Subjective Cognitive Decline PIA:
A Year in Review

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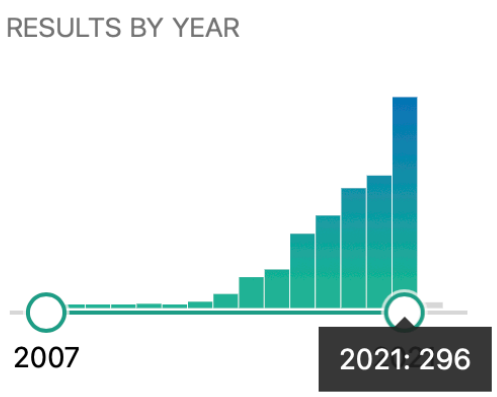
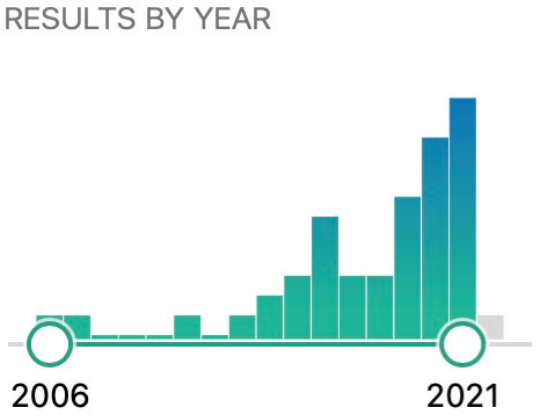
alzheimer's association®

Disclosures: None

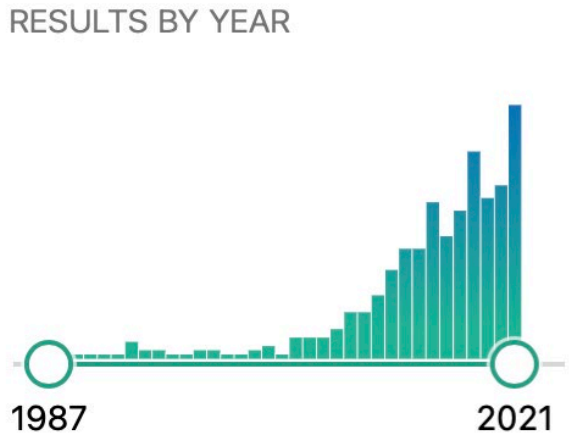
Caveats:



“Subjective cognitive decline”



“Subjective cognitive concerns”



“Subjective cognitive impairment”

Photos and screenshots encouraged!

What is subjective cognitive decline?

- **Self-experienced, persistent decline** in cognitive capacity compared with previously normal cognitive status
  - Unrelated to an acute event

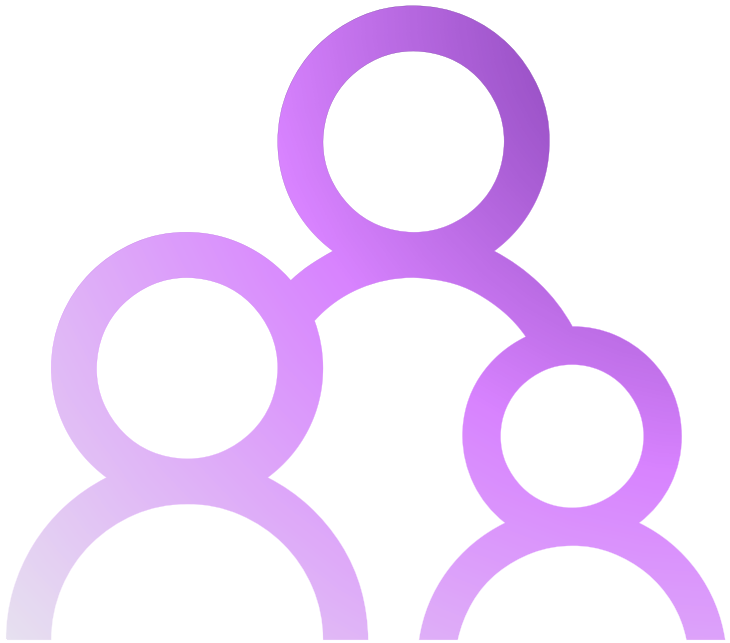
- **Normal performance on standardized cognitive tests** when adjusted for age, sex, and education

- Related terms: subjective cognitive concerns, subjective cognitive impairment

(Jessen et al., *Lancet Neurology*, 2020)

Main Themes in SCD Research - 2021

- Diversity and Inclusion
- Cognition
- Neuroimaging
- Biofluids
- Interventions



Diversity and Inclusion

American Psychological Association

Diversity and Inclusion: Framework and Language Guidelines

https://www.apa.org/about/apa/equity-diversity-inclusion

Inclusive Language in Writing

- General Terms Related to Equity and Power
- Person-First and Identity-First Language
- Identity-Related Terms
  - Age
  - Disability Status
  - Race, Ethnicity, and Culture
  - Sexual Orientation and Gender Diversity
  - Socioeconomic Status

