD, early- onset non-Alzheimer's disease; MMSE, Mini-Mental State Examination.

TABLE 2

Education-, age-, and sex-adjusted cognitive composite domain profiles of the cognitively normal, early-onset Alzheimer's disease, and early-onset non-Alzheimer's disease groups, and group differences after controlling for global cognitive severity.

	CN	EOAD	EOnonAD	CN versus EOAD *β* (SE), *p* value	CN versus EOnonAD *β* (SE), *p* value	EOnonAD versus EOAD *β* (SE), *p* value
N	89	212	70			
Episodic memory	−0.12 (0.8)	−2.38 (1.0)	−1.07(1.3)	−1.72 (0.1), $p < 0.001$	−0.47 (0.1), $p = 0.003$	−0.88 (0.1), $p < 0.001$
Language	−0.08 (0.7)	−1.37(1.9)	−0.80(1.1)	0.06 (0.7), $p = 0.93$	0.05 (0.8), $p = 0.95$	0.26(0.7), $p = 0.70$
Speed/Attention	−0.01 (1.2)	−1.93 (3.9)	−0.70(1.5)	−0.44 (0.3), $p = 0.19$	−0.31(0.2), $p = 0.27$	−0.69 (0.3), $p = 0.02$
Visuospatial	−0.02 (1.0)	−1.42 (4.5)	−0.75 (1.9)	−0.10 (0.5), $p = 0.93$	−0.46 (0.4), $p = 0.27$	−0.60 (0.5), $p = 0.29$
Executive	−0.07 (1.0)	−1.43 (2.1)	−0.59(1.4)	−0.85 (03), $p = 0.005$	−0.29(0.2), $p = 0.27$	−0.64 (0.3), $p = 0.02$

Note: Values represent mean and SD across cognitive domains of robust-standardized cognitive variables. EOAD versus CN, EOnonAD versus CN, an versus EOnonAD represent the beta coefficient (β, *standard error* (SE), and *p* values from the analyses comparing the respective groups after contre education, age, sex, and Mini-Mental State Examination performance.

Abbreviations: CN = cognitively normal, EOAD = early-onset Alzheimer's disease, EOnonAD = early-onset non-Alzheimer's disease; MMSE, Mini State Examination.

TABLE 3

Education-, age-, and sex-adjusted cognitive composite domain profiles of the clinical syndrome subgroups.

	CN	Amnestic	Non-Amnestic	PCA	PPA
N	89	228	23	16	15
% of Clinical Sample	–	81%	8%	6%	5%
Episodic memory	−0.12 (0.8)	−2.21 (1.3)	−1.55 (1.5)	−1.73(1.1)	−1.36 (2.3)
Language	−0.08 (0.7)	−1.17(1.7)	−1.16(2.0)	−2.25 (2.6)	−1.76 (3.1)
Speed/Attention	−0.01 (1.2)	−1.29(2.9)	−1.72 (4.7)	−5.76 (2.4)	−1.28(1.7)
Visuospatial	−0.02 (1.0)	−1.09 (3.2)	−0.69 (3.8)	−6.11 (3.3)	−0.41 (1.4)
Executive	−0.07 (1.0)	−1.06 (2.0)	−1.26(1.5)	−0.87(1.7)	−0.88 (1.8)

Note: Values represent mean *robust Z-Scores* and SD.

Abbreviations: CN, cognitively normal; PCA, posterior cortical atrophy; PPA, primary progressive aphasia.

TABLE 4

APOE allele characteristics (A) and *APOE ε4* carrier status and age at onset (B) of the cognitively normal, early-onset Alzheimer's disease, and early-onset non-Alzheimer's disease groups.

A.	**CN**	**EOAD**	**EOnonAD**	**EOAD versus CN**	**EOnonAD versus CN**	**EOAD versus EOnonAD**
N	89	212	70			
ε2 Heterozygous	7.9%	4.7%	11.4%	0.28	0.45	0.05
ε4 Heterozygous	41.6%	53.8%	41.4%	0.05	0.98	0.07
ε4 Homozygous	9.0%	14.2%	2.9%	0.22	0.11	0.01
B.	EOAD		EOnonAD		Combined	
	APOE ε4−	*APOE ε4+*	*APOE ε4−*	*APOE ε4+*	*APOE ε4−*	*APOE ε4+*
N	98	114	41	29	139	143
Age at onset	54.82 (4.3)	55.81 (4.3)	54.7 (5.8)	55.64 (5.0)	54.79 (4.7)	55.77 (4.4)
Comparison of +/− within Groups	$p = 0.11$		$p = 0.88$		$p = 0.08$	
Comparison of + and − between groups					0.91	0.49

Note: A. Values represent % of CN, EOAD, and EOnonAD samples with the respective allele characteristics. EOAD versus CN, EOnonAD versus CN, and EOAD versus EOnonAD represent *p* values from the post hoc analyses comparing the respective groups following significant *ANOVA* analysis. B. *APOE ε4* represents the absence of an *ε4* allele, and *APOE ε4+* represents the presence of an *ε4* allele. Age at onset represented by age (SD). Comparison of +/− within groups represents results of t-tests comparing age at onset between *APOE ε4-* and *ε4+* carriers within EOAD, EOnonAD, and combined groups. Comparison of + and − between groups represents results of t-tests comparing age at onset of *APOE ε4-* participants between EOAD and EOnonAD groups, and age at onset of *APOE ε4+* participants between EOAD and EOnonAD groups.

