LEADS
Longitudinal Early-Onset Alzheimer's Disease Study

LEADS FAMILY MEETING
Sept. 7 | Indianapolis, IN and Online

LEADS UPDATE

Dustin B. Hammers, PhD, ABPP
Clinical Neuropsychologist, Dept. of Neurology, IU School of Medicine

UCSF Weill Institute for Neurosciences
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POLICIES

Photography is welcome in this presentation.

The information included in this presentation may be shared on other platforms.

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Disclosures and Acknowledgements

Disclosures:

- None

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- **Alzheimer's Association** AARG-22-926940, LDRFP-21-818464, LEADS GENETICS-19-639372

Acknowledgements:

- Thank you to our participants and study partners!
- Thank you to **Liana Apostolova, MD** for her role as PI on the LEADS study, and her contribution to these slides

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LEADS Principal Investigators

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FAAN is an IU Distinguished Professor and the Barbara and Peer Baekgaard Professor
Indiana University

Maria Carrillo, PhD
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Alzheimer's Association

Bradford Dickerson, MD
Professor of Neurology at Harvard Medical School and Tom Rickles Chair in Progressive Aphasia Research
Massachusetts General Hospital

Gil Rabinovici, MD
Edward Fein and Pearl Landrith Endowed Professor in Memory & Aging
University of California, San Francisco

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LEADS Sites and Site PIs

- Butler Hospital (Meghan Riddle)
- Wien Center (Ranjan Duara)
- Banner Sun Health Research Institute (Alireza Atri)
- Georgetown University (Raymond Scott Turner)
- Mayo Clinic Jacksonville (Gregory Day)
- Washington University in St. Louis (Kyle Womack)
- Mayo Clinic (David Jones)
- Columbia University (Lawrence Honig)
- Johns Hopkins University (Chiadi Onyike)
- University of Pennsylvania (David Wolk)
- University of California Los Angeles (Mario Mendez)
- Indiana University (Liana Apostolova)
- Northwestern University (Ian Grant)
- University of California San Francisco (Gil Rabinovici)
- Emory University (Erik CB Johnson)
- Massachusetts General Hospital (Brad Dickerson)
- Houston Methodist (Joseph Masdeu)
- Stanford University (Sharon Sha)

Longitudinal Early-Onset Alzheimer's Disease Study (LEADS)

An estimated 200,000 Americans are currently living with early-onset Alzheimer's disease, meaning an onset of cognitive symptoms before the age of 64.

This is an understudied population often not included in clinical trials for Alzheimer's disease and often experience other barriers due to age of onset.

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Study Recruitment: LEADS recruits participants under the age of 65 across 18 sites in the US

Observational Study: The study participants will be followed for at least two years to study disease progression

Data Collected: Cognitive and behavioral measures, MRI, PET imaging, CSF, blood, and genetics will be collected from the study participants.

Study Updates: LEADS is open for recruitment

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Groups of LEADS Participants

Three groups of participants recruited into LEADS.

1. Cognitively Normal (CN)
2. Cognitively Impaired (CI) – two sub-groups
    1. Early-onset cognitive impairment in the presence of β-amyloid (EOAD)
    2. Early-onset cognitive impairment in the absence of β-amyloid (EOnonAD)

