Modeling Trajectories of Cognitive Function across the Life Course: Integrative Data Analysis (IDA) of Add Health and Other Cohort Studies

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The National Longitudinal Study of Adolescent to Adult Health

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- Collaborators

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Background & Significance

- Cognitive decline and Alzheimer's Disease (AD) is a major public health concern
  - Dementia prevalence globally estimated to double from 20.2 million in 1990 to 43.8 million in 2016
  - AD prevalence in the U.S.: 4.5 million in 2000 →14 million by 2050
- No effective treatments for AD and dementia at present
  - Only for symptoms and none for delaying the disease process
- Prevention and interventions addressing cognitive deficits at the very early preclinical phases are critical

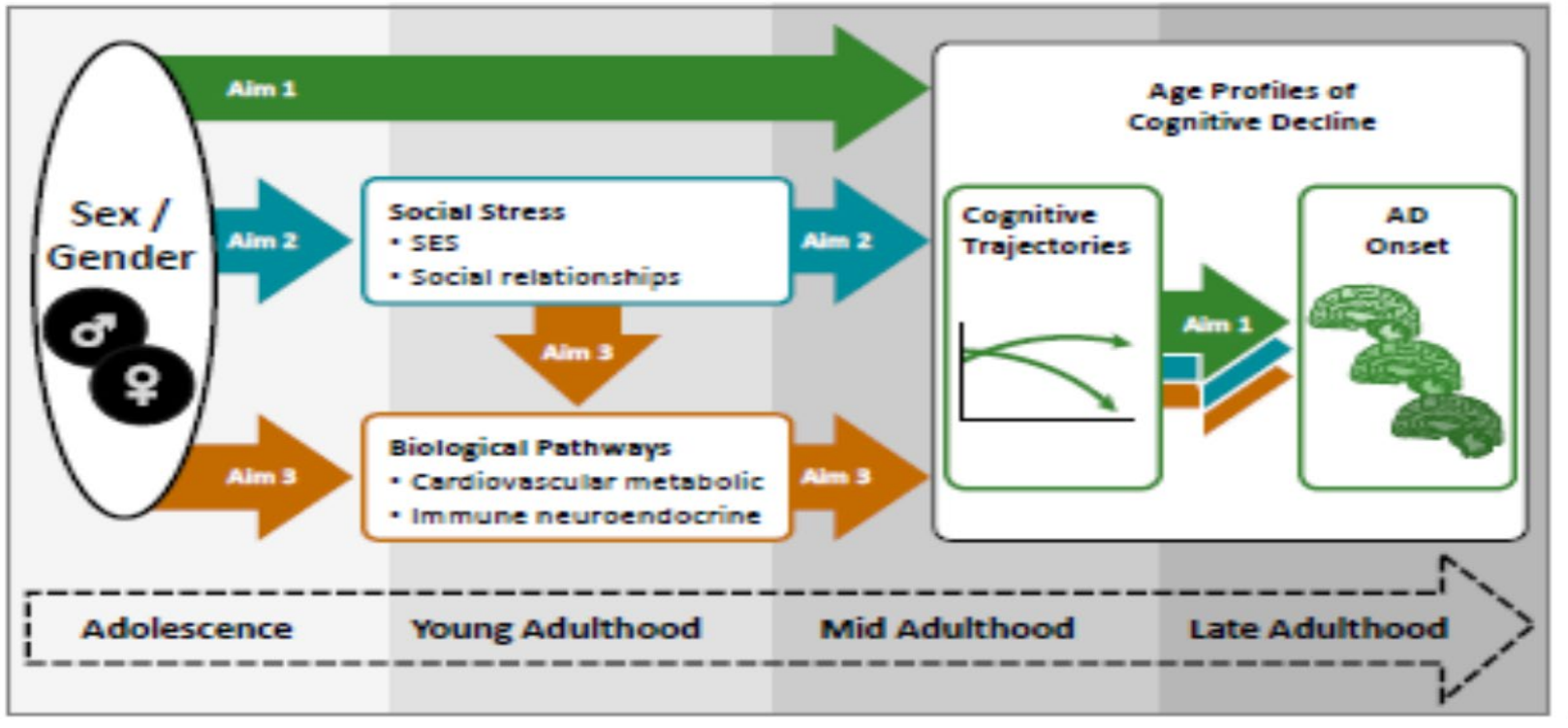
Research Gaps

- Age-related cognitive change over the life span
  - “Brain/Cognitive Reserve hypothesis” suggests that AD pathophysiology changes occur long before older adulthood but has not been not properly tested.
  - Lack of data on early and mid-life exposures and risks.
  - Analyses focused on rates or levels at a point in time, but rarely assessed change with age across multiple life stages.
  - Limited tests of the patterns of variation restricted to small, regional samples with short-term follow-ups.

Research Gaps

- Social status and disparities in cognitive decline over the life course
  - The links between early-life social disadvantages (e.g., related to gender, race/ethnicity, and education) and later-life cognitive decline are not established.
  - The life course mechanism underlying the link are not clear: when do the cognitive impacts of social status emerge in life and how long do they last?
  - Previous research is limited to cross-sectional data or a single life stage (e.g., old age).
  - No knowledge of how the social disparities unfold or change over the full life course.
  - Extensive longitudinal studies of life course social status in association with cognitive decline are mandatory to addressing these gaps.

