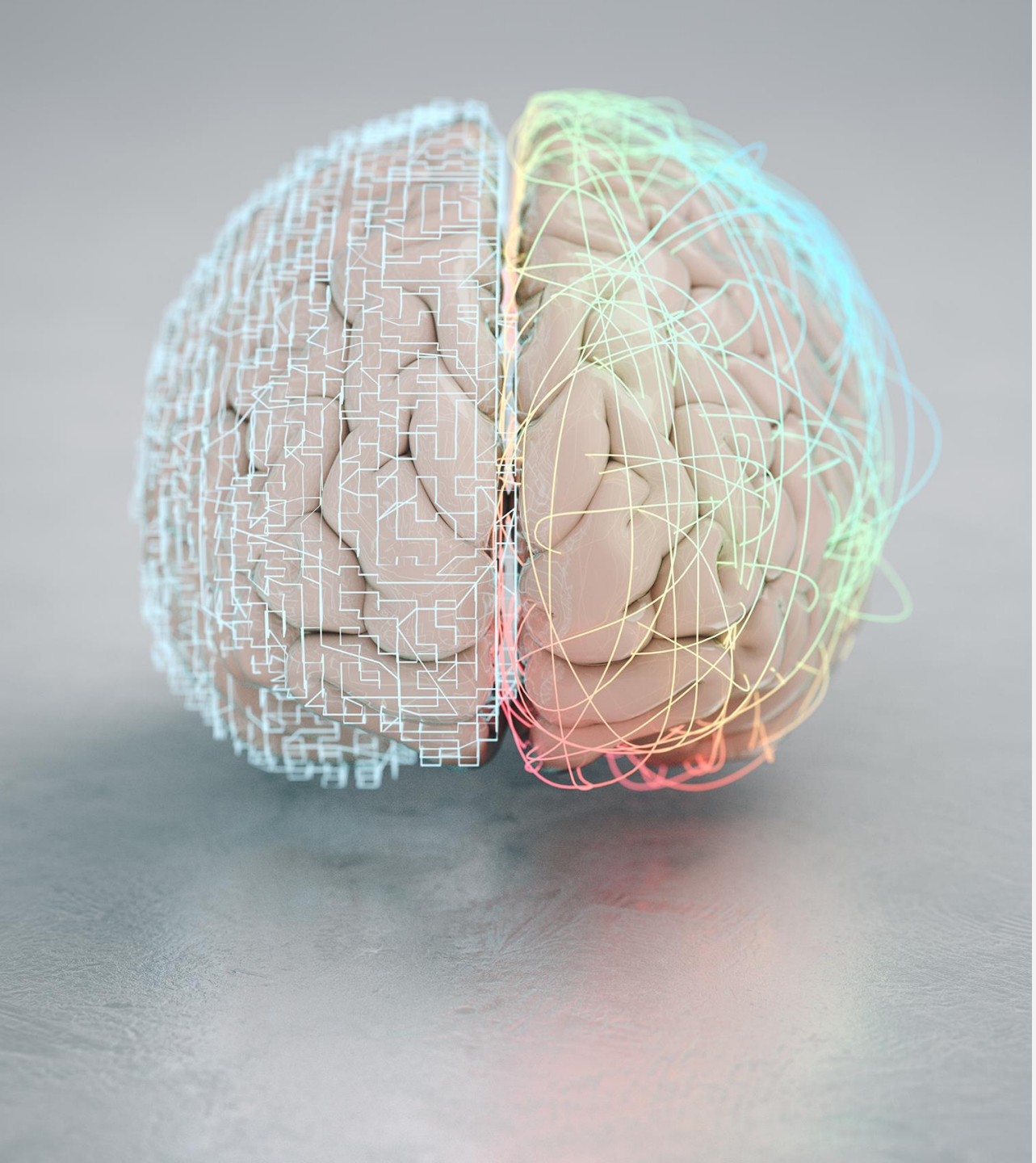


NATURE, NURTURE AND NEURODEGENERATION:

RISK AND PROTECTION IN AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE

Yakeel T. Quiroz, PhD
Professor
Psychological & Brain Sciences, Neuroscience
Boston University

Neuroimaging Researcher
Massachusetts General Hospital

October 24, 2025

FRANCISCO LOPERA, MD

Friend, Mentor and Collaborador

1951-2024

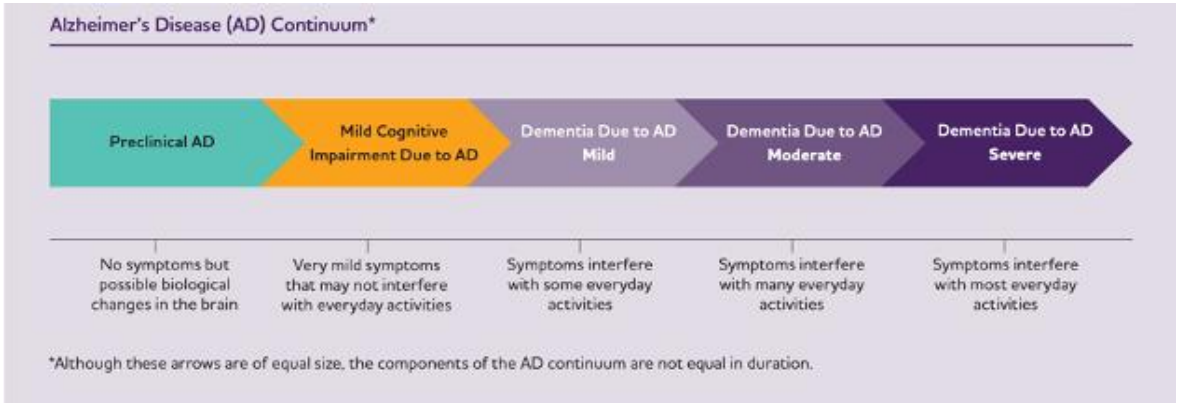
"La enfermedad y la cura para el Alzhéimer están en la naturaleza... La cura está en imitar a la naturaleza"

