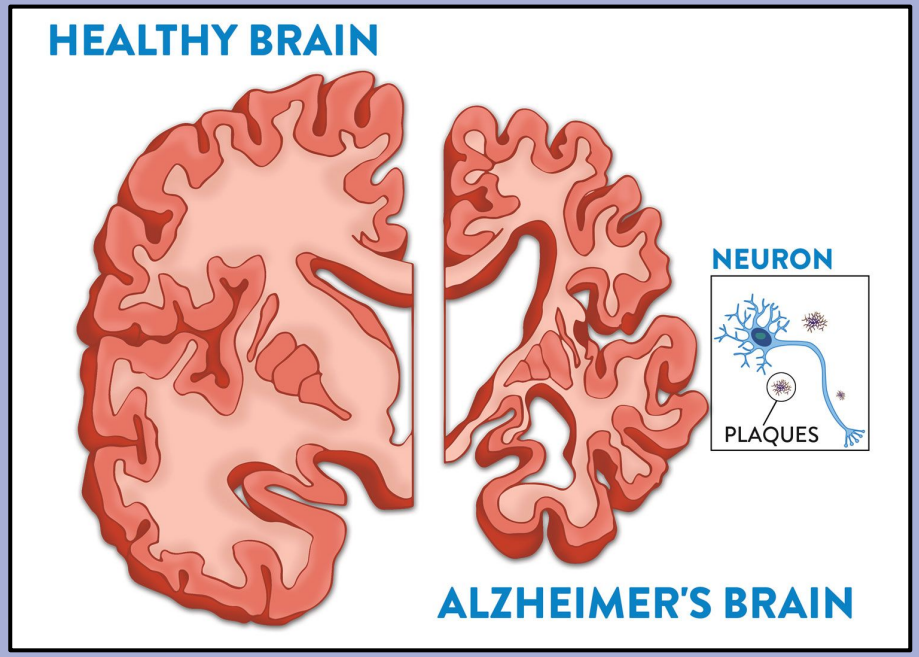
Neuropsychiatric Symptoms in Down Syndrome and Late-Life Alzheimer's Disease

Srisai Saavarni Chilukuri, Ryan Kuhlman, Lidio Jaimes Jr, Noah McMahon, Casie Lin

Mentors: Dr. Daniel Gillen, Dr. David Sultzer, Christina Magana-Ramirez, Tiffany Hu

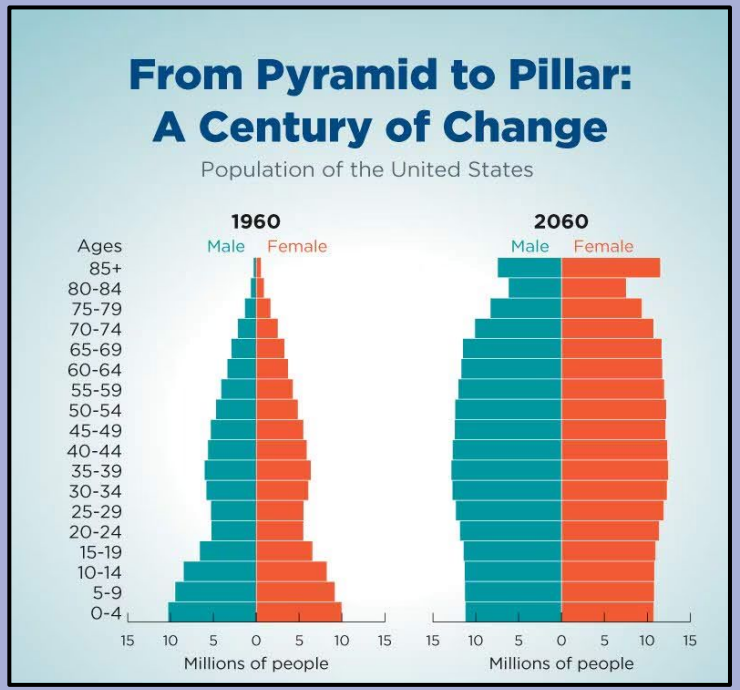
What Characterizes Alzheimer's?

- **Amyloid plaques** and **Tau tangles** can accumulate over time
- Hinder cell communication, inflammatory response, neuronal death
- Memory loss, disinhibition, difficulty with communication



Outlook and Prediction

- Aging population in the US, Alzheimer's expected to become a **major healthcare issue**
- Increased focus on early warning signs
- **Neuropsychiatric Symptoms (NPS)** include anxiety, depression, apathy, irritability, and other symptoms



Alzheimer's and Down Syndrome

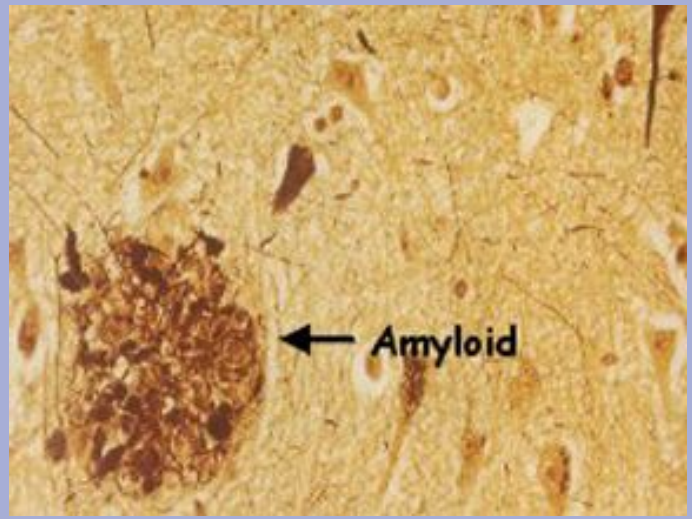
- Extra chromosome 21 leads to overexpression of amyloid precursor protein
- **50%** of individuals with Downs will develop dementia
- By 40, nearly all will experience brain changes consistent with Alzheimer’s

