

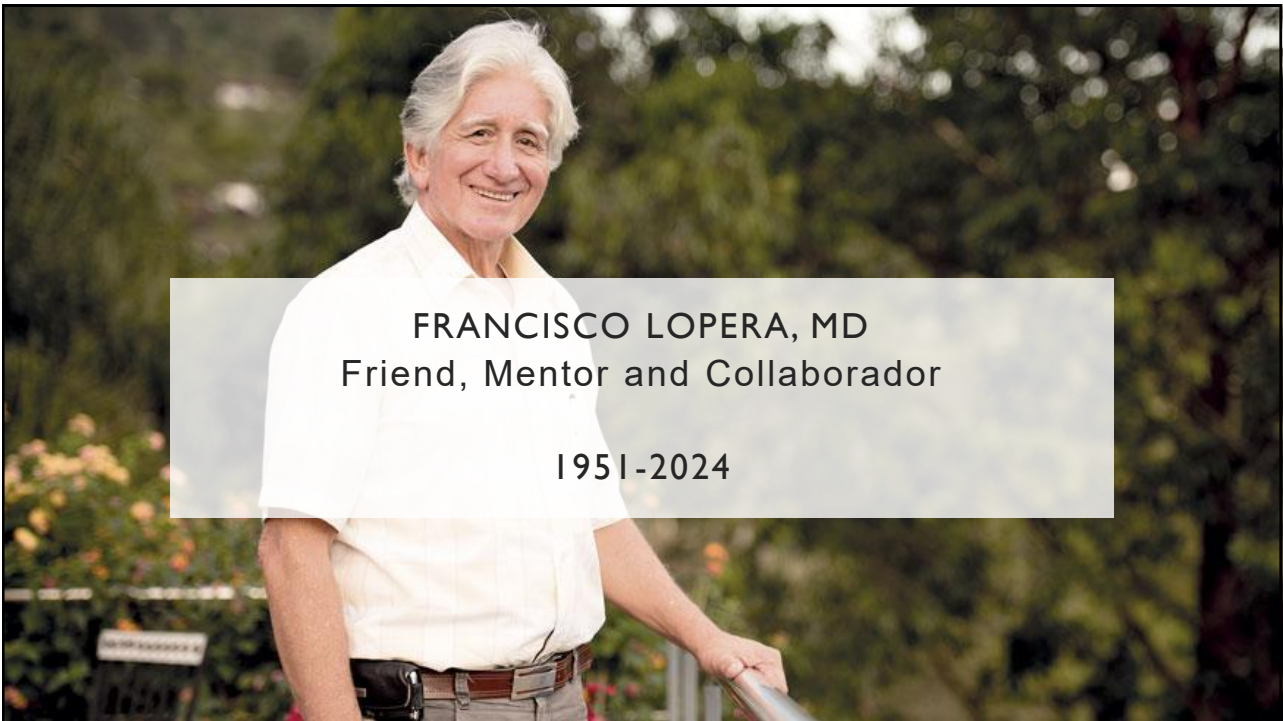
**RISK AND PROTECTIVE
FACTORS IN AUTOSOMAL
DOMINANT ALZHEIMER'S
DISEASE: FINDINGS FROM
THE COLBOS STUDY**

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Boston University

Neuroimaging Researcher
Massachusetts General Hospital

September 19, 2025

1



FRANCISCO LOPERA, MD
Friend, Mentor and Collaborator

1951-2024

2

DISCLOSURES

Dr. Quiroz has served as consultant for Biogen

3

OUTLINE

1. Overview: Dementia, autosomal dominant AD (ADAD), and biomarkers in the preclinical stage of the disease
2. Early detection of ADAD
3. COLBOS: Tau pathology and biomarkers in preclinical AD
4. Risk factors in ADAD
5. COLBOS Extreme: Protective factors and cognitive resilience in ADAD
6. Other ongoing/new projects

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DEMENTIA

Umbrella term for loss of memory and other thinking abilities severe enough to interfere with daily life.

- Alzheimer's:
60-80%
- Lewy Body Dementia:
5-10%
- Vascular Dementia:
5-10%
- Frontotemporal Dementia:
5-10%
- Others:
Parkinson's,
Huntington's

Mixed dementia:
Dementia from more than one cause

Number and Ages of People 65 or Older with Alzheimer's Dementia, 2023*

Age Group	Number of People (Million)	Percentage
Total	6.7	100%
65-74 years	1.79	26.7%
75-84 years	2.54	37.9%
85+ years	2.37	35.4%

*Percentages do not total 100 due to rounding.
Created from data from Rajan et al.^{62, 2022}

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Alzheimer's Disease (AD) Continuum*

Stage	Description
Preclinical AD	No symptoms but possible biological changes in the brain
Mild Cognitive Impairment Due to AD	Very mild symptoms that may not interfere with everyday activities
Dementia Due to AD Mild	Symptoms interfere with some everyday activities
Dementia Due to AD Moderate	Symptoms interfere with many everyday activities
Dementia Due to AD Severe	Symptoms interfere with most everyday activities

*Although these arrows are of equal size, the components of the AD continuum are not equal in duration.

Cognitive Functions vs Age

The graph shows a downward curve of cognitive functions over age. Key points include: Preclinical, Mild Cognitive Impairment, and Dementia. Annotations include 'Delay clinical onset' (shifting the curve right), 'Aging' (the overall downward trend), and 'Current treatments' (flattening the curve).

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ALZHEIMER'S DISEASE

Sporadic AD: 90-95% of cases

*Generally diagnosed in individuals over the age of 65.

*The most important risk factors—age, family history and heredity (APOE4, the major genetic risk factor).

Familial AD: <2% of cases

*Autosomal-dominant mutations: Presenilin 1 and 2, Amyloid precursor protein (APP) genes

