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Cerebrospinal fluid biomarkers in the Longitudinal Early-onset Alzheimer's Disease Study

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Abstract

Introduction: One goal of the Longitudinal Early Onset Alzheimer's Disease Study (LEADS) is to define the fluid biomarker characteristics of early-onset Alzheimer's disease (EOAD).

Methods: Cerebrospinal fluid (CSF) concentrations of Aβ1–40, Aβ1–42, total tau (tTau), pTau181, VILIP-1, SNAP-25, neurogranin (Ng), neurofilament light chain (NfL), and YKL-40 were measured by immunoassay in 165 LEADS participants. The associations of biomarker concentrations with diagnostic group and standard cognitive tests were evaluated.

Results: Biomarkers were correlated with one another. Levels of CSF Aβ42/40, pTau181, tTau, SNAP-25, and Ng in EOAD differed significantly from cognitively normal and early-onset non-AD dementia; NfL, YKL-40, and VILIP-1 did not. Across groups, all biomarkers except SNAP-25 were correlated with cognition. Within the EOAD group, Aβ42/40, NfL, Ng, and SNAP-25 were correlated with at least one cognitive measure.

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CONFLICT OF INTEREST STATEMENT

Dr. Dage is an inventor on patents or patent applications of Eli Lilly and Company relating to the assays, methods, reagents, and/or compositions of matter related to measurement of P-tau217. Dr. Dage has served as a consultant for Abbvie, Genotix Biotechnologies Inc., Gates Ventures, Karuna Therapeutics, AlzPath Inc., and Cognito Therapeutics, Inc., founder of Monument Biosciences, and received research support from ADx Neurosciences, Fujirebio, AlzPath Inc., Roche Diagnostics, and Eli Lilly and Company in the past 2 years. Dr. Dage serves on a scientific advisory board for Eisai. Dr. Dage has received speaker fees from Eli Lilly and Company. Dr. Fagan has received research funding from Biogen, Centene, Fujirebio, and Roche Diagnostics. Dr. Fagan is a member of the scientific advisory boards for Roche Diagnostics, Genentech, and Diadem. Dr. Fagan consults for DiamiR and Seimens Healthcare Diagnostics Inc. Dr. Mendez, and Ms. Gray, Faber and Snoddy have no conflicts of interest to report. Dr. Schindler serves on a scientific advisory board for Eisai. Dr. Day is supported by the National Institutes of Health (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 (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. Dr. Day's institution has received support from Eli Lilly for Dr. Day's development and participation in an educational event promoting early diagnosis of symptomatic AD. Dr. Wingo is as a cofounder of revXon. Dr. Apostolova has received personal compensation for serving as a consultant for Biogen, Two Labs, Florida Department of Health, Genentech, NIH Biobank, Eli Lilly, GE Healthcare, Eisai, and Roche Diagnostics and for serving on a data safety and monitoring board for IQVIA. Dr. Apostolova receives research support from the National Institute on Aging, the Alzheimer's Association, Roche Diagnostics, AVID Radiopharmaceuticals, Life Molecular Imaging, and Eli Lilly. All other authors had nothing to report. Author disclosures are available in the supporting information.

CONSENT STATEMENT

IRB approval was obtained for LEADS through a central IRB overseen by Indiana University, and informed consent was obtained in written form from all study participants or authorized representatives.

SUPPORTING INFORMATION

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

Discussion: This study provides a comprehensive analysis of CSF biomarkers in sporadic EOAD that can inform EOAD clinical trial design.

Keywords

Alzheimer's disease; amyloid; astrogliosis; Aβ42/40; biomarkers; CSF; dementia; neurogranin; NfL; pTau181; SNAP-25; tau; tTau; VILIP-1; YKL-40

1 | BACKGROUND

Alzheimer's disease (AD) is characterized by the presence of amyloid plaques and tau neurofibrillary tangles in the brain and is the most common cause of dementia.[1] Although there are rare autosomal dominant cases, most sporadic cases (95%) of AD are late-onset Alzheimer's disease (LOAD), with symptom onset occurring after the age of 65 years. About 5% of sporadic cases have an onset of symptoms before the age of 65 years and are referred to as sporadic early-onset Alzheimer's disease (EOAD).[2,3] Patients with sporadic EOAD have been included along with LOAD in many clinical trials despite reported differences in neuropsychological presentation, progression rates, density and distribution of tau pathology, and genetic risk factors.[4–7] The Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) was launched in 2018 to study this population.[8] One goal of LEADS is to characterize cerebrospinal fluid (CSF) biomarkers in the sporadic EOAD population. Understanding the effect size associated with an AD diagnosis on each of these measures and the amount of variation that exists in a sporadic EOAD population is essential to enable clinical trials for this understudied patient group. These CSF biomarker data can be used to calculate the sample size or power when designing proof-of-concept clinical trials in the EOAD population where these biomarkers may be useful as disease-related endpoints.