DSAD versus LOAD

- **Alzheimer's due to Down syndrome (DSAD)** vs. **Late-life onset Alzheimer's (LOAD)** share presence of amyloid plaques

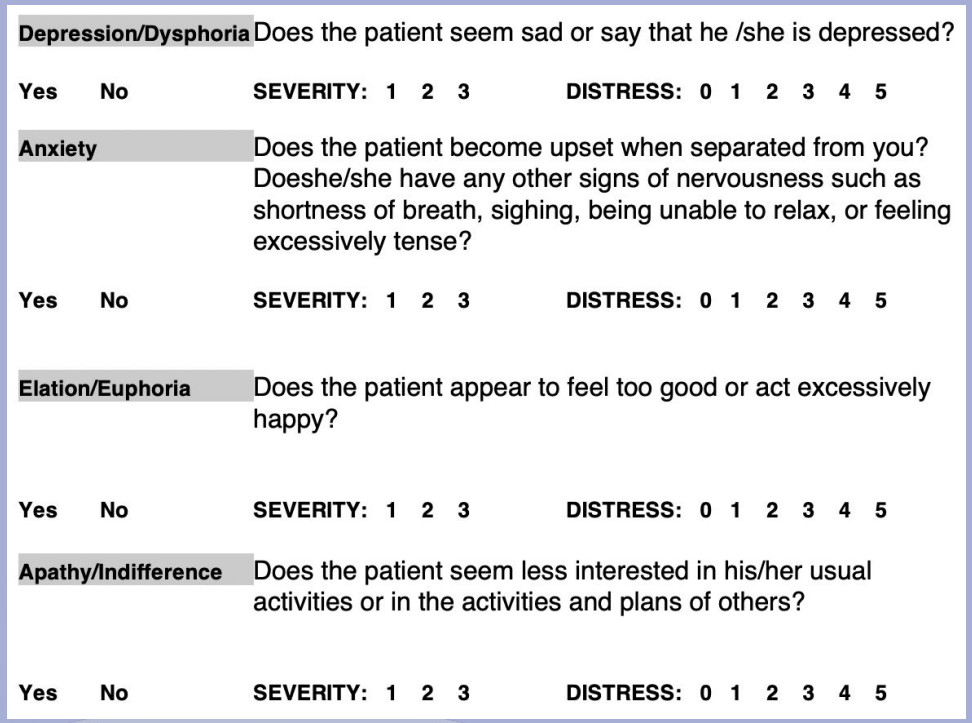
- DSAD has a "purer" form with fewer mixed brain pathologies, additional conditions like sleep apnea

- Similar NPS in DSAD and LOAD suggest linked amyloid pathology; different NPS would indicate other factors are involved



Our response variable: NPI scores

- The Neuropsychiatric Inventory (NPI) is a survey that assess patients' neuropsychiatric symptoms.
- The **NPI-Q (LOAD)** is an abridged version of the **NPI (DSAD)**.
  - **NPI** measures the frequency and severity but **NPI-Q** only measures severity
- A co-participant—e.g. caretaker, family member, or friend—takes the survey for the patient



Depression/Dysphoria	Does the patient seem sad or say that he /she is depressed?	
Yes **No**	**SEVERITY: 1 2 3**	**DISTRESS: 0 1 2 3 4 5**
Anxiety	Does the patient become upset when separated from you? Doeshe/she have any other signs of nervousness such as shortness of breath, sighing, being unable to relax, or feeling excessively tense?	
Yes **No**	**SEVERITY: 1 2 3**	**DISTRESS: 0 1 2 3 4 5**
Elation/Euphoria	Does the patient appear to feel too good or act excessively happy?	
Yes **No**	**SEVERITY: 1 2 3**	**DISTRESS: 0 1 2 3 4 5**
Apathy/Indifference	Does the patient seem less interested in his/her usual activities or in the activities and plans of others?	
Yes **No**	**SEVERITY: 1 2 3**	**DISTRESS: 0 1 2 3 4 5**

Our response variable: NPI scores

We are looking at 2 NPI scores:

- Presence/absence of 12 symptoms
  - Maximum **sum of symptoms**: 12
- Severity ranging from 1-3 for each symptom
  - Maximum **sum of severity**: 12*3 = 36
- We will be using the **sum of severity** for our analyses

Neuropsychiatric Symptoms	
- Delusions	- Disinhibition
- Hallucinations	- Irritability
- Agitation	- Motor behaviors
- Depression	- Nighttime disturbances
- Anxiety	
- Elation	- Appetite disturbances
- Apathy	

Objectives

To better understand the patterns of NPS in the course of AD we will:

1. Identify and compare the pattern of NPS in individuals with **DSAD** and **LOAD** at 3 levels of cognitive impairment

2. Quantify the longitudinal change in NPS over a 6.5 year period in those with **DSAD** and **LOAD**.

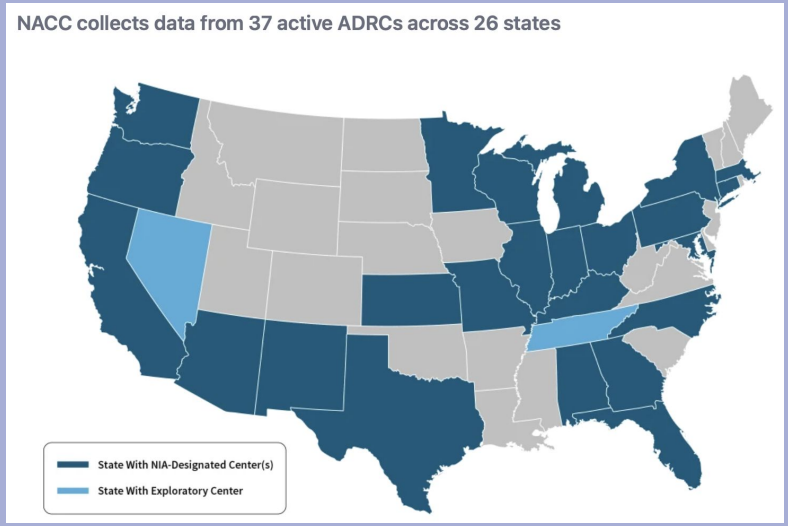
1

NACC Data

NACC Data

The **National Alzheimer's Coordinating Center** (NACC) is the centralized data repository and collaboration hub for the National Institute of Aging's (NIA's) Alzheimer's Disease Research Centers (ADRC) Program