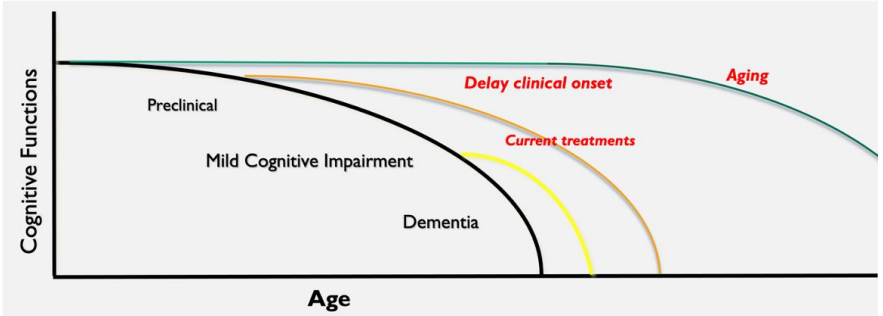
DISCLOSURES

Dr. Quiroz has served as consultant for Biogen

OUTLINE

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


Alzheimer's Disease (AD) Continuum*
Preclinical AD
Mild Cognitive Impairment Due to AD
Dementia Due to AD Mild
Dementia Due to AD Moderate
Dementia Due to AD Severe
No symptoms but possible biological changes in the brain
Very mild symptoms that may not interfere with everyday activities
Symptoms interfere with some everyday activities
Symptoms interfere with many everyday activities
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
Preclinical
Mild Cognitive Impairment
Dementia
Delay clinical onset
Aging
Current treatments
Age

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

EARLY DETECTION OF AD-RELATED CHANGES

A 30+YEAR JOURNEY…

Clinical Trials

Neuroimaging/ Biomarkers

Genetic characterization

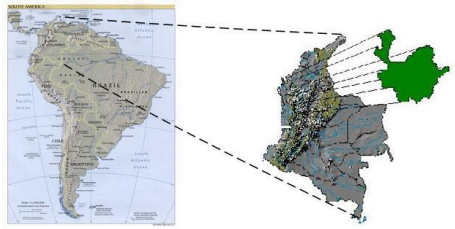
Clinical assessments

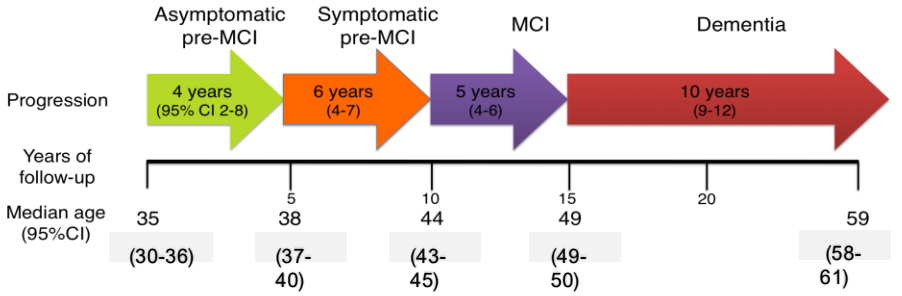
- Alzheimer's disease
- Frontotemporal
- Huntington
- CADASIL

Families from Antioquia

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

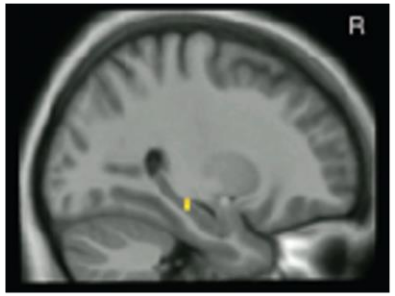
What are the earliest biological and physiological changes associated with the predisposition to Alzheimer's disease?

Colombia-Boston (COLBOS)

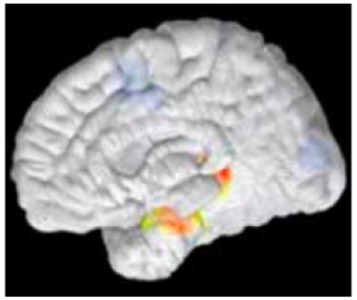
Biomarker study of autosomal dominant Alzheimer's disease

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

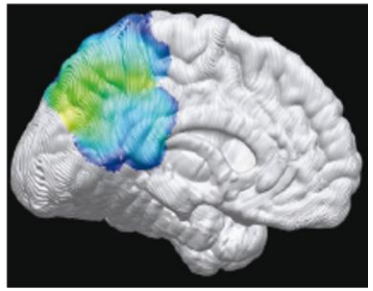
Hippocampal hyperactivation, and less deactivation of parietal regions



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

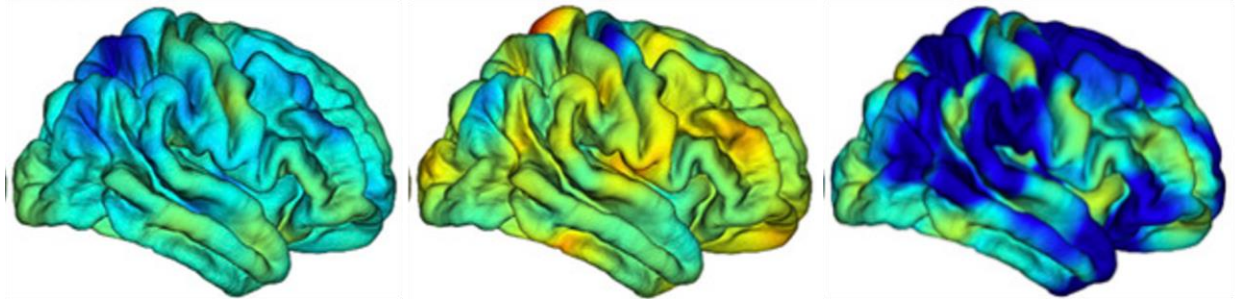


Carriers (18-25yo)
Reiman* et al. (2012)



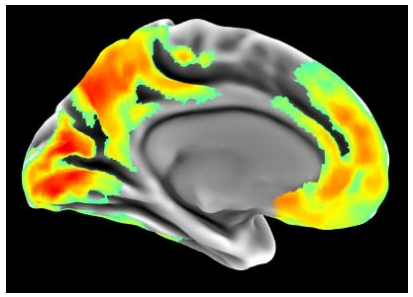
Children/Adolescents (9-18yo)
Quiroz et al., (2015)

Cortical thinning

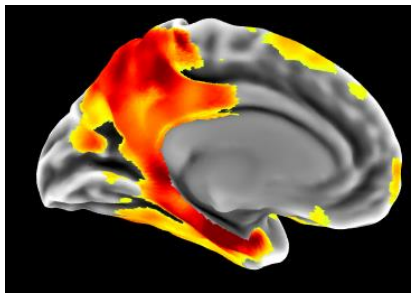


Two cut-points
at ~17 and 32 yrs of age
Quiroz et al. (2013)
Fox-Fuller et al (2021)

- 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.



