LIFE COURSE APPROACHES TO COGNITION AND RISK OF DEMENTIA: DATA LINKAGES &NOVEL METHODOLOGIES

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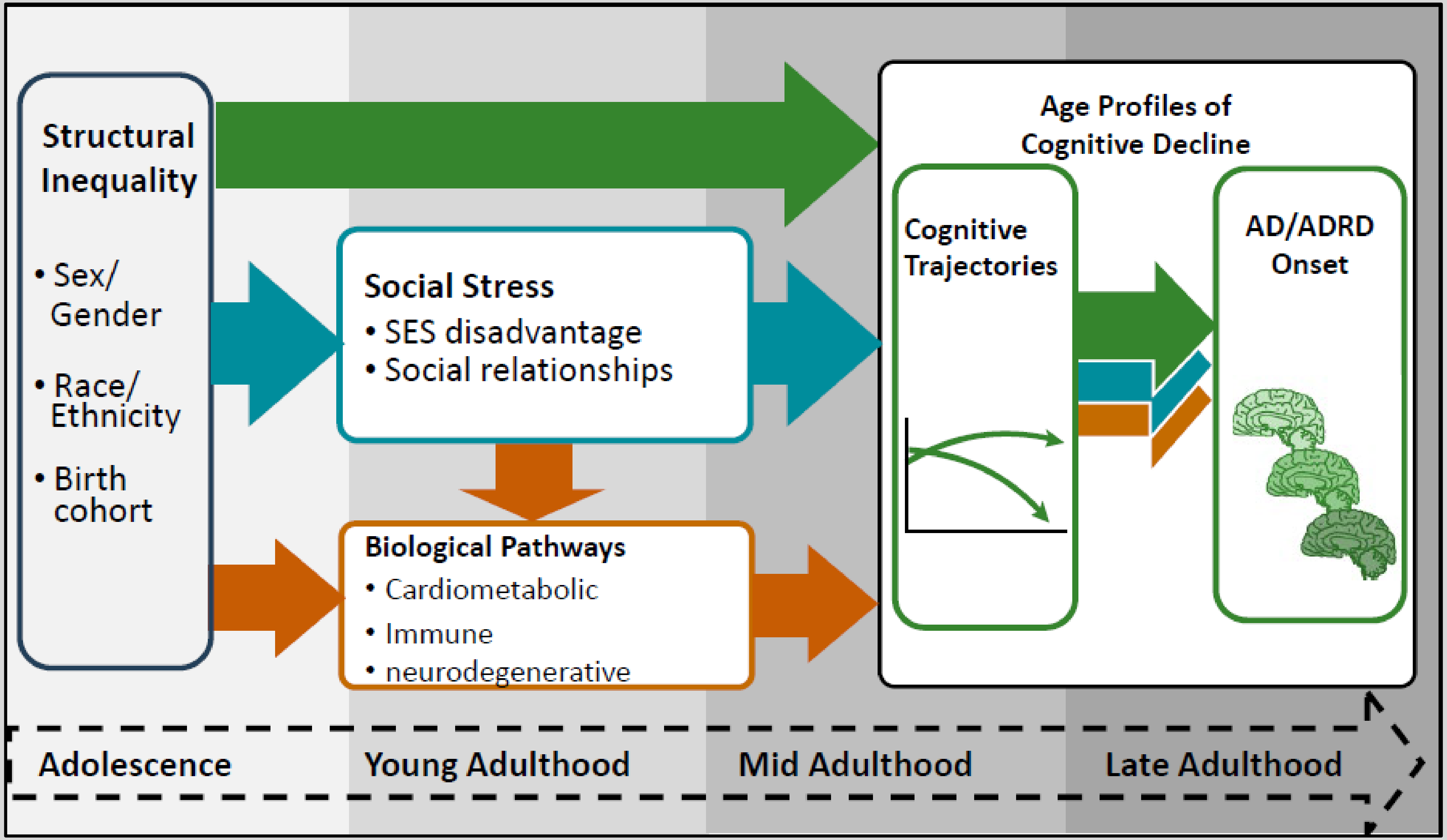
Overview