CSF biomarkers have been used extensively in AD clinical research and clinical practice to aid in diagnosis in patients.[9] The core set of CSF AD biomarkers includes amyloid-β peptides 42 (Aβ42) and 40 (Aβ40), which are usually used as a ratio (Aβ42/40), as well as tau (both total tau [tTau] and tau phosphorylated at threonine 181 [pTau181]). The core CSF AD biomarkers identify those individuals likely to have amyloid pathology as a potential contributor to their cognitive symptoms.[10,11] In addition to this core set of AD biomarkers, other CSF biomarkers have been used in AD clinical research: neurofilament light chain (NfL), for neuroaxonal damage; visinin-like protein 1 (VILIP-1), for neuronal injury; chitinase-3-like protein 1 (YKL-40) and glial fibrillary acid glycoprotein (GFAP), for astrocytic changes; synaptosomal-associated protein 25 (SNAP-25), for presynaptic damage; and neurogranin (Ng), for postsynaptic damage.[9,12] In LOAD studies, these additional CSF biomarkers are correlated with one another and are increased in early AD but may plateau or even decrease in later stages of AD dementia.[13–15] However, most studies have not characterized these CSF biomarkers specifically in the sporadic EOAD population.

The aim of this cross-sectional study was to provide a descriptive analysis of a panel of CSF biomarkers in EOAD compared with cognitively normal (CN) or amyloid positron emission tomography (PET)-negative early-onset cognitively impaired participants (EOnonAD). Achieving this aim will provide information necessary for future clinical trial design

using CSF biomarkers in this population and provide a foundation for understanding the relationship of the CSF biomarkers with the disease course of EOAD. Additionally, this study provides a foundation for future studies using sophisticated modeling techniques to investigate the individual information that each CSF biomarker provides to the overall understanding of the EOAD population.

2 | METHODS

2.1 | Participants

The LEADS design (NCT03507257) was published previously.[8] Institutional Review Board (IRB) approval was obtained through a central IRB overseen by Indiana University, and informed consent was obtained in written form from study participants or authorized representatives. LEADS participants must be age 40 to 64 years at the time of consent. EOAD and EOnonAD participants must meet National Institute of Aging-Alzheimer's Association (NIA-AA) criteria for dementia or mild cognitive impairment (MCI) and have a global Clinical Dementia Rating (CDR) score ≤1 indicative of very mild or mild dementia.[16] 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. Unlike the Alzheimer's Disease Neuroimaging Initiative (ADNI) study and some clinical trials, LEADS does not exclude individuals with predominantly non-amnestic presentations other than motor and behavioral presentations. Individuals meeting criteria for the dysexecutive, logopenic primary progressive aphasia or posterior cortical atrophy variants are eligible for the study.

2.1.1 | Clinical assessments—LEADS clinical assessments included a standardized history of present illness, past medical history, family history, concurrent medication, and detailed general medical and neurological examinations. LEADS uses the NACC Uniform Data Set cognitive battery (UDS 3.0), the NACC Frontotemporal Lobar Degeneration module, the Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADAS-Cog), and several additional cognitive tests tapping into cognitive functions that are commonly impaired in rare AD variants.[17] Clinical diagnosis is established in a multidisciplinary consensus conference at each clinical site following the NIA-AA diagnostic criteria for dementia and MCI. Cognitive screening tests included in this analysis are the Montreal Cognitive Assessment (MoCA), clinical dementia rating sum of boxes (CDR-SB), and ADAS-Cog.[18]

2.1.2 | CSF fluid biomarkers—There were 371 participants included in the LEADS mid-term analysis, but only 165 participant samples were available for this analysis since the lumbar puncture (LP) was optional. Additionally, 11 of the subjects were missing a CSF sample at the baseline visit, so the first collections (10 at 12 months and one at 24 months) were included for this analysis. Samples were distributed blinded to the Knight Alzheimer's Disease Research Center Fluid Biomarker Core laboratory at Washington University in St. Louis in May 2022 after being randomized prior to analysis for age, sex, and diagnosis

by the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD).

Concentrations of Aβ40, Aβ42, tTau, and pTau181 were measured using the Lumipulse G1200 Chemiluminescent Enzyme Immunoassay platform according to the manufacturer's instructions. The Lumipulse platform is an automated analysis system based on chemiluminescent enzyme immunoassay (CLEIA) technology. Fujirebio kit-provided controls and in-house fluid biomarker core CSF controls were used for quality control purposes (see supplemental materials for assay measurement range and quality control performance in Tables S6, S7, S8, and S9). VILIP-1, SNAP-25, and Ng were measured by quantitative fluorescent two-site immunoassays with Single Molecule Counting (SMC) technology using antibodies and protocols developed in the laboratory of Dr. Jack Ladenson at Washington University in St. Louis, as was previously described.[14,19–21] Samples and in-house CSF controls (Tables S10 and S11) were analyzed over 7 days, 27 samples per day.

NfL and YKL-40 were measured with plate-based commercial Enzyme-Linked Immunosorbent Assays (ELISAs) manufactured by Uman Diagnostics and Quidel, respectively, and as previously described.[22,23] Measuring range and control values are in supplemental materials (Table S12, S13, and S14).

2.2 | Statistical analysis

Statistical analysis was conducted in JMP Pro version 16 or GraphPad Prism (version 9.5). Mean differences in demographic variables and cognitive test results by diagnostic groups were evaluated using post hoc pairwise comparisons and Tukey-Kramer to limit type I error.[24] To facilitate comparisons between biomarkers, CSF biomarker data were standardized using the mean and standard deviation of the CN group after using an outlier box plot to identify and remove outliers (supplemental methods Table S1). Once the standardized values were calculated, all participant results were included in the analyses. Non-parametric correlation analyses (Spearman's correlation) were performed due to the skew of fluid biomarker data and non-linear nature of the associations. Spearman's correlation means and bias-corrected (BC) confidence limits were determined through bootstrap resampling ($n = 2500$) in JMP Pro.[25] Comparisons of CSF biomarkers by diagnostic group were performed by ANOVA with a Kruskal-Wallis test for overall significance and post hoc, pariwise Dunn's multiple-comparisons tests. Data transformation, as well as adjustments for age, sex, or *APOE* e4 carrier status, was outside the scope of these analyses as the influence of these factors will be best understood in focused studies of the specific clinical uses of each CSF biomarker.

