MAY 3, 2023

TEXAS
The University of Texas at Austin

Drivers of Disparities in Alzheimer's Disease

Aging Texas Well Advisory Committee
Texas Health and Human Services

Alexandra L. Clark, Ph.D.
Assistant Professor
Department of Psychology, The University of Texas at Austin

@alexleighclark

Disclosures

- Professional & Financial:
  - Salaried state employee
  - I receive research funding from the National Institutes of Health, Department of Defense, and Alzheimer's Association

- Personal:
  - Family member and caregiver

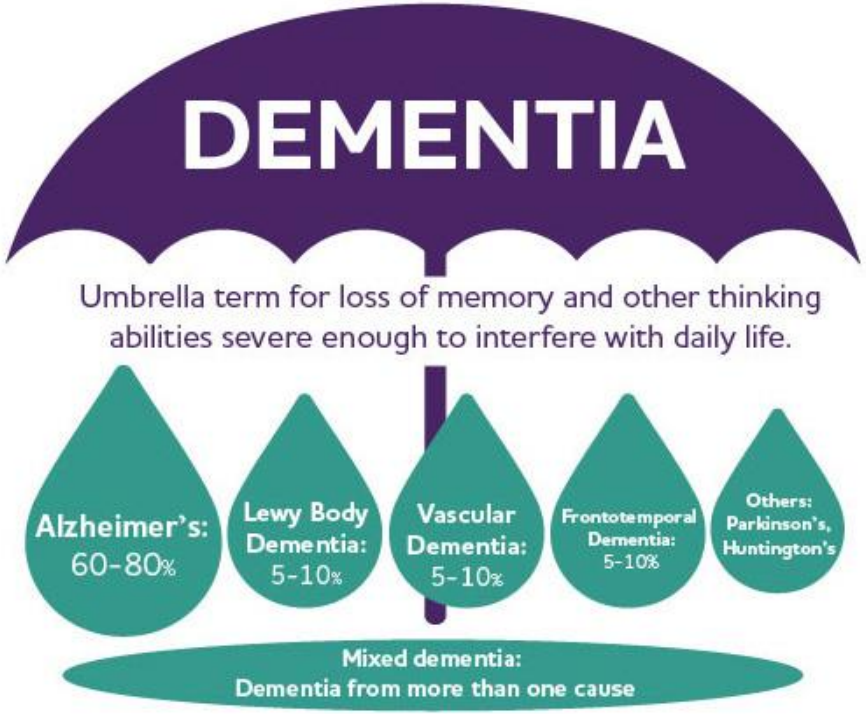
Outline

- Overview of Alzheimer's disease (AD) & racial/ethnic disparities
- Highlight risk factors for AD
- Discuss biology of AD
- Detail assessment & treatment issues in AD

What is Alzheimer's disease (AD)?

- Progressive neurodegenerative condition that results in dementia
- Characterized by pervasive cognitive deficits
  - Memory, attention, reasoning
- Declines in everyday functioning
  - Managing finances, household chores, transportation
  - Dressing, grooming

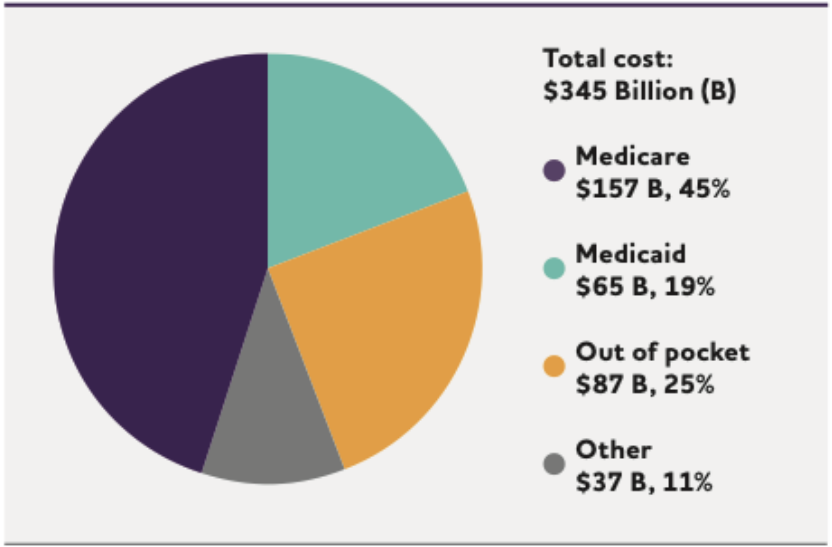
AD/Dementia



Alz Facts & Figures, 2021

AD Cost & Care Burden

Aggregate healthcare cost by payment source for Americans aged 65 and older with AD in 2023.

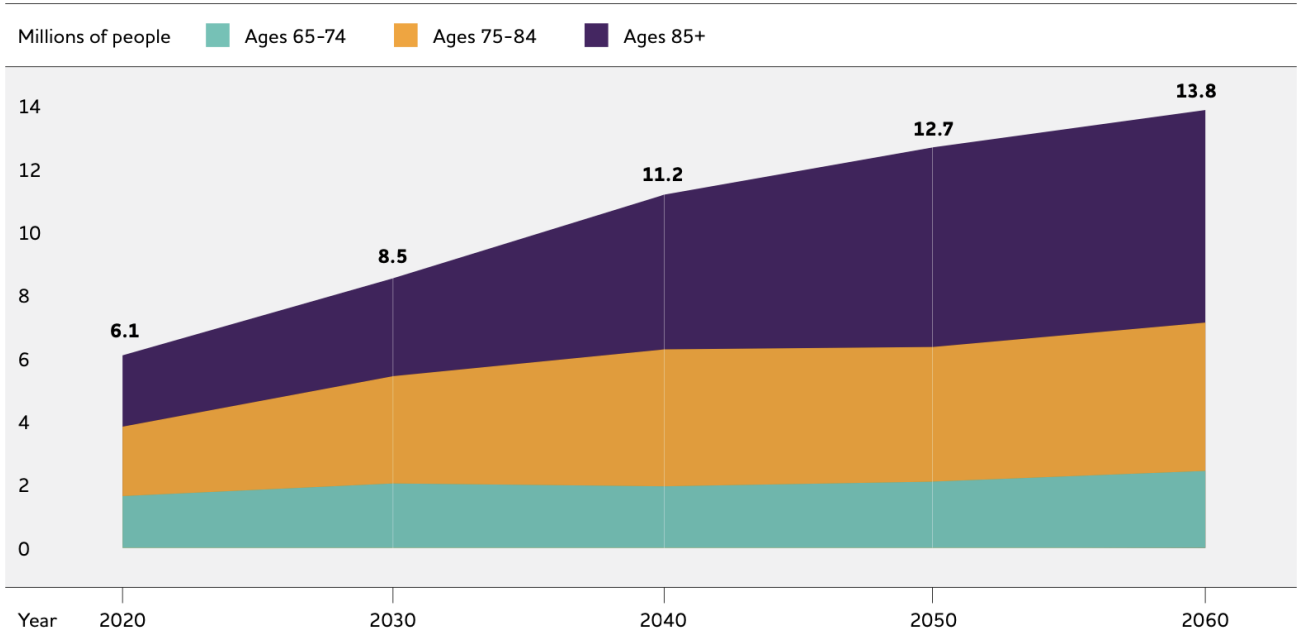


*Data are in 2023 dollars.

- Annual healthcare costs of AD exceed $300 billion
- Estimated that there are more than 11 million unpaid family caregivers
- Limited treatment options

Why should we be concerned about AD?

Projected number of people aged 65 and older in the US population with AD, 2020 to 2060.