1. *The most important midlife social and institutional pathways linking early life social disadvantages with risk for later life cognitive decline and dementia*
   - Life course context: conceptual model, major gaps, and challenge (NIA R01 project)
2. *Most important data sets and methodologies in understanding these life course processes*
   - Creative Data linkages
     - Extensive longitudinal data across the full life course: synthesized cohort sequential design (Add Health, MIDUS, ACL, HRS)
     - Longitudinal trajectories in mid life linked to time-to-event data in late life (HRS-ADAMS)
     - Survey data linked to validated external data for enhanced measures of midlife SES (Add Health and O*NET)
   - Novel Methodologies
     - Longitudinal Integrative Data Analysis (IDA)
     - Joint latent class mixed models (JLCMM)
3. *Most important data & methodological needs in this area of research*
   - Long-term longitudinal cognitive data for harmonization and linkages
   - Multidimensional SES measures in midlife to capture workplace structural contextual factors

PART 1. LIFE COURSE CONTEXT

Conceptual Model, Major Gaps, and Challenge

Figure 1. Conceptual Model of Life Course Process of AD/ADRD and Social Disparities



Adapted from NIA R01AG057800 (PI: Yang). Project Website: https://www.cpc.unc.edu/research-themes/projects/life-course-process-of-alzheimers-disease-sex-difference-and-biosocial-mechanisms/

Major Research Gaps

- **Characterization of age-related cognitive change over the full life span is lacking**
  - "Brain/Cognitive Reserve hypothesis" of early life origins of AD pathophysiology has rarely been tested empirically
  - Longitudinal nature (timing, course, slope) of cognitive changes is predictive of dementia risk in older adults, but not investigated in studies of adults of all ages
- **Social inequalities in cognitive aging are not fully documented or understood**
  - The link between early-life social disadvantage and later-life cognitive trajectory (baseline and rates of change) has not been consistently established
  - Remaining question on the life course pathways: When do the cognitive impacts of social inequality emerge in life? How long do they last?
- **Extensive life course models of population-based data of cognitive aging and its association with life course social inequalities are mandatory to addressing these gaps**

Fundamental Challenge

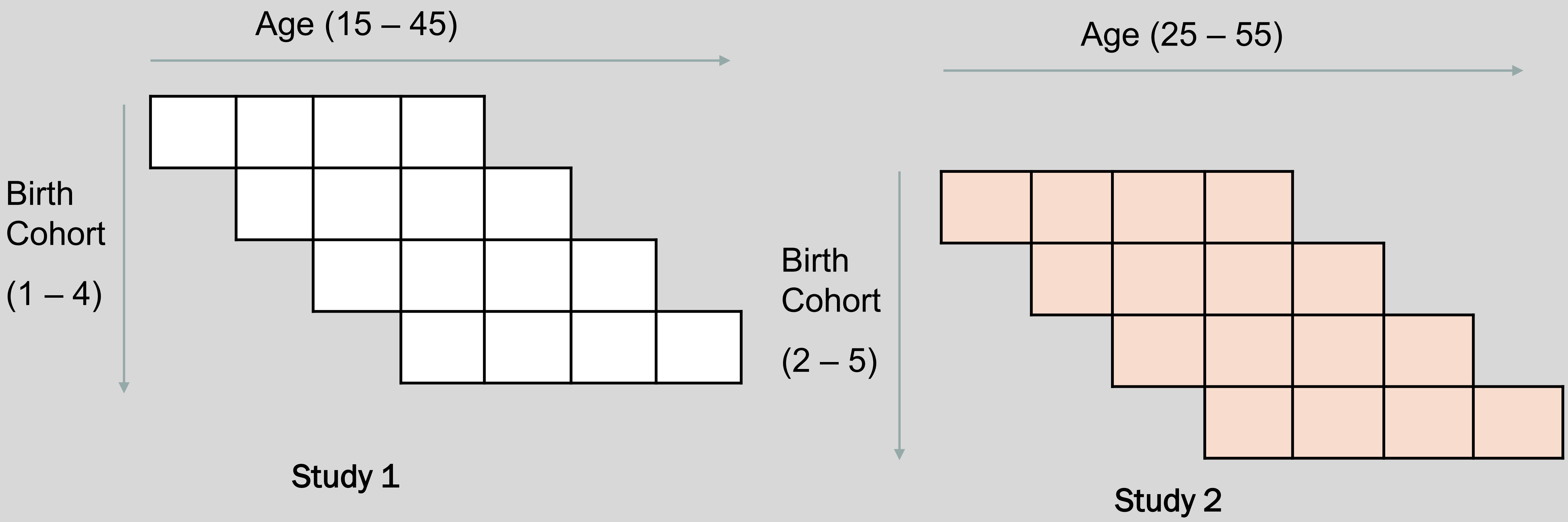
- No single, nationally representative study has observed the full life course that begins in the early-life period preceding the occurrence of peak cognitive performance and extends through old age
  - Lack of data on early and mid-life exposures and risks
  - Limited to small non-representative samples and cross-sectional or short-term longitudinal analyses within a single life stage
  - Confounding of aging and cohort effects