*Before the age of 65

*Nearly 100% penetrance

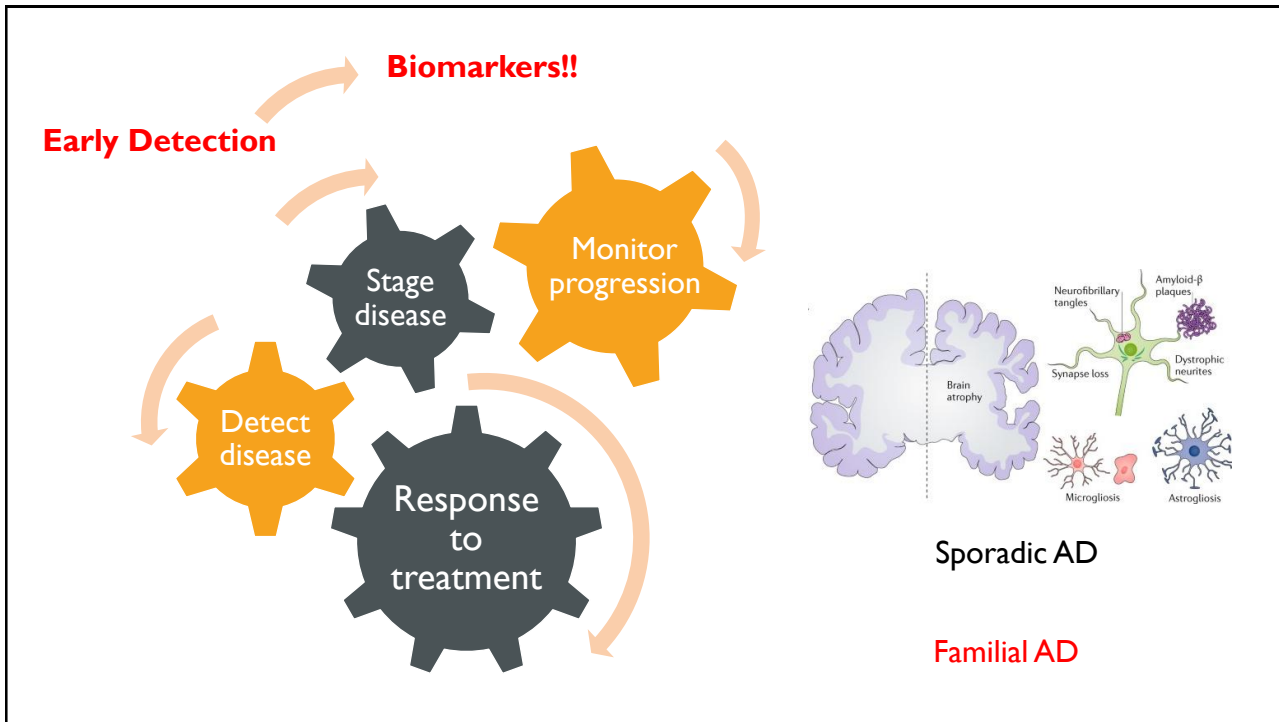
*Specific age of onset



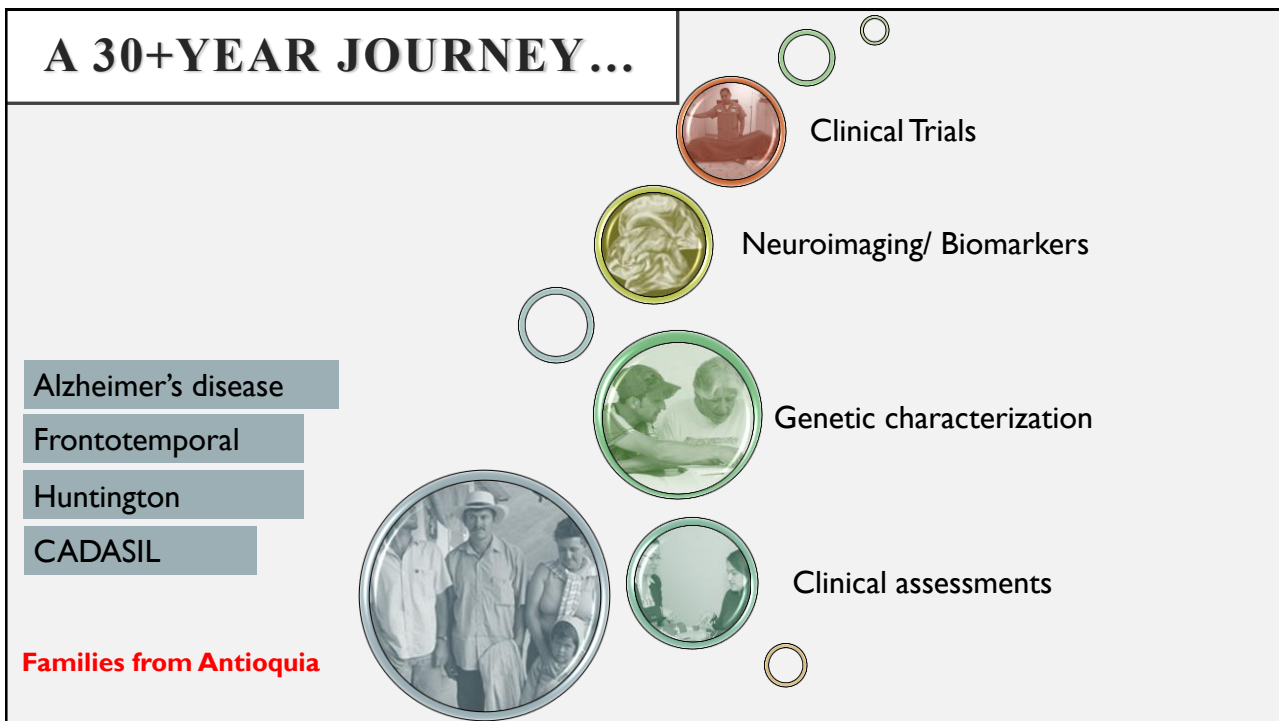
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EARLY DETECTION OF AD-RELATED CHANGES

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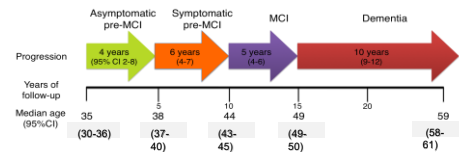
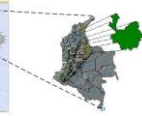
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A LARGE EXTENDED FAMILY WITH EARLY-ONSET ALZHEIMER'S DISEASE (AD) IN ANTIOQUIA, COLOMBIA

- Autosomal dominant AD (ADAD): A unique opportunity to examine early AD-related changes in cognitively-normal individuals.
- Presenilin-1 (*PSEN-1*) mutation carriers develop early-onset AD with near 100% certainty.
- The Colombian kindred (E280A mutation) has a median age of mild cognitive impairment (MCI) at 44 years (95% CI +/- 2 years), and dementia at 49 years (95% CI +/- 2 years).
- Clinical, cognitive and biomarker similarities between ADAD and late-onset Sporadic AD.



Lopera et al, 1997; Acosta-Baena et al, 2011; Fuller et al., 2019


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What are the earliest biological and physiological changes associated with the predisposition to Alzheimer's disease?

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Colombia-Boston (COLBOS)

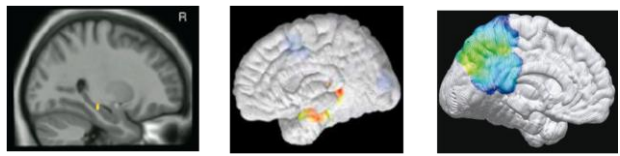
Biomarker study of autosomal dominant Alzheimer's disease



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Evidence for brain changes in cognitively unimpaired carriers, years before clinical onset

Hippocampal hyperactivation, and less deactivation of parietal regions



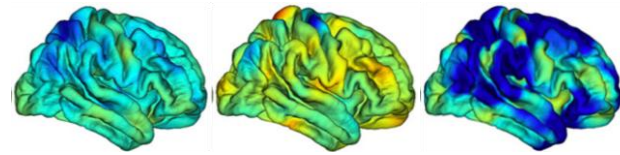
Older Carriers (>25yo)
Quiroz et al. (2010)

Carriers (18-25yo)
Reiman* et al. (2012)

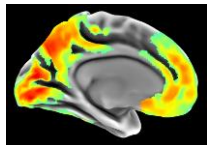
Children/Adolescents (9-18yo)
Quiroz et al., (2015)

Cortical thinning

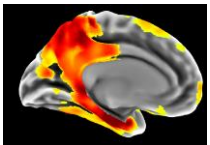
- PSEN1-E280A mutation carriers had elevated amyloid pathology as early as 28 years old.
- PSEN1-E280A mutation carriers showed increased tau pathology in their late-30s, a few years before their clinical onset.
- Tau pathology more closely linked to clinical progression.



Two cut-points at ~17 and 32 yrs of age
Quiroz et al. (2013)
Fox-Fuller et al (2021)



Aβ pathology



Tau pathology

Older Carriers (>28yo)
Quiroz et al. (2018)
Sanchez et al. (2021)

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TAU PATHOLOGY DISRUPTS BRAIN CONNECTIVITY IN ASYMPTOMATIC PSEN1 MUTATION CARRIERS



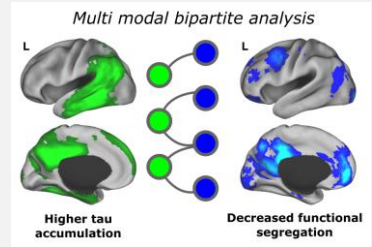
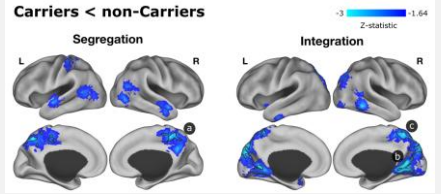
Mutation carriers had less functional segregation and integration in default-mode network (DMN) regions, particularly the precuneus and the retrosplenial cortex.