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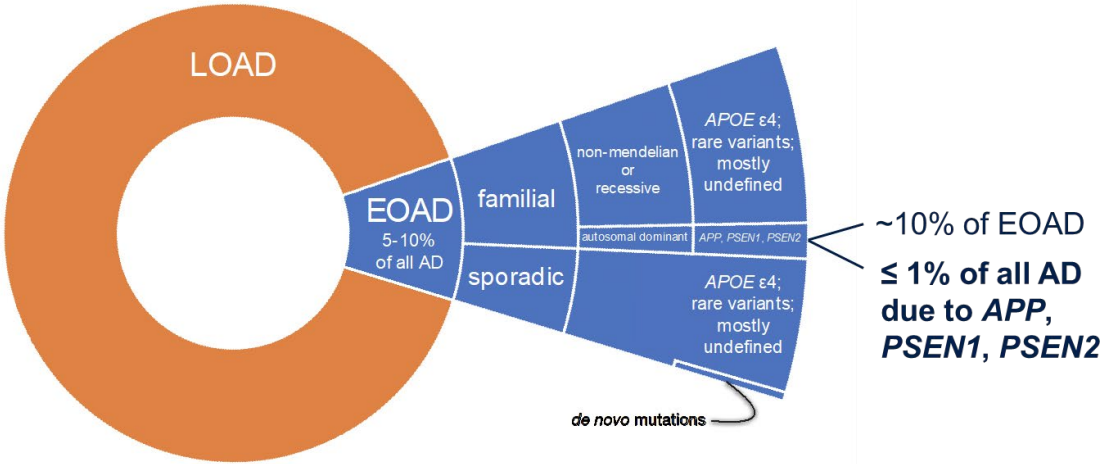
Genetic Contributions to Early-Onset Alzheimer's Disease



LOAD – late-onset AD, age ≥ 65
EOAD – early-onset AD, age < 65
Sporadic – family history not suggestive of inherited dementia
Familial – history of AD/dementia in multiple generations
Autosomal dominant – caused by mutation in a single gene

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Agenda for Updates

- Enrollment
- Research Findings

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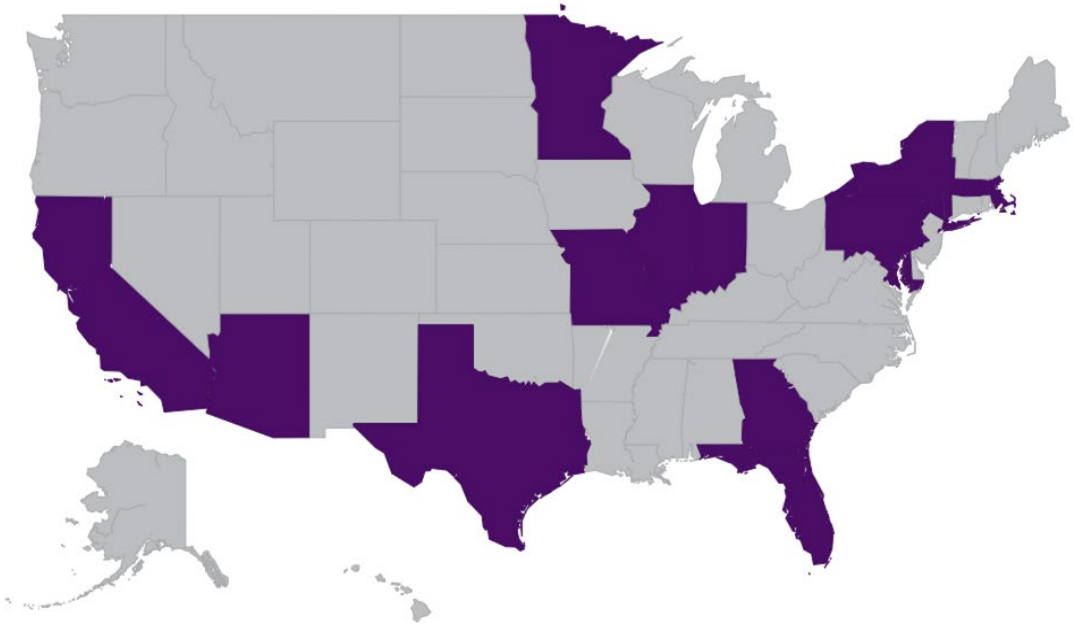
LEADS Sites across the US



Indiana University	Mayo Clinic, Jacksonville
Mayo Clinic, Rochester	University of California, San Diego
Columbia University	Northwestern University
Washington University, St. Louis	University of California, San Francisco
Wien Center for Clinical Research	Georgetown University
Johns Hopkins University	Stanford University
University of Pennsylvania	Banner Sun Health Research Institute
Emory University	Houston Methodist Neurological Institute
University of California, Los Angeles	Massachusetts General Hospital