Abbreviations: *APOE,* apolipoprotein E; CN, cognitively normal; EOAD, early-onset Alzheimer's disease; EOnonAD, early-onset non-Alzheimer's disease.

TABLE 5

Consent for lumbar puncture in the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) sample.

	No	Yes	*p* value	Effect Size
N	150 (40.4%)	221 (59.6%)		
Age, years	57.94 (5.0)	58.03 (5.0)	0.86	0.02
Education, years	15.75 (2.5)	15.69 (2.4)	0.83	0.02
Gender, % female	57.3%	47.1%	0.05	0.10
Race (*n* of Yes/No within racial/ethnicgroup), %			0.59	0.09
Non-Hispanic White	126 (40.4%)	185 (59.6%)		
Hispanic	6 (37.5%)	10 (62.5%)		
Black/African American	11 (45.8%)	13(54.2%)		
Asian	5 (50.0%)	4 (50.0%)		
More than one race	3 (33.3%)	6 (66.7%)		
Diagnostic group (*n* of Yes/No within diagnostic group), %			0.39	0.07
CN	41 (46.1%)	48 (53.9%)		
EOnonAD	25 (35.7%)	45 (64.3%)		
EOAD	84 (39.6%)	128 (60.4%)		
Mini-Mental State Examination	24.31 (5.7)	24.39 (4.9)	0.88	0.02

Note: Values for age, education, and Mini-Mental State Examination represent the mean and inter-quartile range. Gender reflects the percent of participants within either the Yes or No group that were female. Race reflects the number and percent of participants within a particular racial/ethnic category that did or did not provide consent for lumbar puncture. Diagnostic Group reflects the number and percent of participants within a specific diagnostic group that did or did not provide consent for lumbar puncture. *p* values reflect results of t-tests (for continuous variables) and chi-square analyses (for categorical variables) comparing Yes and No groups. Effect sizes were calculated using Cohen's *d* for continuous variables and Cohen's *w* for categorical variables.

Abbreviations: CN, cognitively normal; No, did not provide consent for lumbar puncture; Yes, provided consent for lumbar puncture; EOnonAD, early-onset non-Alzheimer's disease; EOAD, early-onset Alzheimer's disease; LEADS, Longitudinal Early-Onset Alzheimer's Disease Study; MMSE, Mini-Mental State Examination.

TABLE 6

Consent for genetic disclosure in the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) sample.

	No	Yes	*p* value	Effect Size
n	29(10.7%)	242 (89.3%)		
Age, years	58.07 (4.2)	58.73 (4.6)	0.44	0.15
Education, years	15.10(2.5)	15.42 (2.4)	0.52	0.13
Gender, % female	48.3%	47.5%	0.94	0.005
Race (*n* of Yes/No within racial/ethnicgroup), %			0.63	0.10
Non-Hispanic White	29(11.6%)	220 (88.4%)		
Hispanic	0 (0%)	8 (100%)		
Black/African American	0 (0%)	9 (100%)		
Asian	0 (0%)	3 (100%)		
More than one race	0 (0%)	2 (100%)		
Diagnostic group (n of Yes/No within diagnostic group), %			0.28	0.07
CN	N/A	N/A		
EOnonAD	5 (7.3%)	64 (92.7%)		
EOAD	24(11.9%)	178 (88.1%)		
Mini-Mental State Examination	22.97 (5.4)	22.79 (5.1)	0.87	0.03

Note: Gender reflects the percent of participants within either the Yes or No group that were female. Values for age, education, and Mini-Mental State Examination represent the mean and interquartile range. Gender reflects the percent of participants within either the Yes or No group that were female. Race reflects the number and percent of participants within a particular racial/ethnic category that did or did not provide consent for genetic disclosure. Diagnostic Group reflects the number and percent of participants within a specific diagnostic group that did or did not provide consent for genetic disclosure. *p* values reflect results of t-tests (for continuous variables) and chi-square analyses (for categorical variables) comparing Yes and No groups. Effect Sizes were calculated using Cohen's *d* for continuous variables and Cohen's *w*for categorical variables.

Abbreviations: CN, cognitively normal; No, did not provide consent for lumbar puncture; Yes, provided consent for lumbar puncture; EOnonAD, early-onset non-Alzheimer's disease; EOAD, early-onset Alzheimer's disease; LEADS, Longitudinal Early-Onset Alzheimer's Disease Study; MMSE, Mini-Mental State Examination.