Aβ pathology



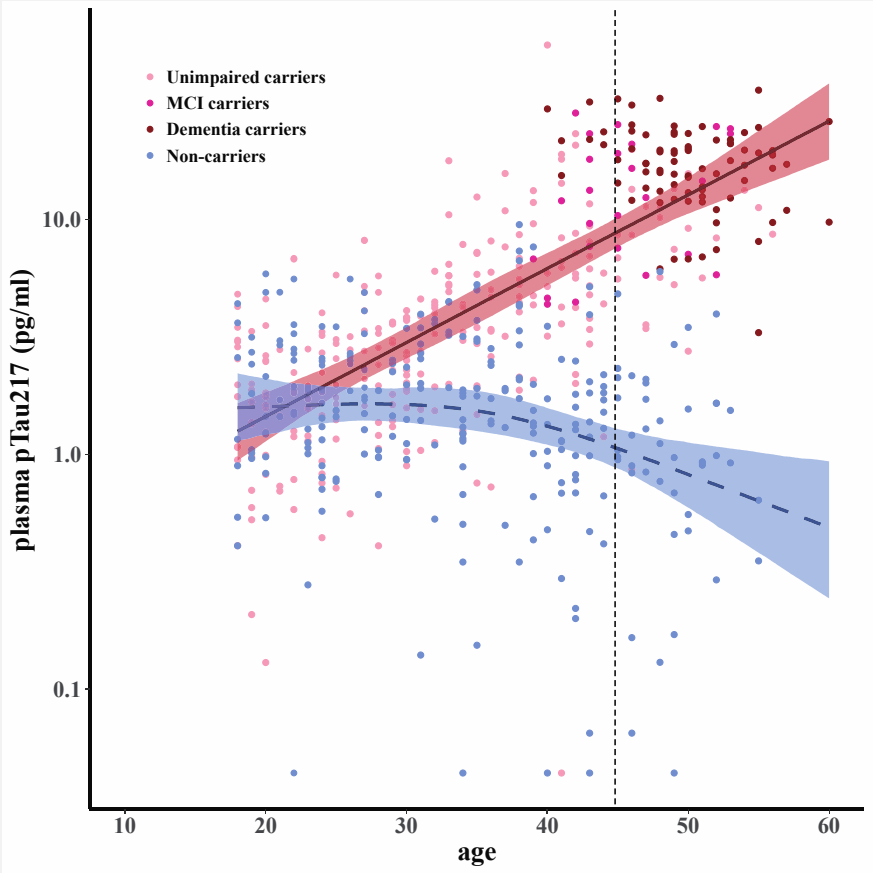
Tau pathology

Older Carriers (>28yo)

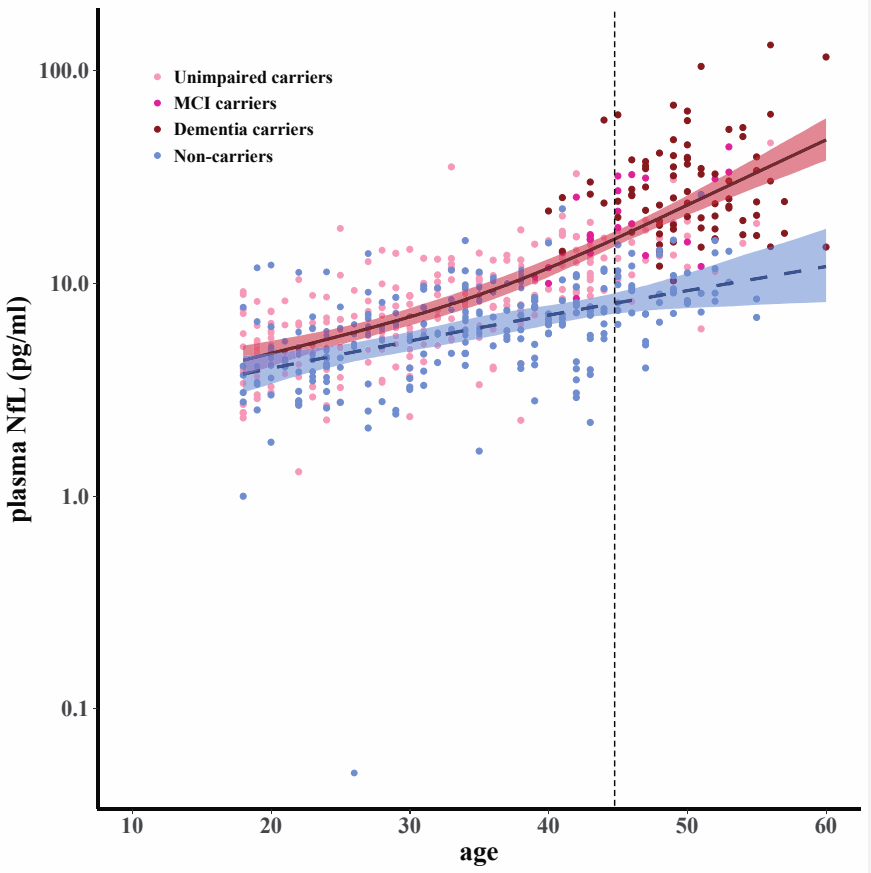
Quiroz et al. (2018)
Sanchez et al. (2021)