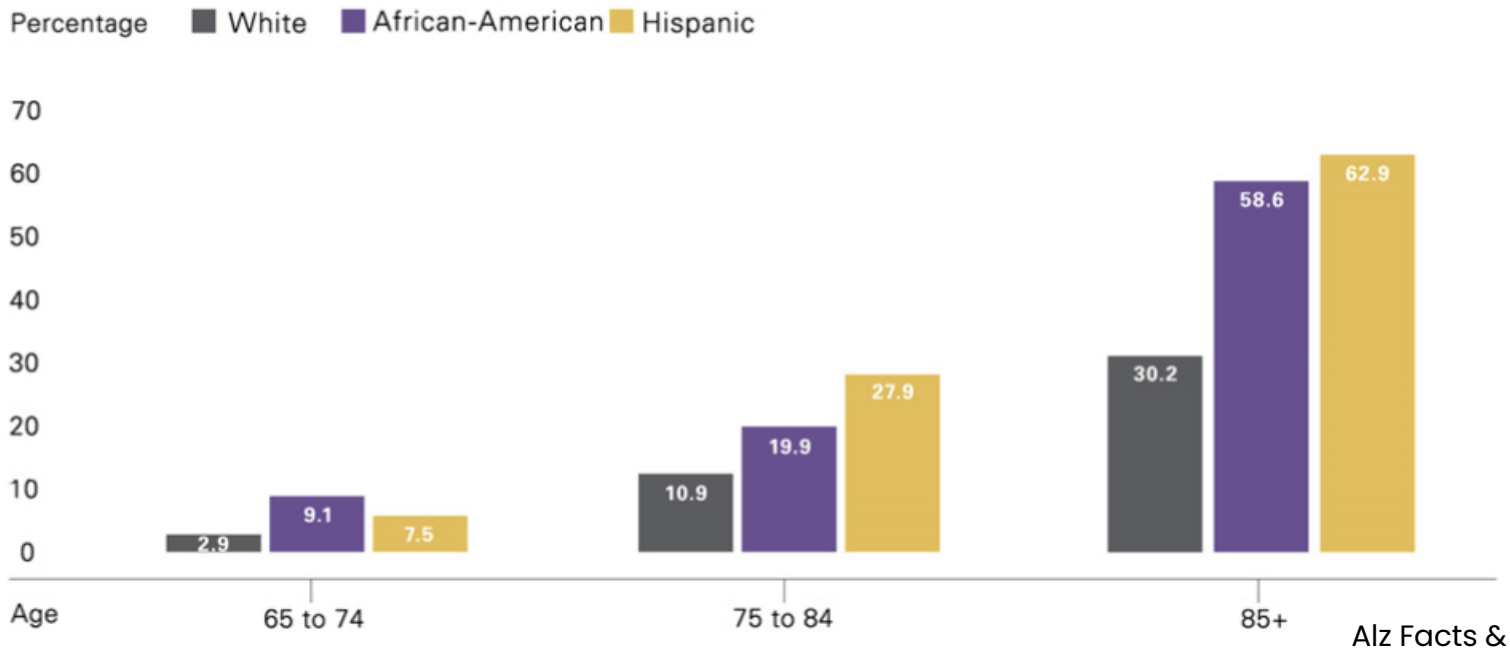


Created from data from Rajan et al.[A6,224]

Alz Facts & Figures, 2023

Racial/ethnic disparities in AD

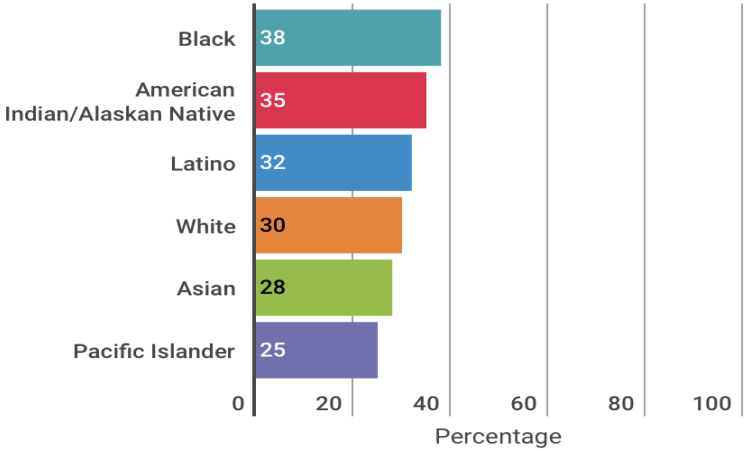
Proportion of people aged > 65 years with Alzheimer's disease (AD) and other dementias by race/ethnicity from the Washington Heights-Inwood Columbia Aging Project, 2006



Alz Facts & Figures, 2012

Racial/ethnic disparities in AD, con't.

Dementia rates for adults above the age of 65 by each major US ethnic and racial groups.



Mayeda et al., 2016

Key point: Exact estimates may slightly vary, but racial/ethnic minorities are disproportionately impacted by AD.

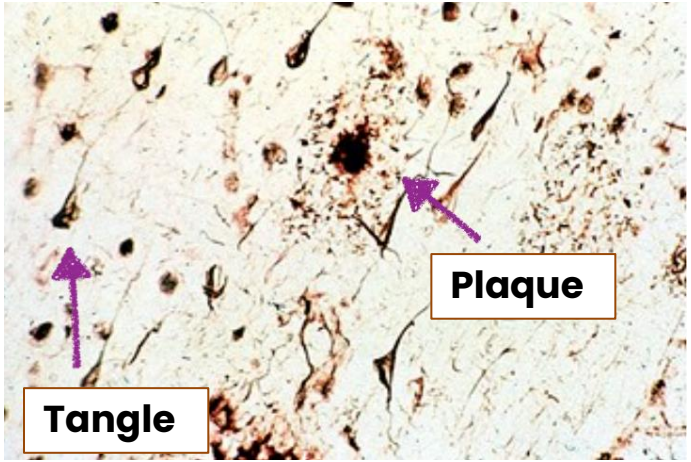
What are racial/ethnic disparities in AD?

- "… a particular type of health difference that is closely linked with economic, social, or environmental disadvantage."
- "…avoidable differences in health between groups of people who are more and less advantaged socially."
- **"…health inequities are health differences that are avoidable, unnecessary, and unjust."**

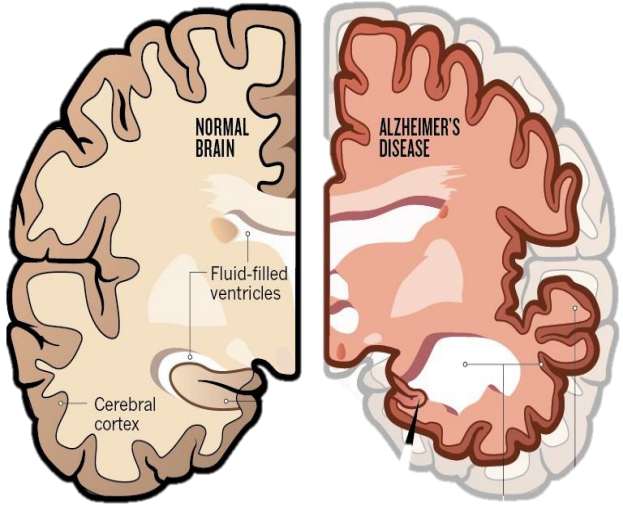
Questions to ponder

Q: Why are certain groups of the population disproportionately impacted by AD?

Biology of AD



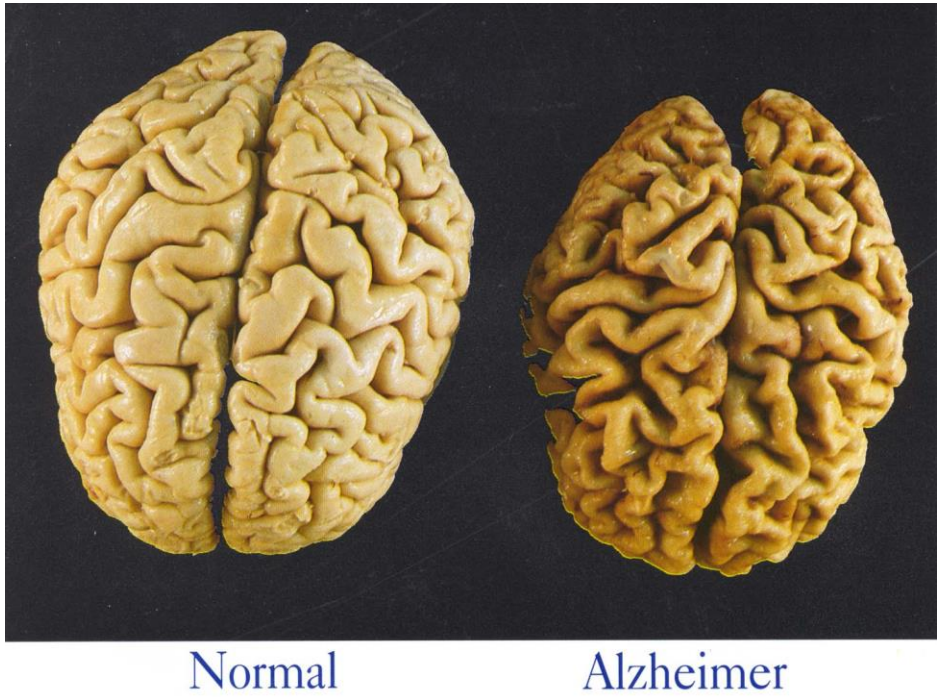
Formation of amyloid plaques & tau tangles

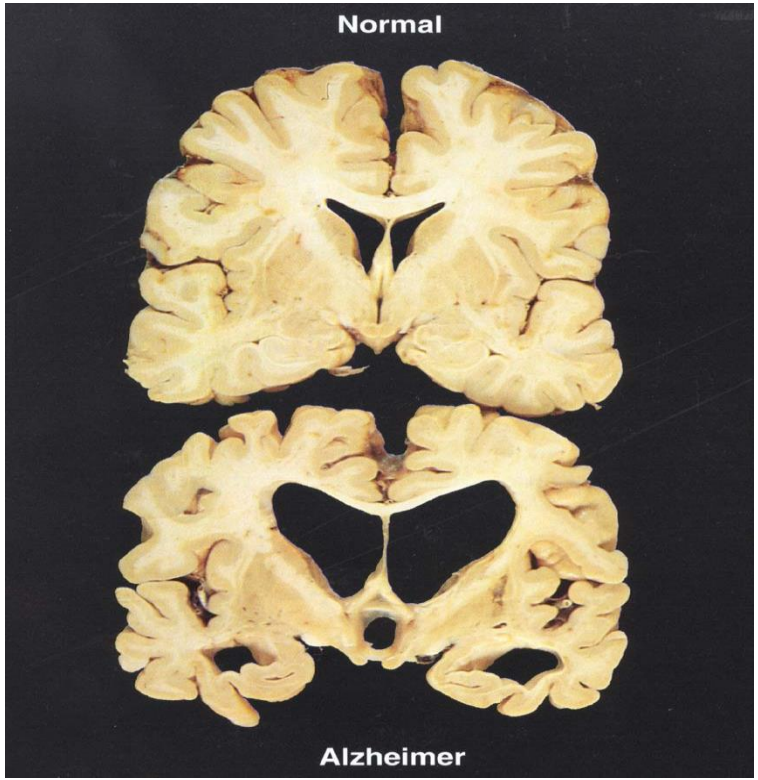


Drew, L. (2018). An age-old story. Nature, 559, S2-S3.