Greater tau burden was associated with lower segregated and integrated functional connectivity of DMN regions, particularly the precuneus and medial prefrontal cortex.



These findings show how tau pathology alters the brain's functional organization years before cognitive impairment occurs.

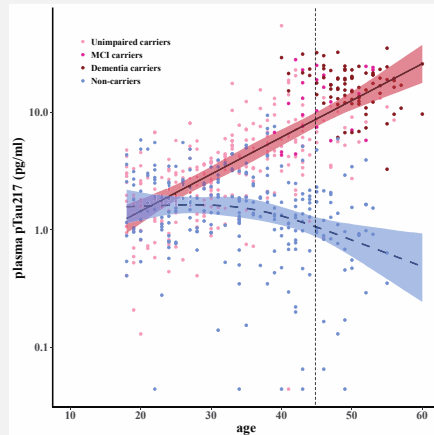


Guzman-Velez, Diez...Quiroz, PNAS 2022

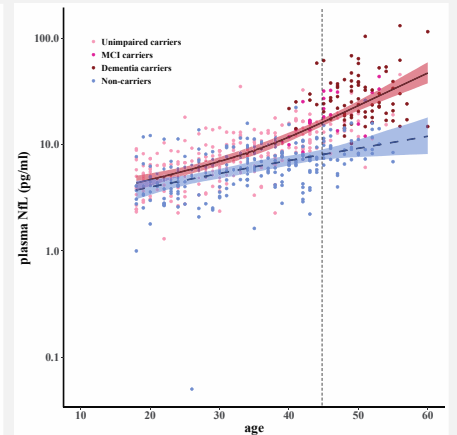
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PLASMA BIOMARKERS

A. Plasma P-tau217 by age



B. Plasma Neurofilament light by age



Quiroz et al., *The Lancet Neurology* 2020 (NFL); Palmqvist et al., *JAMA* 2020 (p-tau217)

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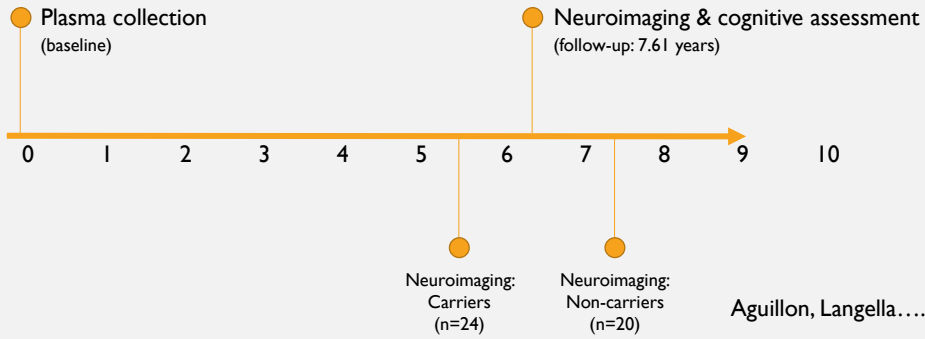
CAN PLASMA P-TAU217 PREDICT SUBSEQUENT LEVELS OF TAU PET PATHOLOGY AND COGNITIVE PERFORMANCE?

Baseline measures:

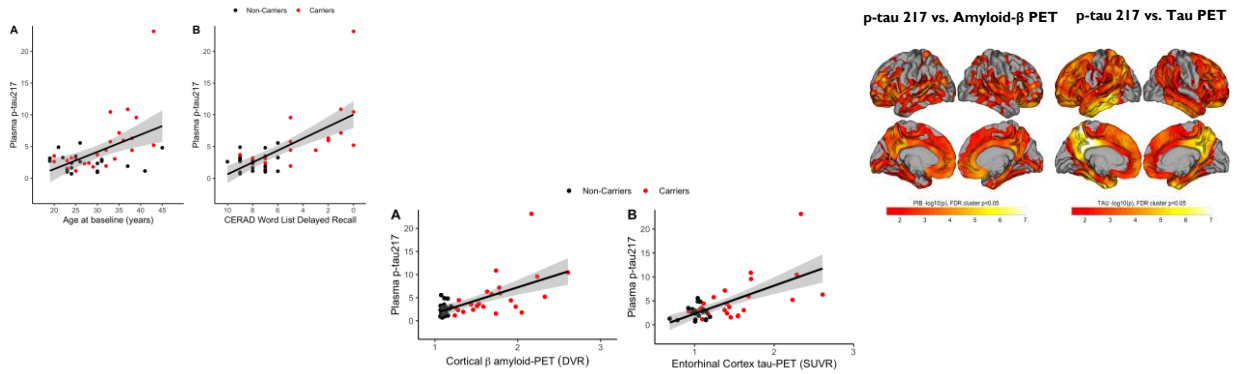
- Plasma p-tau217
- Demographics (age, sex, education)

Follow-up measures:

- Tau-PET ([F18] flortaucipir)
 - ROI: Inferior temporal, entorhinal, precuneus
 - Exploratory vertex wise
- Aβ-PET (11C-Pittsburgh compound B)
 - ROI: Mean cortical uptake
 - Exploratory vertex wise
- MMSE
- CERAD Word List Delayed Recall



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BASELINE PLASMA P-TAU217 IS ASSOCIATED WITH GREATER PET PATHOLOGY BURDEN ~7.5 YRS LATER

Aguillon, Langella et al., 2024

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**REMOTE AND UNSUPERVISED
ASSESSMENTS FOR DETECTION OF
COGNITIVE IMPAIRMENT**

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MAPP REMOTE BATTERY

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Alzheimer's Research & Therapy (2020) 12:104
<https://doi.org/10.1186/s12876-020-01402-9>

Brief Communication


The MAPP Room Memory Test: Examining Contextual Memory Using a Novel Computerized Test in Cognitively-Unimpaired Individuals with Autosomal Dominant Alzheimer's Disease

A. Gaidarov^{1,2}, P.A. Aduen¹, J.T. Fox-Fuller^{1,3}, J.E. Martinez^{1,4}, L.A. Gonzalez^{1,5}, C. Vila-Castelar⁶, A. Barua¹, C. Plante McDevitt^{1,6}, A. Cronin-Golomb⁷, E. Lopez¹, Y.T. Quiroz^{1,14}

¹Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA; ²Department of Psychological and Brain Sciences, Boston University, Boston, MA, USA; ³Department of Psychology, Neuroscience Center and the Boston Medical Center, Boston, MA, USA; ⁴Center for Neuroscience, University of Arizona, Tucson, Arizona; ⁵Department of Psychology, Washington University School of Medicine, St. Louis, MO, USA; ⁶Center for Neuroscience, University of Arizona, Tucson, Arizona; ⁷Department of Psychology, Boston University, Boston, MA, USA; ⁸Department of Psychology, Boston University, Boston, MA, USA; ⁹Department of Psychology, Boston University, Boston, MA, USA; ¹⁰Department of Psychology, Boston University, Boston, MA, USA; ¹¹Department of Psychology, Boston University, Boston, MA, USA; ¹²Department of Psychology, Boston University, Boston, MA, USA; ¹³Department of Psychology, Boston University, Boston, MA, USA; ¹⁴Department of Psychology, Boston University, Boston, MA, USA

Brief Report

Memory for Semantically Related Objects Differentiates Cognitively Unimpaired Autosomal Dominant Mutation Carriers from Non-Carrier Family Members