PLASMA BIOMARKERS

A. Plasma P-tau217 by age



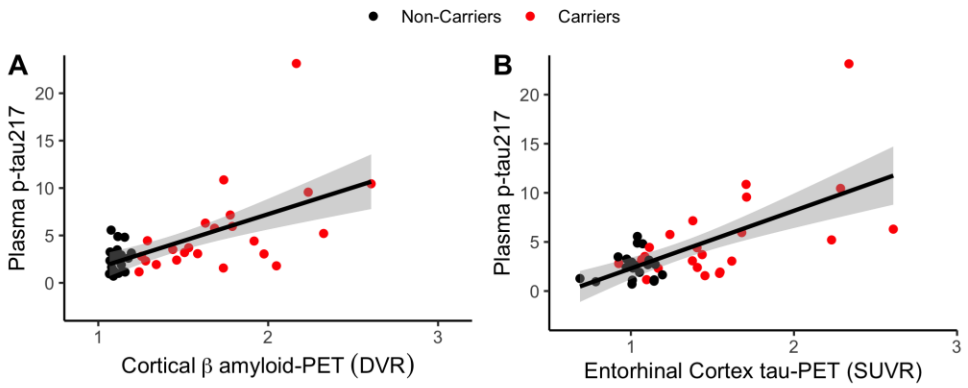
B. Plasma Neurofilament light by age



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

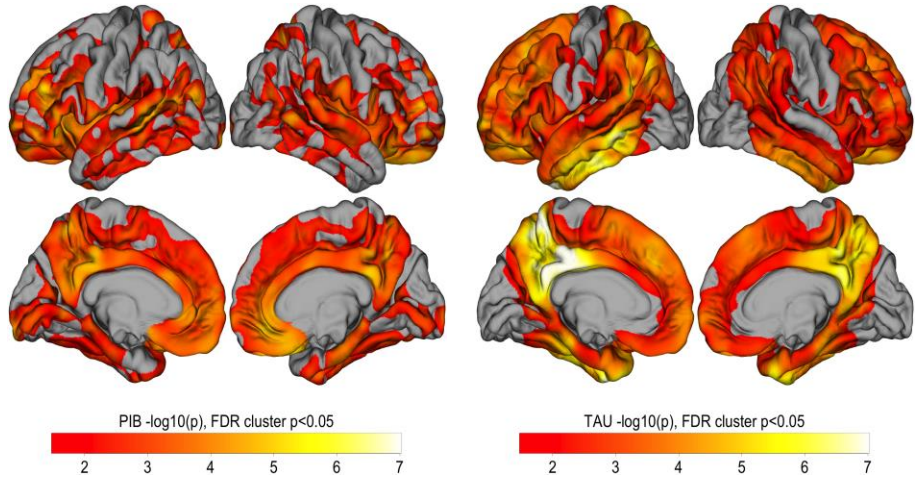
CAN PLASMA P-TAU217 PREDICT SUBSEQUENT LEVELS OF TAU PET PATHOLOGY AND COGNITIVE PERFORMANCE?

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



p-tau 217 vs. Amyloid-β PET

p-tau 217 vs. Tau PET



Aguillon, Langella…. Quiroz, 2022

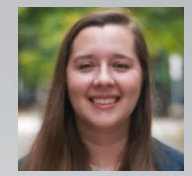
Eye biomarkers

J Miller, MD
Mass Eye and Ear

Genetic factors

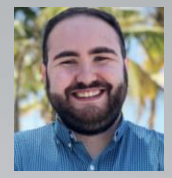
J Arboleda-Velasquez, MD PhD
Mass Eye and Ear

Cognitive markers



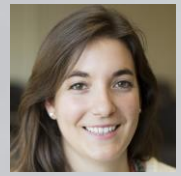
A Giudicessi, MA

N Schwab, PhD



J Fox-Fuller, PhD

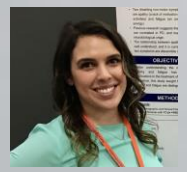
Sex differences



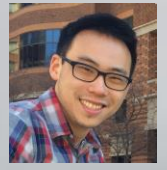
C Vila-Castelar, PhD

Sleep

A. Lam, MD
MGH Neurology

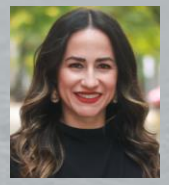


C Pluim, PhD



J. You, MD
MGH Neurology

Physical activity



E Guzman-Velez, PhD

Odor biomarkers

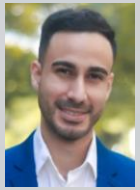
L Ramirez-Gomez, MD
MGH Neurology

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

Cardiovascular factors

Diabetes
Hypertension
Hypercholesterolemia
Smoking
Obesity

Stress



J Martinez, MA

Tau biomarkers

S Langella, PhD

J Sanchez, BS
MGH Neurology

YT Quiroz, PhD

H Jacobs, PhD
MGH Radiology

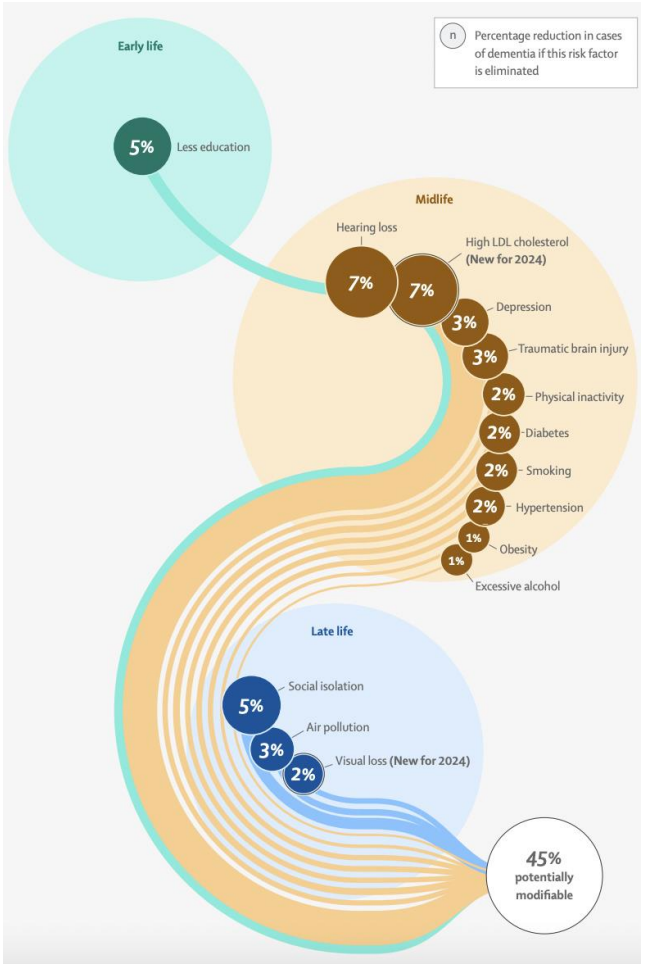
Other studies:

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

J Gatchel, MD PhD

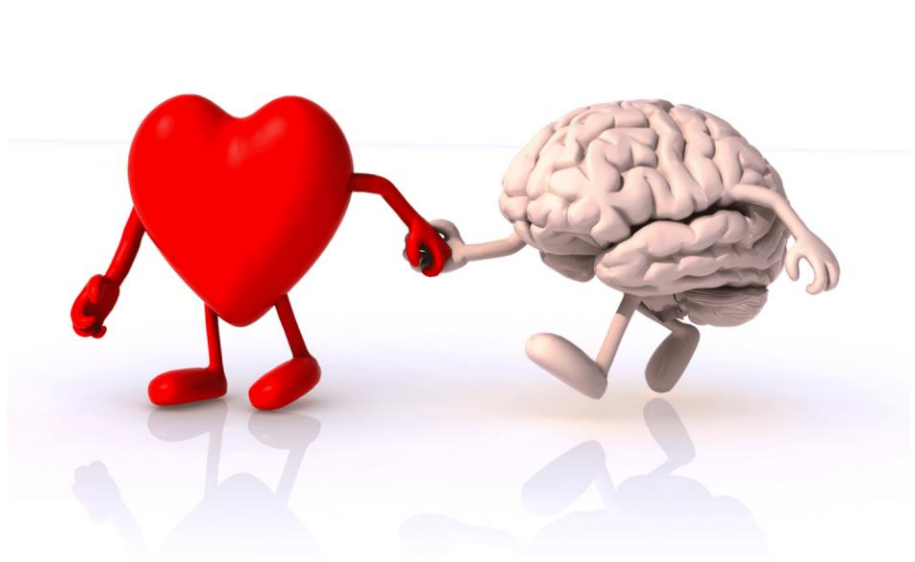
P Vannini, PhD
MGH Neurology


14 Risk Factors
Obesity
Diabetes
High blood pressure
Smoking
Excessive alcohol
Physical inactivity
High LDL cholesterol
Less education
Social isolation
Depression
Hearing loss
Untreated vision loss
Air pollution
Head injury