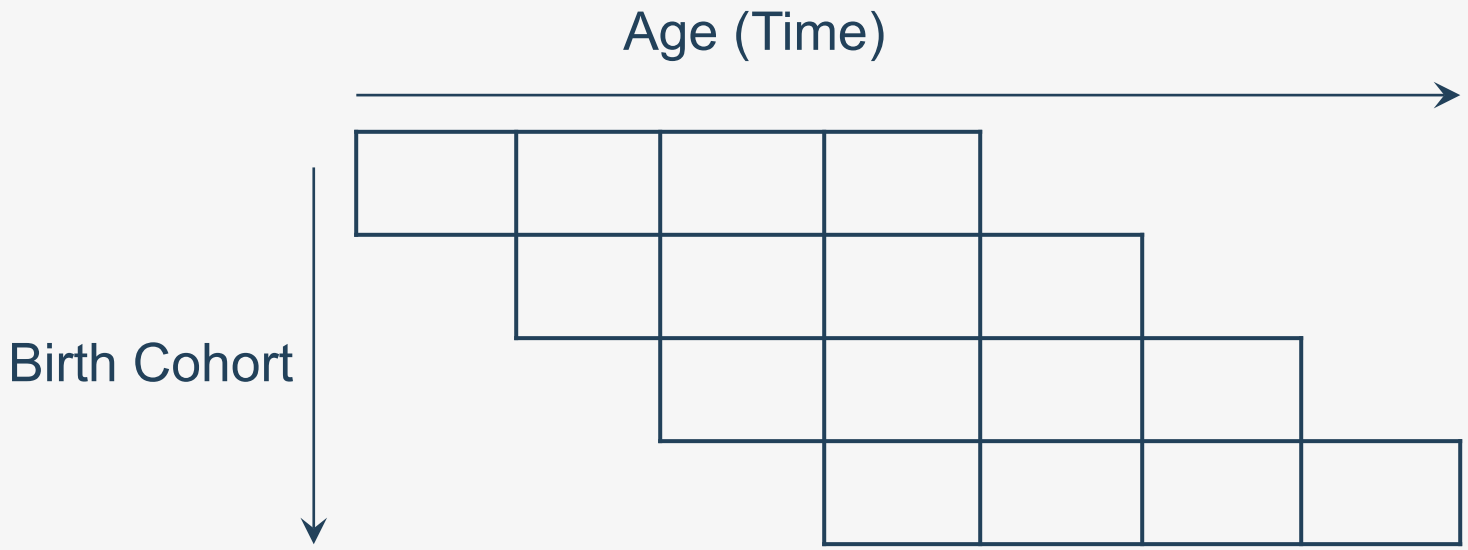
A General Conceptual Framework



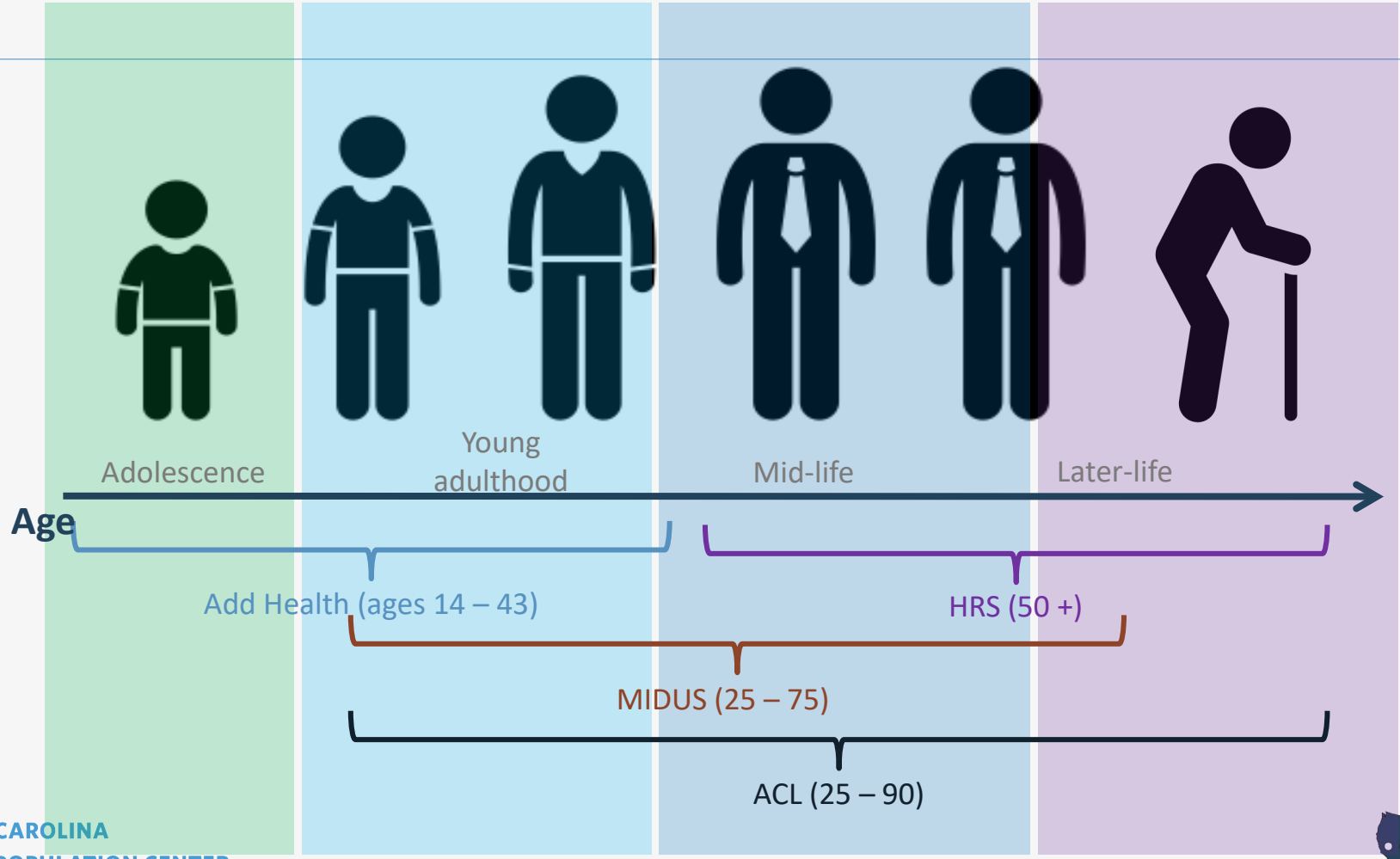
Specific Aims

- Model age trajectories of cognitive function over the life course using a novel application of the Integrative Data Analysis (IDA) methodology for longitudinal data
- Examine gender, race/ethnicity, and education differences in age trajectories of cognitive function over the life course
- Assess variation across a large range of historical birth cohorts to understand the role of secular trends in key risk factors (e.g., gender roles, structural racism, and education).

