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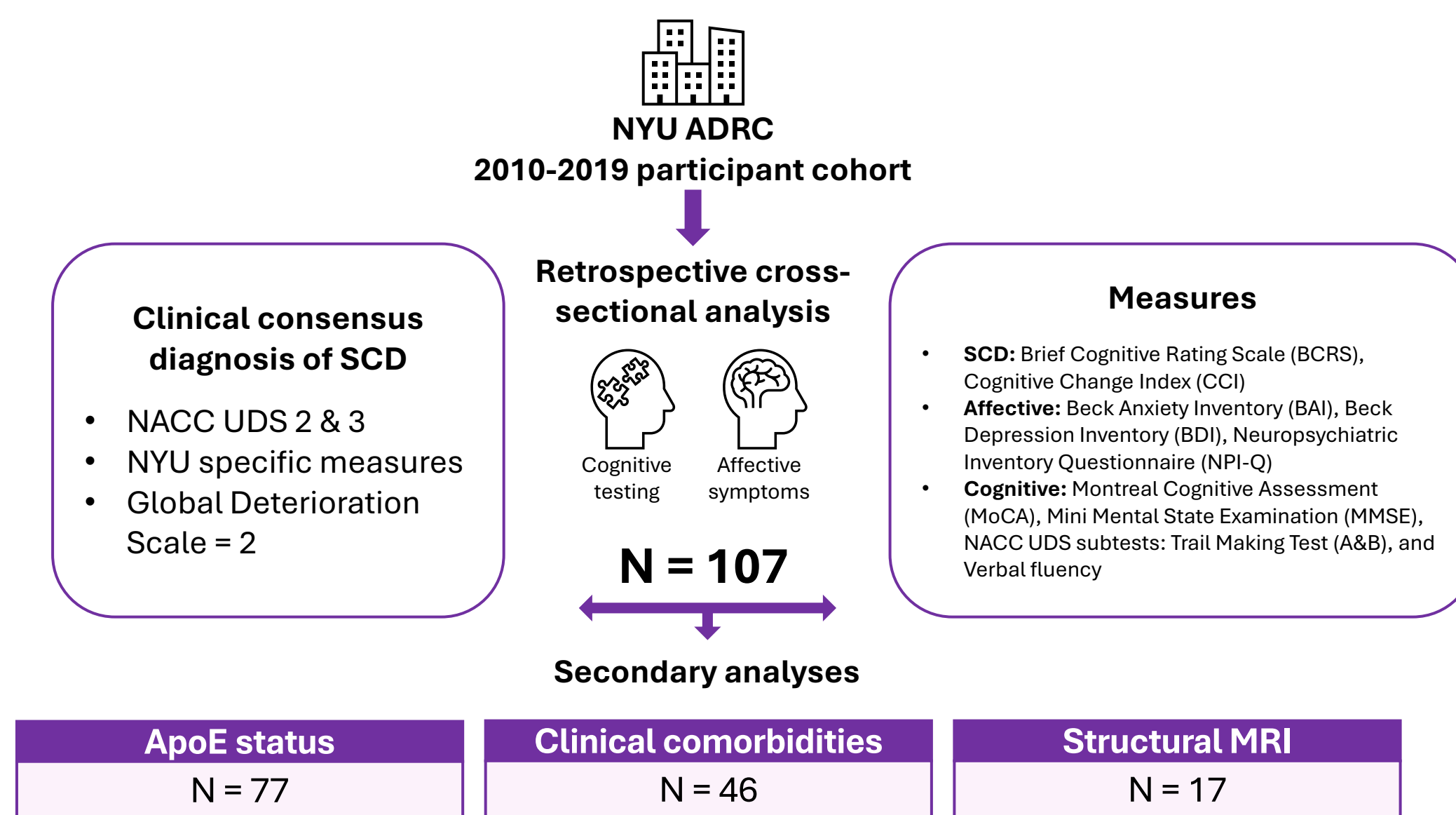
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Background

- Subjective cognitive decline (SCD) is a self-perceived cognitive decline despite normal objective cognition and may represent a preclinical stage of Alzheimer's¹.
- Anxiety and depression are common in early Alzheimer's disease (AD) and are also associated with cognitive decline^{2,3}.
- The combination of SCD and affective symptoms may indicate increased risk for later impairment⁴.
- It is unclear whether anxiety and depression in SCD have distinct clinical and structural imaging correlates.

Methods

Study Design



Statistical analyses

Unpaired t-test for magnitude comparisons, ANOVA for individual responses. Simple and multiple linear regression models when appropriate, with models adjusted for demographic and clinical variables that were statistically significant in the first analysis.