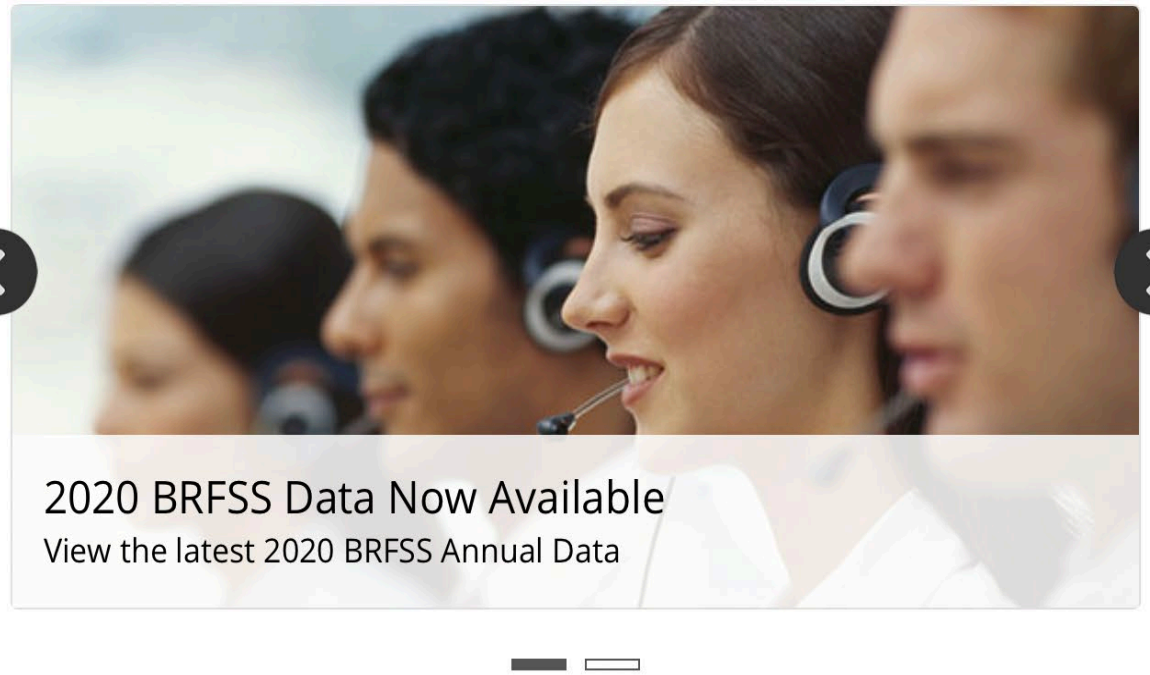
Avoiding Microaggressions in Language

- Culturally Appropriative and Pejorative Language
- Violent Language
- Language That Doesn't Say What We Mean

CDC Behavioral Risk Factor Surveillance System

Module 6: Cognitive Decline:

- E.g., During the past 12mo, have you experienced confusion or memory loss that is happening more often or getting worse?



BRFSS™

The Behavioral Risk Factor Surveillance System (BRFSS) is the nation's premier system of health-related telephone surveys that collect state data about U.S. residents regarding their health-related risk behaviors, chronic health conditions, and use of preventive services. Established in 1984 with 15 states, BRFSS now collects data in all 50 states as well as the District of Columbia and three U.S. territories. BRFSS completes more than 400,000 adult interviews each year, making it the largest continuously conducted health survey system in the world. See More.

www.cdc.gov/brfss

Race/Ethnicity

Sangeeta Gupta, *BMC Public Health*

Delaware State University

- Examination of racial/ethnic disparities in SCD, 2015-2018
- Black, Hispanic participants with SCD more likely to be **younger, less educated, low income, without access to healthcare, living alone, and with functional limitations** vs. White participants
  - Only half discussed cognitive decline with a health care professional

Uyanga Ganbat & Yan Yan Wu, *Asia-Pacific J of Pub Health*

University of Hawai‘i

- SCD **more prevalent in Native Hawaiian/Other Pacific Islanders** vs. Asian and White participants
- **Greater SCD-related functional difficulties** in NHOPI

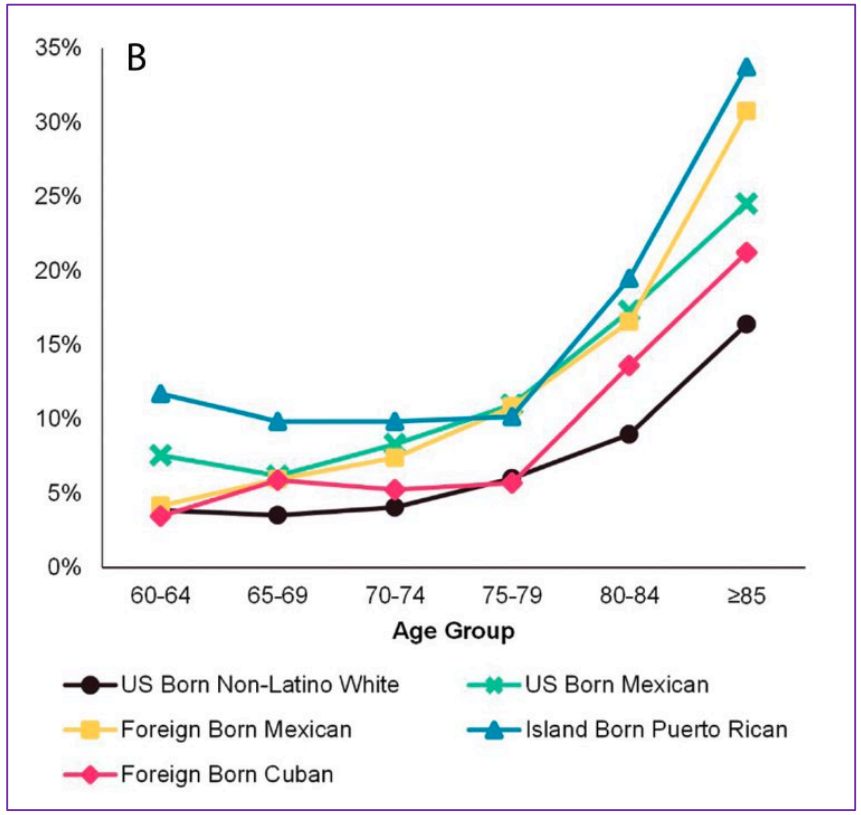
Complementary Readings

Brown & Patterson, *Aging Ment Health*

Zlatar et al., *Alz and Dementia*

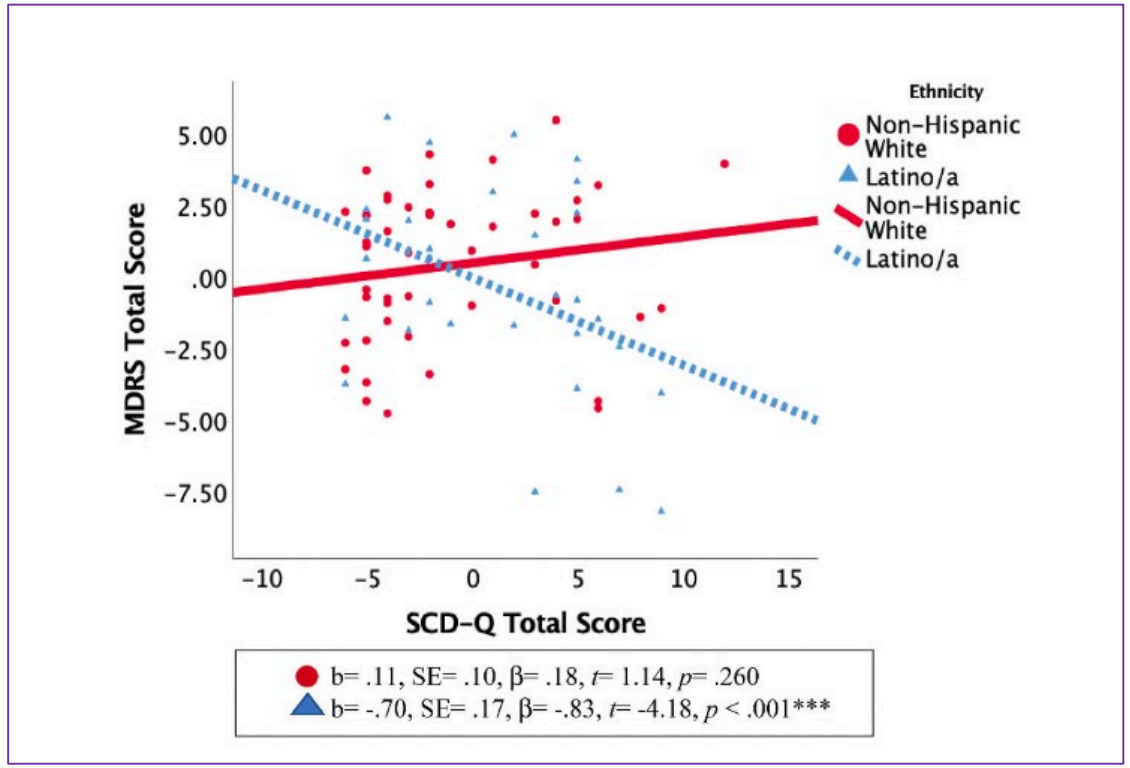
Piña-Escudero et al., *Arch Geront & Geriatr*