3 | RESULTS

3.1 | Participants

This analysis includes participants enrolled in LEADS as of February 2022. The LEADS is ongoing, and the LP procedure is optional. As such, the numbers of participants ($n = 165$) included only those that had undergone at least one LP at the time of samples being identified for analysis (February 2022) and represent about 44% of the overall LEADS

cohort at that time. The characteristics of individuals with CSF data are shown in Table 1 and are divided into diagnostic categories (n = 37 CN, n = 96 EOAD, and n = 32 EOnonAD). Diagnostic groups did not vary by sex, *APOE* carrier status, or race. The EOAD group was older than the CN group and was less ethnically diverse compared with the CN or EOnonAD groups. As expected, the EOAD group performed worse on cognitive tests compared to the CN group in post hoc pairwise comparisons. Additionally, the EOAD group had greater impairment than the EOnonAD group on the MoCA (p < .001) and ADAS-Cog (p = .002), but not the CDR-SB (p = 1.000).

3.2 | Correlation of CSF biomarker levels and association with diagnostic groups

CSF biomarkers were correlated with one another (Figure 1A and Table S2) in the total study population as well as within the EOAD group (Figure 1B and Table S3), except for NfL with SNAP-25 or Aβ42/40 in the EOAD group, and both have p value > .05 and Spearman's rho of −0.104 and 0.186, respectively. Non-parametric densities of the standardized CSF biomarker data allow visual assessment of scatter patterns. There are two distinct density clusters across all associations with Aβ42/40 in the total study population. The NfL scatter plots show seven members of the EOnonAD group and two EOAD with very high levels. The synaptic degeneration markers (Ng and SNAP-25) and VILIP-1 have similar patterns with most of the variation seen in the EOAD group. The correlations between VILIP-1 and Ng or SNAP-25 in the total study population or in the EOAD group are higher than the correlation of VILIP-1 and NfL (Tables S2 and S3).

The standardized levels of individual biomarkers varied across diagnostic groups (Figure 2 and Table 2). AD biomarkers Aβ42/40, tTau, and pTau181 all showed similar patterns, with the EOAD group significantly different from CN and EOnonAD groups (p < .001 in comparisons for each biomarker). However, the CN group was not different from the EOnonAD group (p > .05 for all biomarkers). Other CSF biomarkers showed unique patterns including NfL being elevated in both EOAD and EOnonAD groups compared with CN (p < .001 and p < .05, respectively) and different between EOAD and EOnonAD (p < .001). Levels of SNAP-25, VILIP-1, YKL-40, and Ng were elevated in EOAD compared with CN (p < .05, p < .01, p < .001, p < .001, respectively), only SNAP-25, YKL-40, and Ng were different between EOAD and EOnonAD (p < .05, p < .01, p < .01, respectively).

3.3 | Correlation of CSF biomarkers with cognition (MoCA, CDR-SB, and ADAS-Cog)

The correlations of the three cognitive measures with CSF biomarkers in the overall study population, as well as in the EOAD group, are shown in a forest plot using Spearman's rho and 95% confidence limits (Figure 3). The strongest correlations were seen with NfL, Aβ42/40, tTau, and pTau181. All of these were significant across all three cognitive measures (Table S4). However, the correlation of CSF biomarkers with all three cognitive measures within the EOAD group (Figure 3) showed only NfL remaining significant for the MoCA (p < .001), CDR-SB (p < .001), and ADAS-Cog (p < .008) (Table S5). All biomarkers were correlated with one or more of the cognitive measures in the overall study population, except for SNAP-25, where the bootstrap resampling confidence limits overlapped a Spearman's rho of zero in all three measures. The correlations between CSF biomarkers and cognitive measures were generally weaker in the EOAD group compared

with the overall population. Only NfL maintained significant correlations with all three cognitive measures in the EOAD group.

4 | DISCUSSION

We completed a descriptive analysis of CSF biomarkers in LEADS participants generally and in the sporadic EOAD population specifically. As expected and consistent with the recent US Food and Drug Administration (FDA) approvals for some of these biomarkers, the CSF measures of Aβ42/40 and pTau181 differentiated the EOAD from CN and EOnonAD groups. This result was expected since the EOAD and EOnonAD groups were defined by the presence or absence of amyloid pathology as determined by amyloid PET imaging; however, verification further supports the use of these CSF biomarkers to aid in the diagnosis of EOAD. All the CSF biomarkers correlated with one another, which is very similar to what has been observed in LOAD and autosomal-dominant EOAD.[23] Outside of aiding in diagnosis, it remains unclear what information the other biomarkers might convey as independent measures. Future studies are required to explore this question in detail. It is important to note that the frequency of APOE ε carriers in the CU group (51%) of this CSF substudy was similar to that described in the CN group of LEADS (51%), and both are higher than seen in population-based studies such as the Mayo Clinic Study of Aging (29.1%) in clinically unaffected participants ages 50 to 65.[26] The explanations for this difference are likely related to biased recruitment to clinical research studies compared with population-based studies. Individuals are more likely to be interested in participating in clinical research studies if they have affected family members or have knowledge of their risk profile. We believe this is intensified for early-onset dementia due to the large impact on families.