The Accelerated Longitudinal Cohort Data Structure



An Integrative Life Course Research Design



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Longitudinal Integrative Data Analysis (IDA)

- IDA is a set of statistical tools for analyzing two or more independent samples (Curran & Hussong, 2009; 2013)
- A novel application of IDA to longitudinal modeling of age trajectories (Yang et al., 2021)
  - Jointly modeling multiple cohort studies with an augmented age range from 12 to 90+
  - *Pooled* IDA: combined dataset from separate samples using a *cohort sequential design*
  - *Coordinated* IDA: parallel models are fit to each separate sample and results are compared within and across study

Longitudinal IDA

- Innovative advantages:
  - Test of novel life course hypotheses to address age dynamics over far more extended developmental and historical periods
  - Increase power: larger combined sample sizes and greater representation from across-sample heterogeneity
  - Modeling heterogeneity across studies strengthens internal and external validity about population inferences
  - Support data sharing for a more cumulative science of population health

Data and Study Samples

- Four NIH Population-based Cohort Studies
  - *National Longitudinal Study of Adolescent to Adult Health*: 1994-5 (Wave I), 2008-20 (Wave IV), and 2016-8 (Wave V)
  - *National Survey of the Midlife Development in the United States* (MIDUS): 2005 - 2013 (Waves II and III)
  - *Health and Retirement Study* (HRS): 1996 – 2016
  - *Americans' Changing Lives Study* (ACLs): 1986 – 2011 (Waves 1 – 5)

- Inclusion / Exclusion Criteria
  - Included: At least one wave of cognitive measures
  - Excluded: Add Health age-discordant grade level or school dropout (N = 2,616)
  - Excluded: Non-Hispanic Others (2% - 8%; total N = 2,562)
  - Excluded: Missing data on covariates (<1%; total N = 378)

Table 1. Data and Study Sample for the Pooled Integrative Analysis of Episodic Memory

Survey	N (baseline)	N (person-years)	Survey Years	Length of Follow-Up	# Study Waves
Add Health	12,046	13,134	2008-2018	10 yrs	2
MIDUS	3,817	6,067	2009-2013	4 yrs	2
HRS	35,278	184,481	1996-2016	20 yrs	10
Combined	**51,141**	**203,682**	**1996-2018**	**22 yrs**	**14**

Table 2. Data and Study Samples for the Coordinated Integrative Analysis of Overall Cognitive Function

Survey	N (baseline)	N (person-years)	Survey Years	Length of Follow-Up	# Data Waves
Add Health	12,039	13,127	1994-2018	24 yrs	3*
MIDUS	3,820	6,185	2009-2013	4 yrs	2
HRS	32,985	124,299	1996-2016	20 yrs	10
ACL	3,532	11,623	1986-2011	25 yrs	5

*Includes Wave I where an additional cognitive measure, Picture Vocabulary Test (PVT), was collected. We used it for a cross-sectional analysis of adolescence cognitive ability for the 12,039 respondents in the longitudinal sample with cognitive measures in Waves IV and V.

Supplement Table A. Cognitive Measures across Four Longitudinal Studies

Study	Overall Cognition		Episodic Memory		Executive / Attention / Orientation	
	Total Score	Range	Test Item	Range	Test Item	Range
Add Health	Memory	0-37	Immediate word recall Delayed word recall	0-15 0-15	Digits backward Picture Vocabulary Test	0-7 13-146
MIDUS	BTACT	-2.9-3.6	Immediate word recall Delayed word recall	0-15 0-15	Digits backward Category fluency Stop & Go Accuracy Number Series Backward Counting	0-8 0-42 0-40 0-5 -13-100
ACL	SPMSQ	0-5	n/a		Serial 3's subtraction Date naming Day of week Current president Previous president	0-1 0-1 0-1 0-1 0-1
HRS	TICS	0-35	Immediate word recall Delayed word recall	0-10 0-10	Backward counting Serial 7's subtraction Date naming Object naming President/VP	0-2 0-5 0-4 0-2 0-2

Outcome Measures

- Verbal Episodic Memory
  - Immediate and delayed word recall tests (Add Health, MIDUS, and HRS)
  - Harmonized measure: standardized each score, summed, and standardized to derive the final score (Yang et al., 2020; Stebbins et al. 2022)

- Overall Cognitive Function
  - Total score of all cognitive tests (different across 4 studies)
  - Harmonized measure: standardized total score

Covariates

- *Age* (in years) and *Birth Cohort* (-1905 – 1984)
- *Gender*: Men or Women
- *Race/ethnicity*: Non-Hispanic (NH) White, NH Black, and Hispanic
- *Educational Attainment*: <12, 12-15, and 16+ years
- *Attrition/Lost to follow-up*: death or nonresponse; remained
- *Immigrant status*: US-born or foreign-born
- *Study Membership*: Add Health, MIDUS, or HRS

Sample Characteristics:

Table 3. Baseline Descriptive Statistics for the Pooled Integrative Analysis of Episodic Memory

Variable	All N = 51,141	Add Health N = 12,046	MIDUS N = 3,817	HRS N = 35,278
Study Membership (%)	100	24	7	69
Age, mean (SD)	53.30 (16.53)	28.39 (2.42)	55.19 (12.50)	59.62 (9.52)
Birth year (range)	1890-1983	1976-1983	1920-1971	1890-1965
Female (%)	56	52	54	51
Race/ethnicity (%)				
Non-Hispanic White	68	73	88	78
Non-Hispanic Black	19	15	7	12
Hispanic	13	12	4	10
Education (%)				
Less than high school	20	6	8	20
High school degree	55	60	62	54
College degree or higher	25	34	30	25
Foreign-Born (%)	10	3	4	10
Immediate recall, mean (SD)	5.96 (1.92)	6.73 (2.01)	6.69 (2.26)	5.74 (1.69)
Delayed recall, mean (SD)	4.65 (2.16)	5.30 (2.06)	4.30 (2.61)	4.61 (2.03)
Episodic memory, mean (SD)	0.19 (1.03)	0.58 (1.01)	0.31 (1.25)	0.12 (0.94)