Ethnicity



Marc Garcia, et al., *Innov in Aging*
Syracuse University

- Higher rates of self-reported cog. impairment **among all disaggregated Latino subgroups** vs. US-born Whites



Marina Nakhla et al., *J Clin Exp Neuropsych*
SDSU/UCSD Joint Doctoral Program

- **Ethnicity as a moderator of SCD, global cognition**
- SCD associated with worse global cognition in Latinos/as, not NH/White group

Sexual Orientation and Gender

Variable	Sexual and gender minority adults (weighted n = 1,882,629)			Heterosexual, cisgender adults (weighted n = 57,855,821)			
	Unweighted N	% (95% CI)	RSE	Unweighted N	% (95% CI)	RSE	*P*
SCD	507	15.7 (13.1–18.2)	8.30%	11,724	10.5 (10.1–10.9)	1.84%	< .0001
Functional limitations due to SCD	213	60.8 (52.2–69.3)	7.20%	4039	47.8 (45.9–49.7)	2.03%	.0048

Abbreviations: Abbreviations: BRFSS, Behavioral Risk Factor Surveillance System; CI, confidence interval; RSE, relative standard error; SCD, subjective cognitive decline; SGM, sexual and gender minority.

Jason Flatt, et al., *Alz & Dementia: Transl Res & Clin Int*

University of Nevada

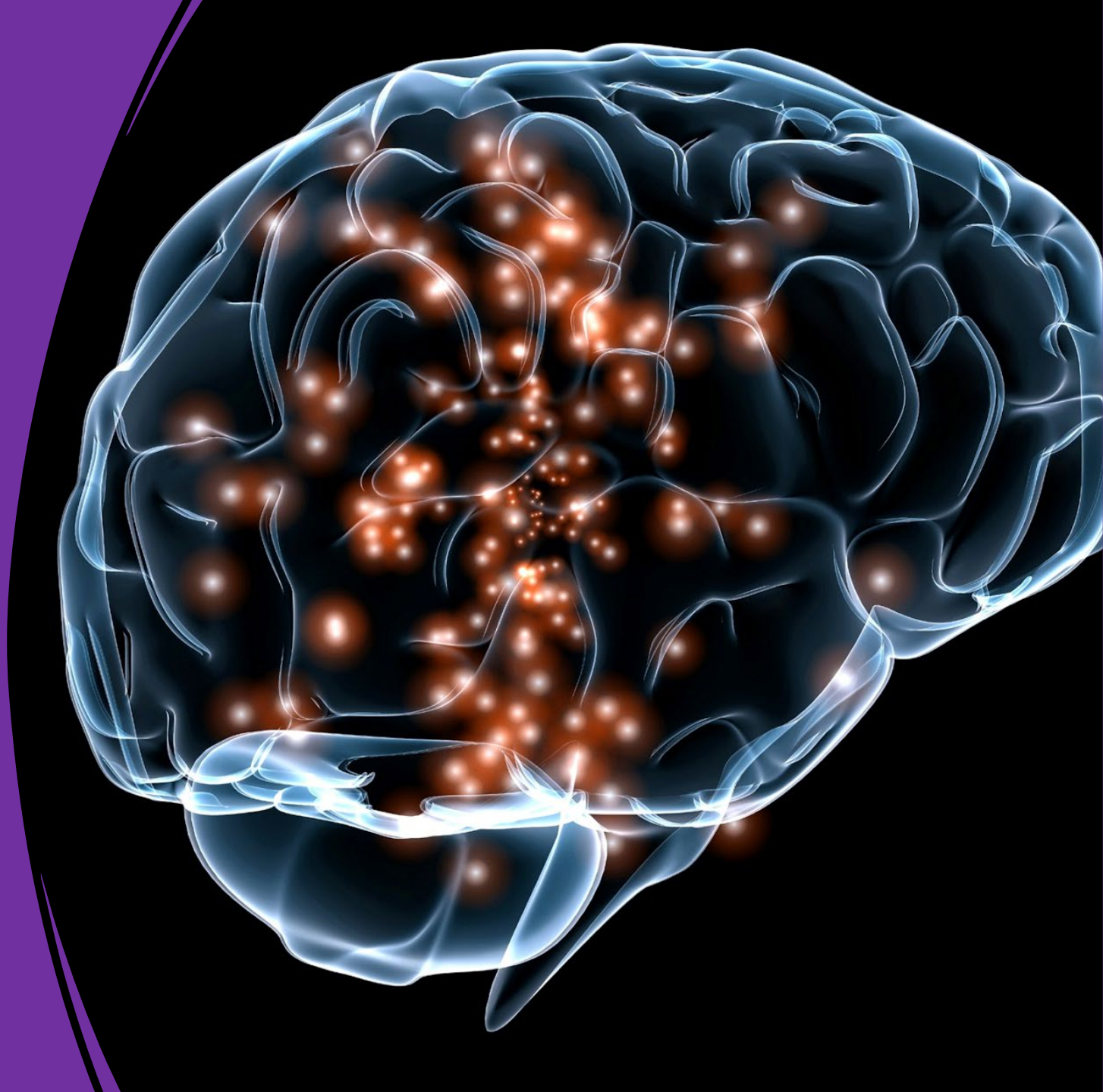
Diversity and Inclusion in SCD: *Take Home Points*

- **Elevated rates of SCD** seen in racial, ethnic, and sexual/gender minority groups