Cortical atrophy, neuron loss, & synapse loss

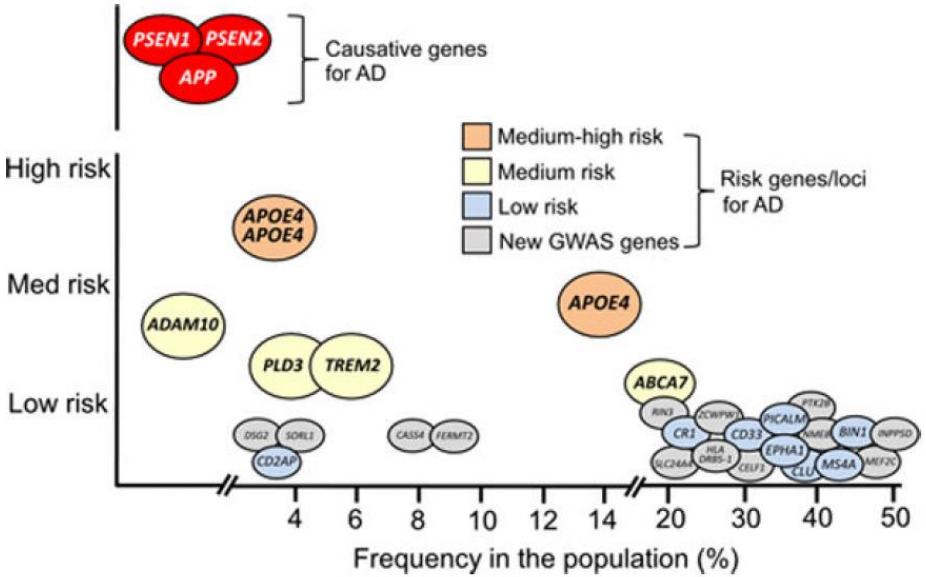
Biology of AD, cont'd.





Genetic risk factors for AD

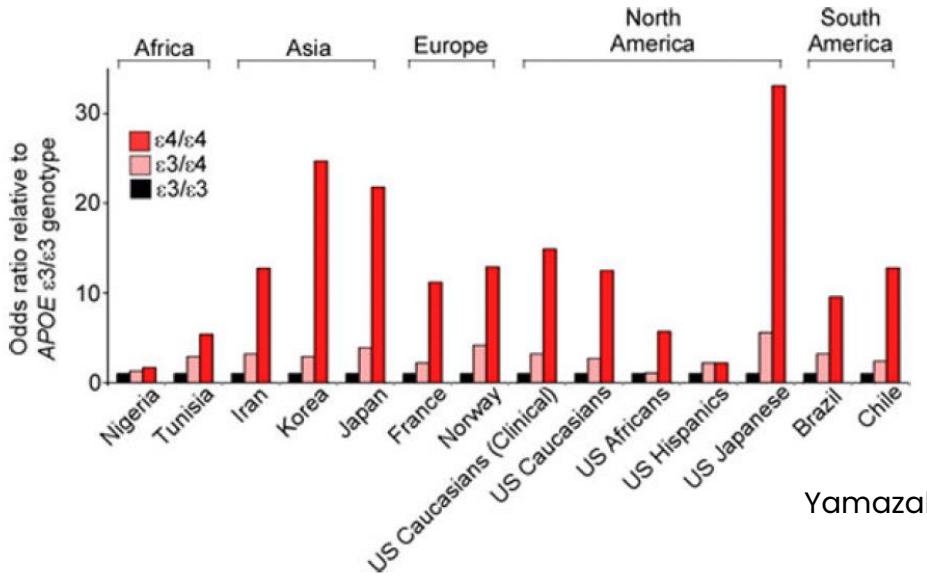
Genetic causative/risk factors for AD identified in large scale



Yamazaki et al., 2016

Genetic risk factors for AD, cont'd.

The relative odds for developing AD according to APOE allelic

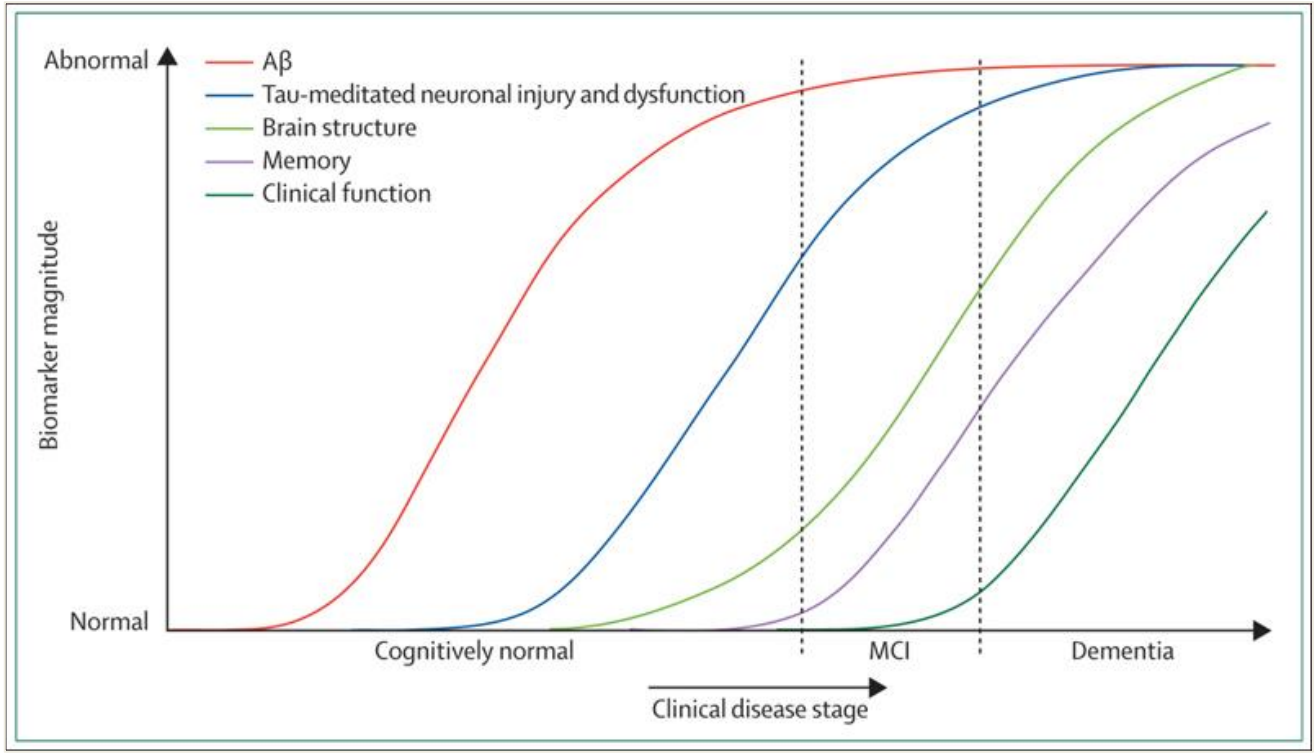


Yamazaki et al., 2016

Key point: Racial/ethnic disparities in AD **are not** simply due to genetic risk factors.

Conceptual model of AD cascade

Hypothetical model of dynamic biomarkers of the AD pathological cascade (Jack et a., 2010).



Amyloid & tau are important, but so is other pathology

The neuropathology of probably Alzheimer Disease and Mild Cognitive Impairment (Schneider et al., 2000).

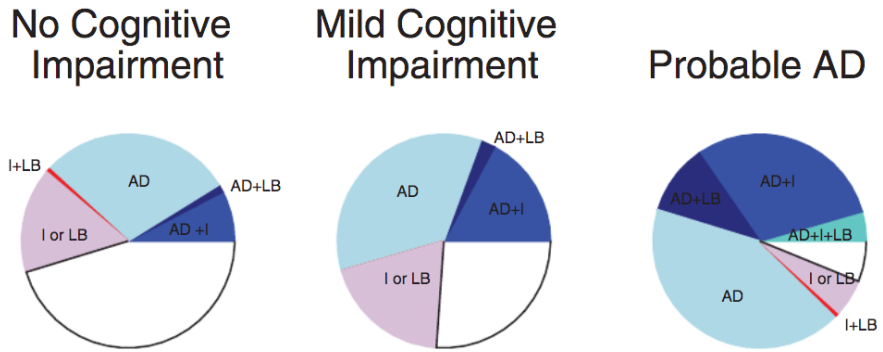


Fig. Pathology by clinical status proximate to death. (Blue shades) Pathologic diagnosis of Alzheimer disease (AD). Clockwise: light blue = pathologic diagnosis of AD only; dark blue = pathologic diagnosis of AD and neocortical Lewy bodies (LB); medium blue = pathologic diagnosis of AD and cerebral infarcts (I); aqua = pathologic diagnosis of AD, I, and LB. (Red shades) I and/or LB (with no pathologic diagnosis of AD). Clockwise: pink = I or LB; red = I and LB. (White) No pathologic diagnosis of AD, no I, no LB.