Sample Characteristics:

Table 4. Baseline Descriptive Statistics (Weighted) for the Coordinated Integrative Analysis of Overall Cognitive Function

Variable	Add Health N = 12,039	MIDUS N = 3,820	HRS N = 32,985	ACL N = 3,532
Age, mean (SD)	28.39 (2.42)	55.24 (12.54)	60.34 (9.57)	47.32 (16.52)
Birth year (range)	1976-1983	1920-1971	1890-1965	1890-1961
Female (%)	52	54	51	53
Race/ethnicity (%)				
Non-Hispanic White	73	88	78	82
Non-Hispanic Black	15	7	12	11
Hispanic	12	4	10	7
Education (%)				
Less than high school	6	8	21	26
High school degree	60	62	54	55
College degree or higher	34	30	25	20
Foreign-Born (%)	3	4	10	8
Total Cognitive Score, mean (SD)	16.28 (4.37) R: 0—37	-0.01 (1.23) R: -2.9—3.6	23.29 (4.86) R: 0—35	4.27 (0.91) R: 0—5

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Analytic Methods

- The first study modeling the life course trajectories of cognitive function in the U.S. adult population from adolescence to old age
  - A *pooled* IDA of verbal episodic memory
  - A *coordinated* IDA of overall cognitive ability
- Adjust for study heterogeneity due to
  - Measures: harmonized and commensurate
  - Sampling design: modeling *Study Membership* as fixed effect with test of *study-by-covariate interactions*
  - Historical time: longitudinal cohort analysis accounts for period differences with *age-by-cohort interactions*, fixed effects of *study membership*, and *cohort-by-study interactions*

Analytic Methods

- Linear Mixed Effects-Growth Curve Models

$$Y_{ti} = (\gamma_{00} + X'_{ik}\gamma_{0k} + u_{0i}) + (\gamma_{10} + X'_{ik}\gamma_{1k} + u_{1i})*AGE_{ti} + (\gamma_{20} + X'_{ik}\gamma_{2k} + u_{2i})*AGE_{ti}^2 + \varepsilon_{ti}$$

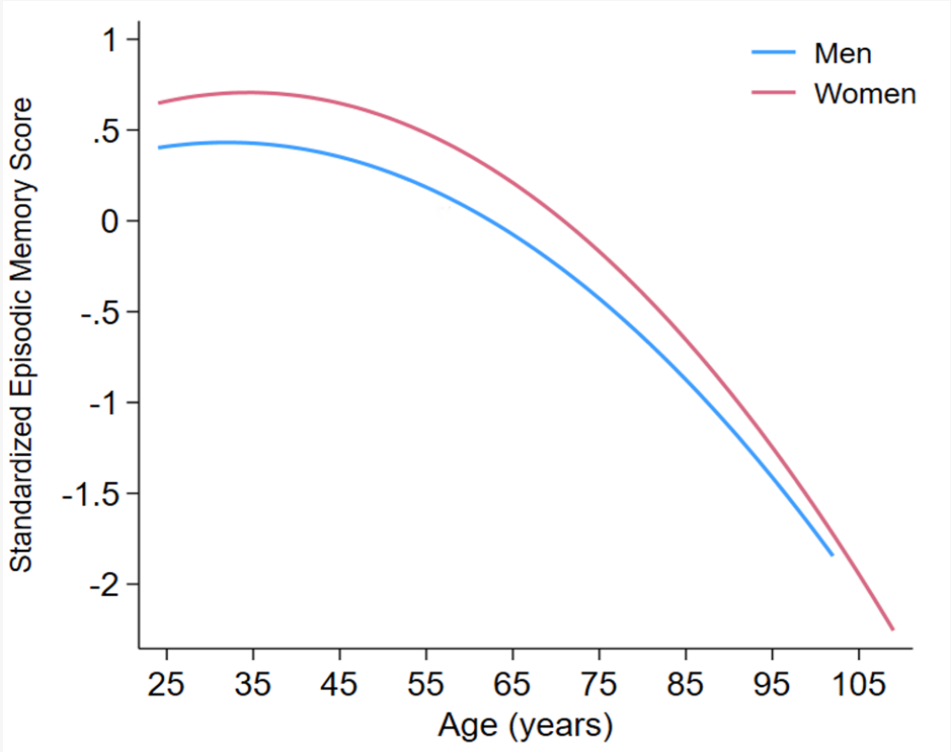
Y_{ti}: the cognitive outcome (e.g., episodic memory or overall cognitive score) for respondent *i* at time *t, for i* = 1,…,*n* and *t* =1…,T_i

γ_{00}, γ_{10}, and γ_{20}: fixed effects of the intercept, linear slope AGE_{ti} (centered around cohort median), quadratic slope AGE_{ti}^2

X'_{ik} $(k = 1, \ldots, K)$: a vector of individual-level characteristics, including *birth cohort*, *gender*, *race/ethnicity*, *education*, and the *interactions*; γ_{0k}, γ_{1k} and γ_{2k}: associated fixed effects for the intercept, linear slope, and quadratic slope models

u_{0i}, u_{1i}, and u_{2i}: random effects of the intercept, linear and quadratic terms for individual *i*, assumed to have a multivariate normal distribution; and $\varepsilon_{ti} \sim N(\ , \sigma^2)$: residual error

Figure 1. Predicted Trajectories of Episodic Memory: Gender and Cohort Differences