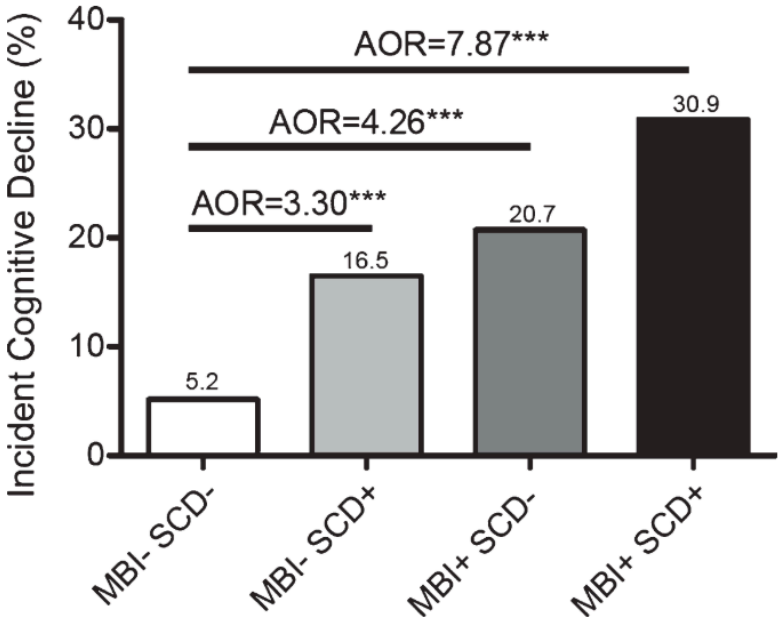
- Research suggests there are **greater SCD- related functional challenges**, **different relationships between SCD and cognitive performance** in these groups

- Despite greater SCD and functional challenges, minority groups have **equal or lower rates of discussing SCD with healthcare providers**

Cognition



Cognition and Mood/Behavior



Zahinoor Ismail et al., *JAD*

University of Calgary

Cumming School of Medicine

- **Mild behavioral impairment + SCD** associated with **greatest risk of cognitive decline**

Nikki Hill et al., *JAD*

Pennsylvania State University

- Depressive symptoms **partially mediated** relationship between SCD and longitudinal cognitive performance

Complementary Readings

Jenkins et al., *JAD*

Ahn et al., *J Nurs Scholarship*

Sabatini et al., *Aging, Neuropsy, and Cog*

Schwilk et al., *Int J Geri Psychiatr*

Eikelboom et al., *Neurology*

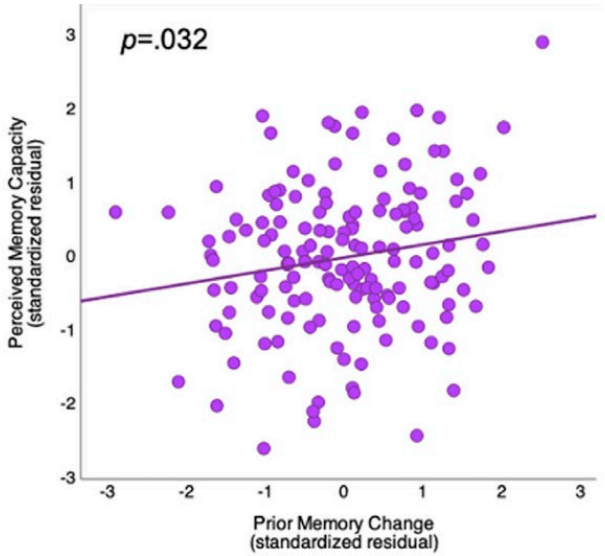
Teles & Shi, *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*

Cognition and Amyloid

Xi Chen, et al., Neurobio of Aging

University of Texas at Dallas/University of California Berkeley

- **Increased SCD** associated with **greater prior memory decline**, **amyloid deposition**
- SCD also associated with **decreased hippocampal activation during encoding**



Yun Jeong Hong et al., *Dem Geriatr Cog Disord*

The Catholic University of Korea

- Aβ+ SCD group showed **faster memory decline over 2 years** vs. Aβ- SCD group in a clinic-based sample

Complementary Readings

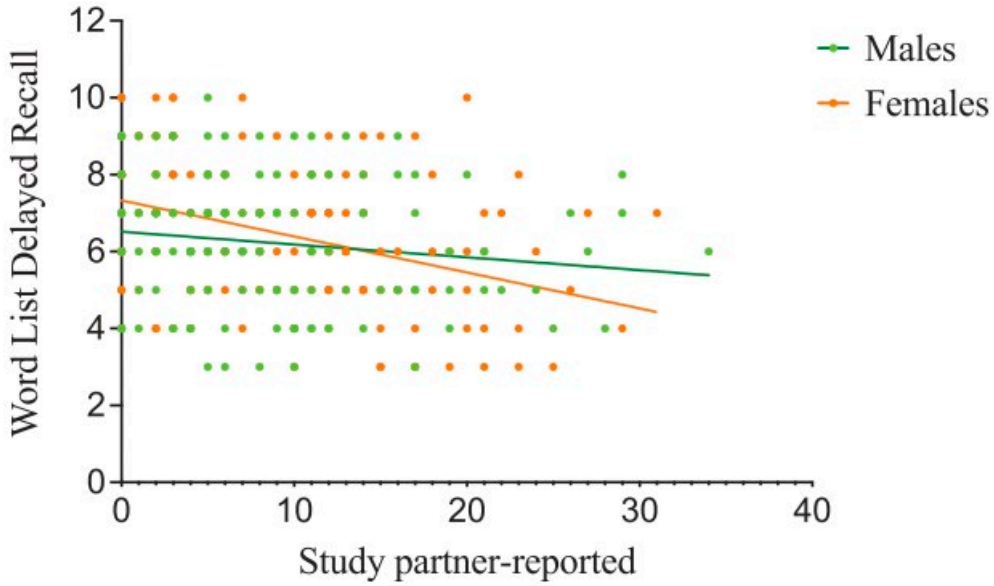
Tort Merino et al., *Int J of Geri Psychiatr*

Cognition and Genetics

Jairo Martinez et al., *JINS*

Massachusetts General Hospital/ Harvard Medical School

- Female PSEN-1 mutation carriers showed association between **greater self- and study-partner-reported concerns and worse verbal memory**



Knut Hestad et al., *Front Psych*

Inland Norway University of Applied Sciences

- Dose-reponse pattern seen in ApoE ε4 carriers with SCD in a clinic- based sample
  - **Greater number of ε4 alleles associated with worse delayed recall**

Cognition in SCD:
Take Home Points

- Factors like **mood, sex** may influence or mediate cognitive performance in SCD

- Cognition appears to **decline faster and is associated with structural brain changes** in SCD individuals with higher amyloid levels

- Presence of **genetic markers (e.g., ApoE ε4, PSEN-1)** may be associated with greater concerns and worse memory performance in individuals with SCD

Neuroimaging

Structural Alterations

Lorenzo Pini & Alexandra Wennberg, *Exp Geront*

University of Padova

- **Community-based samples** - consistent atrophy in hippocampus & temporal/parietal cortices
- **Clinic-based samples** - atrophy in temporal/parietal cortices, but more heterogeneous/complex pattern

Nira Cedres et al., *Aging*

Karolinska Institute/Stockholm University

- Greater SCC -> **reduced hippocampal** vol, **frontal/temporal/insular** thinning, and **higher mean diffusivity** across entire WM skeleton (sparing occipital)

	SCC	Age	Average MD
Age	0.37***	-	-
Average MD	0.36***	0.55***	-
Average cortical thickness	-0.49***	-0.60***	-0.47***
Hippocampal volume	-0.14*	-0.29***	-0.40***

SCC, subjective cognitive complaints; MD, mean diffusivity; ***p<0.001; *p<0.05.