- 1024 recorded variables, ranging from general demographic background to medical history to active symptoms.
  - We focused on 8 of these variables: **age, race, sex, Alzheimer's meds, antidepressant, living situation, sleep apnea, thyroid issues**
  - We are interested in the potential relationships between these variables and subjects' NPI-Q Scores.



Data includes over 183,000 individual visits

Inclusion Criteria

Initial NACC sample size

N = 183097

Isolated observations to first visit

N = 49412

Removed participants under age 55 and with Down Syndrome

N = 46625

Relationship variable subsetted to include only spouse/partner, child, sibling

N = 37750

Removed participants that are Impaired-Non-MCI

N = 36211

NACC Table 1

- Sample Size: 36,211
- Stratified by diagnosis:
  - Normal cognition
  - Mild Cognitive Impairment (MCI)
  - Dementia
- Age increases as cognition declines
- In general, more female than male
- Non-Hispanic White are most represented in data

	Normal cognition (N=13309)	MCI (N=8614)	Dementia (N=14288)	Overall (N=36211)
Age at first NPI (years)				
Mean (SD)	71.1 (8.15)	73.1 (8.07)	73.3 (9.10)	72.5 (8.58)
Median [Min, Max]	70.0 [55.0, 101]	73.0 [55.0, 101]	74.0 [55.0, 103]	72.0 [55.0, 103]
Race and ethnicity				
Hispanic Other	305 (2.3%)	227 (2.6%)	500 (3.5%)	1032 (2.9%)
Non-Hispanic Asian	422 (3.2%)	292 (3.4%)	317 (2.2%)	1031 (2.8%)
Non-Hispanic Black	1871 (14.1%)	1071 (12.4%)	1414 (9.9%)	4356 (12.0%)
Non-Hispanic Other	887 (6.7%)	628 (7.3%)	861 (6.0%)	2376 (6.6%)
Non-Hispanic White	9824 (73.8%)	6396 (74.3%)	11196 (78.4%)	27416 (75.7%)
Sex				
Male	5118 (38.5%)	4649 (54.0%)	7072 (49.5%)	16839 (46.5%)
Female	8191 (61.5%)	3965 (46.0%)	7216 (50.5%)	19372 (53.5%)
Sleep apnea				
No	12385 (93.1%)	7850 (91.1%)	13579 (95.0%)	33814 (93.4%)
Yes	924 (6.9%)	764 (8.9%)	709 (5.0%)	2397 (6.6%)

2

ABC-DS Data

ABC-DS Data

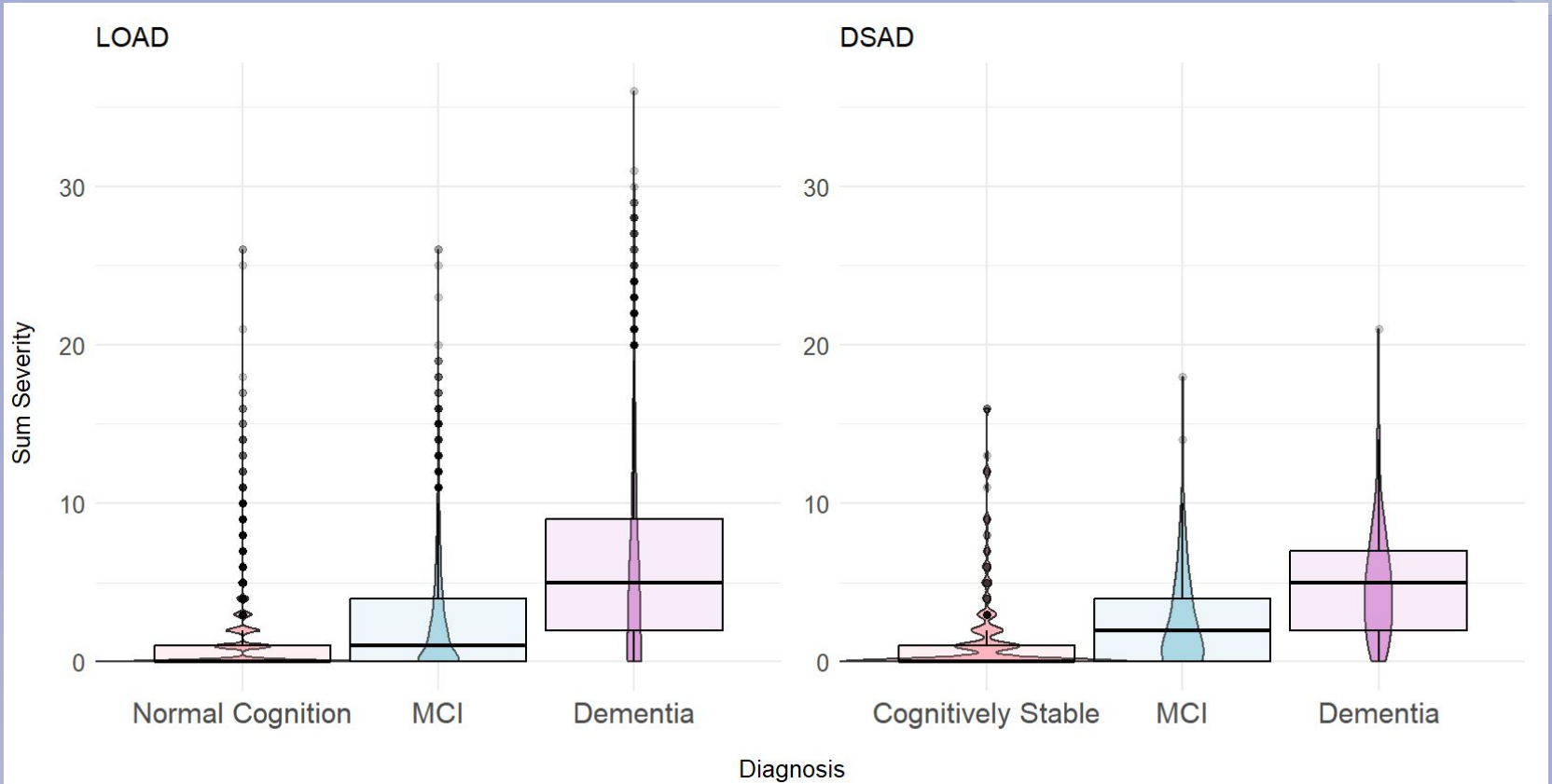
- **Alzheimer Biomarkers Consortium-Down Syndrome** is a longitudinal study
- Data collected at 10 different sites
- Goal: follow a cohort of adults with DS to identify early markers that may herald the onset of AD
- Interested in demographics, health history, NPS, and NPI score