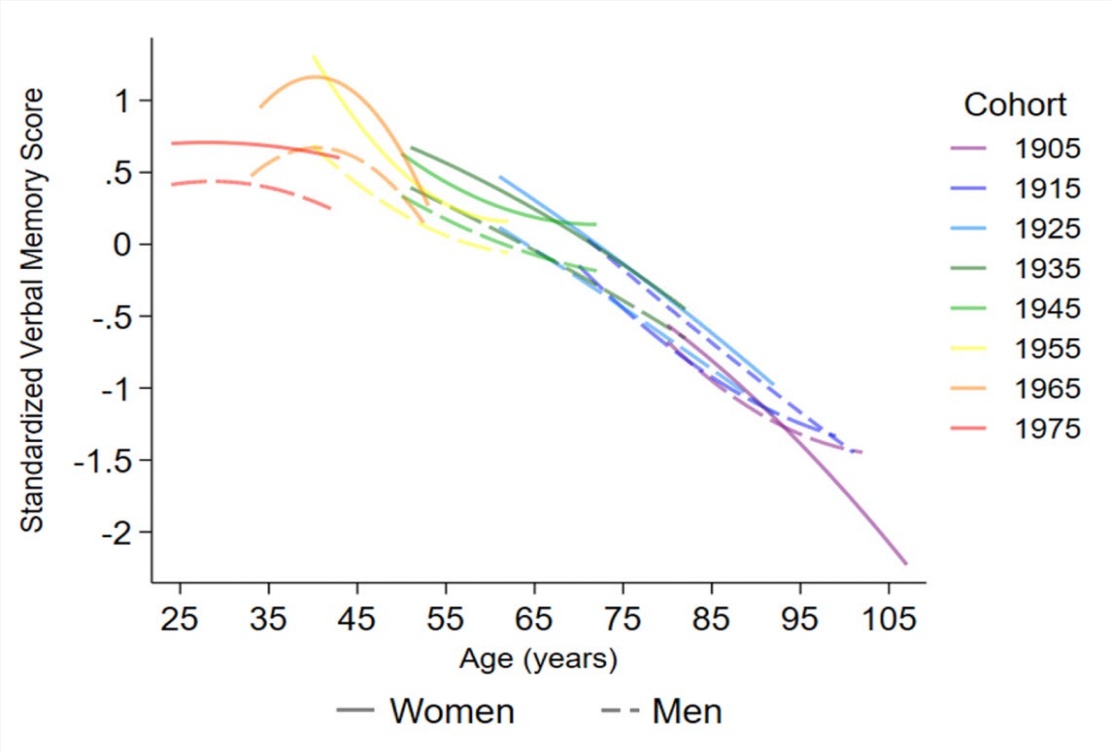
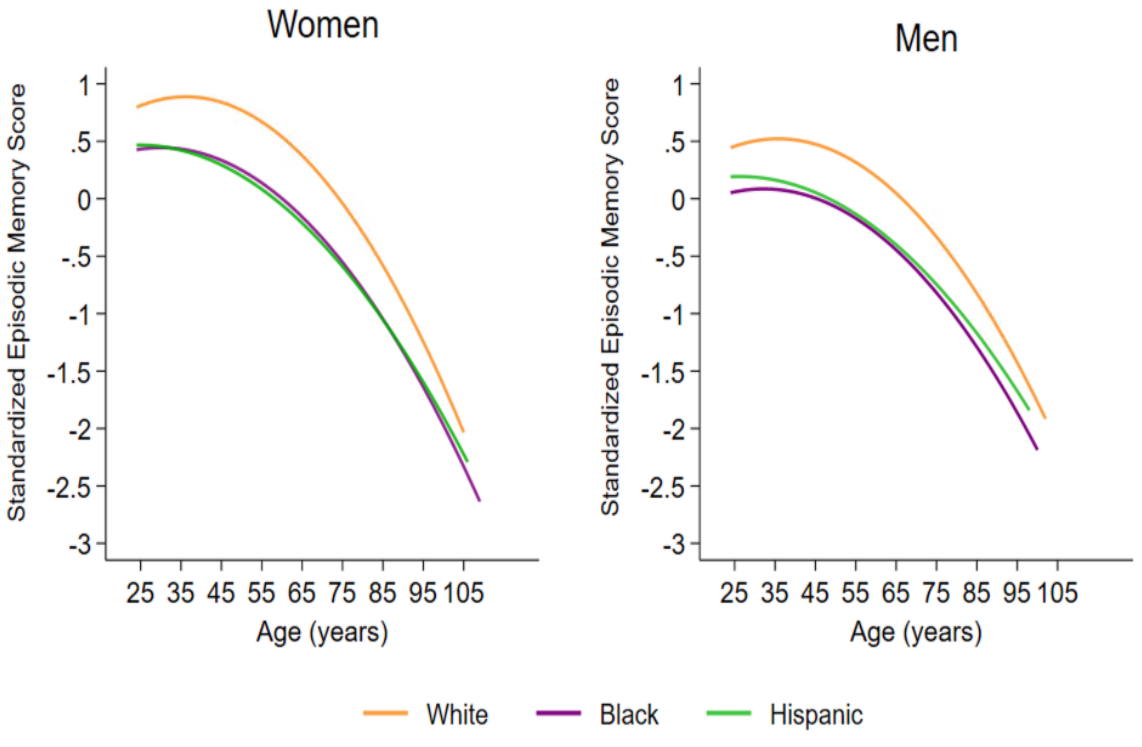