Complementary Readings

Chen et al., *Int J Neuropsychopharm*

Cheng et al., *Psychophysiology*

Hansen et al., *Front Aging Neurosci*

Liang et al., *NeuroImage: Clinical*

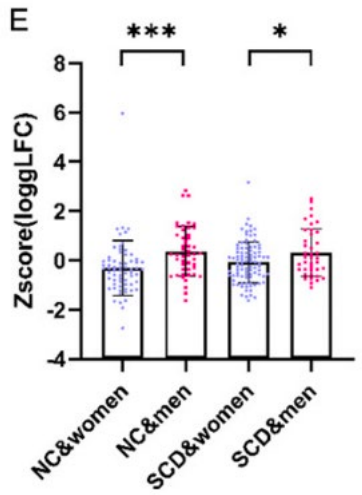
Tao et al., *Front Aging Neurosci*

Wen et al., *NeuroImage*

Functional Connectivity

Wenying Du et al., *JAD*

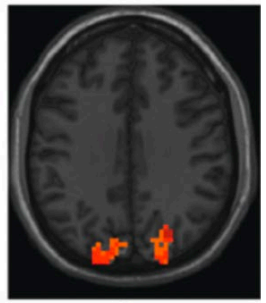
Xuanwu Hospital of Capital Medical University

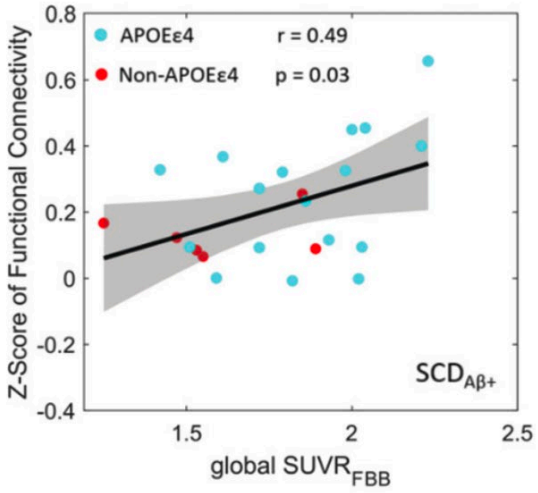


- In SCD and NC, **women showed lower global left frontal connectivity** vs. men

Shumei Li, Marcel Daamen, et al., *JAD*

German Center for Neurodegen. Diseases/ University Hospital Bonn





- Funct. changes in **precuneus** regions related to **amyloid** in Aβ+ SCD in clinic-based sample

Complementary Readings

Corriveau-Lecavalier et al., NeuroImage: Clinical

Fogel et al., *Front Neurol*

Fu et al., *Front Aging Neurosci*

Lei et al., *Med Imag Analysis*

Liu et al., *JAD*

Liang et al., *Alz Res Ther*

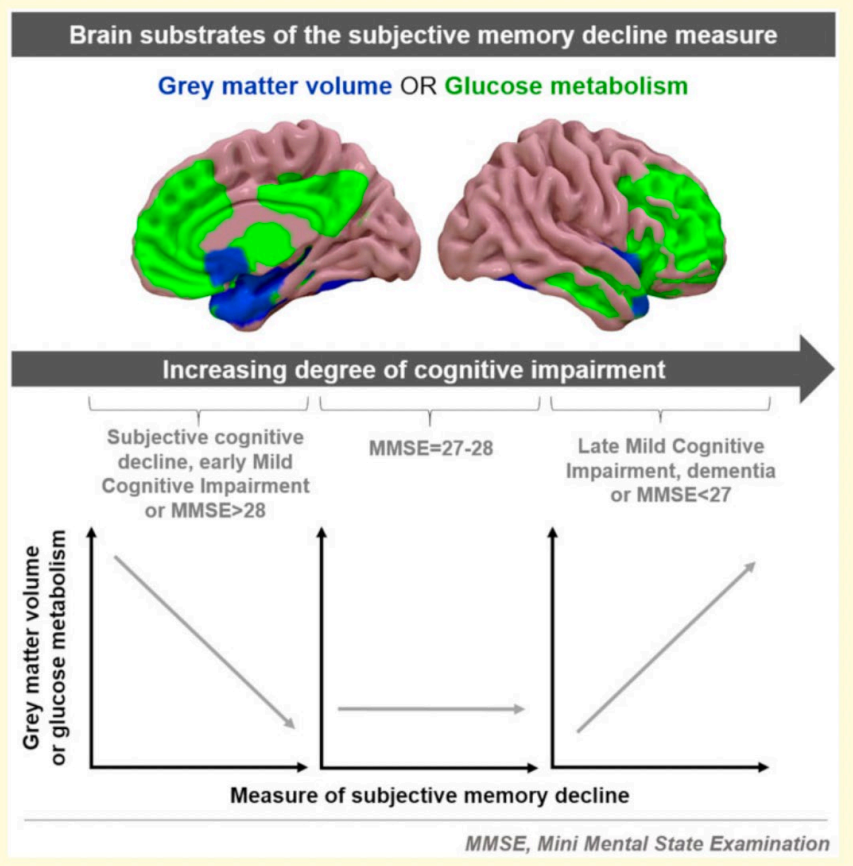
Ribaldi et al., *Alz Res Ther*

Xu et al., *Front Aging Neurosci*

Neuroimaging Biomarkers

Elizabeth Kuhn et al., *Brain Communications*

Normandie University



- In a clinic-based group of SCD individuals, **higher SMD score associated with lower glucose metabolism in frontal/temporal cortices, insula, and putamen**
- Opposite relationships seen in MCI/AD groups

Complementary Readings

Amariglio et al., *J Prev Alz Dis*

Bullich et al., *Alz Res & Ther*

Ebenau et al., *Euro J Nuc Med Mol Im*

Dong et al., *Alz Res & Ther*

Ortega et al., *Alz Res & Ther*

Pavisic et al., *J Neurol, Neurosurg, Psychiatr*

Wang et al., *Brain Imag Beh*

Neuroimaging in SCD:
Take Home Points

- Correlations seen between **SCD individuals and structural/functional changes** in the brain
  - May be moderating factors, such as **sex, neuropathology, and setting** (e.g., clinic vs. community)