International Sites will be discussed in the next presentation

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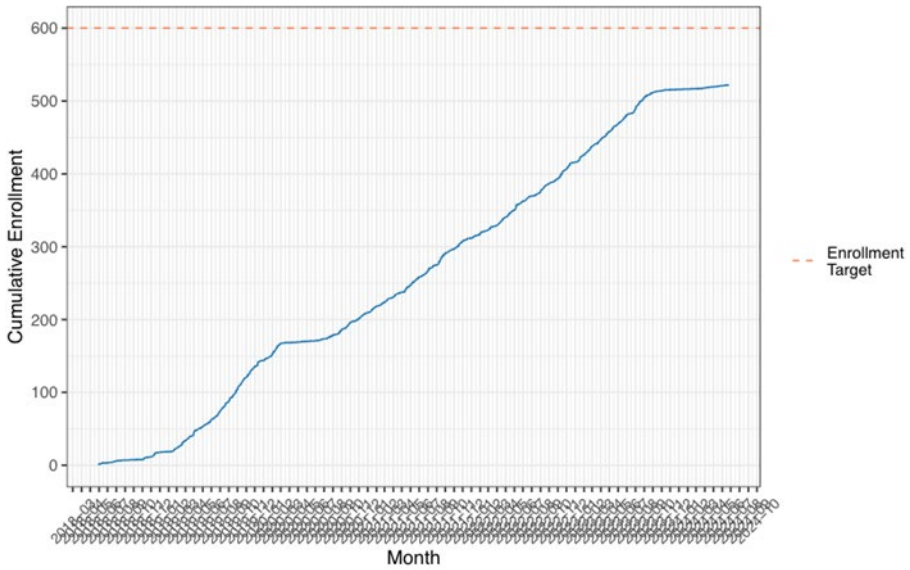
Enrollment Update = 61%

Target enrollment = 650 EOAD and 100 CN + up to 200 EOnonAD



	Enrolled		
	EOAD	EOnonAD	CN
Aug 2024	*400*	122	100

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Completed Annual Visits

BASELINE	12M	24M	36M	48M
622	430	237	83	24

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Participant Discontinuation Rate = 31%

- Participant not able or willing to participate anymore (n=86)
- Starting Clinical Trial (n=24)
- Deceased (n=25)
- Lost to follow-up (n=27)
- Study partner unable/unwilling to participate (n=8)
- Site PI/Study Physician Recommendation (n=9)
- Non-Compliance (n=1)
- Covid Pandemic Disruption (n=1)
- Other (n=12)

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Enrollment requirements: Key Eligibility Criteria

Inclusion Criteria:

- 40-64 years old
- Meets criteria for MCI due to AD or probable AD dementia
- Must have a study partner who spends a minimum average of 10 hours per week with the participant

Exclusion Criteria:

- History of schizophrenia, mania, or bipolar disorder
- Previous enrollment in a drug trial targeting amyloid or tau
  - Note: Clinical use of anti-amyloid treatment is permitted

The study team will further assess all items on the eligibility checklist.

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Screening & Baseline Visits

Screening Visit – (1 visit):

- Informed Consent – Participant & Study Partner (2 hours)
- Neurological & Physical Exam (1 hour)
- Clinical Dementia Rating (CDR) Assessment (30-60 mins)
- MRI (1 hour)
- Safety Labs (blood draw) (20-30 mins)
- Vital Signs
- Questionnaires (30 mins):
    - Demographics
    - Family History
    - Medical History
    - Medications

If eligible, proceed to baseline visit.

Baseline Visit – (2-3 visits):

- Cognitive Testing (4-5 hours)
- Amyloid PET Scan (2 hours)
- Tau PET Scan (2 hours)
- Blood Draw (30 mins)
- Questionnaires (30 mins)
- Lumbar Puncture (optional) (1 hour + 30 min rest)
- Brain donation discussion
- Genetic testing discussion

Results:

- Receive Amyloid PET results
- Receive Tau & FDG PET Scan Results

If negative Amyloid results, complete FDG PET Scan.