n
Percentage reduction in cases of dementia if this risk factor is eliminated
Early life
5%
Less education
Midlife
Hearing loss
7%
High LDL cholesterol (New for 2024)
7%
3%
Depression
3%
Traumatic brain injury
2%
Physical inactivity
2%
Diabetes
2%
Smoking
2%
Hypertension
1%
Obesity
1%
Excessive alcohol
Late life
5%
Social isolation
3%
Air pollution
2%
Visual loss (New for 2024)
45%
potentially modifiable

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

Dorothee Schoemaker[1,2], Lina Velilla[3], Yesica Zuluaga[3], Ana Baena[3], Carolina Ospina[3], Yamile Bocanegra[3], Sergio Alvarez[4], Martin Ochoa-Escudero[4], Edmarie Guzmán-Vélez[1], Jairo Martinez[1], Francisco Lopera[2], Joseph F. Arboleda-Velasquez[2], 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

Received: 25 April 2024 | Revised: 21 August 2024 | Accepted: 23 August 2024

DOI: 10.1002/trc2.70003

Alzheimer's & Dementia
Translational Research & Clinical Interventions

RESEARCH ARTICLE

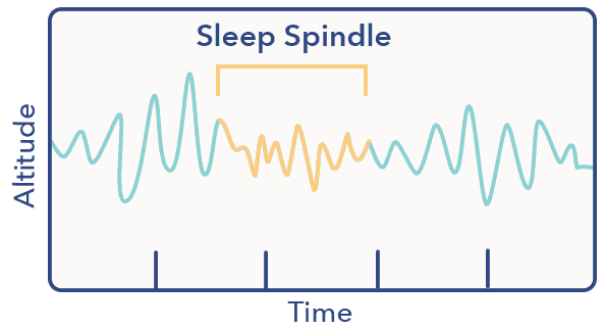
Relationship between physical activity and biomarkers of pathology and neuroinflammation in preclinical autosomal-dominant Alzheimer's disease

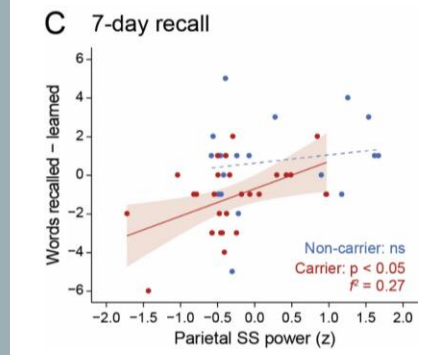
Edmarie Guzmán-Vélez[1] | Angelys Rivera-Hernández[2] | Sofia Fabrega[1] | Gabriel Oliveira[1] | Jairo E. Martínez[1,3] | Ana Baena[4] | Glen Picard[5,6] | Francisco Lopera[4] | Steven E. Arnold[7] | J Andrew Taylor[5,6] | Yakeel T. Quiroz[1,4,7]

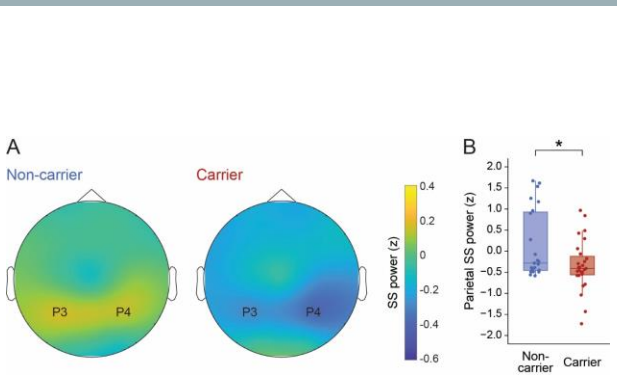
PHYSICAL ACTIVITY

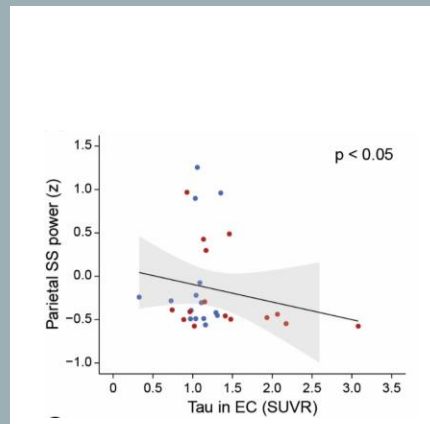
- PA was measured using a wrist-worn FitBit Charge 4.
- Participants were instructed to wear the FitBit on either wrist for at least 3 weeks in Colombia.
- PA was not associated with cognition or plasma biomarkers.
- Participants engaged very little in moderate to vigorous PA. Therefore, light PA may not exert a significant protective effect in preclinical AD.

Guzman-Velez et al., 2024



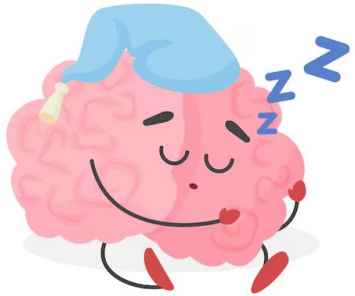






SLEEP AND ACCELERATED LONG-TERM FORGETTING

- While carriers and non-carriers performed similarly on 20-minute recall, carriers showed worse performance on 7-day recall.
- Carriers demonstrated reduced parietal sleep spindle (SS) power compared to non-carriers.
- **In carriers only, parietal SS power was associated with 7-day recall, thus implicating its role in ALF.**