Figure 2. Predicted Trajectories of Episodic Memory: Race and Cohort Differences



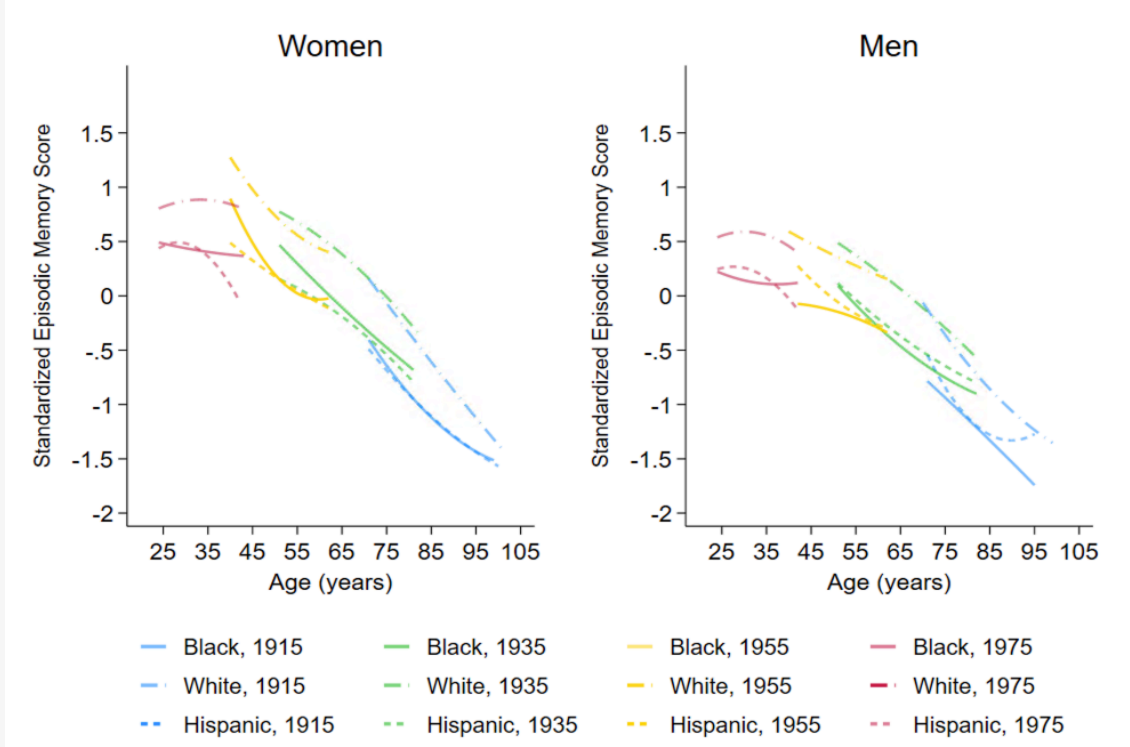


Figure 3. Predicted Trajectories of Episodic Memory: Education and Cohort Differences

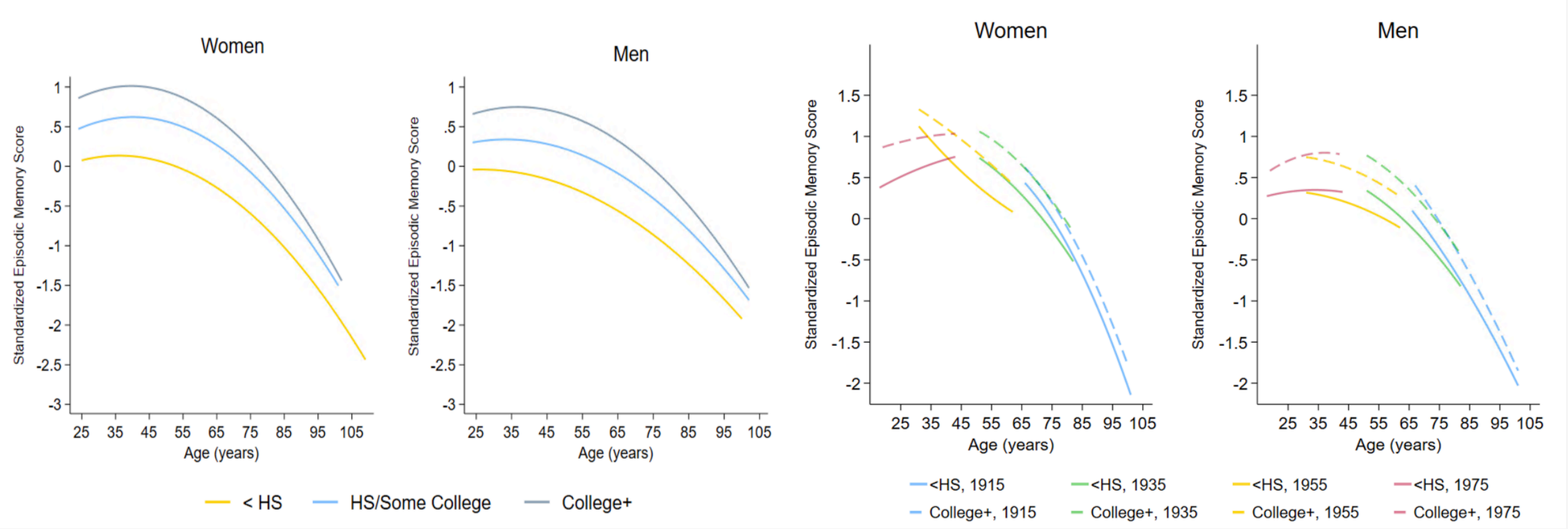


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Figure 4. Predicted Trajectories of Episodic Memory: Race by Education Differences