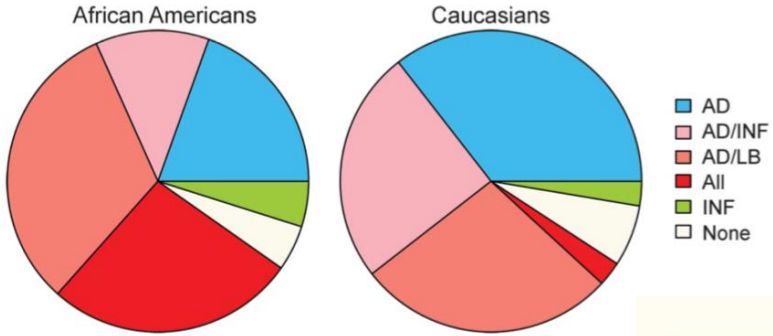
(2009) *Annals of Neurology.*

- AD = amyloid & tau
- I = Infarcts/vascular disease
- LB = Lewy Bodies

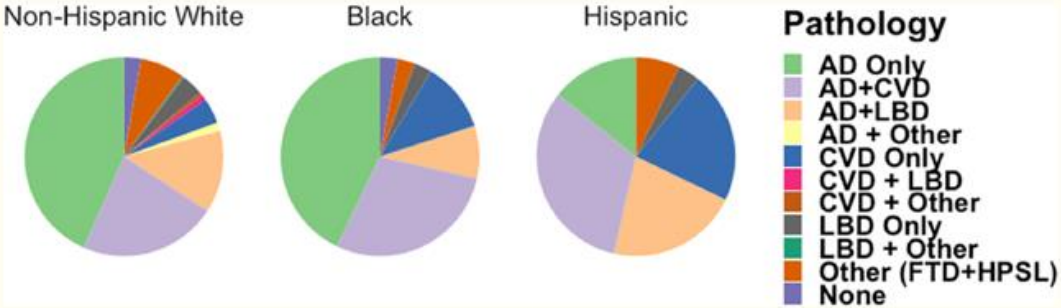
Results: Of the 179 persons with probably AD, 87.7% had pathological confirmed AD and 45.8% has mixed pathologies, most commonly AD with macroscopic infarcts.

Mixed pathology is relevant to racially/ethnically diverse samples

Racial differences in mixed pathology (Barnes et et al., 2015; Filshtein et al., 2020).

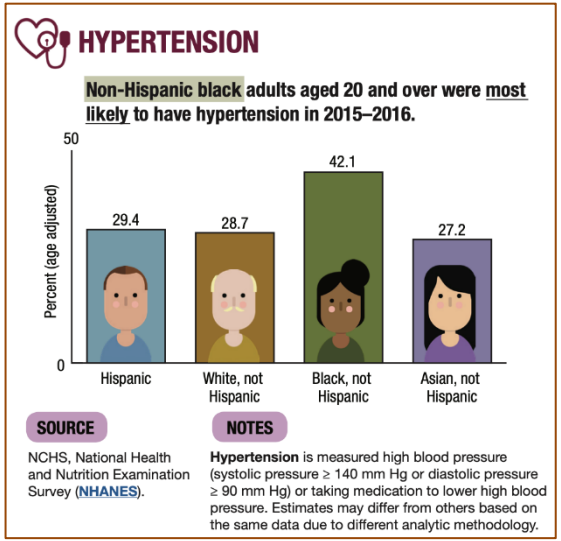


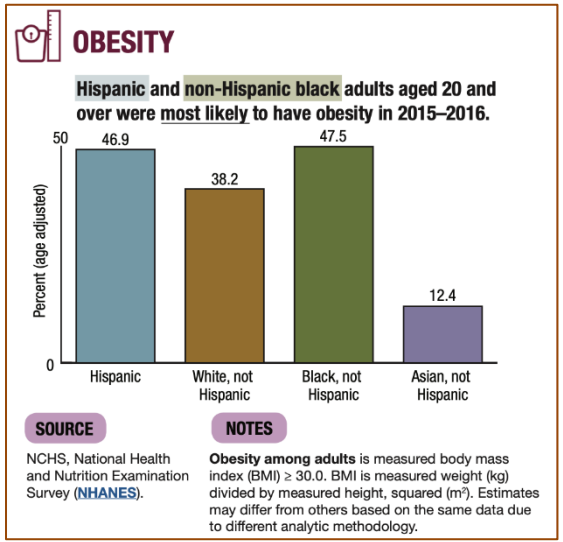
Pie chart shows proportions of individual and mixed pathologies in black
dents with Alzheimer disease (AD) dementia. INF = infarcts; LB = Lewy b

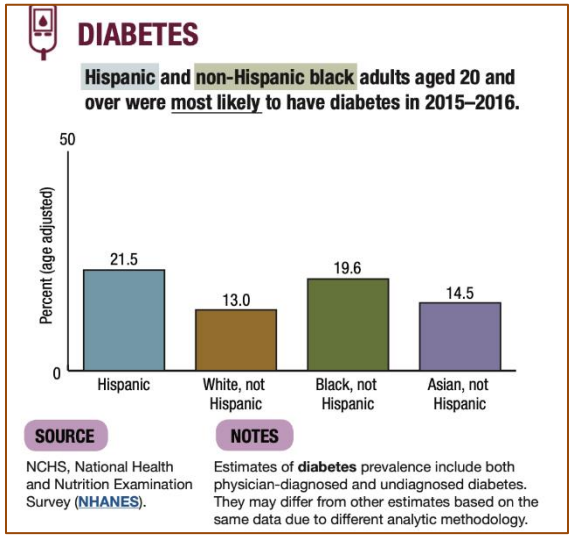


Filshstein et al. (2020) *JAD*.

Racial/ethnic health disparities in vascular drivers of AD



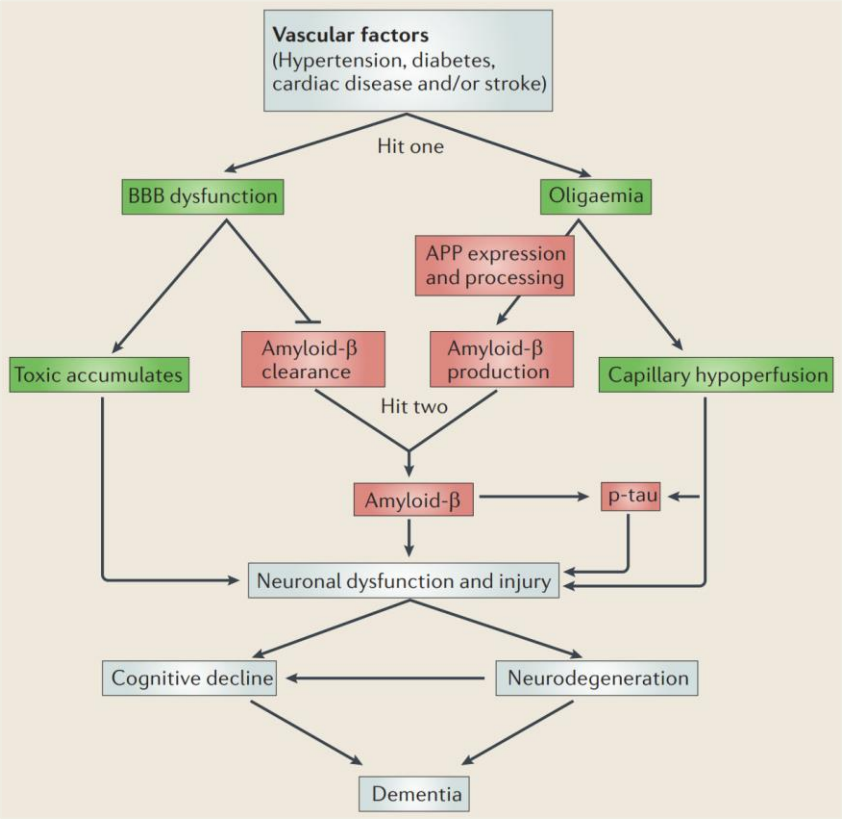




Centers for Disease Control and Prevention. Heart disease risk factors. Atlanta, GA. Available from: https://www.cdc.gov/heartdisease/risk_factors.htm.

Key point: Minoritized groups have **higher rates** of vascular risk factors.