- Cognitive complaints seem to be **differentially associated with brain-based biomarkers in SCD** compared to later stages of cognitive impairment (e.g., higher SCC -> hypometabolism)

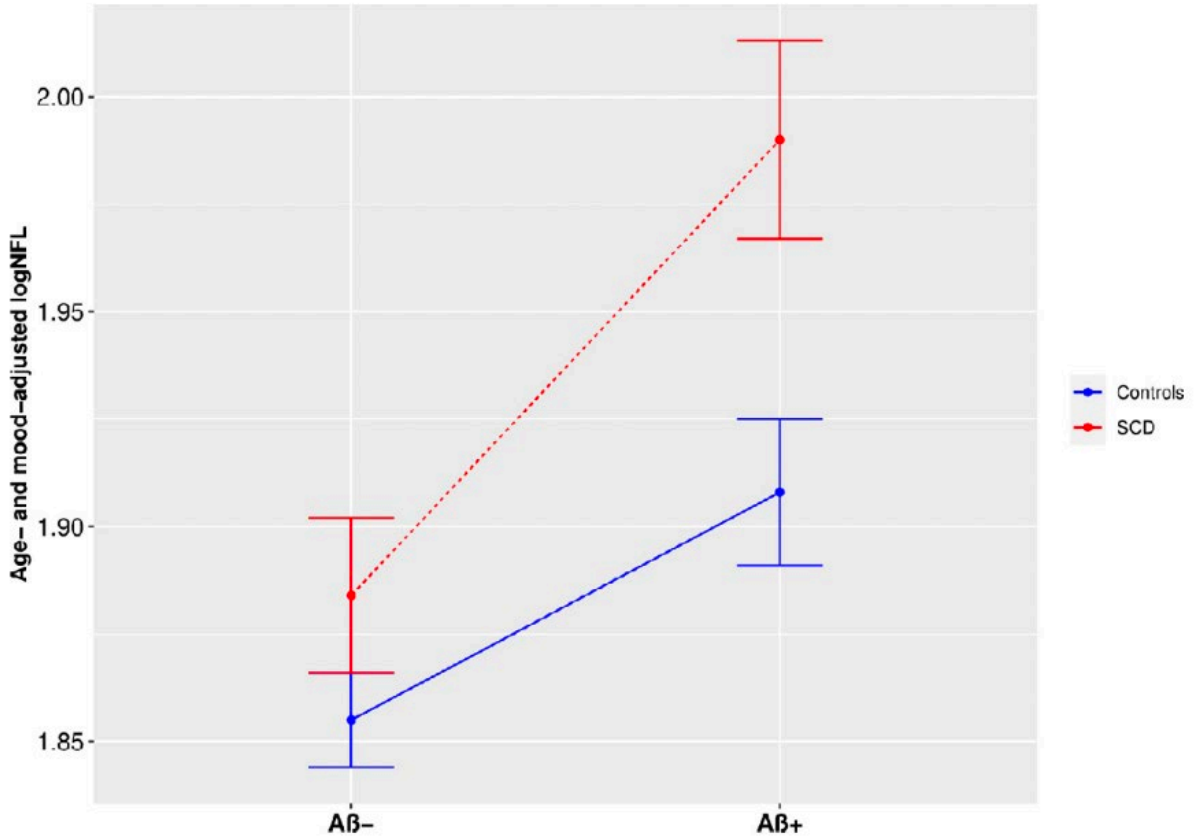
Biofluids

Cerebrospinal fluid

Gonzalo Sánchez-Benavides et al., *Neurobio Aging*

BBRC-FPM/IMIM Hospital del Mar/Medical Research Institute

- SCD associated with **greater levels of CSF neurofilament light chain** (NFL)
  - Moderated by Aβ status
- **Higher NFL associated with lower hippocampal volume** in Aβ+ individuals with SCD