ABC-DS Table 1

- Sample size of 482
  - After removing patients (n=21) who didn't receive a diagnosis
- Age increases as cognition decreases
- Most individuals are Non-Hispanic White
- More male than female

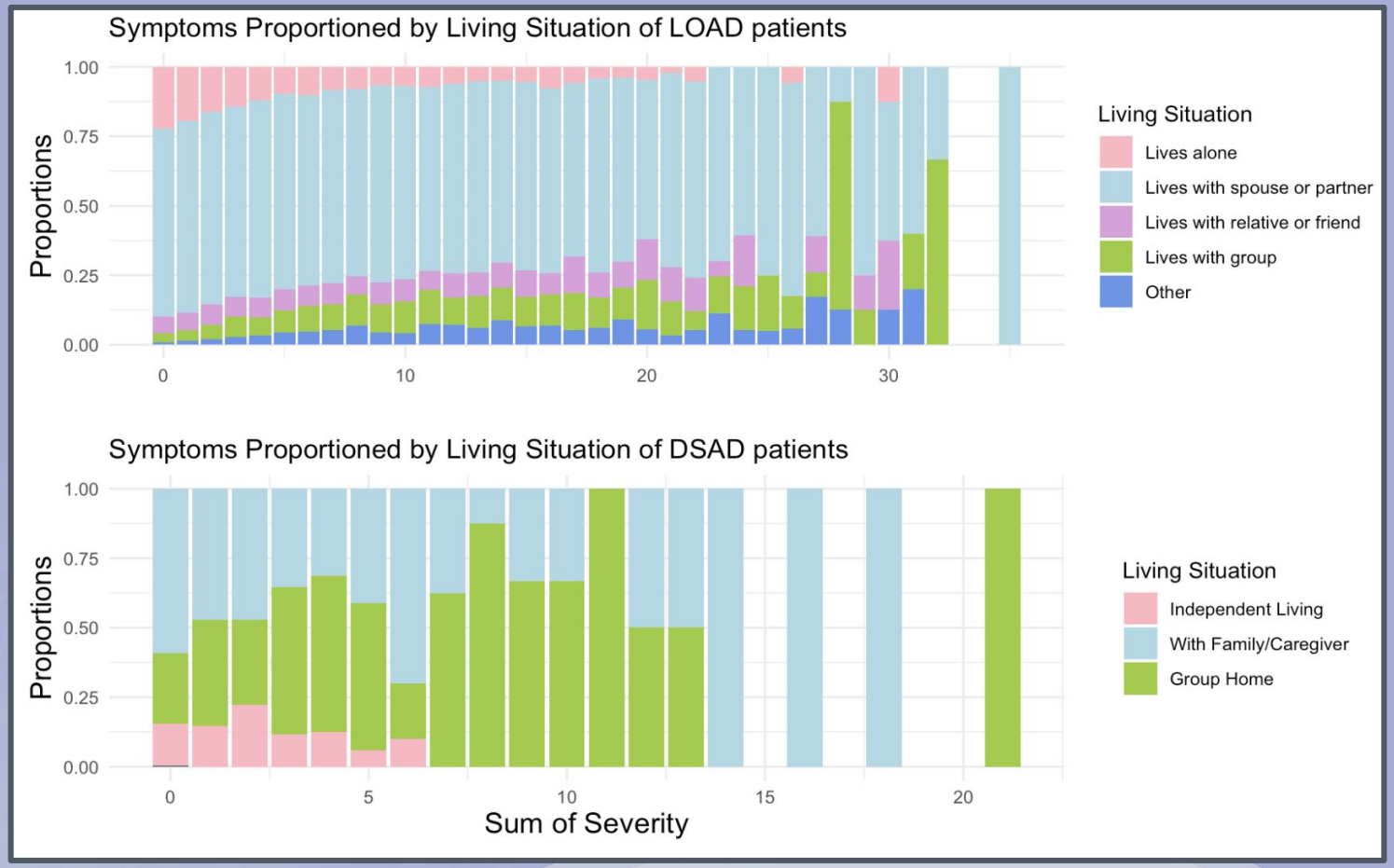
	Cognitively Stable (N=369)	MCI (N=59)	Dementia (N=54)	Overall (N=482)
Age at first NPI (years)				
Mean (SD)	42.2 (8.65)	53.6 (7.22)	54.8 (6.04)	45.2 (9.69)
Median [Min, Max]	41.0 [25.0, 72.0]	53.0 [40.0, 81.0]	55.0 [40.0, 67.0]	44.0 [25.0, 81.0]
Missing	70 (19.0%)	7 (11.9%)	8 (14.8%)	85 (17.6%)
Race and ethnicity				
Non-Hispanic White	334 (90.5%)	55 (93.2%)	50 (92.6%)	439 (91.1%)
Hispanic White	21 (5.7%)	1 (1.7%)	1 (1.9%)	23 (4.8%)
Non-Hispanic Black	3 (0.8%)	2 (3.4%)	2 (3.7%)	7 (1.5%)
Non-Hispanic Asian	5 (1.4%)	1 (1.7%)	0 (0%)	6 (1.2%)
Non-Hispanic Mixed	5 (1.4%)	0 (0%)	1 (1.9%)	6 (1.2%)
Hispanic Mixed	1 (0.3%)	0 (0%)	0 (0%)	1 (0.2%)
Sex				
Male	196 (53.1%)	39 (66.1%)	27 (50.0%)	262 (54.4%)
Female	173 (46.9%)	20 (33.9%)	27 (50.0%)	220 (45.6%)
Sleep apnea				
Absent	229 (62.1%)	35 (59.3%)	43 (79.6%)	307 (63.7%)
Active/Inactive	140 (37.9%)	24 (40.7%)	11 (20.4%)	175 (36.3%)