Many studies have investigated core CSF AD biomarkers (Aβ42/40, pTau181, tTau, and NfL) in broad populations and have found support for the use of these biomarkers to aid in the diagnosis of AD or related dementias in individuals aged at least 50 years.[27] The CSF and plasma biomarkers have been similarly used as exploratory endpoints or post hoc studies of investigational amyloid removal therapies in both autosomal-dominant AD and LOAD.[28,29] However, few studies have characterized investigational markers (Ng, VILIP-1, SNAP-25, and YKL-40) in sporadic EOAD populations and evaluated how these biomarkers relate to one another. The effect sizes and data in Table 1 can be used to model sample size and power for the use of these CSF biomarkers as clinical trial endpoints in the EOAD population, supporting the idea that these data may inform the design of clinical trials in the EOAD population or provide confidence in their use in the 50-and-over population.

In a recent study of LOAD, Pereira et al. showed that synaptic markers, including SNAP-25 and Ng, were associated with amyloid deposition and memory dysfunction, while NfL levels continued to increase with worse global cognition.[30] Our results are consistent in EOAD, also showing associations of cognition with NfL. Pereira et al. also observed reductions in Ng with decreased memory performance, as was replicated in our EOAD group.[30] Other CSF biomarker trajectory analyses have been conducted in autosomal-dominant AD[23,31] and LOAD[14] that have shown early changes followed by a plateau or even reductions in levels, but these trajectories may differ depending on the comparison with amyloid PET, tau PET,

or cognitive symptoms. The changes in biomarker levels by disease stage will be important factors to control for when using these CSF biomarkers in clinical trials.

4.1 | Limitations

This study had several limitations. This constitutes an interim assessment of an ongoing study, and additional enrollment could affect the findings. The EOnonAD group is likely heterogeneous, including likely subjects with Lewy body disease and frontotemporal dementias, among other potential diagnoses. LEADS is a multisite longitudinal study, but the analysis is baseline only and, thus, only a cross-sectional analysis. The findings should be confirmed once the study is completed and longitudinal follow-up is incorporated into the analyses. This was a descriptive analysis and used non-parametric approaches in data analysis. Future studies incorporating data transformations and covariates into parametric models can be performed to allow for more specific hypotheses to be evaluated.

Although there similarities were noted between EOAD and LOAD, direct comparative analyses adjusting for covariates are necessary to generalize biomarker similarities and differences between the populations. The generalizability of the findings and observations to a diverse non-White or Hispanic population remains unknown due to the low enrollment of these populations in LEADS. LEADS is funded to increase enrollment of diverse subjects, and future analyses will need to be completed to evaluate our results in a more diverse population. Finally, future studies should evaluate each of these CSF biomarkers for specific contexts of use.

5 | CONCLUSION

CSF biomarkers were associated with diagnostic groups and cognition in LEADS. It remains to be seen whether they will be associated with cognitive decline. Future studies investigating longitudinal CSF biomarker trajectories and differences between EOAD and LOAD are needed to define the utility of these CSF biomarkers for monitoring unique aspects of disease progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Li X, Feng X, Sun X, Hou N, Han F, Liu Y. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2019. Front Aging Neurosci 2022;14:937486. doi: 10.3389/fnagi.2022.937486 [PubMed: 36299608]
2. Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. J Neurol Neurosurg Psychiatry 2003;74(9):1206–1209. doi: 10.1136/jnnp.74.9.1206 [PubMed: 12933919]
3. 2022 Alzheimer's disease facts and figures. Alzheimers Dement 2022;18(4):700–789. doi: 10.1002/alz.12638 [PubMed: 35289055]