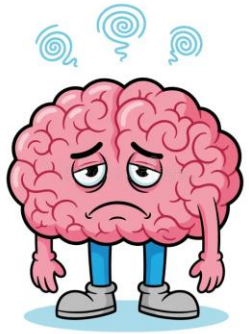


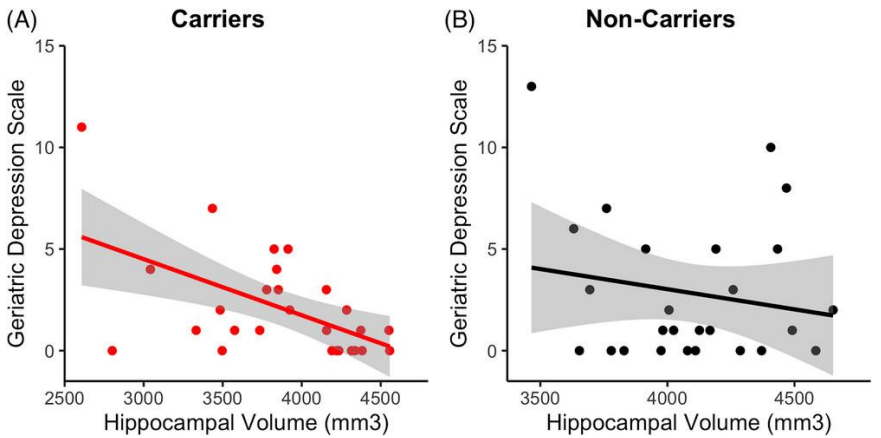
You et al., Under Review

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.





Alzheimer's & Dementia
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION
RESEARCH ARTICLE

Depressive symptoms and hippocampal volume in autosomal dominant Alzheimer's disease

Stephanie Langella[1] | Francisco Lopera[2] | Ana Baena[2] | Joshua T. Fox-Fuller[1,3] | Diana Munera[1] | Jairo E. Martinez[1,3] | Averi Giudicessi[1,3] | Patrizia Vannini[1,4] | Bernard J. Hanseeuw[5,6] | Gad A. Marshall[1,4] | Yakeel T. Quiroz[1,2] | Jennifer R. Gatchel[1,7,8,9]

Langella et al., 2023

STRESS COPING STRATEGIES

Short Communications

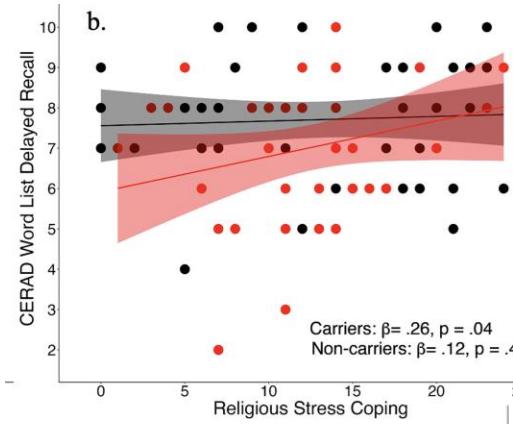
Religious stress coping is associated with lower entorhinal tau pathology and better memory performance in autosomal dominant Alzheimer's disease

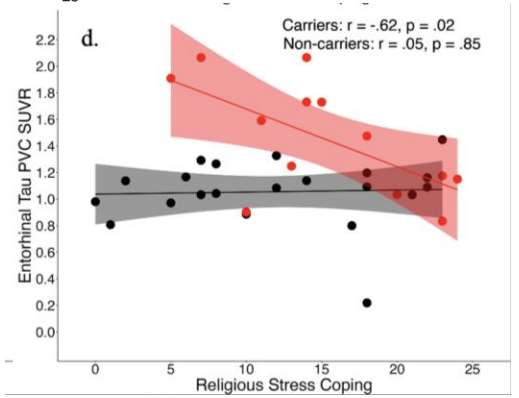
Jairo E Martinez [1,2], Yamile Bocanegra [3], Ana Baena [3], Stephanie Langella [1], Averi Giudicessi [1,2], Justin S Sanchez [1], David Aguillon [3], Alice Cronin-Golomb [2], and Yakeel T Quiroz [1,2,3,4]

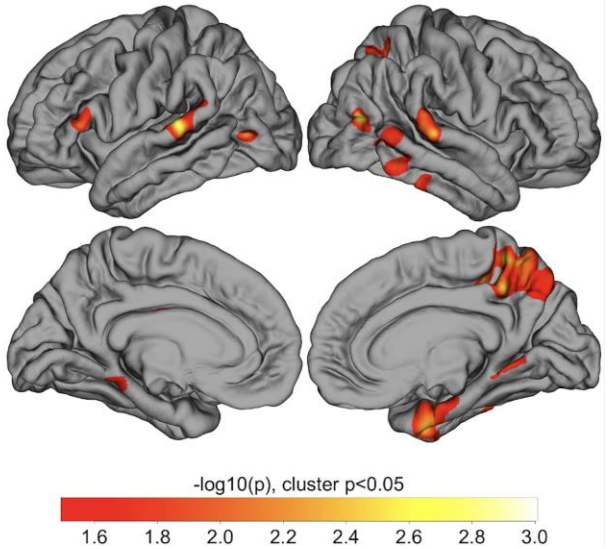
Stress Coping Strategies Questionnaire (CAE)

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," and 6) "I went to church to place candles or pray."