Complementary Readings

Jacobs et al., *Mol Psychiatr*

Willemse et al., *Alz Res & Therapy*

Ma et al., *JAD*

Ayton et al., *Prog in Neurobio*

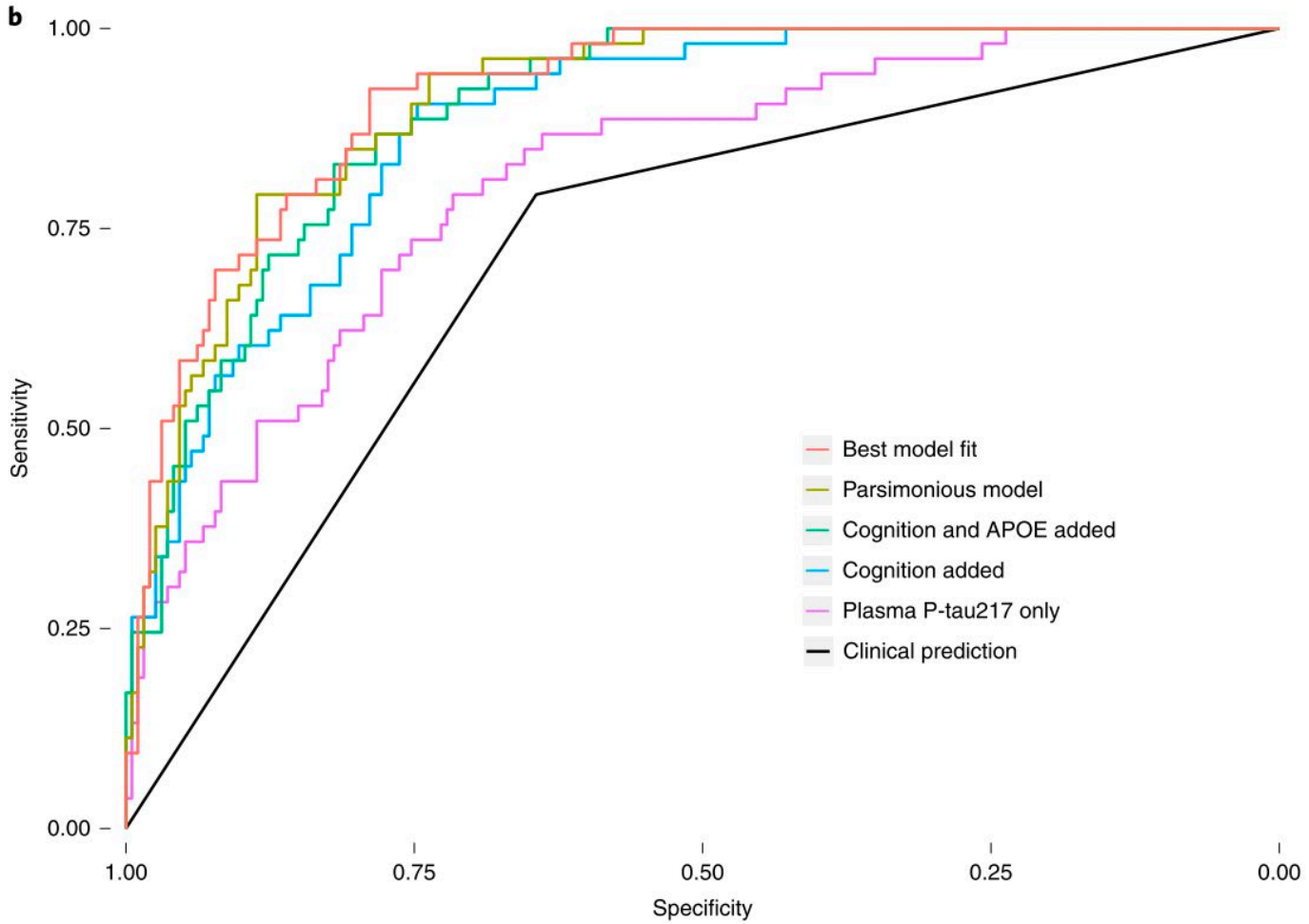
Cicognola et al., *Alz Res & Therapy*

Scarth et al., *JAD*

Plasma

Sebastian Palmqvist et al., *Nature Medicine*

Lund University/Skåne University

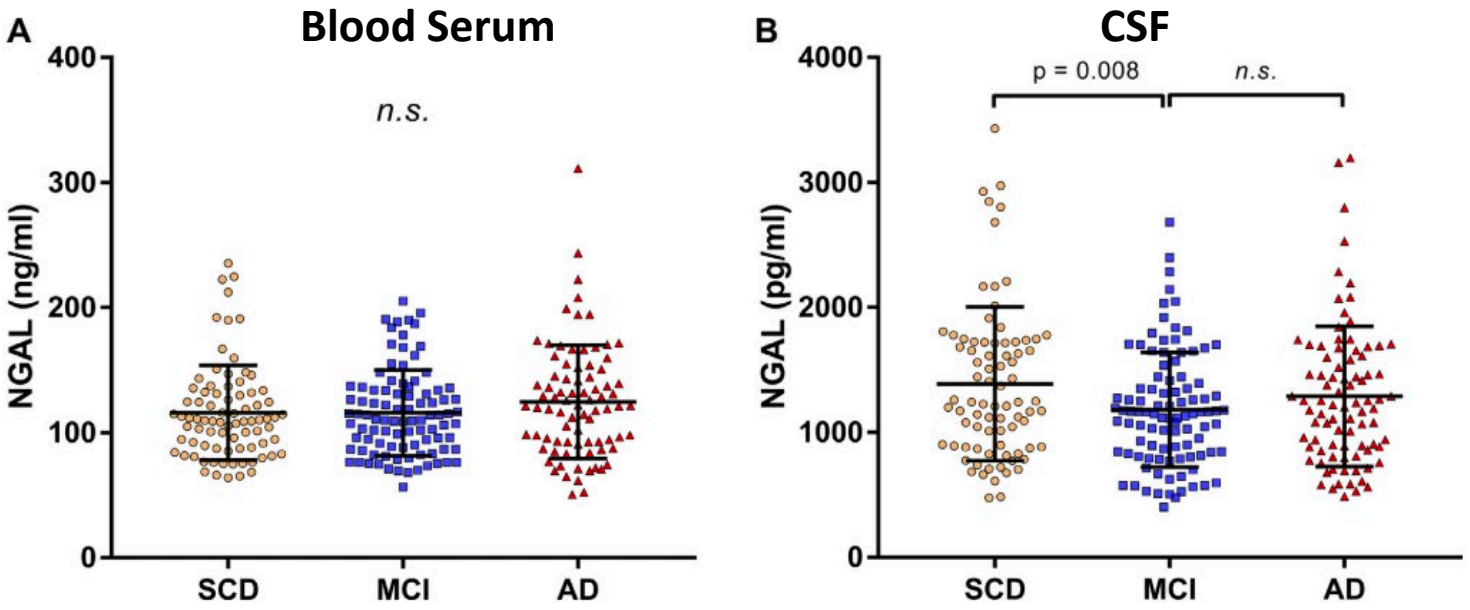


- **Plasma P-tau217 predicted AD accurately within 4 years** in SCD & MCI from clinic-based BioFINDER study (lilac)
  - More accurate than clinical prediction (black)
  - Adding **memory** (ADAS-Cog DR), **executive functioning** (TMT-B, ”Animals”), and **APoE** produced higher accuracy (green)
- Similar results in ADNI using plasma P-tau181

Plasma

Petrus Naudé et al., *Neurobio of Aging*

University of Groningen/University of Cape Town



- **No differences seen in serum Neutrophil gelatinase-associated lipocalin (NGAL)** across diagnostic groups
- **CSF NGAL significantly higher in SCD vs. MCI group**