4. Yoon B, Shim YS, Park HK, Park SA, Choi SH, Yang DW. Predictive factors for disease progression in patients with early-onset Alzheimer's disease. J Alzheimers Dis 2016;49(1):85–91. doi: 10.3233/jad-150462 [PubMed: 26444786]
5. Cho H, Choi JY, Lee SH, et al. Excessive tau accumulation in the parietooccipital cortex characterizes early-onset Alzheimer's disease. Neurobiol Aging 2017;53:103–111. doi: 10.1016/j.neurobiolaging.2017.01.024 [PubMed: 28254589]
6. Marra C, Bizzarro A, Daniele A, et al. Apolipoprotein E epsilon4 allele differently affects the patterns of neuropsychological presentation in early- and late-onset Alzheimer's disease patients. Dement Geriatr Cogn Disord 2004;18(2):125–131. doi: 10.1159/000079191 [PubMed: 15211066]
7. Toyota Y, Ikeda M, Shinagawa S, et al. Comparison of behavioral and psychological symptoms in early-onset and late-onset Alzheimer's disease. Int J Geriatr Psychiatry 2007;22(9):896–901. doi: 10.1002/gps.1760 [PubMed: 17343292]
8. Apostolova LG, Aisen P, Eloyan A, et al. The Longitudinal Early-onset Alzheimer's Disease Study (LEADS): framework and methodology. Alzheimers Dement 2021;17(12):2043–2055. doi: 10.1002/alz.12350 [PubMed: 34018654]
9. Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: current status and prospects for the future. J Intern Med 2018;284(6):643–663. doi: 10.1111/joim.12816 [PubMed: 30051512]
10. Willemse EAJ, Tijms BM, van Berckel BNM, et al. Comparing CSF amyloid-beta biomarker ratios for two automated immunoassays, Elecsys and Lumipulse, with amyloid PET status. Alzheimers Dement (Amst) 2021;13(1):e12182. doi: 10.1002/dad2.12182 [PubMed: 33969174]
11. Willemse EAJ, van Maurik IS, Tijms BM, et al. Diagnostic performance of Elecsys immunoassays for cerebrospinal fluid Alzheimer's disease biomarkers in a nonacademic, multicenter memory clinic cohort: the ABIDE project. Alzheimers Dement (Amst) 2018;10:563–572. doi: 10.1016/j.dadm.2018.08.006 [PubMed: 30406175]
12. Olsson B, Lautner R, Andreasson U, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol 2016;15(7):673–684. doi: 10.1016/s1474-4422(16)00070-3 [PubMed: 27068280]
13. Galasko D, Xiao M, Xu D, et al. Synaptic biomarkers in CSF aid in diagnosis, correlate with cognition and predict progression in MCI and Alzheimer's disease. Alzheimers Dement (N Y) 2019;5:871–882. doi: 10.1016/j.trci.2019.11.002 [PubMed: 31853477]
14. Sutphen CL, McCue L, Herries EM, et al. Longitudinal decreases in multiple cerebrospinal fluid biomarkers of neuronal injury in symptomatic late onset Alzheimer's disease. Alzheimers Dement 2018;14(7):869–879. doi: 10.1016/j.jalz.2018.01.012 [PubMed: 29580670]
15. Mattsson N, Insel PS, Palmqvist S, et al. Cerebrospinal fluid tau, neurogranin, and neurofilament light in Alzheimer's disease. EMBO Mol Med 2016;8(10):1184–1196. doi: 10.15252/emmm.201606540 [PubMed: 27534871]
16. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43(11):2412–2414. doi: 10.1212/wnl.43.11.2412-a
17. Besser L, Kukull W, Knopman DS, et al. Version 3 of the National Alzheimer's Coordinating Center's Uniform Data Set. Alzheimer Dis Assoc Disord 2018;32(4):351–358. doi: 10.1097/WAD.0000000000000279 [PubMed: 30376508]
18. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141(11):1356–1364. doi: 10.1176/ajp.141.11.1356 [PubMed: 6496779]
19. Sutphen CL, Jasielec MS, Shah AR, et al. Longitudinal cerebrospinal fluid biomarker changes in preclinical Alzheimer disease during middle age. JAMA Neurol 2015;72(9):1029–1042. doi: 10.1001/jamaneurol.2015.1285 [PubMed: 26147946]
20. Crimmins DL, Herries EM, Ohlendorf MF, et al. Double monoclonal immunoassay for quantifying human visinin-like protein-1 in CSF. Clin Chem 2017;63(2):603–604. doi: 10.1373/clinchem.2016.263236 [PubMed: 27986783]
21. Willemse EAJ, De Vos A, Herries EM, et al. Neurogranin as cerebrospinal fluid biomarker for Alzheimer disease: an assay comparison study. Clin Chem 2018;64(6):927–937. doi: 10.1373/clinchem.2017.283028 [PubMed: 29523639]

22. Aschenbrenner AJ, Li Y, Henson RL, et al. Comparison of plasma and CSF biomarkers in predicting cognitive decline. Ann Clin Transl Neurol 2022;9(11):1739–1751. doi: 10.1002/acn3.51670 [PubMed: 36183195]
23. Schindler SE, Li Y, Todd KW, et al. Emerging cerebrospinal fluid biomarkers in autosomal dominant Alzheimer's disease. Alzheimers Dement 2019;15(5):655–665. doi: 10.1016/j.jalz.2018.12.019 [PubMed: 30846386]
24. Smith RA. The effect of unequal group size on Tukey's HSD procedure. Psychometrika 1971;36(1):31–34. doi: 10.1007/BF02291420
25. Bootstra RubinDBThe. Ann Stat 1981;9(1):130–134. 5.
26. Neth BJ, Graff-Radford J, Mielke MM, et al. Relationship between risk factors and brain reserve in late middle age: implications for cognitive aging. Front Aging Neurosci 2019;11:355. doi: 10.3389/fnagi.2019.00355 [PubMed: 31998113]
27. Molinuevo JL, Ayton S, Batrla R, et al. Current state of Alzheimer's fluid biomarkers. Acta Neuropathol 2018;136(6):821–853. doi: 10.1007/s00401-018-1932-x [PubMed: 30488277]
28. Pontecorvo MJ, Lu M, Burnham SC, et al. Association of donanemab treatment with exploratory plasma biomarkers in early symptomatic Alzheimer disease: a secondary analysis of the TRAILBLAZER-ALZ randomized clinical trial. JAMA Neurol 2022;79(12):1250–1259. doi: 10.1001/jamaneurol.2022.3392 [PubMed: 36251300]
29. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. N Engl J Med 2023;388:9–21. doi: 10.1056/NEJMoa2212948 2022 [PubMed: 36449413]
30. Pereira JB, Janelidze S, Ossenkoppele R, et al. Untangling the association of amyloid-beta and tau with synaptic and axonal loss in Alzheimer's disease. Brain 2021;144(1):310–324. doi: 10.1093/brain/awaa395 [PubMed: 33279949]
31. Fagan AM, Xiong C, Jasielec MS, et al. Longitudinal change in CSF biomarkers in autosomal-dominant Alzheimer's disease. Sci Transl Med 2014;6(226):226ra30. doi: 10.1126/scitranslmed.3007901

RESEARCH IN CONTEXT

Systematic review:

Cerebrospinal fluid (CSF) biomarkers are commonly used in Alzheimer's disease (AD) research and clinical practice.Using PubMed, we identified only a few reports that describe their use in the sporadic form of early-onset Alzheimer's disease (EOAD).Additionally, we did not identify any studies in sporadic EOAD that included CSF biomarkers of astrogliosis, neuronal damage, or synaptic dysfunction along with those for amyloid and tau pathology.