J.T. Fox-Fuller^{1,3}, J.E. Martinez^{1,4}, A. Barua¹, N. Londono¹, D. Munera¹, D. Noriega¹, C. Vila-Castelar⁶, P.A. Aduen¹, E. Lopez¹, A. Cronin-Golomb⁷, Ysabele T. Quiroz^{1,14} & 

Show more

Research | Open Access | Published: 10 September 2020

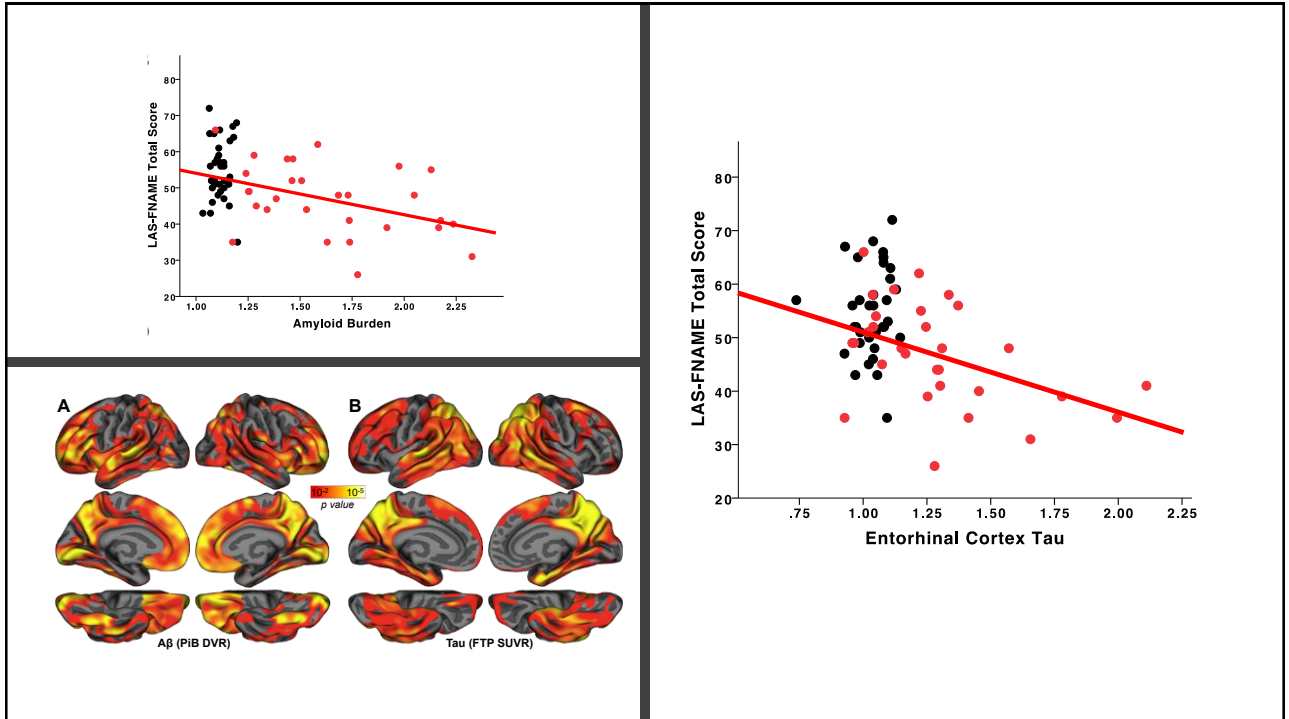
The Latin American Spanish version of the Face-Name Associative Memory Exam is sensitive to cognitive and pathological changes in preclinical autosomal dominant Alzheimer's disease

Clara Vila-Castelar, Nathalia Muñoz, Kathryn V. Papp, Rebecca E. Amariglio, Ana Baena, Edmarie Guzmán-Vélez, Yamile Socarraga, Justin S. Sanchez, Eric M. Reiman, Keith A. Johnson, Reina A. Sorling, Francisca Lopez, Doreen M. Rentz & Ysabele T. Quiroz

Alzheimer's Research & Therapy 12, Article number: 104 (2020) | [View this article](#)

MAPP REMOTE COGNITIVE BATTERY

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CONCLUSION


Findings across studies consistently demonstrate that the LAS-FNAME, along with the MESERO and MAPP Room Memory Test, effectively distinguish cognitively unimpaired carriers from non-carriers, **several years before symptom onset.**

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Eye biomarkers




J. Miller, MD
Mass Eye and Ear




J. Arboleda-Velasquez, MD PhD
Mass Eye and Ear

Sex differences




C. Vila-Castelar, PhD


Sleep



A. Lam, MD
MGH Neurology




C. Plum, PhD




J. You, MD
MGH Neurology

Physical activity

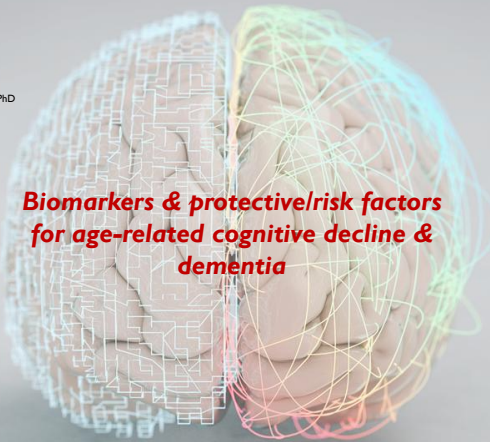


E. Guzman-Velez, PhD

Odor biomarkers




L. Ramirez-Gomez, MD
MGH Neurology




Biomarkers & protective/risk factors for age-related cognitive decline & dementia