Sum of Severity by Diagnosis



Clear progression from few symptoms in normal cognition to more severe and variable symptoms in dementia

Sum of Severity Proportioned by Living Situation



Model

- **Cross-sectional model** of relationship between NPI and diagnosis
- Same model for both datasets
- We used **robust variance estimator** to cover potential violations of heteroscedasticity

$$E[NPI_i] = \beta_0 + \beta_1 MCI_i + \beta_2 Dem_i + \overrightarrow{\gamma}^T \overrightarrow{z_i}$$

Stratified Regression Table

Covariate	LOAD		DSAD	
	Est. (95% CI)	p-Val	Est. (95% CI)	p-Val
Diagnosis				
- CN/CS	Referent		Referent	
- MCI	1.74 (1.60, 1.88)	<.001	1.26 (0.06, 2.46)	0.040
- Dementia	4.62 (4.40, 4.85)	<.001	3.50 (2.12, 4.87)	<.001
Sex (Male vs. Female)	0.63 (0.50, 0.77)	<.001	-0.23 (-0.87, 0.40)	0.471
Age (per 10yrs)	-0.24 (-0.33, 0.15)	<.001	0.22 (-0.23, 0.67)	0.333
Race/Ethnicity				
- NH White	Referent		Referent	
- Hispanic	1.42 (1.01, 1,84)	<.001	0.51 (-1.22, 2.24)	0.562
- NH Black	0.40 (0.19, 0.60)	<.001	0.92 (-0.12, 1.96)	0.081
- NH Asian	0.62 (0.29, 0.95)	<.001	3.31 (-1.45, 8.08)	0.172
- Other	0.60 (0.35, 0.84)	<.001	2.38 (-0.58, 5.34)	0.115
Thyroid (Yes vs. No)	0.06 (-0.10, 0.21)	0.473	-0.70 (-1.28, -0.12)	0.018
Antidepressants (Yes vs. No)	1.40 (1.25, 1.55)	<.001	1.42 (0.38, 2.44)	0.007
Sleep Apnea (Yes vs. No)	0.36 (0.19, 0.53)	<.001	0.88 (0.24, 1.53)	0.001

Stratified Regression Table

Covariate	LOAD		DSAD	
	Est. (95% CI)	p-Val	Est. (95% CI)	p-Val
Diagnosis				
- CN/CS	Referent		Referent	
- MCI	1.74 (1.60, 1.88)	<.001	1.26 (0.06, 2.46)	0.040
- Dementia	4.62 (4.40, 4.85)	<.001	3.50 (2.12, 4.87)	<.001
Sex (Male vs. Female)	0.63 (0.50, 0.77)	<.001	-0.23 (-0.87, 0.40)	0.471
Age (per 10yrs)	-0.24 (-0.33, 0.15)	<.001	0.22 (-0.23, 0.67)	0.333
Race/Ethnicity				
- NH White	Referent		Referent	
- Hispanic	1.42 (1.01, 1,84)	<.001	0.51 (-1.22, 2.24)	0.562
- NH Black	0.40 (0.19, 0.60)	<.001	0.92 (-0.12, 1.96)	0.081
- NH Asian	0.62 (0.29, 0.95)	<.001	3.31 (-1.45, 8.08)	0.172
- Other	0.60 (0.35, 0.84)	<.001	2.38 (-0.58, 5.34)	0.115
Thyroid (Yes vs. No)	0.06 (-0.10, 0.21)	0.473	-0.70 (-1.28, -0.12)	0.018
Antidepressants (Yes vs. No)	1.40 (1.25, 1.55)	<.001	1.42 (0.38, 2.44)	0.007
Sleep Apnea (Yes vs. No)	0.36 (0.19, 0.53)	<.001	0.88 (0.24, 1.53)	0.001