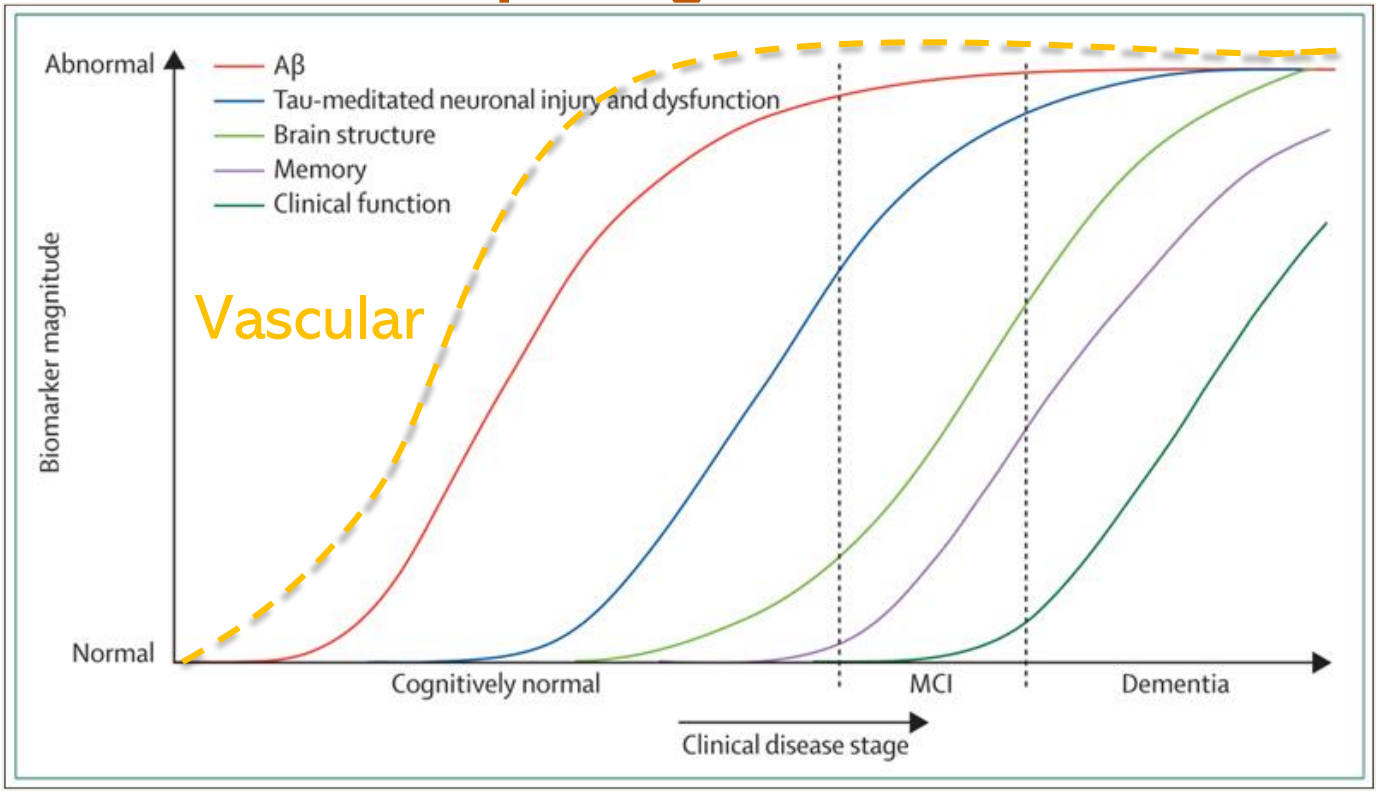
Upstream process: Vascular drivers of AD



Key point: These chronic cardiovascular conditions are key initiators of the AD pathologic change.

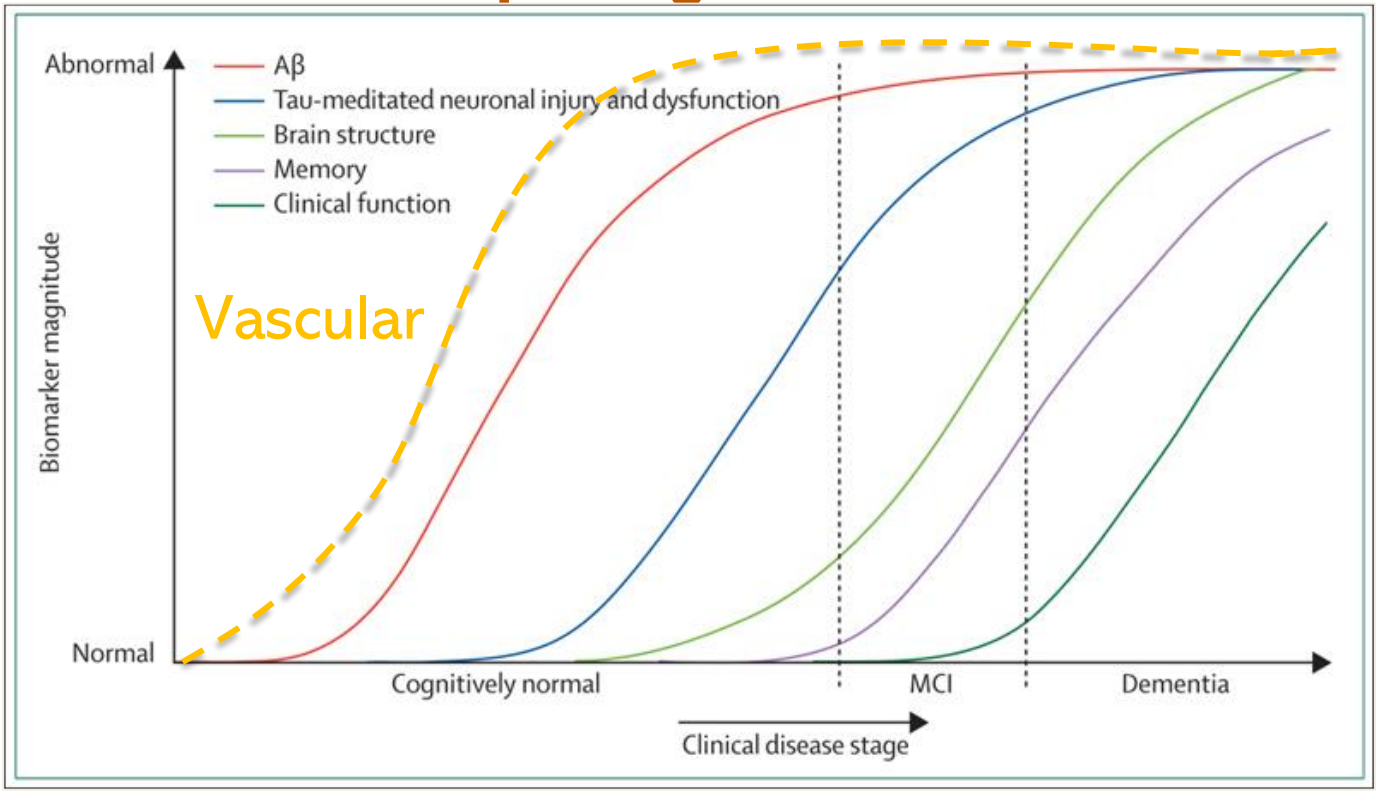
Zlokovic (2011), *Nature Rev Neurocsi*

Conceptual model of AD pathogenesis



Clark et al. (2021), *Journal of Alzheimer's Disease*

Conceptual model of AD pathogenesis, cont'd.



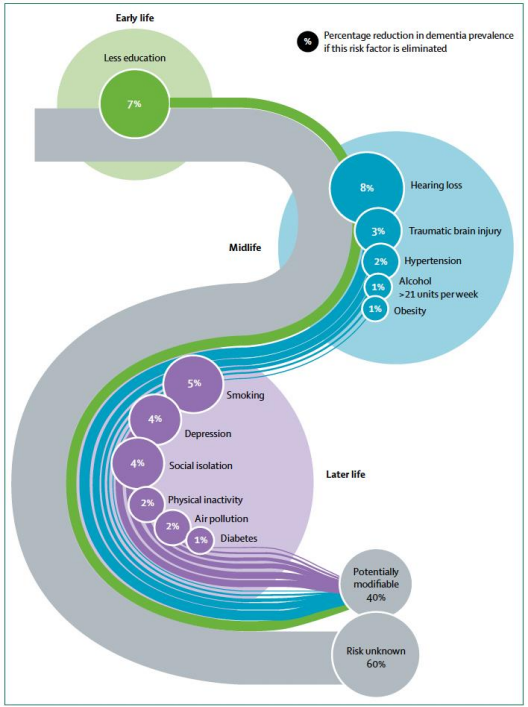
Key point: Vascular dysfunction is one of the **earliest markers** of pathologic aging & may be especially relevant in **racially/ethnically diverse samples**.

Q: Why are certain groups of the population at increased risk for dementia?

Higher rates of chronic vascular health conditions

Modifiable risk factors for AD

Population attributable fraction of potentially modifiable risk factors for dementia.



- Growing evidence that a sizable amount of dementia risk is modifiable!
- There are many other lifestyle factors can be targeted for important for prevention & intervention efforts.
- Risk is shaped across the life course & begins early.

Livingston et al., 2020

How do these modify risk for AD?

Factors all affect cognitive & brain health

- Brain structure
- Brain function
- Development of cognitive skills
- The accumulation of pathologic proteins (amyloid and tau)
- Cognitive and brain reserve (resistance to damage)

Other critical risk factors for AD

The NIA Health Disparities Research Framework (Hill et al., 2015).