Cognitive markers



A. Giudicessi, MA




N. Schwab, PhD




J. Fox-Fuller, PhD


Tau biomarkers




S. Langella, PhD



J. Sanchez, BS
MGH Neurology




YT Quiroz, PhD




H. Jacobs, PhD
MGH Radiology


Stress



J. Martinez, MA



J. Gatchel, MD PhD



P. Vannini, PhD
MGH Neurology

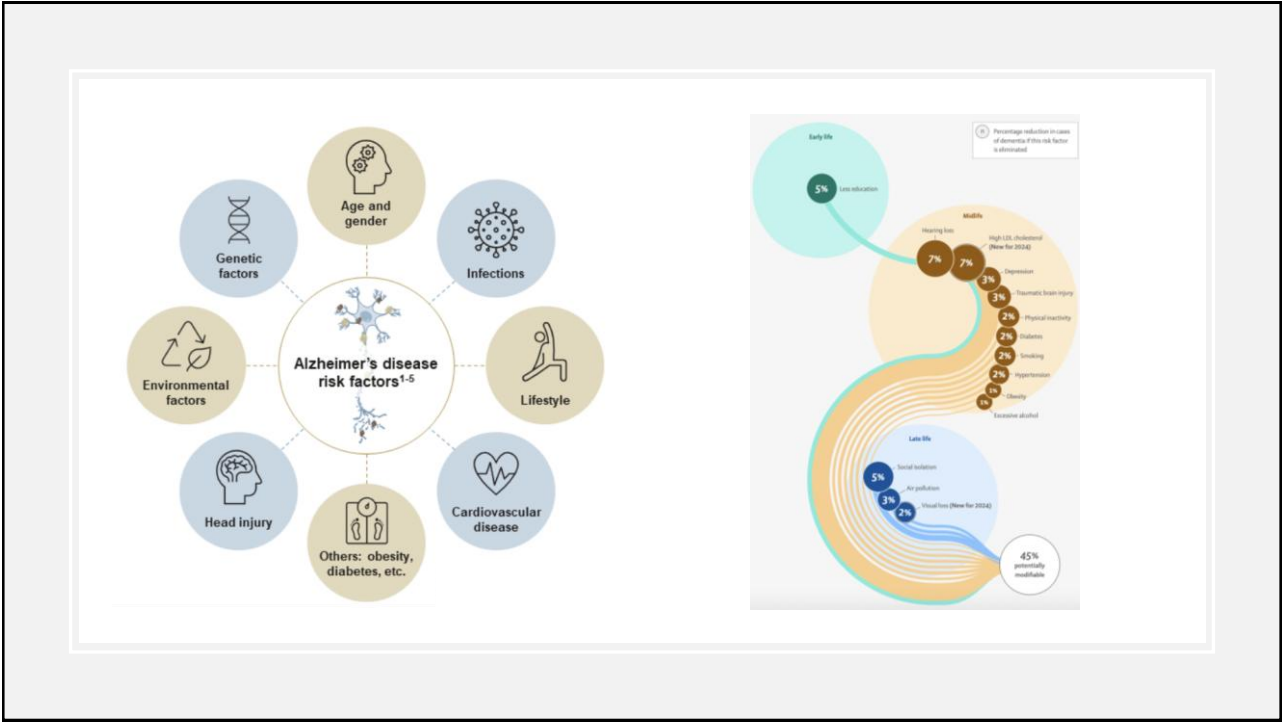
Cardiovascular factors

- Diabetes
- Hypertension
- Hypercholesterolemia
- Smoking
- Obesity

Other studies:

- Neuropsychiatric Symptoms
- Subjective cognitive decline
- Awareness of memory function
- Education
- Environmental toxins
- Comorbidities, etc.

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Global cardiovascular risk profile and cerebrovascular abnormalities in presymptomatic individuals with CADASIL or autosomal dominant Alzheimer's disease

Dorothee Schoemaker^{1,2}, Lina Velilla³, Yesica Zuluaga³, Ana Baena³, Carolina Ospina³, Yamile Bocanegra³, Sergio Alvarez⁴, Martín Ochoa-Escudero⁴, Edmarie Guzmán-Vélez¹, Jairo Martínez¹, Francisco Lopera², Joseph F. Arboleda-Velasquez², Yakeel T. Quiroz^{1,3,5}

CARDIOVASCULAR RISK FACTORS

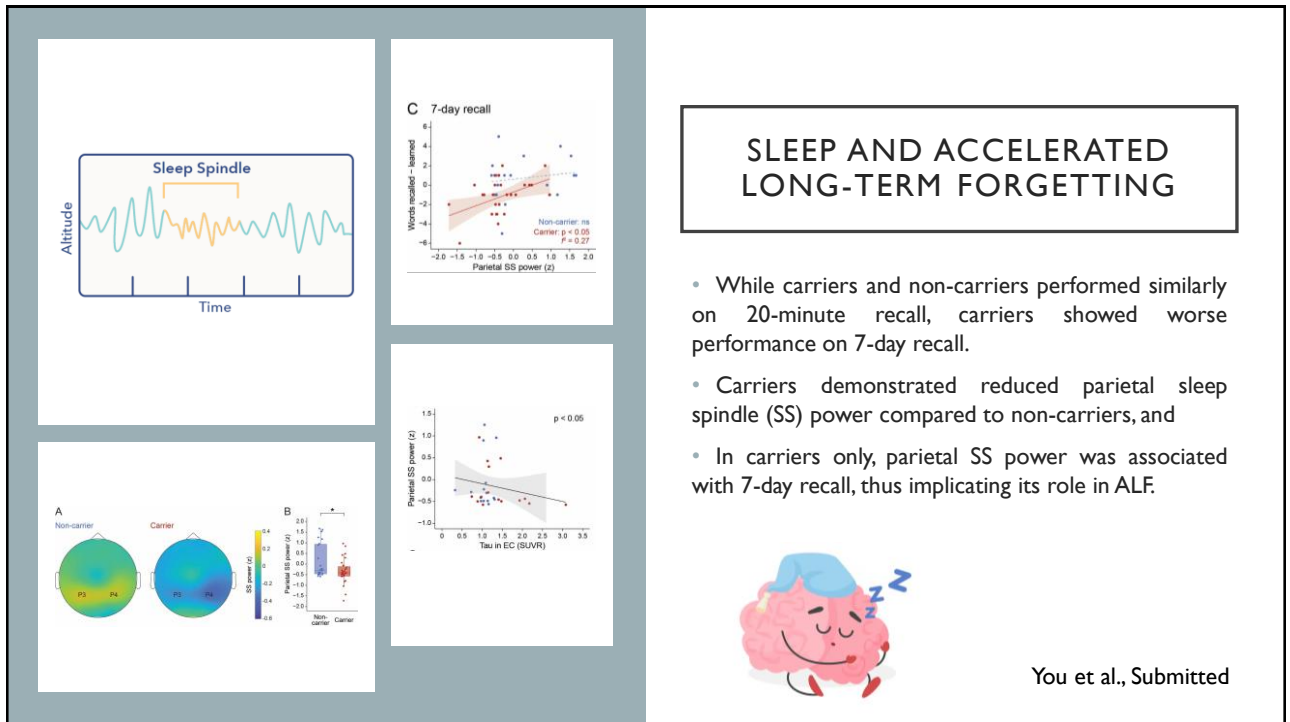
Global cardiovascular risk profile was estimated using the office-based Framingham Cardiovascular Risk Profile (FCRP) score

Age, sex, total cholesterol, HDL cholesterol, systolic blood pressure, smoking status, and diabetes status to estimate a person's 10-year risk of developing cardiovascular disease .

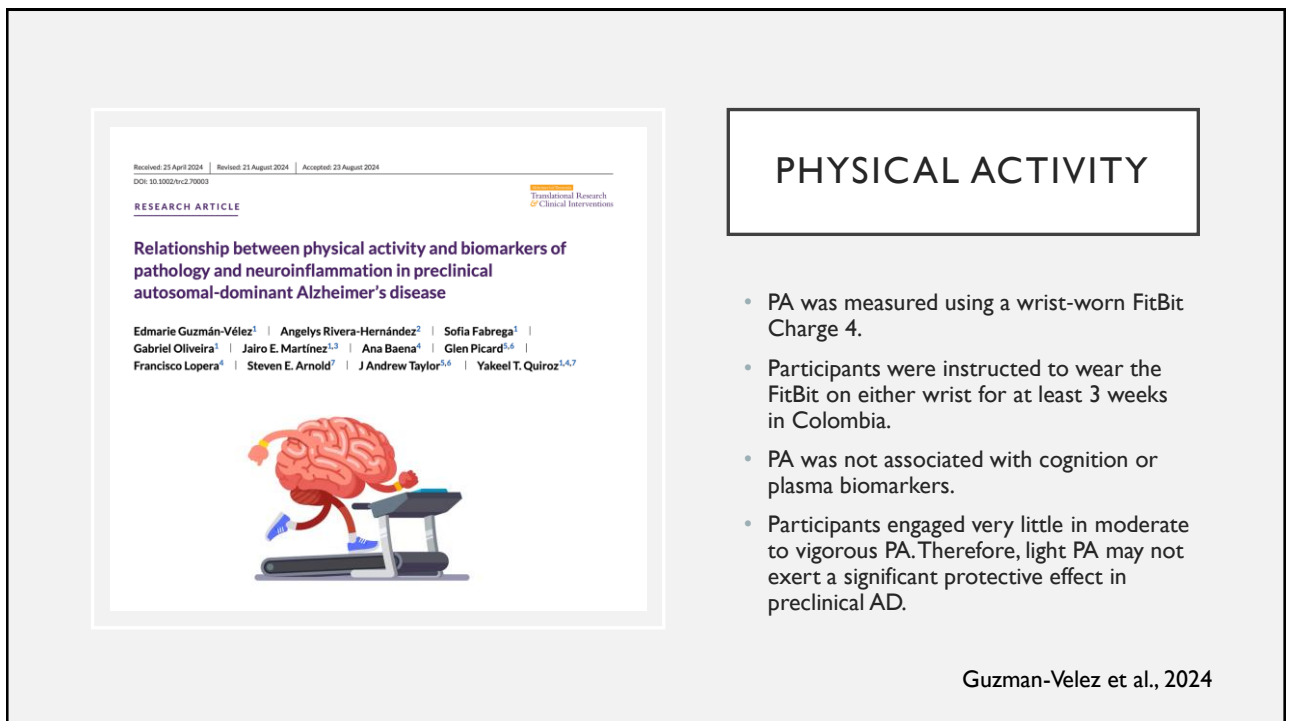
No significant associations between the FCRP score and neuroimaging measures were found in presymptomatic ADAD or non-carrier subjects.