Interpretation:

A broad scope of CSF biomarkers were measured in research participants enrolled in the Longitudinal Early Onset Alzheimer's Disease study (LEADS).We provide a descriptive analysis of how CSF biomarkers differ in relation to diagnosis and how they relate to one another in individuals with EOAD.

Future directions:

LEADS is ongoing, and longitudinal data and samples are being collected.Future analyses will investigate the relationship of CSF biomarkers with plasma biomarkers, genomics, imaging, and cognitive decline.

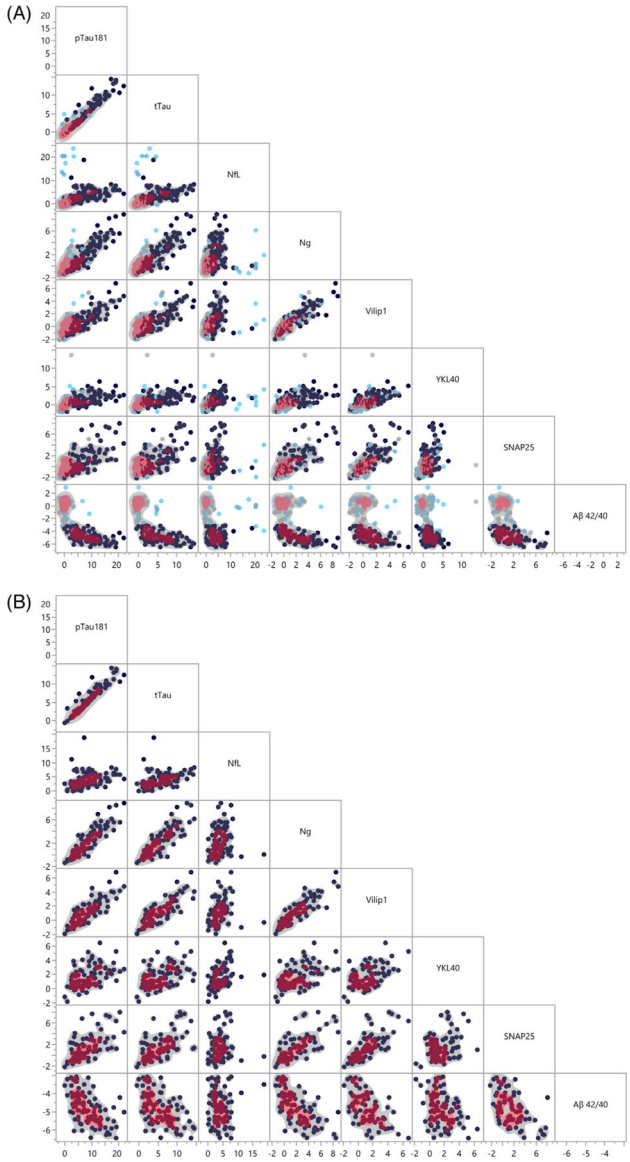

FIGURE 1.

Correlation analysis of standardized CSF biomarkers in (A) LEADS and (B) EOAD group. Individual values for CN (gray), EOAD (dark blue), and EOnonAD (light blue) are shown by filled circles. The non-parametric densities are shown by red shading (0.90) and gray shading (0.50). The opposite side of the correlation map is masked to avoid duplication of scatter plots.