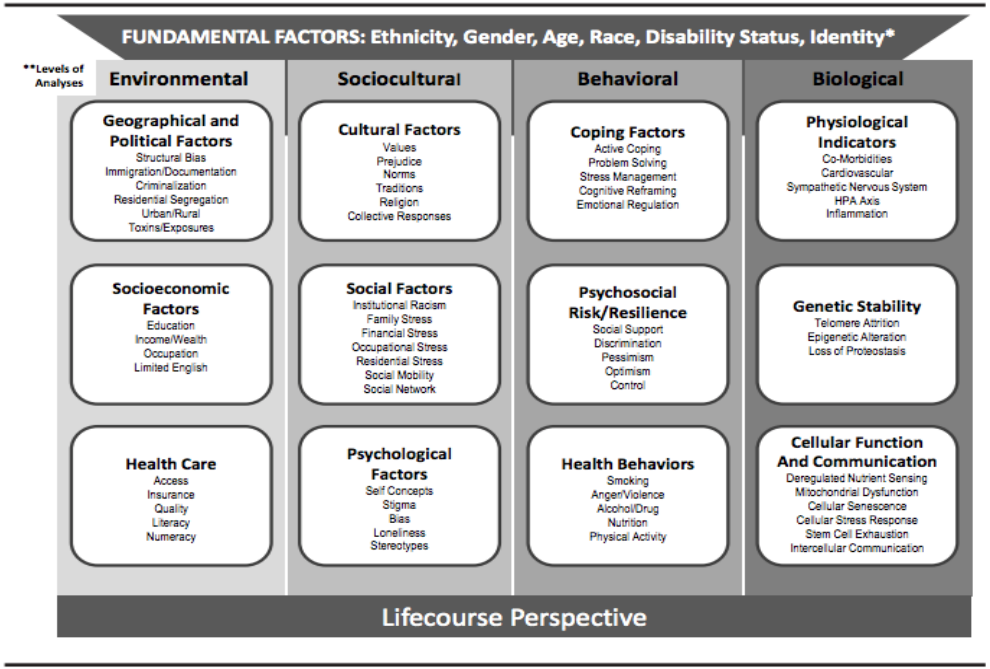


Figure 2. NIA Health Disparities Research Framework

Key point: Factors in each of these domains leads to disparities in AD.

Life course models of AD

- NIA framework acknowledges health outcomes differ as a function of race/ethnicity, class, gender, & disability status in this country

- This is largely a function of different:
  - Access to resources
  - Exposure to adverse conditions
  - Chronic or repeated stress due to either of these things can have a profound impact on health

- Research into social causes of disease is essential (AMA, 2021).

Using census data to characterize environmental risk factors

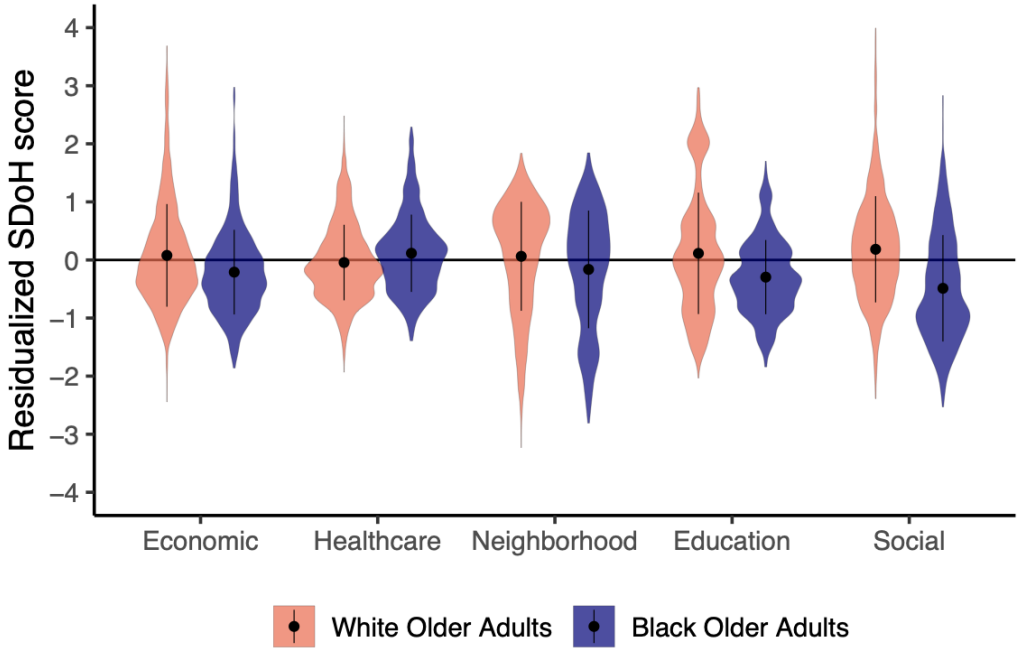
	Economic Stability/Status Factor (16.7%)	Healthcare Access and Quality (14.2%)	Educational Access and Quality (14.0%)	Neighborhood and Built Environment (12.2%)	Social and Community Context (10.6%)
% with College degree	X				
Sports and recreation instruction	X				
Median home value	X				
Median rent	X				
Pharmacies and drug stores		X			
Physician offices		X			
Services for elderly and disabled		X			
Supermarkets and other grocery stores		X			-X
Years of education			X		
Reflected occupational "data" codes			X		
Reflected occupational "people"			X		
Reflected occupational "thing"			-X		
Owner occupancy				X	
Single unit dwellings				X	
Golf courses and country clubs					X
% White residents in neighborhood					X

Note. See Clay et al., 2022 for complete listing of factor loading weights. X = indicated positively loaded onto factor, -X = indicates negatively loaded on factor

Clark et al., 2022

Racial group differences in resources

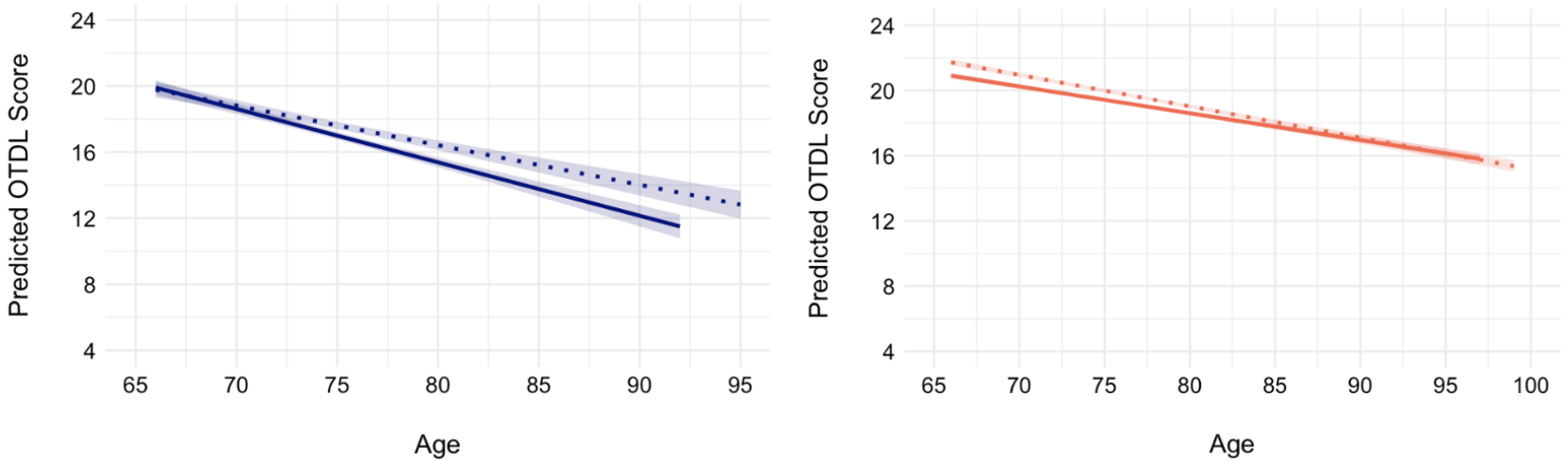
Figure 1. Residualized SDoH scores for Black/African American and White older adults.



Clark et al., 2022

Impact of community-level economic resources

Figure 3. Effect of economic stability/status (dotted line – high; solid line – low) on OTDL trajectories within Black/African American older adults (left, navy) and White older adults (right, red). High vs. low economic stability was determined based on median split.