Schoemaker et al., 2021

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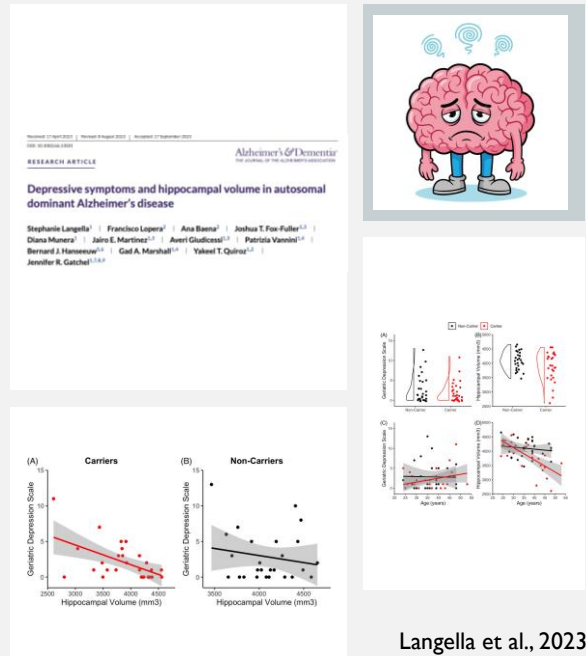


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DEPRESSION

Carriers and non-carriers did not differ in depressive symptoms or hippocampal volume.

Within carriers, lower hippocampal volume was associated with greater depressive symptoms. This relationship was not significant in non-carriers.

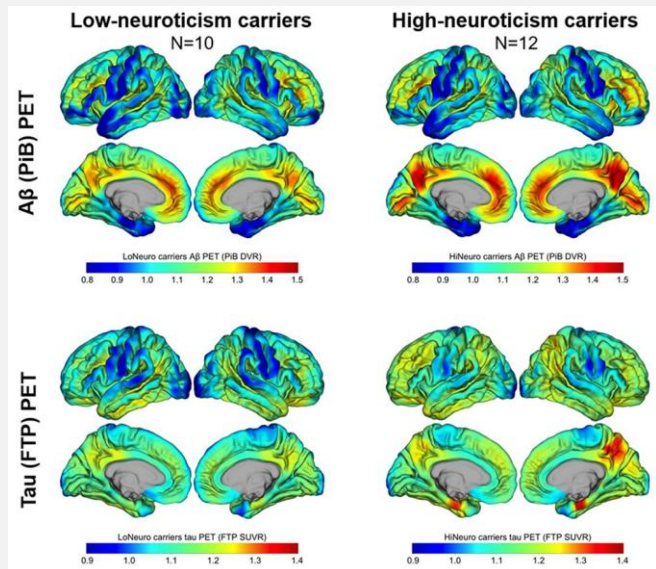


Langella et al., 2023

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NEUROTICISM

- Participants completed the NEO Five-Factor Personality Inventory.
- Carriers reported higher neuroticism relative to non-carriers.
- Neuroticism was positively correlated with entorhinal tau levels only in carriers, but not with amyloid levels.



Baena et al., 2021

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COPING STRATEGIES

Stress Coping Strategies Questionnaire (CAE)

Responses are scored on a 4-point scale (0 = Never, 1 = Rarely, 2 = Sometimes, 3 = Frequently, and 4 = Almost Always)

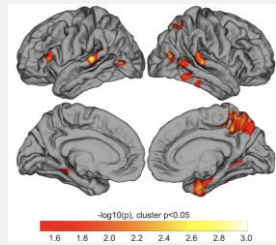
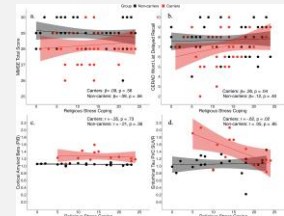
The religious coping items are as follows:

- 1) "I attended church,"
- 2) "I asked a religious person (priest, etc.) for spiritual help,"
- 3) "I went to church to pray/ask for the problem to be resolved,"
- 4) "I had faith that God would remedy the situation,"
- 5) "I prayed,"
- 6) "I went to church to place candles or pray."

Short Communications

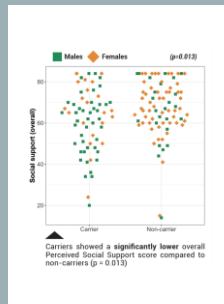
Religious stress coping is associated with lower entorhinal tau pathology and better memory performance in autosomal dominant Alzheimer's disease

Jairo E. Martinez ^{1,2}, Yamile Bocanegra ³, Ana Beana ³, Stephanie Langella ¹, Averi Giudicessi ^{1,2}, Justin S Sanchez ¹, David Aguillon ³, Alice Cronin-Golomb ², and Yakeel T Quiroz ^{1,2,3,4}



Martinez et al., 2025

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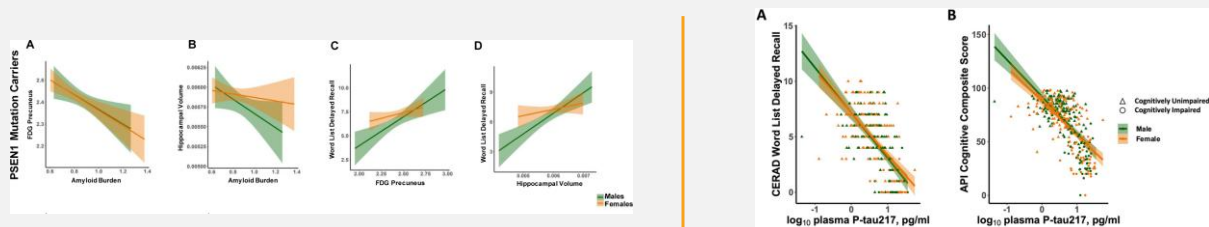
PERCEIVED SOCIAL SUPPORT

- Participants completed the Multidimensional Scale of Perceived Social Support (MSPSS).
- Carriers reported lower PSS—mainly from family and significant others—a difference that remained significant after adjusting for depressive symptoms.
- PSS was not statistically associated with cognition, age, or education.

Ospina Lopera et al., in preparation

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SEX EFFECT



- In PSEN1 carriers only, sex did not affect the relationship between amyloid burden and glucose metabolism or hippocampal volume.

Sex effect observed:

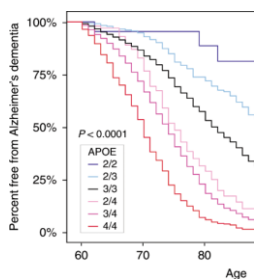
- At any given precuneus glucose metabolism level, females showed better delayed recall than males

- As plasma P-tau217 levels increase, cognitively unimpaired female carriers showed better cognitive performance than cognitively unimpaired male carriers.