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Demographics by Group

	Cognitively Normal N=100	EOAD N=399	EOnonAD N=122	Combined N=621
Age (Years)	56.8 (5.9)	59.0 (4.1)	58.3 (5.9)	58.5 (4.9)
Sex				
M	36 (36%)	188 (47%)	73 (60%)	298 (48%)
F	64 (64%)	211 (53%)	49 (40%)	324 (52%)
Education (Years)	16.7 (2.2)	15.6 (2.4)	15.7 (2.7)	15.8 (2.5)
Minority				
Minority	37 (37%)	52 (13%)	27 (22%)	117 (19%)
Not Minority	63 (63%)	347 (87%)	95 (78%)	505 (81%)
Race				
Am Indian/Alaskan	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Asian	7 (7%)	10 (3%)	3 (2%)	20 (3%)
Hawaiian/Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Black or African American	18 (18%)	23 (6%)	9 (8%)	50 (8%)
White	71 (71%)	358 (91%)	100 (83%)	530 (86%)
More than one race	0 (0%)	2 (1%)	1 (1%)	3 (0%)
Unknown	1 (1%)	2 (1%)	7 (6%)	10 (2%)
Ethnicity				
Hispanic or Latino	12 (12%)	14 (4%)	12 (12%)	38 (6%)
Not Hispanic or Latino	88 (88%)	385 (96%)	88 (88%)	584 (94%)
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)

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Publications with LEADS Data

- As of January 2024, LEADS had published 12 manuscripts on Early-Onset AD
- Prior to LEADS, publications on EOAD were from small samples usually from a single hospital
- Since January:
    - 1 accepted
    - 8 currently in process

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Publication Topics

- Manuscripts recently published or in the process looking at the comparison of early-onset AD (EOAD) with late-onset AD (LOAD)

Research Questions	Researcher
Comparison of cognition at the first visit for study participants with EOAD compared to LOAD	Dustin Hammers
Comparison of brain shrinkage on an MRI scan for study participants with EOAD compared to LOAD	Yuta Katsumi and Alexandra Touroutoglou
Comparison of β-amyloid and tau burden on PET scans	Julien Lagarde (amyloid) and Konstantinos Chiotis (amyloid and tau)

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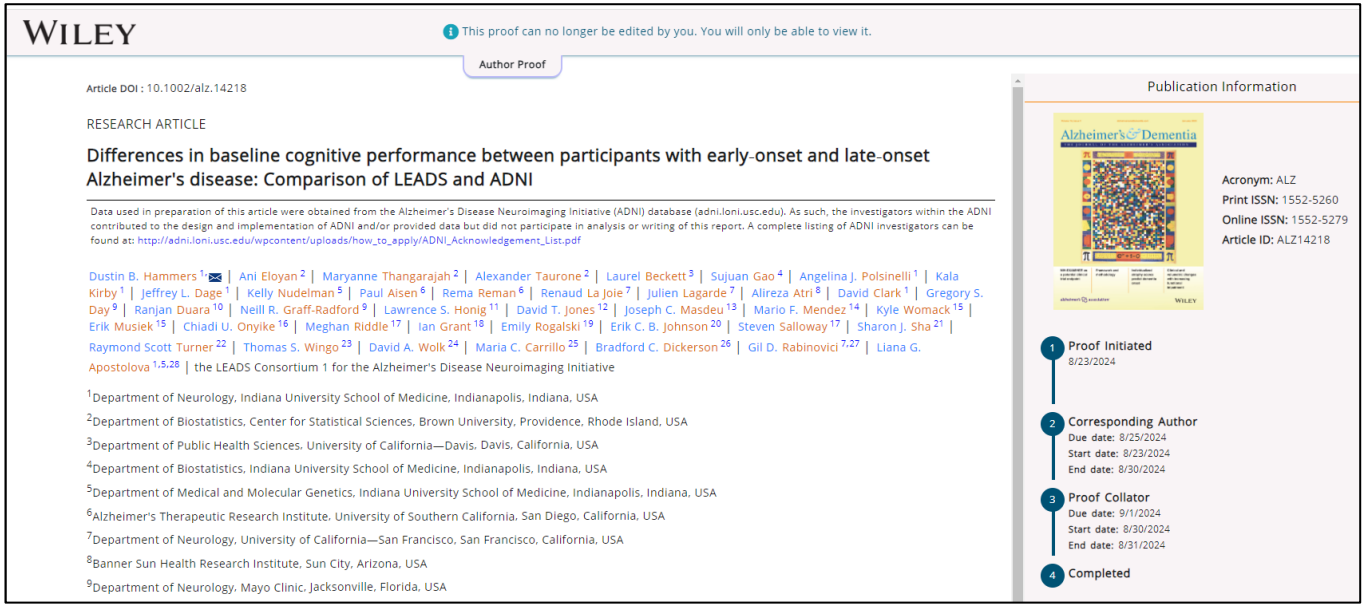
LEADS Research in Detail