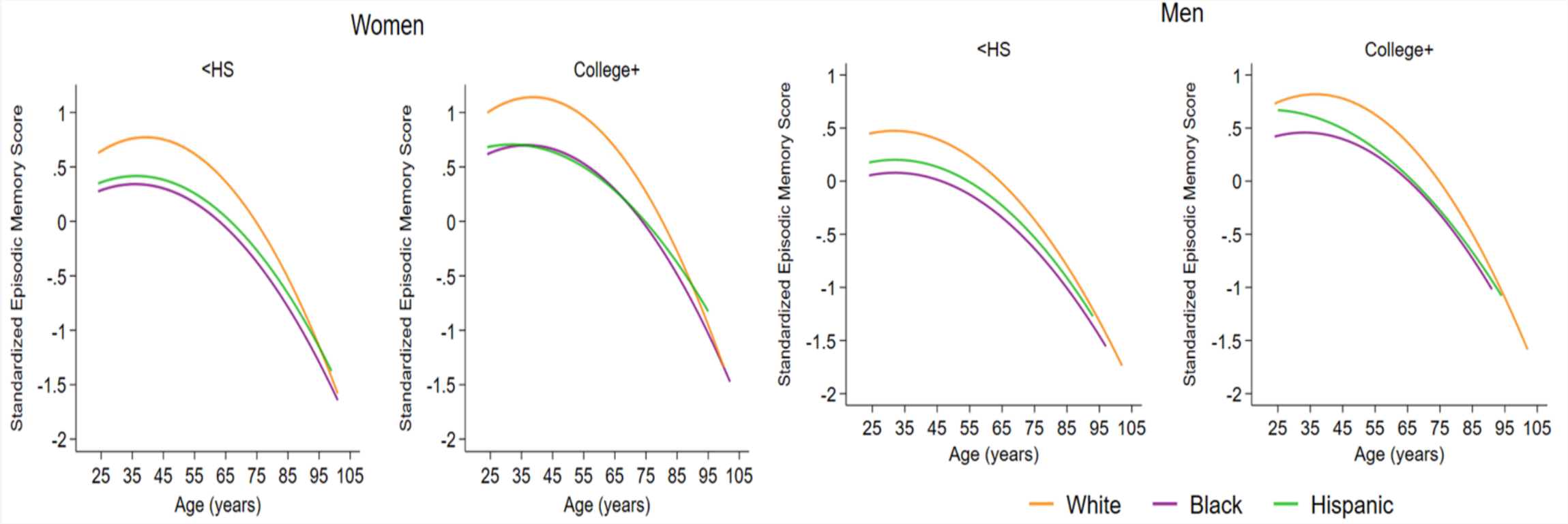
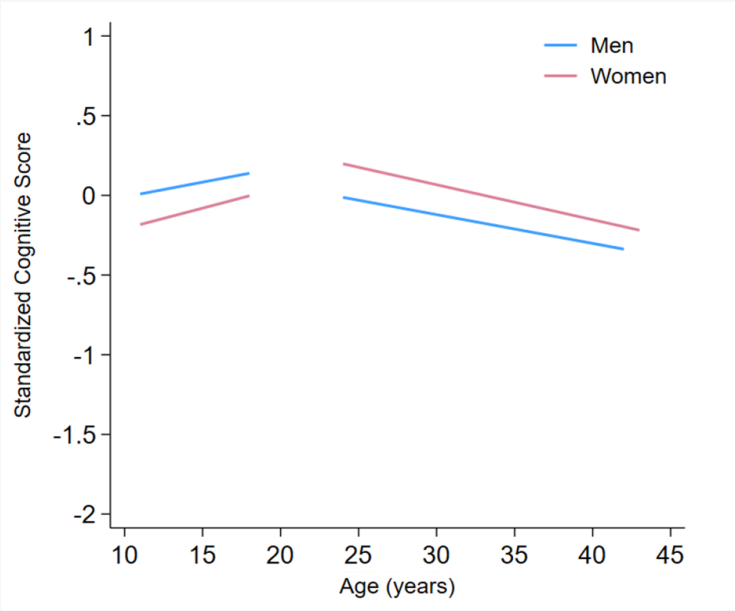
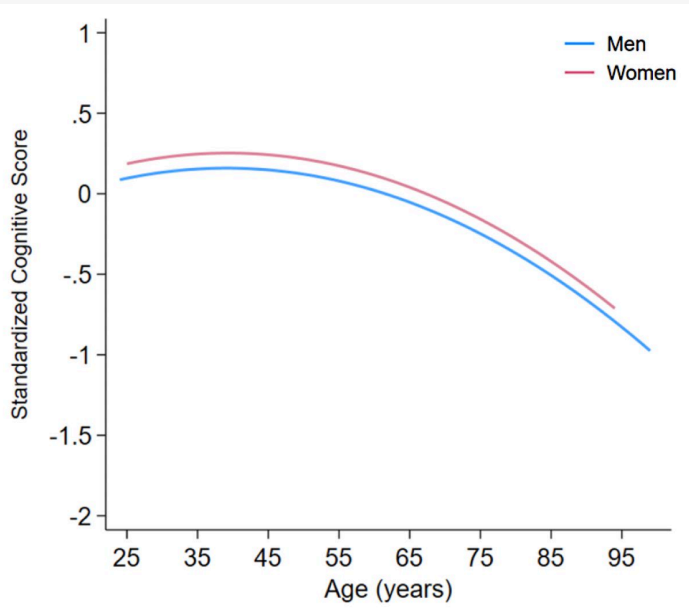


Figure 5. Predicted Trajectories of Overall Cognitive Function: Gender Differences by Study

Add Health



ACL



HRS

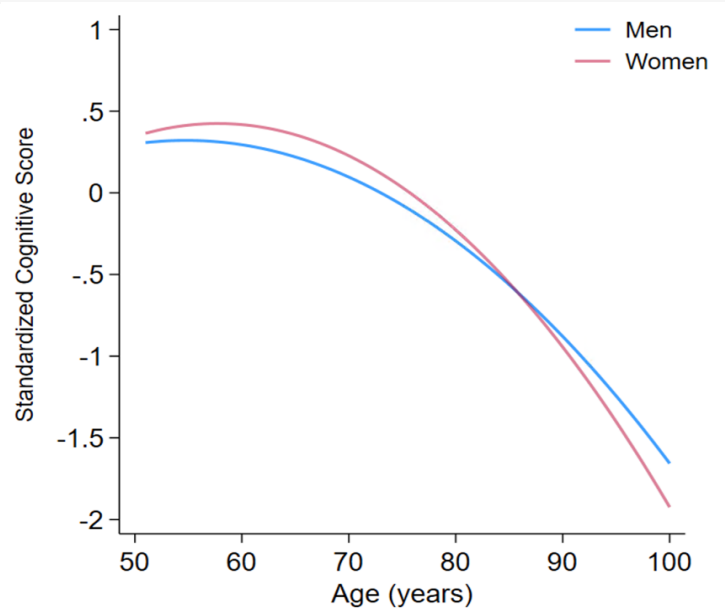


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Figure 6. Predicted Trajectories of Overall Cognitive Function: Race Differences by Study