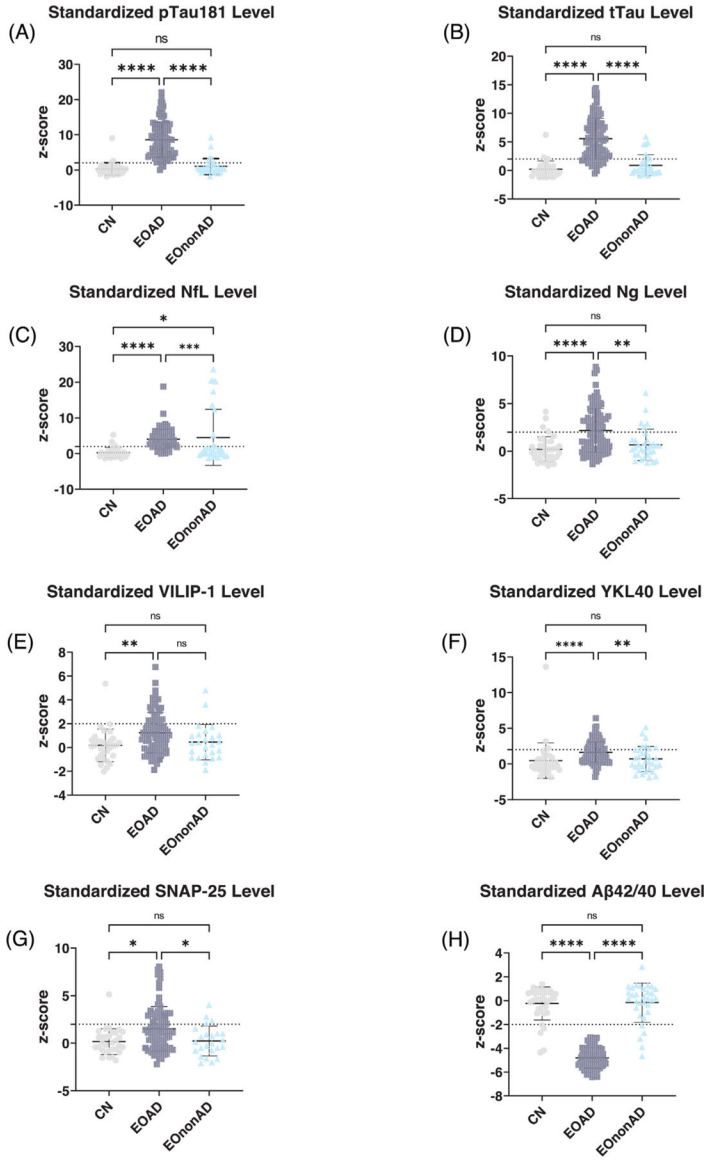

FIGURE 2.

Standardized CSF biomarker values by diagnostic group: (A) pTau181, (B) tTau, (C) NfL, (D) Ng, (E) VILIP-1, (F) YKL-40, (G) SNAP-25, and (H) Aβ42/40. Individual values for CN (gray), EOAD (dark blue), and EOnonAD (light blue) are shown by filled circles, squares, and triangles, respectively. Error bars showing the mean and standard deviation. Significance (p values) is determined by Kruskal–Wallis test for significance and Dunn's multiple comparisons test. $*p < 0.05$; $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$.

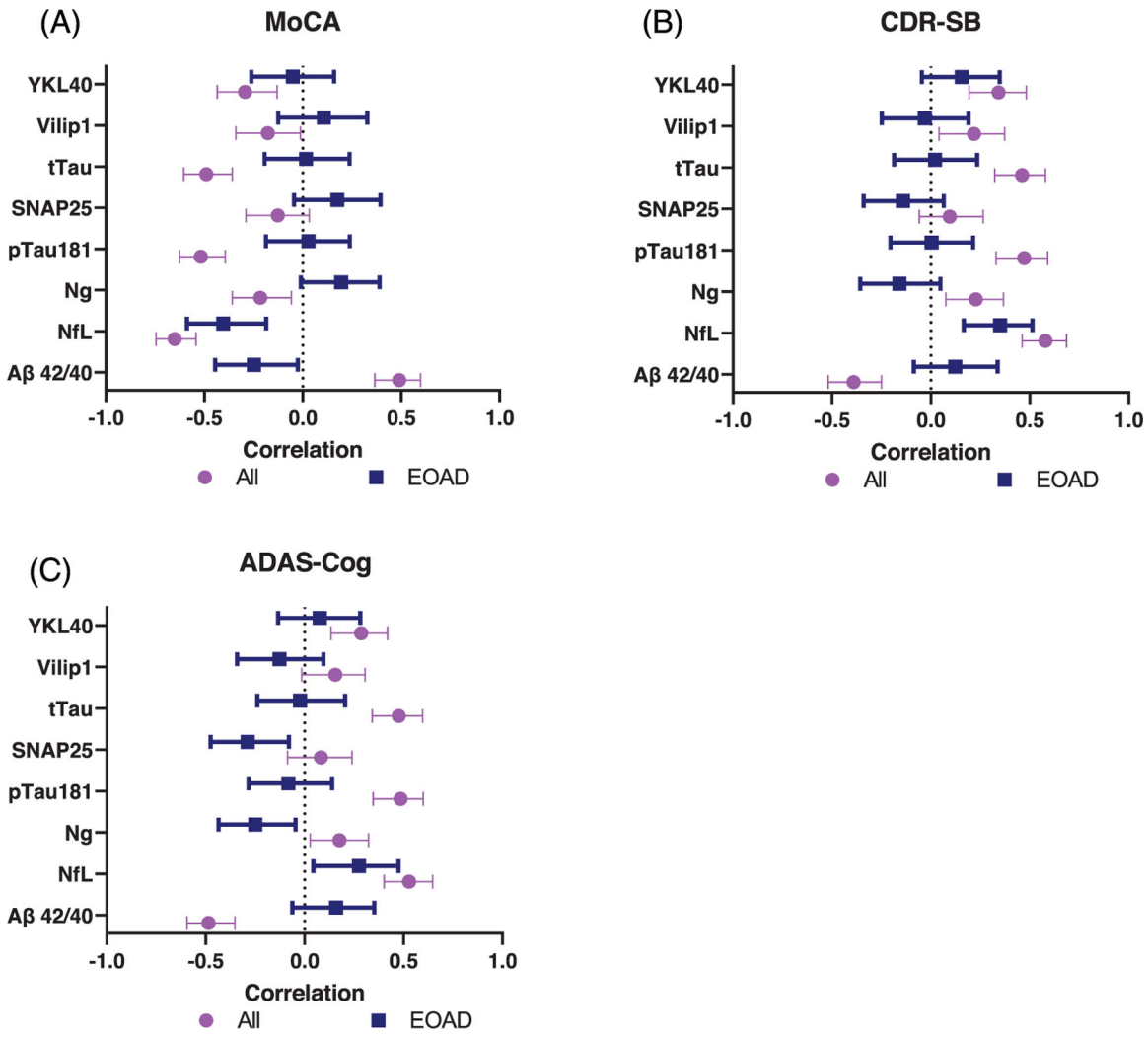

FIGURE 3.