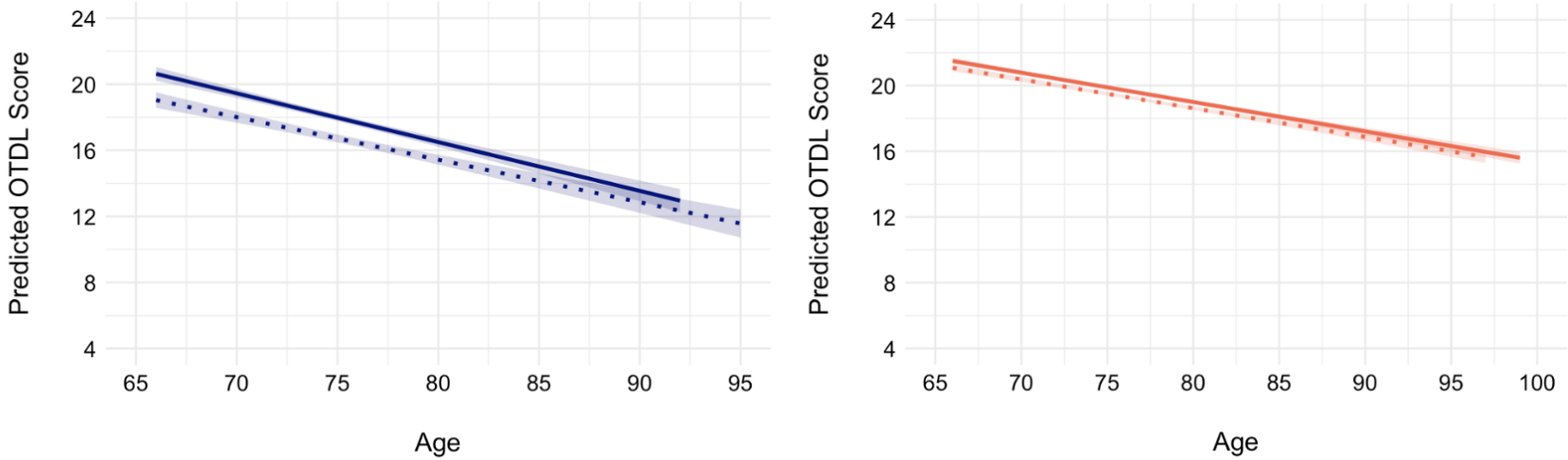


Key point: **Lower economic stability/status** (β=.07, p=.04) is associated with accelerated declines in everyday functioning in Black participants, but not in White participants (*ps*>.30).

Clark et al., 2022

Impact of community-level social resources

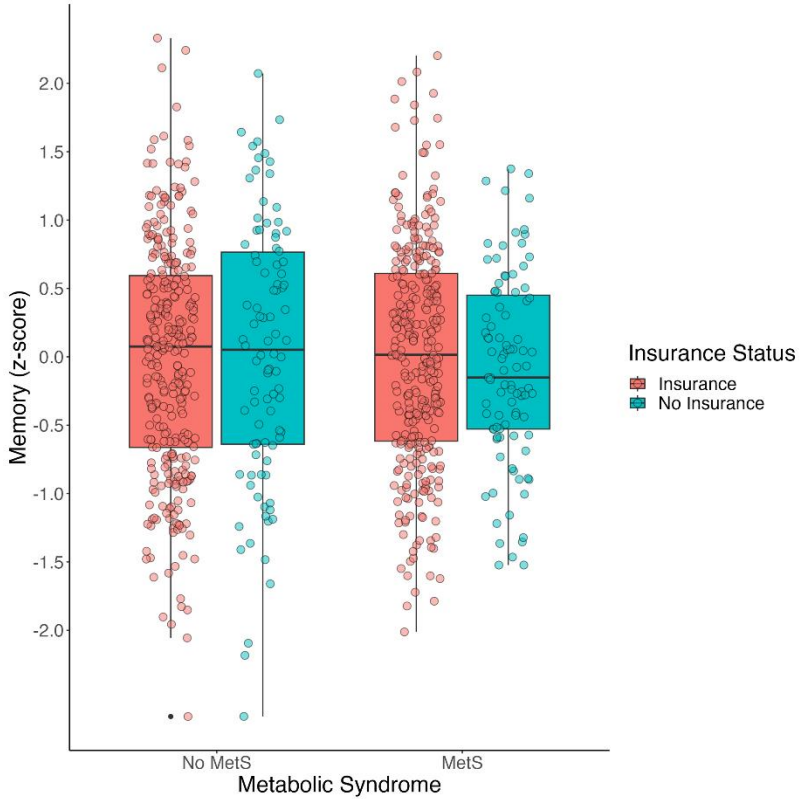
Figure 4. Effect of social and community context (dotted line – high; solid line – low) on OTDL trajectories within Black/African American older adults (left, navy) and White older adults (right, red). High vs. low economic stability was determined based on median split.



Key point: **Lower social and community context** (β=.08, p=.002) was associated accelerated declines in everyday functioning in Black participants, but not in White participants (*ps*>.30).

Clark et al., 2022

More evidence that resources matter

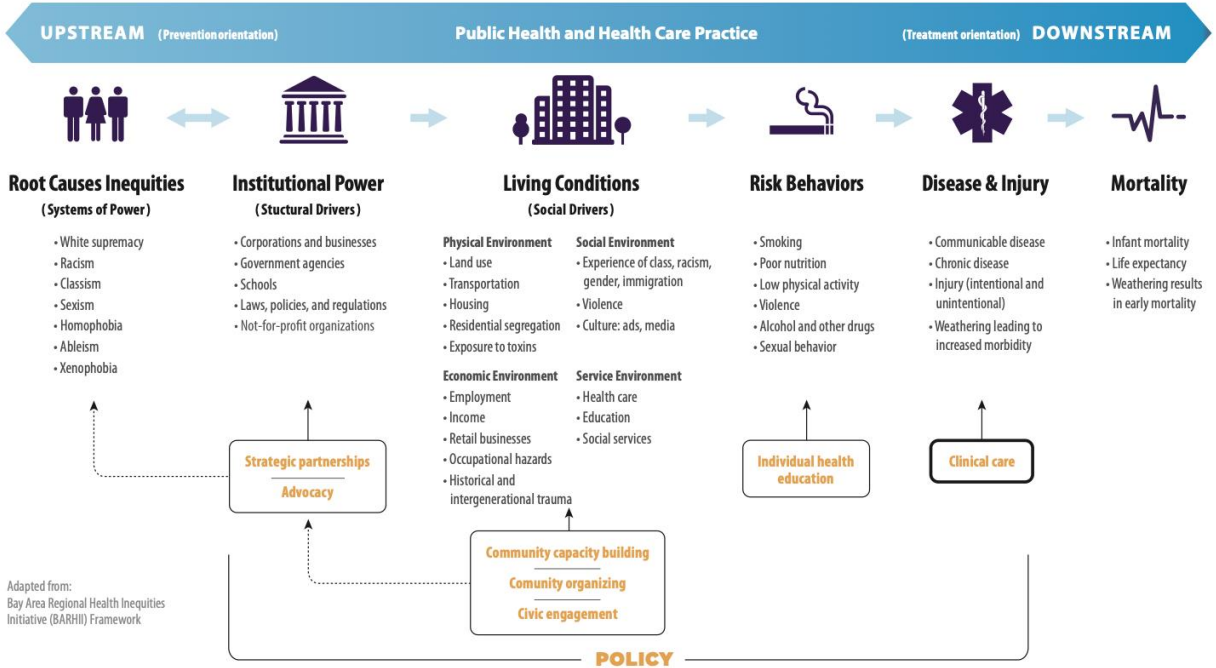


- Underinsured Latinos with existing health issues (MetS) display poorer memory outcomes than those with health insurance.
- Increasing access & affordability of health care coverage may prevent cognitive decline in vulnerable groups.

Breton, Foret, Hamlin, & Clark, (in prep)

AMA Health Equity Plan

Figure 3. What Creates Health Framework



AMA, 2019

Q: Why are certain groups of the population at increased risk for dementia?

- Higher rates of chronic vascular health conditions
- Increased exposure to adverse risk factors
- Limited access to resources