3

Combined Cross-Sectional Analysis

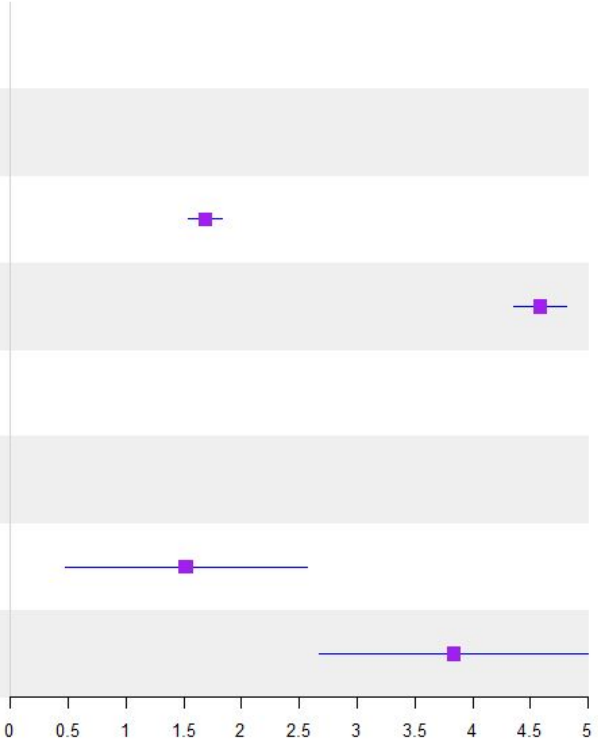
Combined Regression Equation

$$E[NPI_i] = \beta_0 + \beta_1 MCI_i + \beta_2 Dementia_i + \beta_3 Downs_i +$$
$$\beta_4 \mathbf{Downs_i : MCI_i} + \beta_5 \mathbf{Downs_i : Dementia_i} + \overrightarrow{\gamma}^{\mathbf{T}} \overrightarrow{z_i}$$

We are looking to investigate if there is a difference in NPI score-diagnosis relationship, dependent upon whether or not an individual is LOAD or DSAD.

Combined Forest Plot

Covariates	Est.	95% C.I.	P-Val
LOAD			
CN/CS		Referent	
MCI	1.6827	(1.5396 , 1.8258)	< 0.001
Dementia	4.5819	(4.3572 , 4.8066)	< 0.001
DSAD			
CN/CS		Referent	
MCI	1.518	(0.47 , 2.566)	0.005
Dementia	3.837	(2.673 , 5.001)	< 0.001



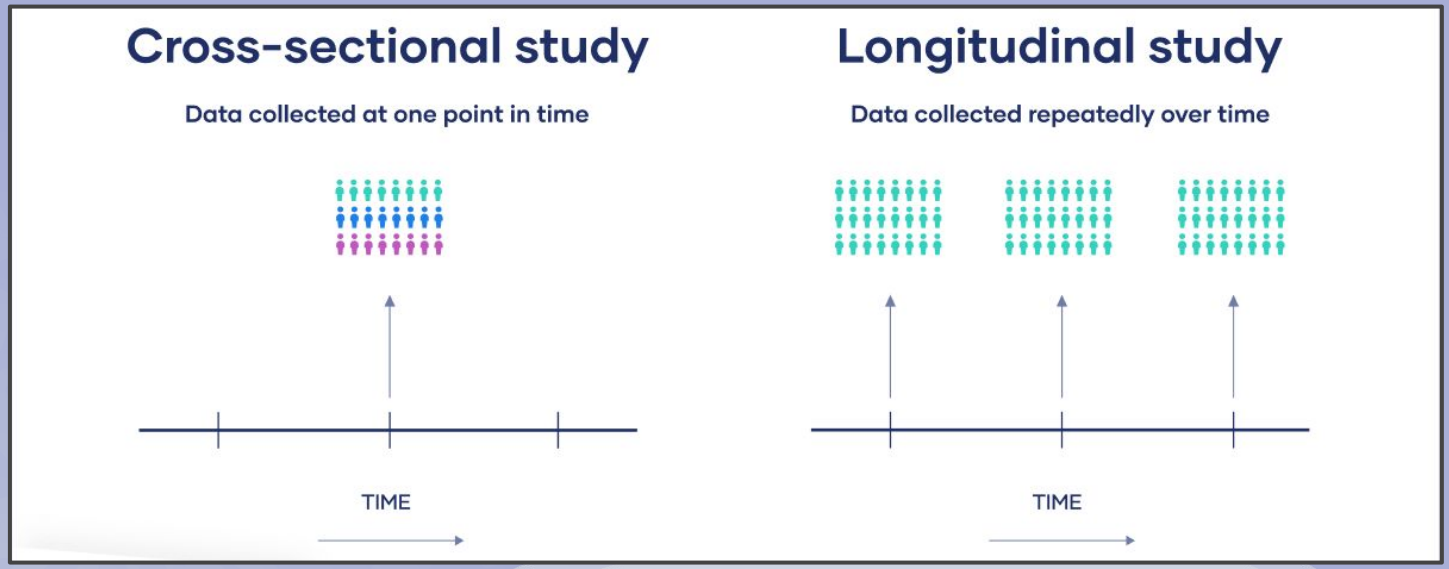
Wald Test for Interaction results in a P-value of 0.46