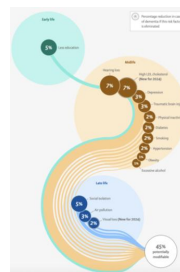
Vila-Castelar et al., 2022, 2023

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The e4 allele on the apolipoprotein (APOE) gene is the strongest genetic risk factor for sporadic AD, whereas the e2 allele is protective



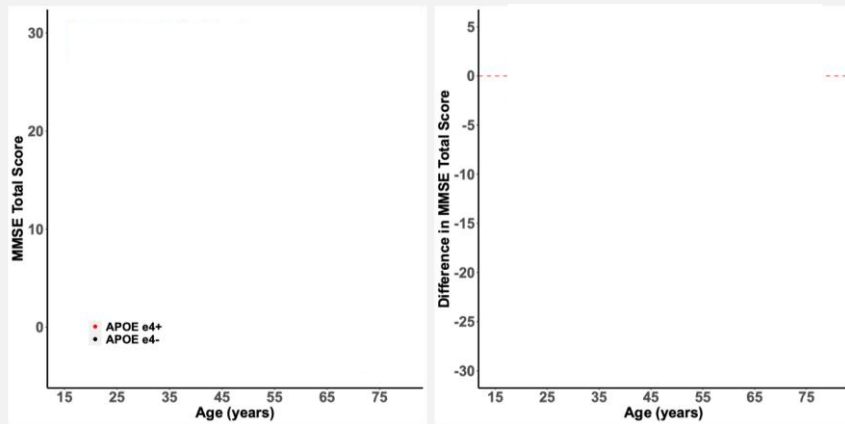
Higher educational attainment is associated with reduced risk for cognitive decline and later clinical onset



Langella et al., Nature Comms 2023

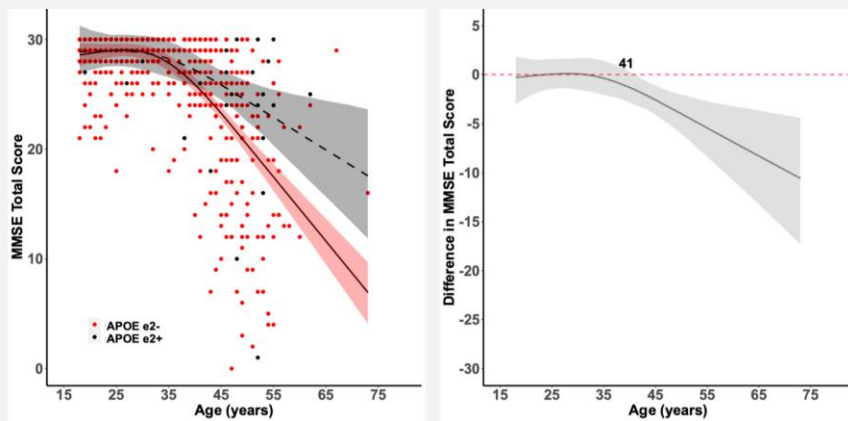
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APOE E4 is associated with accelerated onset of age-related cognitive decline in PSEN1 carriers



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APOE E2 is associated with delayed onset of age-related cognitive decline in PSEN1 carriers

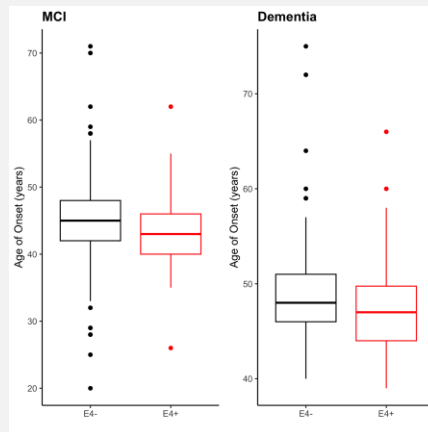


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APOE genotype influences age of clinical onset in *PSEN1* carriers

Average age of onset

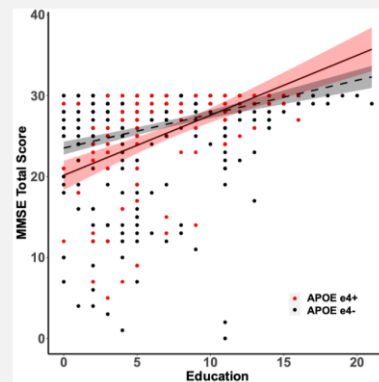
	APOE e4-	APOE e4+
MCI onset	45.09	43.20
Dementia onset	49.17	47.45



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Education is protective and moderates the effects of APOE genotype

Predictor	<i>PSEN1</i> E280A Carriers		<i>PSEN1</i> E280A Non-Carriers	
	β	p	β	p
APOE	-3.37	.001	-0.17	.66
Education	0.41	<.001	0.16	<.001
APOE x Education	0.32	.005	-0.003	.94



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Age-related cognitive decline may be accelerated in ADAD mutation carriers who are also APOE e4+ and delayed in those who are APOE e2+



Higher educational attainment has a protective effect against cognitive impairment, even in the presence of strong genetic risk factors



These results provide support for development of APOE-based treatments and early educational interventions to delay or prevent Alzheimer's disease dementia

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Resistance




Resilience



**COLBOS EXTREME
PROTECTION AGAINST DEMENTIA**

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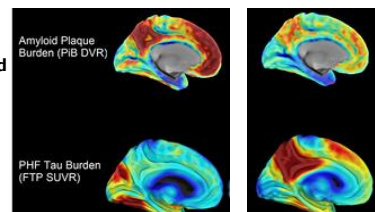


Ms. Aliria Piedrahita	
Genetics	Carrier for PSEN1 E280A mutation, which causes early-onset AD
MCI onset	Age 72
Clinical findings	Hyperlipoproteinemia Type 3

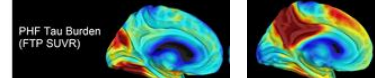
Brain Imaging

- High amyloid- β plaque burden
- Limited tau pathology
- Limited Neurodegeneration

Amyloid



Tau



Genetic analysis

- Homozygous for the rare *APOE3* Christchurch mutation

Arboleda-Velasquez.... Quiroz, *Nature Medicine* 2019

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WHAT WE KNOW ABOUT CHC

Reduced interaction with HSPGs:

- APOE3* Christchurch shows reduced binding to heparan sulfate proteoglycans (HSPGs), limiting tau accumulation in AD-affected regions like the medial temporal lobe (Arboleda-Velasquez et al., 2019). This may help modulate pathways that drive neurodegeneration.

iPSC-based/ Mice studies (Nelson et al., 2023)

- Neurons derived from human/mouse iPSCs carrying *APOE4* and *APOE4ChC* reveal protective effects of Christchurch
- Homozygous *APOE4ChC*:** Protected against tau pathology, neurodegeneration, and neuroinflammation.
- Heterozygous *APOE4ChC*:** Partial protection—reduced neurodegeneration and neuroinflammation, but not tau pathology.