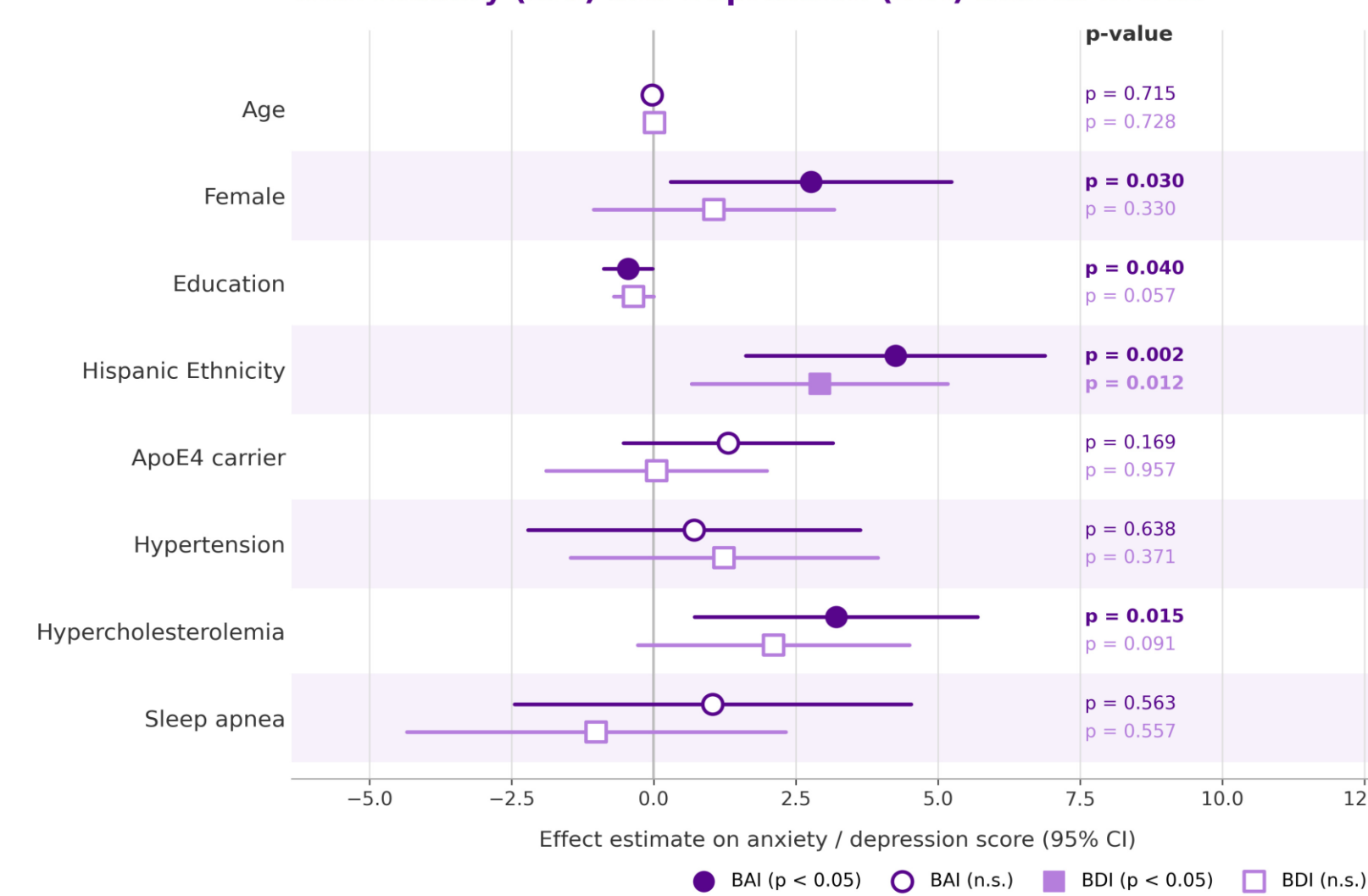
Table 1. Distribution of demographic characteristics and comorbidities (n=107)

Characteristic	Mean	SD
Age (yrs)	67.7	7.8
Education (yrs)	16.7	2.5
N		%
Sex		
Female	82	75.70
Male	25	23.40
Ethnicity		
Hispanic	20	18.69
Non-Hispanic	87	81.31
ApoE status (n=77)		
E4 carriers	27	35.06
E4 non-carriers	50	64.94
Comorbidities (n=46)		
Diabetes	0	0.00
Hypertension	35	76.09
Hypercholesterolemia	17	36.96
Sleep apnea (n=39)	7	17.95

Results

Demographic and vascular factors were primarily associated with anxiety. Hispanic ethnicity associated with both anxiety and depression.

Figure 1. Association of Demographic Characteristics and Comorbidities with Anxiety (BAI) and Depression (BDI) Scores in SCD



Depressive symptoms had a stronger correlation with subjective cognitive complaints. CCI and BCRS items significantly associated with **higher depression scores**. Specific domains associated with both anxiety and depression: psychomotor function, praxis and calculation.