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Author Proof

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RESEARCH ARTICLE

Differences in baseline cognitive performance between participants with early-onset and late-onset Alzheimer's disease: Comparison of LEADS and ADNI

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Dustin B. Hammers [1] | Ani Eloyan [2] | Maryanne Thangarajah [2] | Alexander Taurone [2] | Laurel Beckett [3] | Sujuan Gao [4] | Angelina J. Polsinelli [1] | Kala Kirby [1] | Jeffrey L. Dage [1] | Kelly Nudelman [5] | Paul Aisen [6] | Rema Reman [6] | Renaud La Joie [7] | Julien Lagarde [7] | Alireza Atri [8] | David Clark [1] | Gregory S. Day [9] | Ranjan Duara [10] | Neill R. Graff-Radford [9] | Lawrence S. Honig [11] | David T. Jones [12] | Joseph C. Masdeu [13] | Mario F. Mendez [14] | Kyle Womack [15] | Erik Musiek [15] | Chiadi U. Onyike [16] | Meghan Riddle [17] | Ian Grant [18] | Emily Rogalski [19] | Erik C. B. Johnson [20] | Steven Salloway [17] | Sharon J. Sha [21] | Raymond Scott Turner [22] | Thomas S. Wingo [23] | David A. Wolk [24] | Maria C. Carrillo [25] | Bradford C. Dickerson [26] | Gil D. Rabinovici [7,27] | Liana G. Apostolova [1,5,28] | the LEADS Consortium 1 for the Alzheimer's Disease Neuroimaging Initiative

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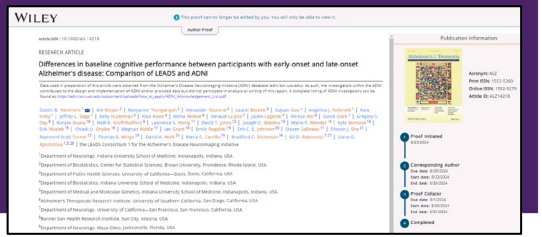

Comparing cognition in EOAD vs. LOAD

	EOAD	LOAD
N	311	314
Processing Speed/Attention	-2.94 (5.9)	-1.27 (2.0)
Visuospatial Skills	-27.12 (26.2)	-2.94 (5.6)
Executive Functioning	-7.92 (6.1)	-2.17 (4.9)
Immediate Memory	-2.22 (1.1)	-2.08 (1.3)
Delayed Memory	-2.25 (0.9)	-2.21 (1.0)
Language	-0.47 (3.1)	-2.01 (4.6)

Value < -1.5 equals clinical impairment in that area

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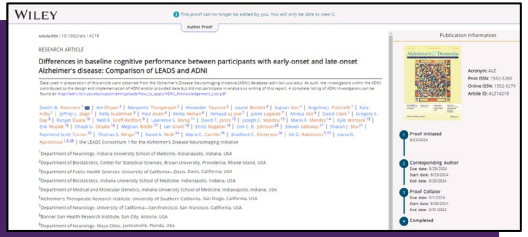