7C11 antibody (Marino et al. 2024):

- Targets the R136 heparin-binding domain of ApoE3.
- Reduced tau phosphorylation in *APOE4* knock-in mice.
- Decreased tau pathology in MAPTP301S mice

Mouse model findings:

- APOE3ChC* mice show reduced amyloid pathology, amyloid-induced tauopathy, and tau-driven neurodegeneration (Chen et al., 2024)
- Improved microglial response.
- APOE3ChC* decreased tau load and protected against tau-induced synaptic loss, myelin loss, and reduction in hippocampal theta and gamma power (Naguib et al. 2025)

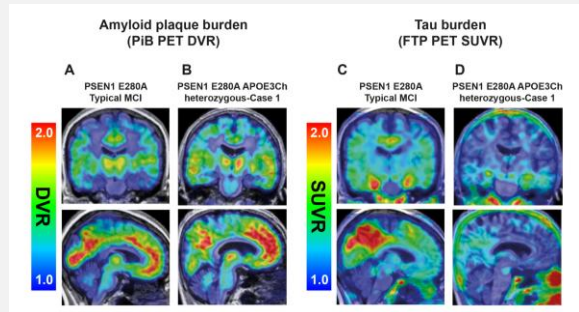
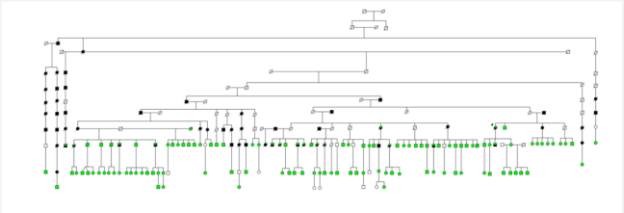
See review: Marino et al, *Lancet Neurology* 2025

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IS APOE3 A PROTECTIVE GENETIC MUTATION IN HETEROZYGOTES?

- We identified 121 family members with the APOE3Ch variant, including 27 carriers who also had the PSEN1-E280A variant.
- APOE3Ch carriers had a 5-year delay in the onset of mild cognitive impairment (MCI) with a median onset of 52 years.
- An APOE3Ch + PSEN1 E280A carrier at the age of 51 years: despite high Aβ plaque burden, had limited tau burden in brain regions affected in AD.



Quiroz, Aguillon, Vasquez, Aguirre-Acevedo et al, NEJM 2024

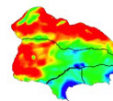
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Male subject

Genetics	Carrier for PSEN1 E280A mutation, which causes early-onset AD <i>Sister developed MCI at age 58, died at age 73</i>		
MCI onset	70 years	AD onset	72 years
Clinical findings	Healthy except for hypertension		

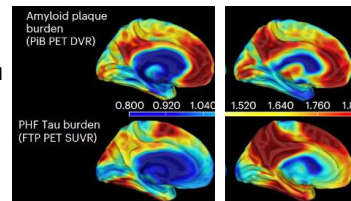
Brain Imaging

- High amyloid-β plaque burden
- Tau tangles in some brain regions
- Very limited Tau pathology in the entorhinal cortex, in contrast to controls



Case #2

Control



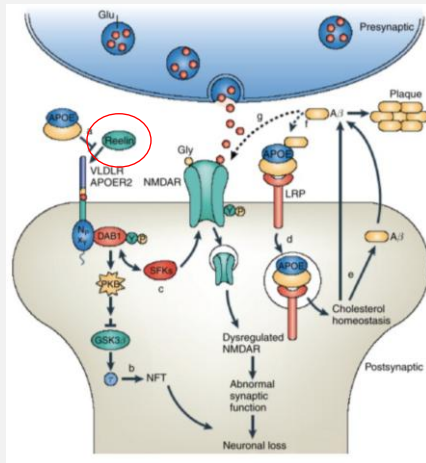
Genetic analysis

- Mutation in Reelin gene (Reelin-COLBOS)

Lopera...Quiroz, Nature Medicine 2023

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REELIN-COLBOS MUTATION LEADS TO GAIN OF FUNCTION IN REELIN

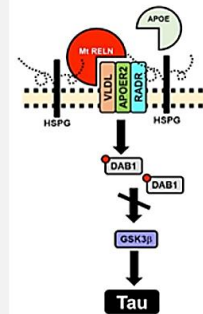


Lopera, Marino et al, Nature Medicine 2023

- Reelin is a ligand that competitively binds to the same receptors as ApoE
- **Reelin signaling has been implicated in AD**
- The Reelin-COLBOS mutation is located near HSPG-binding areas of Reelin

Reelin-COLBOS leads to greater phosphorylation and greater activity in one of its binding partners (Dab1), which in turn reduces Tau phosphorylation

Reelin Gain-of-function



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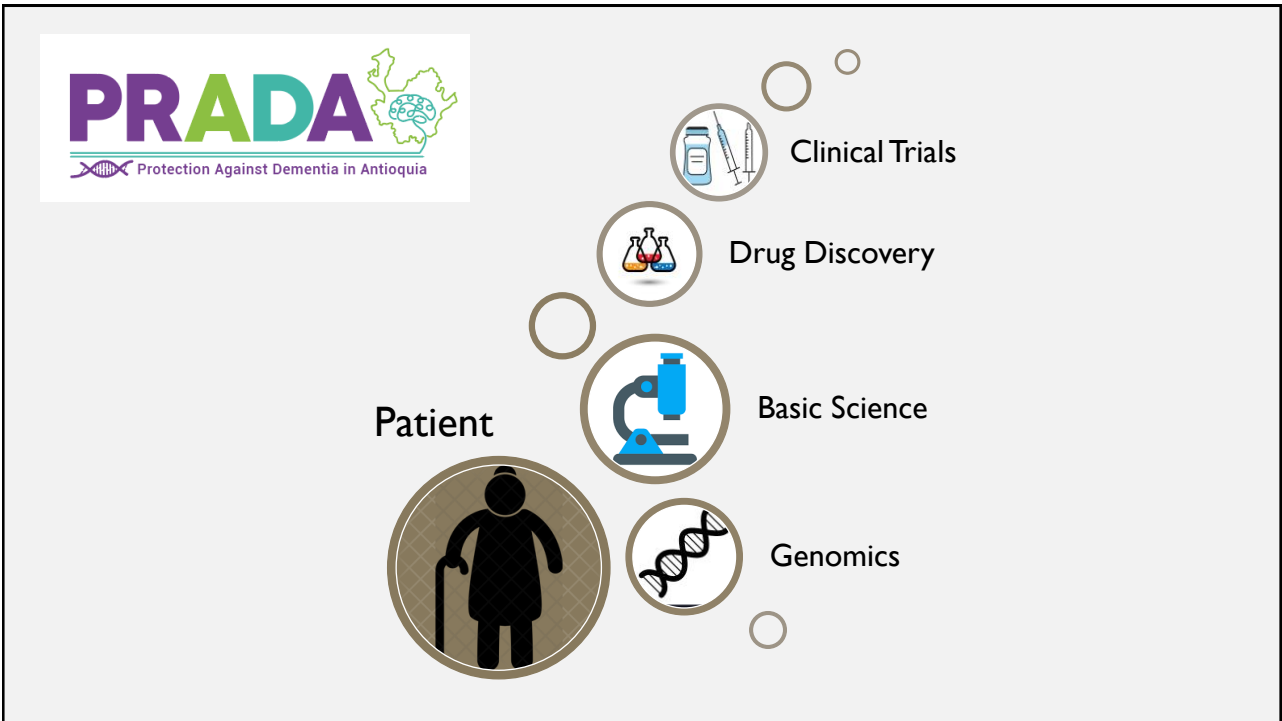
OVERALL CONCLUSIONS

- Families with autosomal dominant mutations provide a unique opportunity to study disease risk and progression (from preclinical to clinical stages), develop/improve measures for early detection, and identify novel therapeutic targets and conduct clinical trials.
- Future longitudinal studies of these populations are needed to further characterize the biomarker and cognitive trajectory of specific genetic mutations.
- There is more to learn from *escapees* of autosomal dominant mutations - those who remain unimpaired at older ages.

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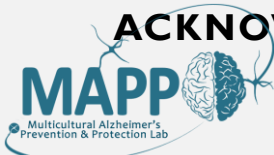
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- Research from the US shows that older Latino individuals are disproportionately more likely to have Alzheimer's disease and related dementias (ADRD) than non- Latino individuals.
- BLAST seeks to investigate the impact of various AD risk and protective factors on cognition, brain function and molecular markers of AD pathology in individuals older than 55yo.



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PSENI
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