Diagnosis, assessment, & treatment issues

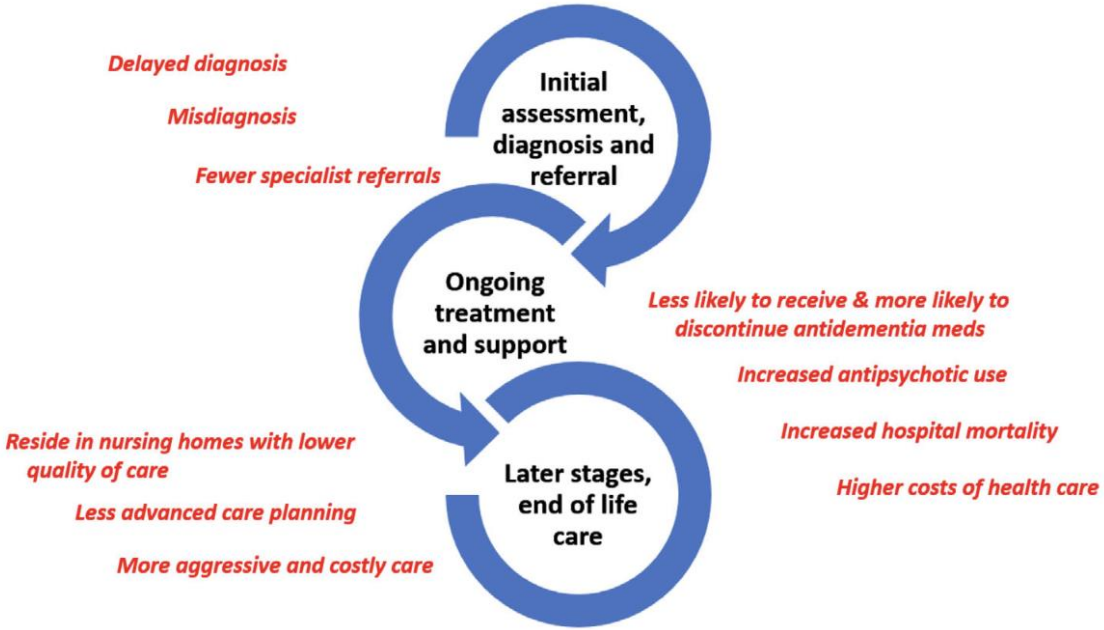


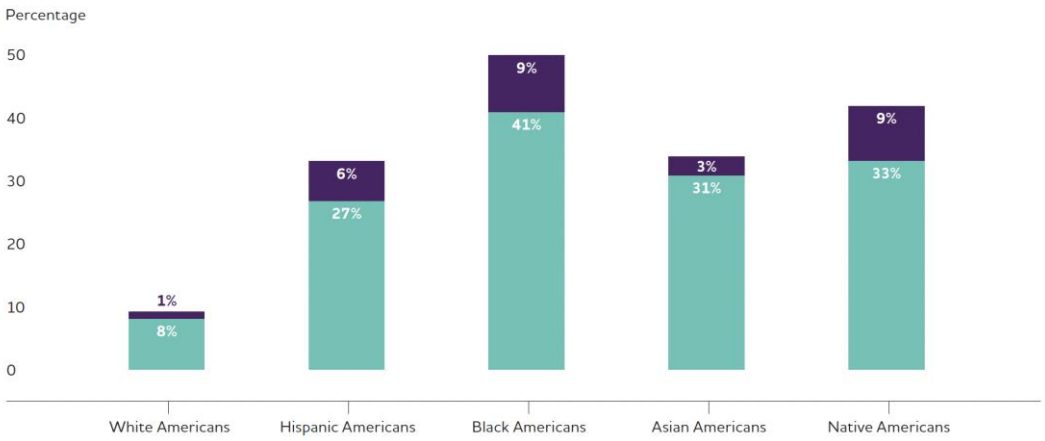
FIGURE 2 Emerging evidence of care disparities for African-American and Latinx persons living with dementia

Aranda et al., 2021

Alz Association Special Report

FIGURE 18

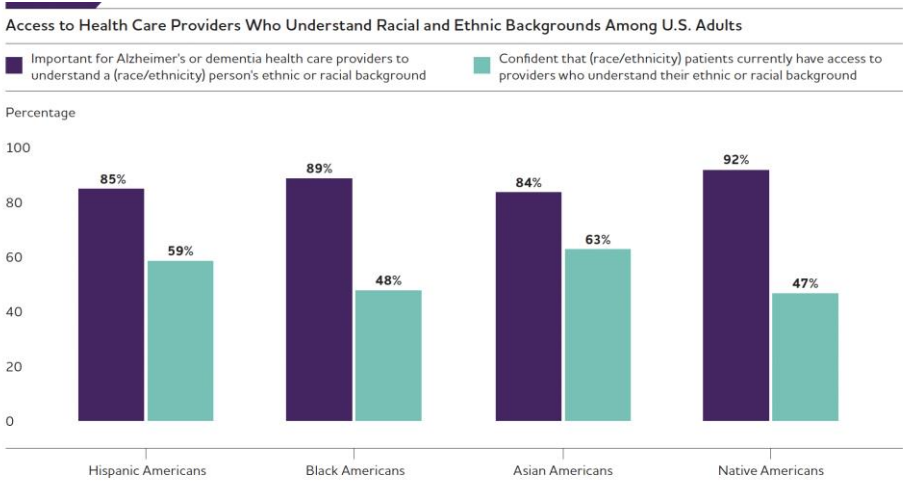
Percentage of U.S. Adults Who Have Experienced Racial or Ethnic Discrimination When Seeking Health Care



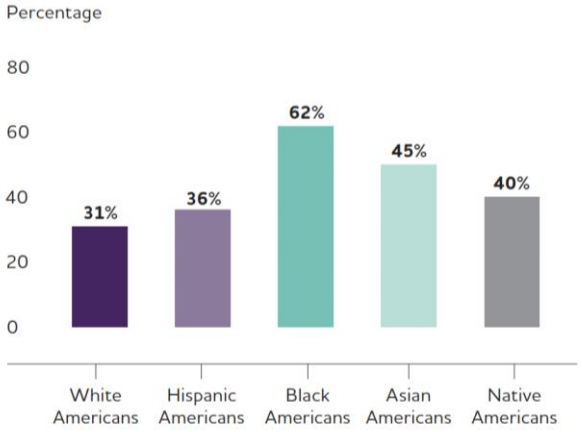
Alz Facts & Figures, 2021

Alz Association Special Report

Access to health care providers who understand Racial/ethnic backgrounds among US adults.



Percent of US adults who believe medical research is biased against people of color



Alz Facts & Figures, 2021

Poor representation in clinical trials

Diversity in Alzheimer's disease drug trials: The important of eligibility criteria (Franzen et a., 2022)

Results: In the 101 included AD trials, participants were predominantly White (median percentage: 94.7%, interquartile range: 81.0–96.7%); and this percentage showed no significant increase or decrease over time (2001–2019). Eligibility criteria such as exclusion of persons with psychiatric illness (78.2%), cardiovascular disease (71.3%) and cerebrovascular disease (68.3%), obligated caregiver attendance (80.2%), and specific Mini-Mental State Examination scores (90.1%; no significant increase/decrease over time) may have led to a disproportionate exclusion of ethnoracially diverse individuals.

Discussion: Ethnoracially diverse participants continue to be underrepresented in AD clinical trials. Several recommendations are provided to broaden eligibility criteria.

Our clinical trials do not include those disproportionately affected by AD!

Drug safety & efficacy concerns

VIEWPOINT

What the Aducanumab Approval Reveals About Alzheimer Disease Research

Jennifer J. Manly, PhD
Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Department of Neurology, Columbia University Irving Medical Center, New York, New York.

M. Maria Glymour, ScD
Department of Epidemiology and Biostatistics, University of California, San Francisco.

The US Food and Drug Administration (FDA) recently provided accelerated approval for aducanumab to treat Alzheimer disease (AD). The decision was controversial within and outside the FDA because of inadequate evidence of medication efficacy. The Peripheral and Central Nervous System Drugs Advisory Committee voted against recommendation of aducanumab and several committee members resigned after approval. FDA approval was based on trials that were not inclusive of the people who bear a disproportionate burden of disease.[1] Only 0.6% (ie, 19 individuals) of participants identified as Black, 3% as Hispanic, 0.03% (1 person) as American Indian or Alaska Native, and 0.03% as Native Hawaiian or Pacific Islander. Of the 9% identified as Asian, 94% were recruited in Asia.[2] Older Black adults are estimated to have AD incidence up to double the rates in older White people. Despite this, Biogen reported that only 6 Black people were randomized to the treatment dose approved by the FDA.

The omission of Black patients from the aducanumab trials is particularly troubling given these racial health inequities. Vascular disease may exacerbate the common adverse events attributed to aducanumab, including microhemorrhages and vasogenic edema, ie, amyloid-related imaging abnormalities (ARIA). People with recent strokes or transient ischemic attacks were excluded from the trials, presumably for safety considerations, but these are not contraindications to prescription on the FDA-approved medication label. Adverse events were also far more common for *APOE e4* allele carriers. Most research indicates that—compared with White individuals—*APOE e4* is more common, although less strongly associated with AD risk,

Q: Why are certain groups of the population at increased risk for dementia?

- Limited access to resources
- Increased exposure to adverse risk factors
- Higher rates of chronic vascular health conditions
- Inequitable assessment & treatment issues

What do we need to do?

- Policies that increase access, resources, & reduce exposure to risk factors
- Acknowledge that dementia risk is partially modifiable & our work occurs begins in early childhood AND late adulthood
- Inclusive workforce and science initiatives must continue if we want to reduce avoidable disparities
- We MUST work together: Bridge gap between science, policy, & those impacted by AD.

Thank you!

Jordana Breton
PhD Student

Abbey Hamlin
PhD Student

The University of Texas at Austin
Department of Psychology

The University of Texas at Austin
Texas Aging & Longevity Center

Key Collaborators

Dr. Stephanie Grasso,
UT Austin

Dr. Andreana
Haley,
UT Austin

Dr. Audrey
Duarte,
UT Austin

Dr. Sid O'Bryant,
UNT

Dr. Kelsey Thomas,
UC San Diego

Other UT Aging Labs

Aphasia Research Lab & Multilingual Aphasia and Dementia Research Lab

- Provide free speech-language interventions to individuals with aphasia
- What is aphasia?
  - Difficulty with language caused by
    - Stroke
    - Neurodegenerative disorders such as Alzheimer's
    - Mild cognitive impairment
    - Other neurological conditions
- We provide services in English, Spanish, and Catalan
- To learn more visit our websites:
- https://slhs.utexas.edu/research/aphasia-research-treatment-lab
- https://slhs.utexas.edu/research/multilingual-aphasia-and-dementia-research-lab/about-lab

- Adult Family Project
- Dr. Karen L. Fingerman
- Contact with: adultfamily@austin.utexas.edu

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Questions?