Comparing cognition in EOAD vs. LOAD

	EOAD vs LOAD	EOAD vs LOAD Significance
Processing Speed/Attention	EOAD <<< LOAD	*p*<.001
Visuospatial Skills	EOAD <<< LOAD	*p*<.001
Executive Functioning	EOAD <<< LOAD	*p*<.001
Immediate Memory	EOAD >>> LOAD	*p*<.001
Delayed Memory	EOAD >>> LOAD	*p*=.006
Language	EOAD >>> LOAD	*p*<.001

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Research Take-Home Message

- EOAD and LOAD appear to possess unique cognitive profiles
- These findings hint that EOAD and LOAD may be somewhat distinct clinical entities despite sharing a common neuropathology
- Future work within LEADS is underway to examine more-closely genetic, fluid biomarker, and imaging distinctions between EOAD and LOAD
- Clinicians and patients should be aware of non-memory impairments in younger populations to ensure proper identification and intervention using disease modifying treatments

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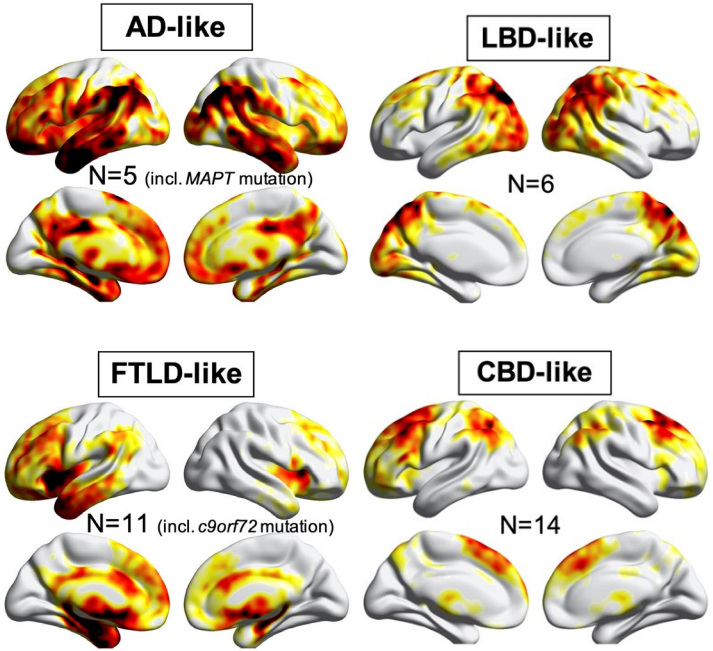
Focus on amyloid-negative patients

Lagarde et al., 2024. AAIC Presentation

- ~25% of patients with clinically diagnosed EOAD are amyloid-PET-negative
- 51% percent of amyloid-negative EOnonAD patients in LEADS had normal brain activity, milder clinical impairment, normal brain structure, and normal blood biomarker values, suggesting non-neurodegenerative etiologies.
- Patients with abnormal brain activity suggested multiple causes including Lewy body disease, FTLD, or corticobasal degeneration.



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LEADS Manuscripts

Profiling baseline performance on the LEADS cohort near the midpoint of data collection	Dr. Hammers
Learning slopes in EOAD	Dr. Hammers
Influence of amyloid and diagnostic syndrome on non-traditional memory scores in EOAD	Dr. Bushnell
Baseline neuropsychiatric symptoms and psychotropic medication use midway through data collection of the LEADS cohort	Dr. Polsinelli
Sex and APOE ε4 carrier effects on atrophy, amyloid PET, and tau PET burden in EOAD	Ms. Nemes
White matter hyperintensities are higher among early-onset Alzheimer's disease participants than their cognitively normal and early-onset nonAD peers: LEADS	Dr. Eloyan
Amyloid and tau-PET in early-onset AD: Baseline data from LEADS	Dr. Cho
Cerebrospinal fluid biomarkers in LEADS	Dr. Dage
Developments in understanding EOAD	Dr. Griffin
The Sporadic Early-Onset Alzheimer's Disease Signature of Atrophy: Preliminary findings from the LEADS Cohort	Dr. Touroutoglou
Familial Alzheimer's Disease Genetic Variants in LEADS	Dr. Nudelman