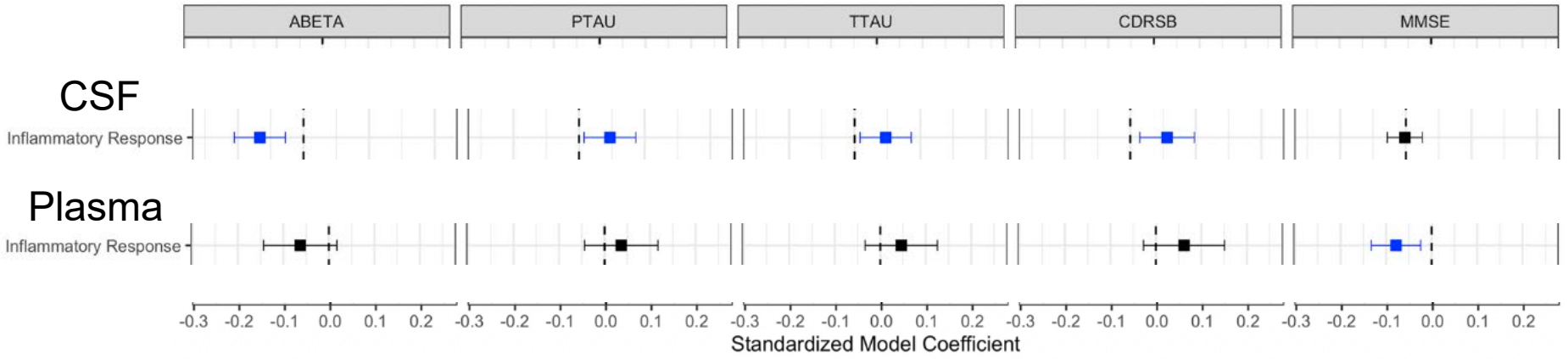
Complementary Readings

Janelidze et al., *JAMA Neurology*

Plasma

Nicholas Cullen et al., *Scientific Reports*

Lund University

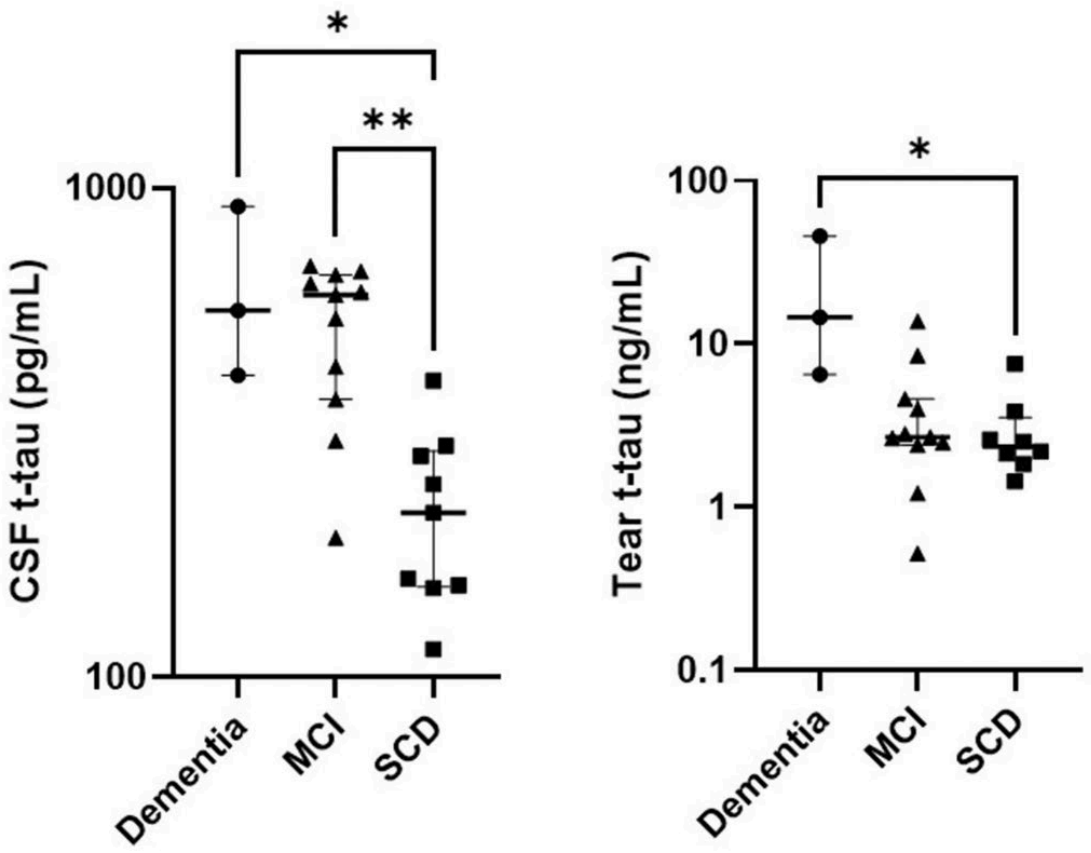


- Elevated **CSF** inflammatory levels seen in **AB-, SCD group**
- **Plasma-based** inflammatory levels only increased in **AD group**

Complementary Readings

Janelidze et al., *JAMA Neurology*

Tear fluid



Marlies Gijs et al., *Scientific Reports*

Maastricht University

- **CSF t-tau** levels differentiated **SCD from MCI and dementia groups**
- **Tear fluid t-tau** levels only differentiated **SCD vs. dementia group**

Biofluids in SCD:
Take Home Points

- Other markers (e.g., **NFL**) are being studied in CSF and show **relationships with cognitive concerns and amyloid** levels

- **Plasma tau seems predictive of cognitive decline** in earlier stages of preclinical AD/MCI

- Data with **other plasma markers and other non-CSF biofluids are less sensitive in unimpaired**, SCD populations

Interventions

Underlined studies are registered clinical trials

- **Cognitive Training**
  - Computerized/Virtual Reality cognitive training
    - Kang et al., *J Med Internet Res*
    - Senczyszyn et al., *Front in Psychiatr*
    - Hu et al., *J Neurology*
  - Cognitive Training + Exercise
    - Salisbury et al., *Trials*
    - Pang & Kim, *Brain Sciences*
    - Boa Sorte Silva, *Front Aging Neurosci*

→ Positive effects on functional connectivity, mixed results on cognitive performance

- **Transcranial Direct-Current or Magnetic Stimulation**
  - Brooks et al., *Mindfulness*
  - Vaqué-Alcázar et al., *Front Aging Neuro*
  - Liu et al., *Front Aging Neurology*

→ Feasible, safe
Some improvements seen in cognition

- **Nutrition**
  - β-Lactolin – Kanatome et al., *JAD*
  - Dietary supplements – Gutierrez et al., *Nutrients*
  - Lifestyle + EGCG supplements – Forcano et al A&D, *Translational Research…*
  - Shentai Tea polyphenols – Ni et al., *JAD*

→ Improved neural activity, verbal fluency

→ Mixed; stronger evidence for polyphenols/combos of nutrients, lower evidence for Vitamin D, specific proteins, amino acids, other supplements

- **Behavioral/Educational/Lifestyle**
  - Cooper et al., *Dementia*
  - Roheger et al., *A&D Translational Research…*
  - Innes et al., *JAD Reports*
  - Liou et al., *Brain Sciences*
  - Marchant et al., *Psychotherapy and Psychosomatics*

→ Feasible
Improved cognition with education programs
Some improvement in compensatory strategy use, anxiety symptoms, and functioning

Opportunities for 2022

- More data on discrepancies between self- and informant-reported cognitive concerns
- Improved diagnostic processes, possibly utilizing biomarker data
- More research on blood based biomarker data
- Additional research on SCD in cross-cultural settings
- Further explore the impact of cognitive reserve
- Better understand the link between SCD and affective/mood symptoms
- Assess the utility of SCD as an outcome measure in clinical trials
- Examine effects of cognitive and psychological interventions on SCD

Thank you!

- All volunteers, patients, and caregivers involved in research programs
- Harvard Aging Brain Study colleagues
- Survey Responders

alzheimer's association®

Presentation Bibliography and Extended Reading List:
https://docs.google.com/document/d/19_q7jrrTaCcaA21TozX7wt6XEeQSU5VxZT_S9DYVVN8/edit?usp=sharing