4

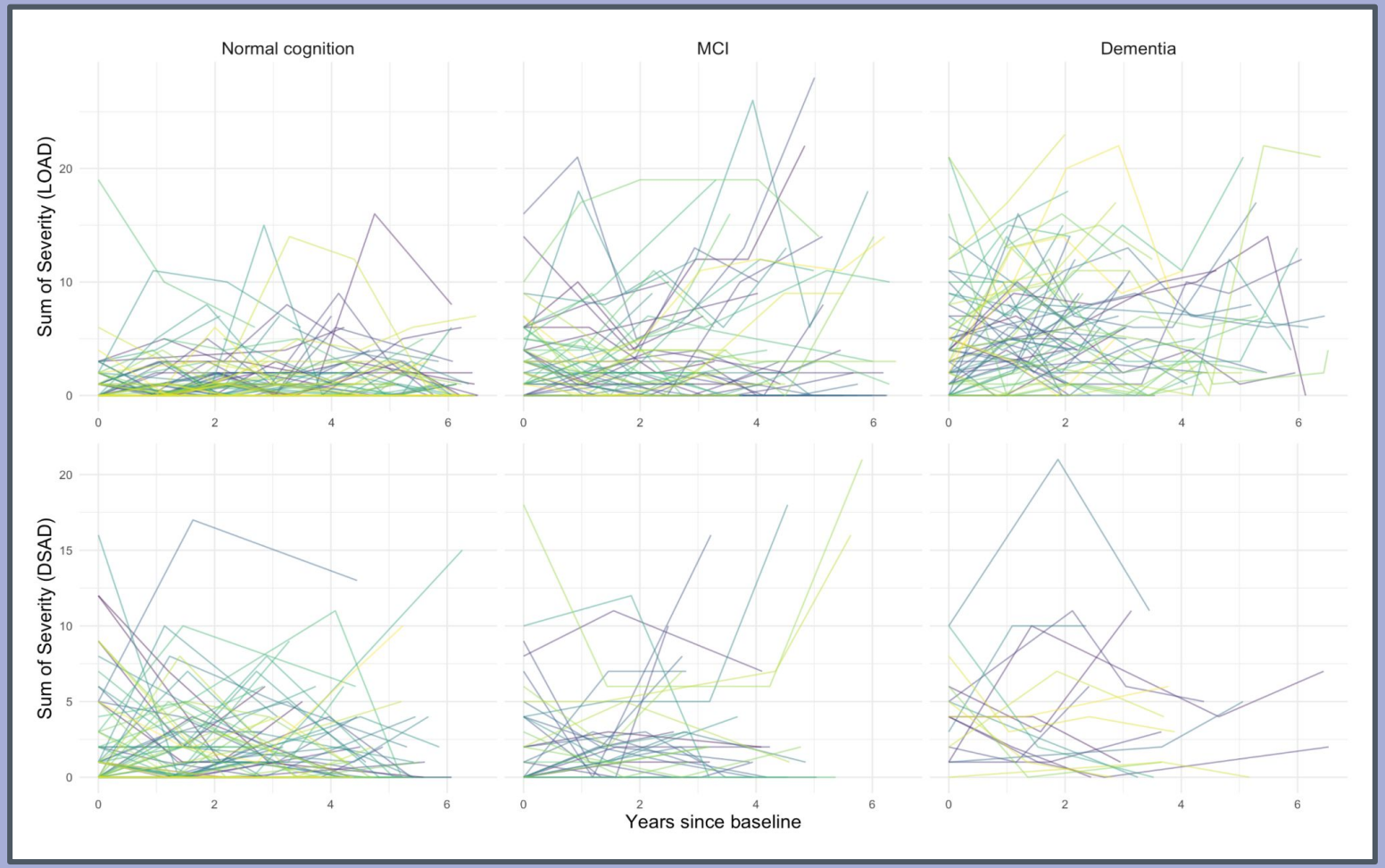
Longitudinal Analysis

Subsetting

- Wanted individuals with at least three visits
  - To visualize actual **change over time**
- Subsetted to individuals who stayed with either study for max of 6.5 years



Sum of Severity Across Time for DSAD and LOAD Patients by Diagnosis



Analysis

- Can no longer account for independence
  - For each patient, each visit will not be independent from their other visits
- **Generalized estimating equation** model
- **AR1** (first-order autoregressive) correlation structure with a robust variance estimator

$$E[NPI_{ij}] = \beta_0 + \beta_1 MCI_{ij} + \beta_2 Dem_{ij} + \beta_3 time_{ij}$$
$$+\beta_4 MCI_{ij} \times time_{ij} + \beta_5 \times Dem_{ij} \times time_{ij} + \overrightarrow{\gamma}^T \overrightarrow{z_i}$$

GEE Table

Estimand	LOAD		DSAD	
	Est. (95% CI)	p-Val	Est. (95% CI)	p-Val
Mean NPI at Baseline				
- CN/CS	1.93 (1.56, 2.30)	<.001	2.41 (1.14, 3.67)	<.001
- MCI	3.32 (2.94, 3.70)	<.001	3.00 (1.38, 4.62)	<.001
- Dementia	4.96 (4.57, 5.35)	<.001	3.70 (2.27, 5.12)	<.001
Mean Change in NPI per Year				
- CN/CS	0.00 (-0.01, 0.01)	0.936	-0.35 (-0.58, -0.13)	0.002
- MCI	-0.05 (-0.07, -0.02)	0.001	-0.43 (-0.80, -0.06)	0.021
- Dementia	0.21 (0.18, 0.24)	<.001	0.20 (-0.28, 0.68)	0.409