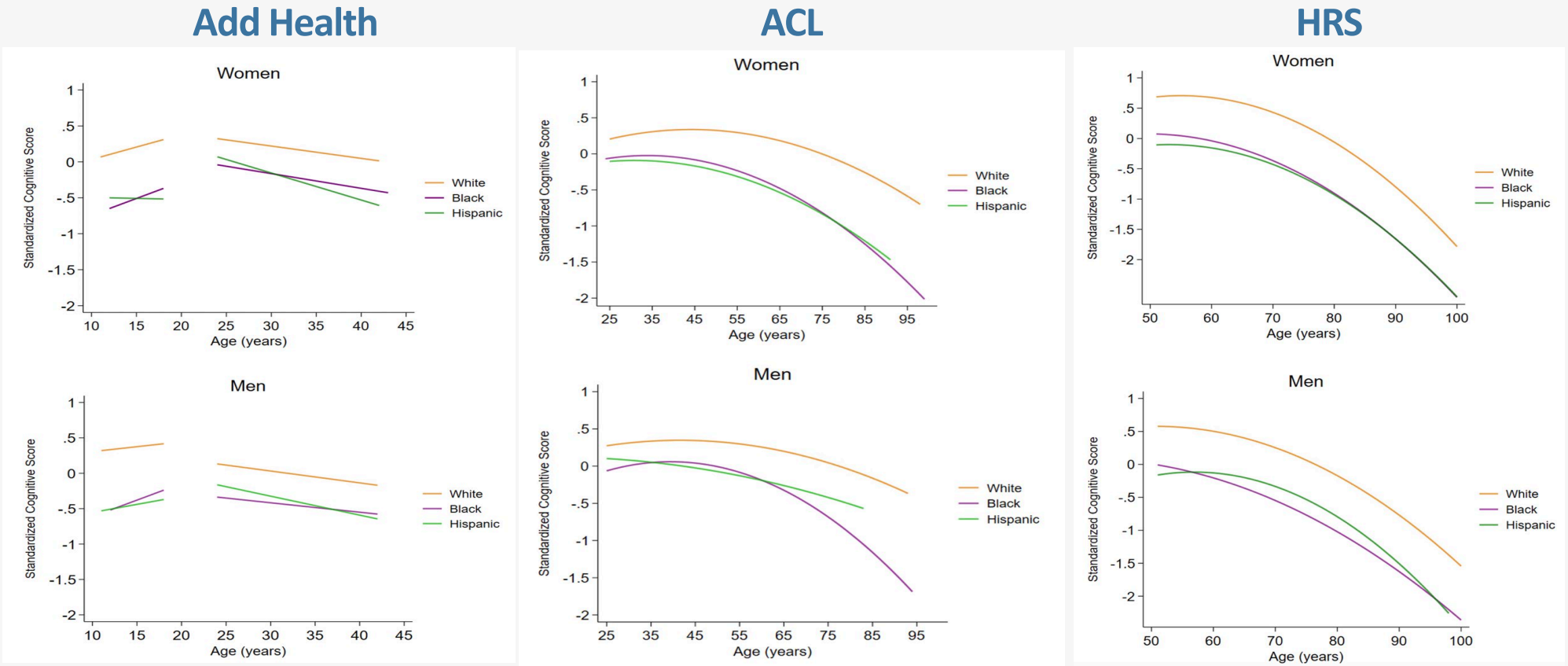
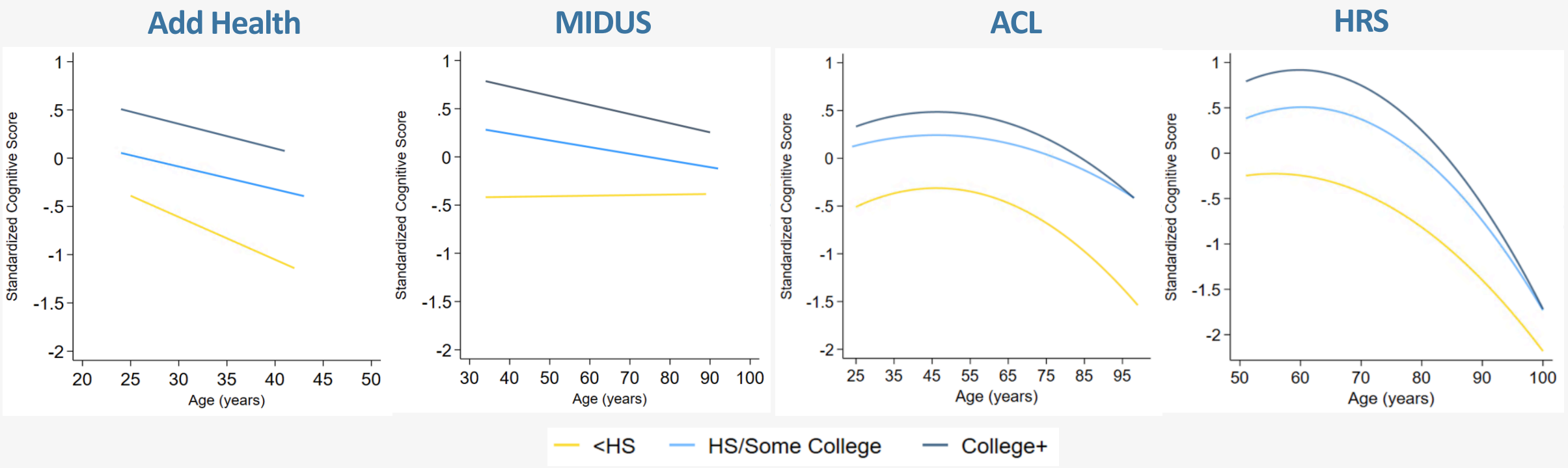


Figure 7. Predicted Trajectories of Overall Cognitive Function: Education Differences by Study – Women



Summary and Conclusions

- Age-related cognitive declines start as early as 30s
  - Early-life cognitive change is essential for predicting mid to late life declines
- There are substantial gender, race/ethnicity, and education differences in cognitive trajectories over the life course
  - Cognitive disadvantages of men, non-Whites, and poorly educated emerge in adolescence and young adulthood and largely persist into late life
- More recent birth cohorts had better cognitive function and slower declines
  - Improved education contributed to improved cognition across cohorts, particularly in women

Summary and Conclusions

- The extensive longitudinal study using the IDA helped to fill existing gaps
  - Establishing early and later-life links improves understanding of the etiology and course of development of dementia
- Future research is needed:
  - Harmonizing measures of cognitive function not shared by studies using advanced methods of psychometrics (e.g., CFA)
  - More longitudinal follow-ups of the Add Health respondents into mid-life
  - Explanatory mechanisms underlying the social disparities in cognitive decline