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Data Sharing

Approved Studies

University of Pennsylvania
Duke University
UCLA
Emory University
Mass General Hospital
UC - San Francisco

Lund University- x2
University of Gothenburg
Amsterdam University Med Center – x2

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Thank you to LEADS participants and family members!

Together, we can improve early diagnosis, deepen our understanding, and ultimately build the foundation for a cure for early-onset AD

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trialmatch
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Learn more about how to get involved with LEADS and find a LEADS Sites near you through alz.org/TrialMatch

790	Alzheimer's disease
384	Mild Cognitive Impairment
38	Vascular Dementia
128	Other Dementia

*As of September 2024

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Additional Study Opportunities

- Connected speech and language in amyloid-positive EOAD
  - Will evaluate language abilities during spontaneous speech in EOAD.
  - Storytelling abilities and more complex language and communication, which is not data that is collected as part of the current LEADS protocol
    - Approximately 90 minutes at Baseline, 6 months, and 12 months

- Contact Dr. Stark at: bcstark@iu.edu

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Understanding Care Partner Needs in Early Onset Alzheimer's

- There is a need for age- and life-stage appropriate training interventions for care partners of people living with EOAD
- We want to hear from past and current care partners about their caregiving needs, services they wished existed to support them and their families, and gaps that need to be addressed by medical professionals in the care of persons with EOAD.
- This information will be used to develop a series of care partner skills-training interventions specifically designed for EOAD at different stages of disease (mild, moderate, late)
- Contact Dr. Polsinelli at: apolsine@iu.edu

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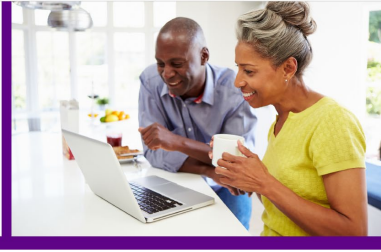
LITES



LIFESTYLE INTERVENTIONS FOR THE TREATMENT OF EARLY-ONSET ALZHEIMER'S DISEASE STUDY

- Randomized clinical trial to look at a combined cognitive training & exercise intervention
- Outcomes: cognition, functioning, and mood
- Current LEADS participants classified as **amyloid-positive EOAD** (*n* = 60) will be recruited
- All aspects of this proposed study will be conducted **remotely**

Interested participants can contact me or Jane Musema

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- jmusema@iu.edu
- (317) 963 4595

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INTERNATIONAL LEADS UPDATES

Courtney Kloske, PhD

Alzheimer's Association

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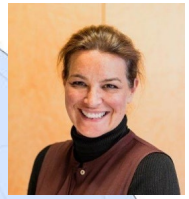
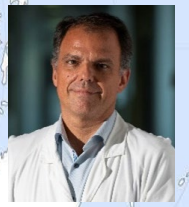


University College London
Catherine Mummery

Amsterdam University Medical Center
Wiesje van der Flier



Sant Pau Memory Unit
Alberto Lleo

FLENI
Ricardo Allegri

Lund University
Oskar Hansson

Funding for the iLEADS Expansion was made possible by the Alzheimer's Association Indiana Chapter

iLEADS international Longitudinal Early-Onset Alzheimer's Disease Study

- **United Kingdom** and Dementia Research Center has nearly 50 EOAD participants, and interest exists in participants to get into LEADS
- **Netherlands** is hoping to begin recruitment in 2025
- **Spain** has a cohort with more than 1,000 individuals, several of whom meet the criteria for LEADS recruitment.
- **Argentina** has identified potential participants for recruitment into the iLEADS site.
- **Sweden** has 150 participants in their Early onset program who are interested in research studies.

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