Figure 2. Heat map of associations between affective symptoms and SCD complaints
(Multiple linear regression adjusted for age, gender, education, and Hispanic ethnicity)

SCD Domain / Complaint	Anxiety (BAI)	Depression (BDI)
Names and faces		p=0.026
New information recall		p=0.003
Problem reasoning		p=0.044
Following stories		p=0.004
Psychomotor function	p=0.038	p=0.022
Praxis	p=0.002	p=0.050
Calculation	p=0.024	p=0.023
Mood and behavior		p=0.006

Overall, cognitive performance measures showed limited and inconsistent associations with affective symptoms after controlling demographics. Lower global cognitive performance (MMSE) was associated with higher anxiety in unadjusted models. No significant associations were observed between MMSE or MoCA scores and depression. Executive function, as measured by TMT-A, was associated with higher anxiety in unadjusted models, but not after adjustment. Depression was associated with poorer performance on verbal fluency (vegetables) in unadjusted analyses.

Table 2. Linear regression analysis to assess cognitive performance and anxiety and depression scores in SCD

Test	Model	BAI			BDI		
		Effect	SE	p value	Effect	SE	p value
MMSE	Model 1	-0.71	0.32	0.029	-0.17	0.27	0.519
	Model 2	-0.58	0.36	0.107	-0.09	0.30	0.772
MoCA	Model 1	-0.64	0.36	0.083	0.02	0.35	0.949
	Model 2	-0.71	0.40	0.085	-0.05	0.42	0.898
Verbal fluency - Animals	Model 1	-0.00	0.09	0.979	0.01	0.08	0.913
	Model 2	0.04	0.10	0.711	0.05	0.09	0.596
Verbal fluency - Vegetables	Model 1	-0.12	0.13	0.980	-0.23	0.10	0.028
	Model 2	-0.06	0.15	0.720	-0.21	0.13	0.116
TMT A	Model 1	0.14	0.04	0.002	0.07	0.04	0.075
	Model 2	0.10	0.05	0.055	0.03	0.05	0.510
TMT B	Model 1	0.01	0.01	0.086	0.01	0.00	0.251
	Model 2	0.00	0.01	0.508	0.00	0.01	0.510

Model 1: unadjusted simple linear regression. **Model 2:** multiple linear regression adjusted for age, gender, education, and Hispanic ethnicity. Values of statistical significance <0.05 in bold.

Greater anxiety and depression were associated with reduced cortical thickness in frontotemporal regions. Specifically, thinner cortex in the right rostral middle frontal gyrus (RMFG) was associated with both higher anxiety and depression across all models. Depression was additionally associated with reduced thickness in the right pars orbitalis. Anxiety was associated with reduced thickness in the right medial orbitofrontal cortex, left caudal anterior cingulate, and left parahippocampal gyrus. These findings remained consistent after adjustment for age and sex.

Table 3. Multiple linear regression models correlating anxiety and depression scores with cortical thickness areas in neuroimaging (n=17)

Cortical area	Model	Anxiety (BAI)			Depression (BDI)		
		Effect	SE	p value	Effect	SE	p value
R rostral middle frontal	Model 1	-25.46	10.94	0.034	-29.68	13.41	0.043
	Model 2	-25.48	11.32	0.041	-29.70	13.88	0.051
	Model 3	-25.31	11.30	0.042	-30.44	13.21	0.037
R pars orbitalis	Model 1	-7.96	4.13	0.073	-13.12	4.44	0.010
	Model 2	-8.26	4.33	0.077	-13.62	4.63	0.011
	Model 3	-8.37	4.26	0.070	-12.61	4.55	0.015
R medial orbitofrontal	Model 1	-16.69	6.09	0.015	-3.72	8.98	0.685
	Model 2	-16.80	6.32	0.019	-3.76	9.33	0.693
	Model 3	-17.18	6.23	0.016	-2.80	9.10	0.762
L caudal anterior cingulate	Model 1	-6.09	2.70	0.039	-5.66	3.49	0.125
	Model 2	-6.13	2.80	0.046	-5.70	3.62	0.137
	Model 3	-6.04	2.80	0.049	-6.05	3.45	0.101
L parahippocampal	Model 1	-6.42	2.35	0.016	-1.34	3.47	0.704
	Model 2	-6.46	2.44	0.019	-1.35	3.60	0.714
	Model 3	-6.71	2.41	0.015	-0.87	3.53	0.808

Multiple linear regression unadjusted (model 1), adjusted for age (model 2), adjusted for sex (model 3). R: Right; L: Left. Values of statistical significance <0.05 in bold.

Conclusions

- Our findings may suggest that although overlapping, anxiety and depression in SCD may reflect partially different clinical and neurobiological processes.
- Hispanic ethnicity was associated with both anxiety and depression, with a stronger effect observed for anxiety.
- Depression is more strongly associated with subjective cognitive complaints.
- Anxiety is associated with frontotemporal cortical thinning and vascular risk factors.

Future directions

- Longitudinal studies are needed to determine whether the distinct cognitive and neuroanatomical profiles associated with anxiety and depression in individuals with SCD predict differential risk for cognitive decline or dementia.
- Further research should investigate the mechanisms underlying these distinct associations and evaluate their potential as early markers of disease progression.

References

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Acknowledgements

This study was funded by NIH P30AG066512 and the Louis J and June E Kay Foundation.