Forest plot of Spearman correlations and 95% confidence limits of CSF biomarkers with cognitive tests in total LEADS population (purple circle) or EOAD group (dark blue square). CDR-SB, Clinical Dementia Rating Scale Sum of Boxes; MoCA, Montreal Cognitive Assessment Total Score; ADAS-Cog, Alzheimer's Disease Cooperative Studies—cognitive behavior subscale. Worse performance in cognitive testing is associated with lower MoCA scores and higher scores on CDR-SB or ADAS-Cog.

TABLE 1

LEADS CSF cohort description.

			Diagnosis categories			
		All	**CN**	**EOAD**	**EOnonAD**	***p* value**
Age	Mean	57.9	56.0	58.8	57.2	0.009
	Standard deviation	5.0	5.4	3.9	6.8	
	N	165	37	96	32	
Sex						0.2
Female	Column %	49%	51%	52%	34%	
Male	Column %	50%	49%	48%	66%	
Race						0.320
Asian	Column %	2%	3%	1%	3%	
Black or African American	Column %	5%	11%	3%	3%	
More than one race	Column %	3%	8%	1%	3%	
Unknown	Column %	2%	3%	1%	3%	
White	Column %	87%	76%	94%	88%	
Ethnicity						0.013
Hispanic or Latino	Column %	6%	14%	1%	6%	
Not Hispanic or Latino	Column %	93%	86%	99%	94%	
APOE e4 carrier						0.593
No	Column %	49%	49%	46%	56%	
Yes	Column %	51%	51%	54%	44%	
Cognitive testing						
MoCA	Mean	19.5	27.5	16.0	21.4	<0.001
	Standard deviation	6.8	2.1	5.5	5.7	
	N	154	33	91	30	
CDR-SB	Mean	2.7	0.0	3.6	3.3	<0.001
	Standard deviation	2.2	0.0	1.8	2.1	
	N	165	37	96	32	
ADAS-Cog	Mean	20.8	14.8	23.9	18.6	<0.001
	Standard deviation	6.6	2.4	6.6	3.5	

		Diagnosis categories			
	All	**CN**	**EOAD**	**EOnonAD**	***p* value**
N	160	37	93	30	

Note: Demographic information for total LEADS CSF cohort and by diagnostic group. Number (*N*) is included for the overall cohort as well as each diagnostic group. Significance (*p* value) was determined between the three diagnostic groups, CN, EOAD, and EOnonAD, using a Kruskal-Wallis test for continuous measures and likelihood ratio for nominal measures.

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale—Cognitive Subscale; CDR-SB, clinical dementia rating scale sum of boxes; CN, cognitively normal; EOAD, early-onset Alzheimer's disease; EOnonAD, amyloid PET negative early-onset cognitively impaired participants; MoCA, Montreal Cognitive Assessment total score.

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TABLE 2

CSF biomarker results in LEADS.

		Diagnosis categories					
		All	**CN**	**EOAD**	**EOnonAD**	***P* value**	**Effect Size**
CSF biomarker results							
Aβ42/40	Mean	0.0569	0.0794	0.0406	0.0800	<0.001	3.3
	Std Dev	0.0217	0.0117	0.0073	0.0140		
	N	163	36	95	32		
pTau181 (pg/mL)	Mean	81.1	32.8	113.8	40.1	<0.001	4.7
	Standard deviation	54.6	17.3	48.3	21.7		
	N	164	37	95	32		
tTau (pg/mL)	Mean	557	275	729	335	<0.001	3.7
	Standard deviation	326	124	303	157		
	N	158	33	94	31		
NfL (pg/mL)	Mean	900	481	995	1060	<0.001	2.6
	Standard deviation	590	195	360	1065		
	N	158	33	94	31		
Ng (pg/mL)	Mean	2947	1773	3659	2212	<0.001	1.5
	Standard deviation	2085	1253	2211	1573		
	N	163	37	94	32		
VILIP-1 (pg/mL)	Mean	227	189	248	204	0.003	0.8
	Standard deviation	93	77	96	83		
	N	138	31	82	25		
YKL-40 (ng/mL)	Mean	240	202	263	214	0.001	0.5
	Standard deviation	99	131	78	93		
	N	165	37	96	32		
SNAP-25 (pg/mL)	Mean	18.1	14.7	20.3	15.0	0.001	1.0
	Standard deviation	8.7	5.5	9.6	6.4		
	N	137	31	82	24		

Note: Some data were not available for each subject; therefore, number (*N*) is included for each variable. Significance (*p* value) was determined between the three diagnostic groups, CN, EOAD, and EOnonAD, using one-way ANOVA. Effect size is Glass's delta and uses the standard deviation from the CN group.

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale—Cognitive Subscale; CDR-SB, Clinical Dementia Rating scale sum of boxes; CN, cognitively normal; EOAD, early-onset Alzheimer's disease; EOnonAD, amyloid PET negative early-onset cognitively impaired participants; MoCA, Montreal Cognitive Assessment total score.