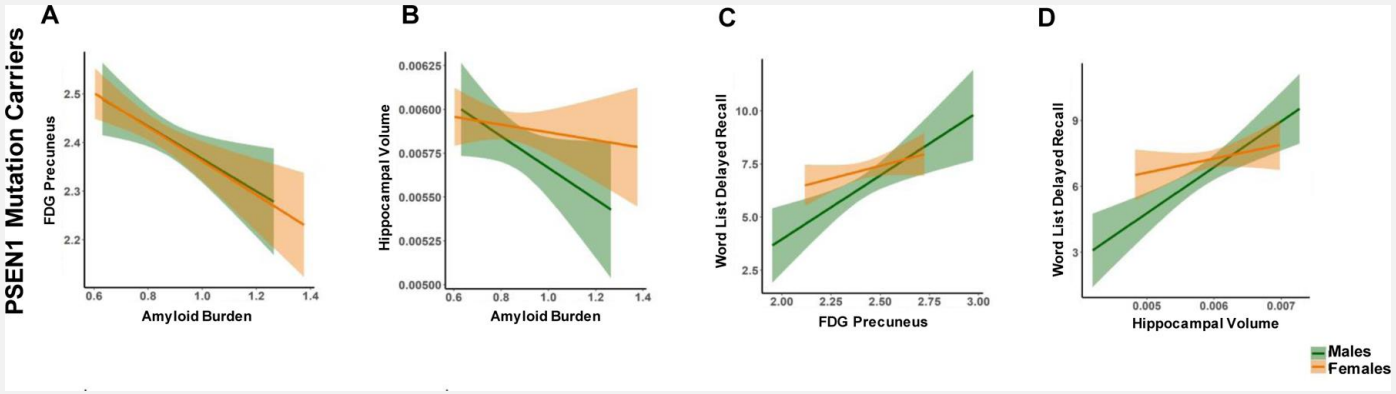


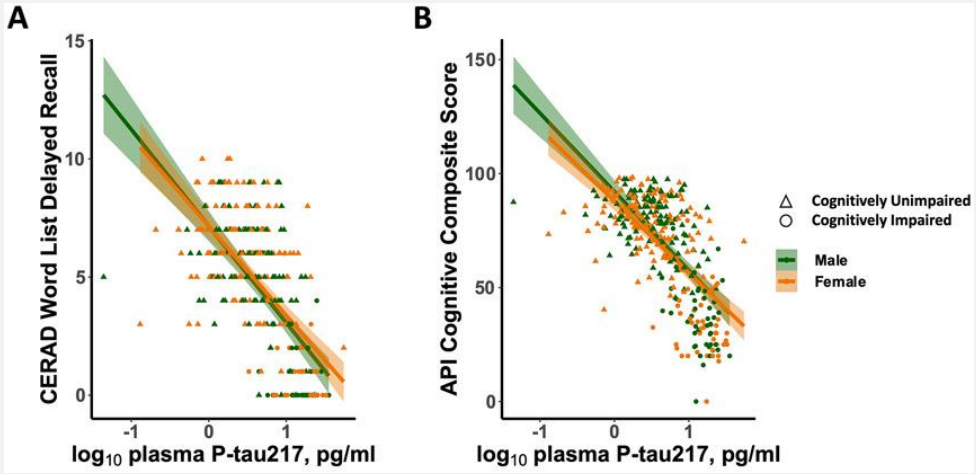




Martinez et al., 2025

SEX EFFECT





- Sex did not affect the relationship between amyloid burden and glucose metabolism or hippocampal volume.

Sex effect observed:

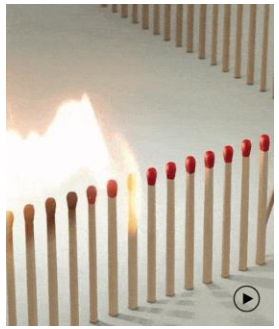
- At any given precuneus glucose metabolism level, females showed better delayed recall than males

- 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

Resistance

Resilience



COLBOS EXTREME

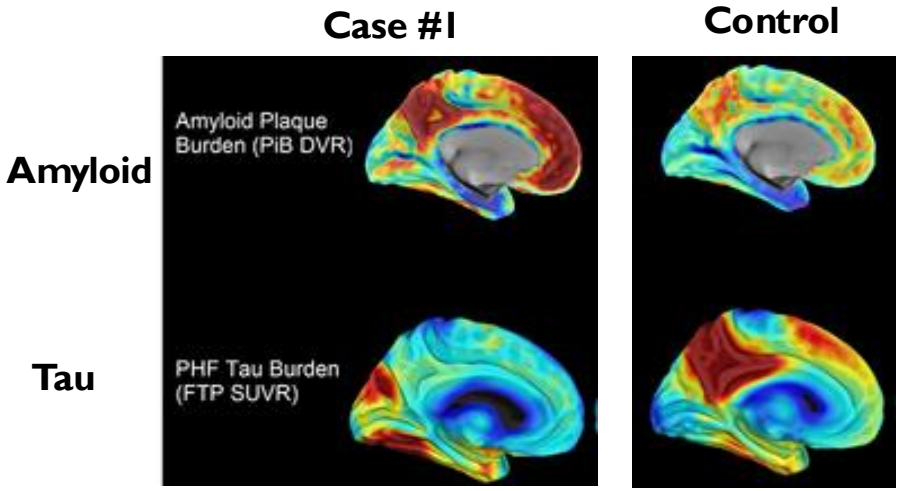
PROTECTION AGAINST DEMENTIA

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



Genetic analysis

- Homozygous for the rare *APOE3* Christchurch mutation

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

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

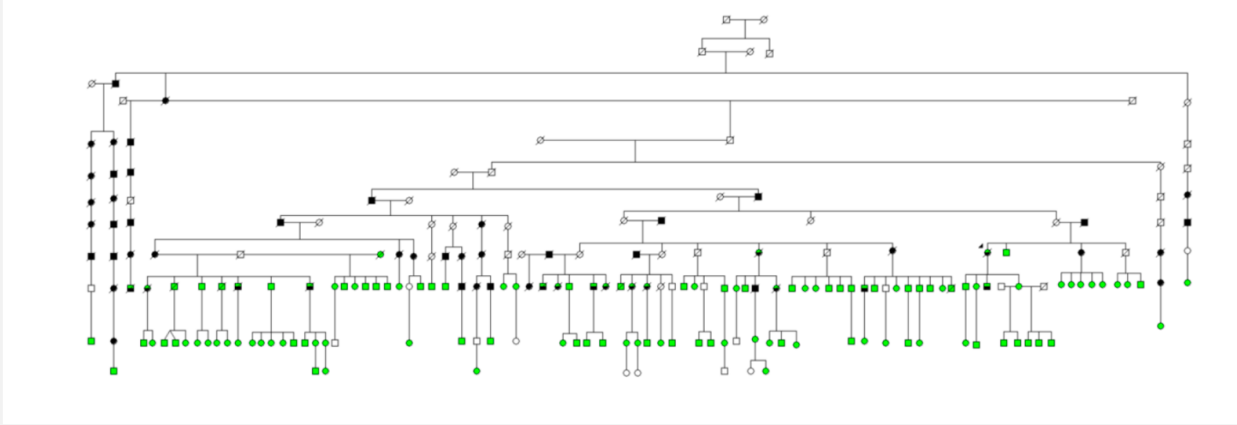
Mouse model findings:

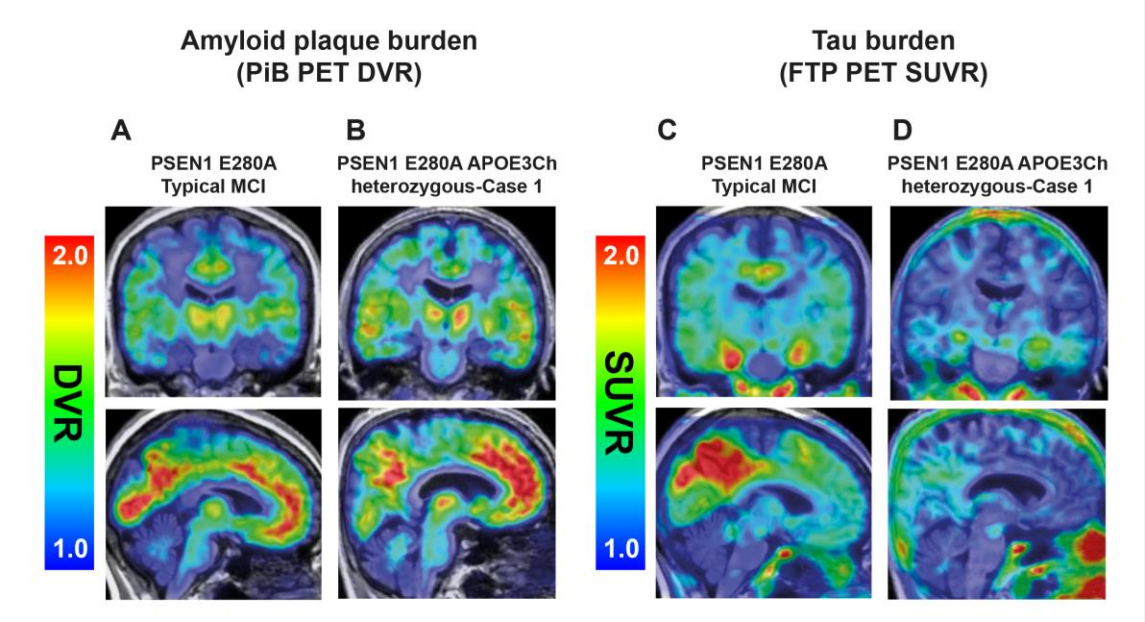
- *APOE3ChC* mice show reduced amyloid pathology, amyloid-induced tauopathy, and tau-driven neurodegeneration (Chen et al., 2024)
- Improved microglial response.
- *APOE3ChC* decreased tau load and protected against tau-induced synaptic loss, myelin loss, and reduction in hippocampal theta and gamma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

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

IS APOECH A PROTECTIVE GENETIC MUTATION IN HETEROZYGOTES?

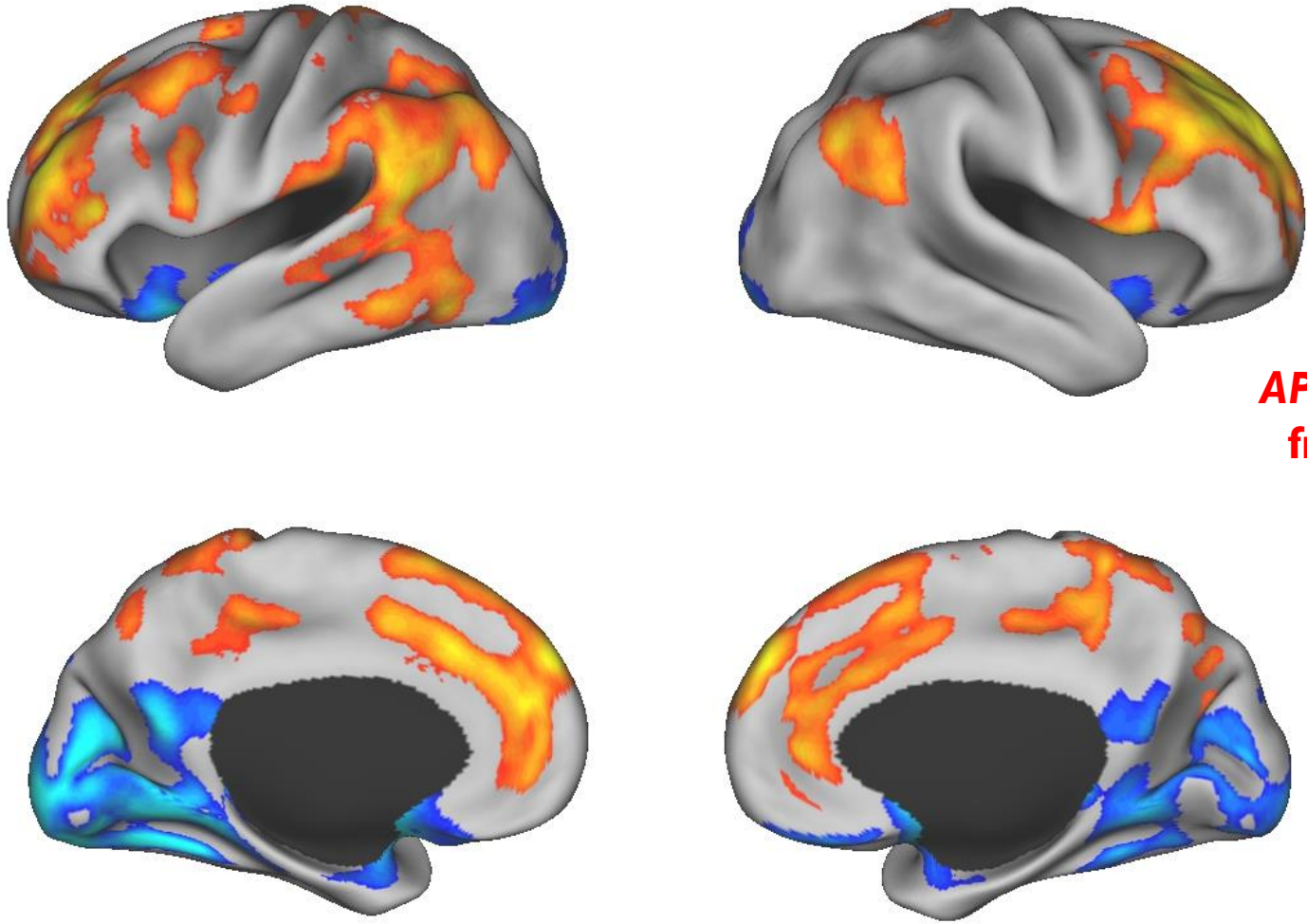
- We identified 121 family members with the APOE3Ch variant, including 27 carriers who also had the PSEN1-E280A variant.
- APOE3Ch carriers had approximately 5-year delay in the onset of mild cognitive impairment (MCI).
- An APOE3Ch + PSEN1 E280A carrier at the age of 51 years: despite high Aβ plaque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





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

CORTICAL THICKNESS IN HETEROZYGOUS APOE3CHC CARRIERS VERSUS NON-CARRIERS



***APOE3ChC* carriers have greater CT in frontoparietal and temporal regions**

Thinner posterior regions

OVERALL CONCLUSIONS

- Families with autosomal dominant mutations offer a unique opportunity to study disease progression, refine early detection, and identify targets for therapy development and trials.
- APOE3ChC may delay age-related cognitive impairment, likely through reduced tau pathology and lower neuroinflammation—pointing to a promising pathway for resilience-based therapies.
- 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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Thank you!!

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