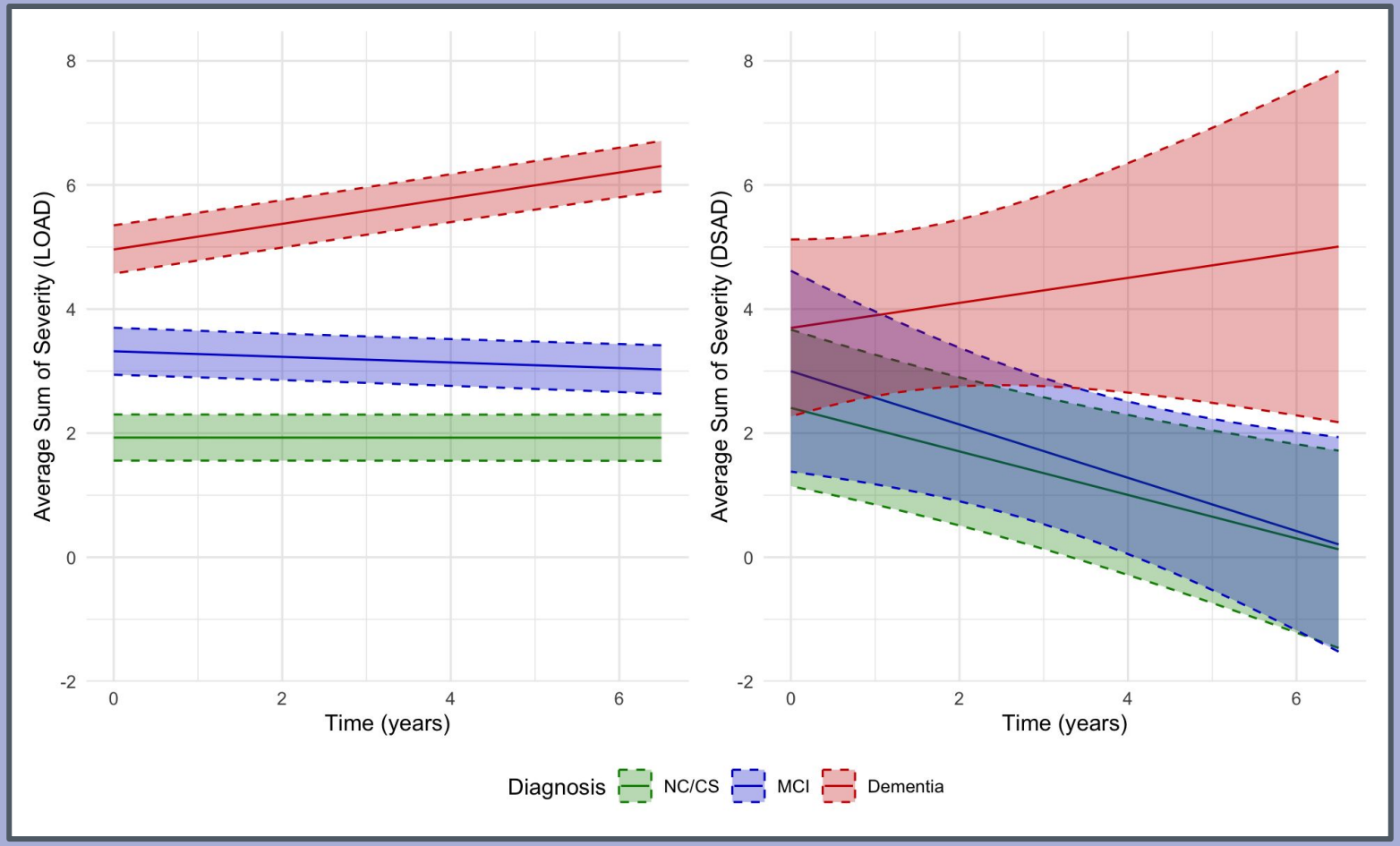
AR1 correlation coefficient: **0.596**
Wald test for interaction results in a P-value of: **0.906**

GEE Table

Estimand	LOAD		DSAD	
	Est. (95% CI)	p-Val	Est. (95% CI)	p-Val
Mean NPI at Baseline				
- CN/CS	1.93 (1.56, 2.30)	<.001	2.41 (1.14, 3.67)	<.001
- MCI	3.32 (2.94, 3.70)	<.001	3.00 (1.38, 4.62)	<.001
- Dementia	4.96 (4.57, 5.35)	<.001	3.70 (2.27, 5.12)	<.001
Mean Change in NPI per Year				
- CN/CS	0.00 (-0.01, 0.01)	0.936	-0.35 (-0.58, -0.13)	0.002
- MCI	-0.05 (-0.07, -0.02)	0.001	-0.43 (-0.80, -0.06)	0.021
- Dementia	0.21 (0.18, 0.24)	<.001	0.20 (-0.28, 0.68)	0.409

AR1 correlation coefficient: **0.378**
Wald test for interaction results in a P-value of: **0.997**

Fitted Average Sum of Severity over time by diagnosis



5

Conclusions

Objective 1:

Identify and compare the pattern of NPS in individuals with **DSAD** and **LOAD** at 3 levels of cognitive impairment

- Interaction Terms between Downs & Diagnosis are **insignificant**
- We cannot conclude that there is a differential association between NPI score and diagnosis based upon whether an individual is LOAD or DSAD
- Presence/severity of NPS across levels of cognitive skills appears to be no different among those with DS compared to older adults with normal cognition or progression to MCI or AD dementia.

Objective 2:

Measure the longitudinal change in NPS over a 6.5 year period in those with **DSAD** and **LOAD**.

- Interaction terms between Time & Diagnosis are **insignificant**
- We cannot conclude that there is a differential association between NPI score and diagnosis based upon what time point or visit is being measured
- The longitudinal analysis is similar for those with dementia, but different for MCI and Normal Cognition.
    - Important because if a cognitively stable or MCI DSAD patient experiences a high sum of severity then something is wrong

References

https://www.nia.nih.gov/research/abc-ds

https://www.census.gov/library/visualizations/2018/comm/century-of-change.html

Alzheimer’s disease facts and figures. Alzheimers Dement 2024;20:3708-3821.

Fortea J, Zaman SH, Hartley S, Rafii MS, Head E, Carmona-Iragui M. Alzheimer's disease associated with down syndrome: A genetic form of dementia. Lancet Neurol 2021;20:930-942.

Tampi RR, Jeste DV. Dementia is more than memory loss: Neuropsychiatric symptoms of dementia and their nonpharmacological and pharmacological management. Am J Psychiatry 2022;179:528-543.

Weissberger GH, Melrose RJ, Narvaez TA, Harwood D, Mandelkern MA, Sultzer DL. 18F-fluorodeoxyglucose positron emission tomography cortical metabolic activity associated with distinct agitation behaviors in Alzheimer disease. Am J Geriatr Psychiatry 2017;25:569-579.

Sultzer DL. Mild behavioral impairment: A new domain of late-life psychiatric symptoms. Am J Geriatr Psychiatry 2019;27:835-837.

Lewis CK, Bernstein OM, Grill JD, Gillen DL, Sultzer DL. Anxiety and depressive symptoms and cortical amyloid-β burden in cognitively unimpaired older adults. J Prev Alzheimers Dis 2022;9:286-296.

Lautarescu BA, Holland AJ, Zaman SH. The early presentation of dementia in people with Down syndrome: A systematic review of longitudinal studies. Neuropsychol Rev 2017;27:31-45.

Questions?