PART 2. DATA LINKAGES AND METHODOLOGIES

2.1 Combining Multiple Cohort Datasets for Longitudinal Integrative Data Analysis (IDA)

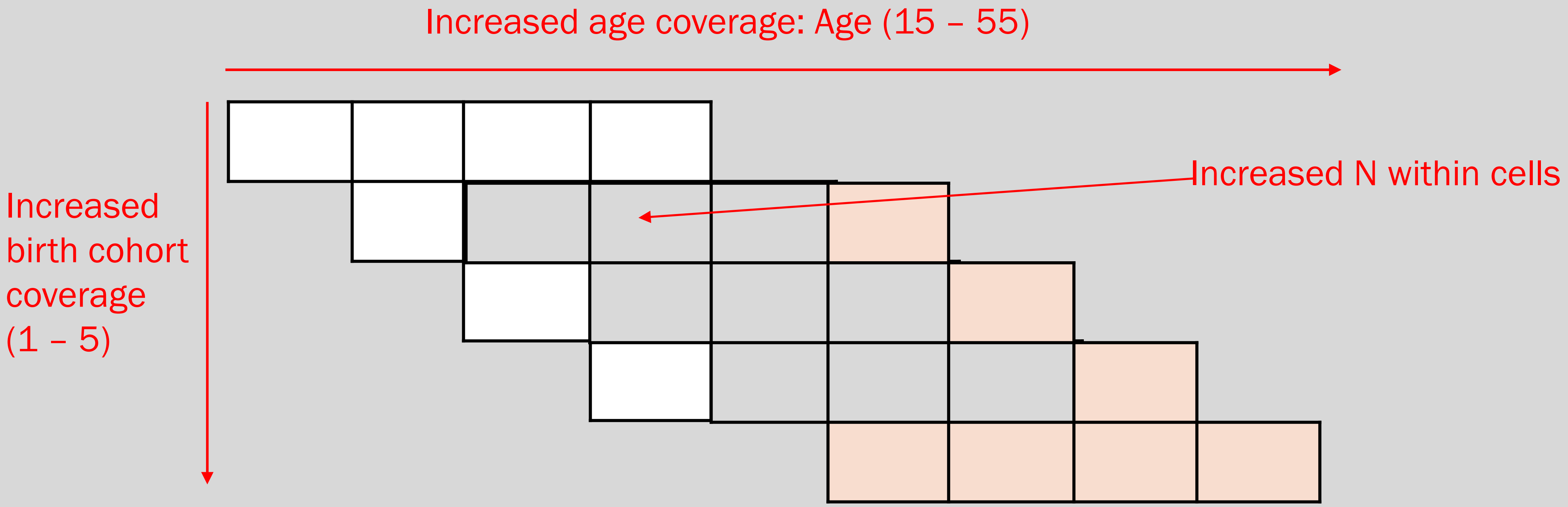
Extensive Life Course Longitudinal Design

- Accelerated longitudinal cohort panels



Extensive Life Course Longitudinal Design

- Synthesized cohort sequential design

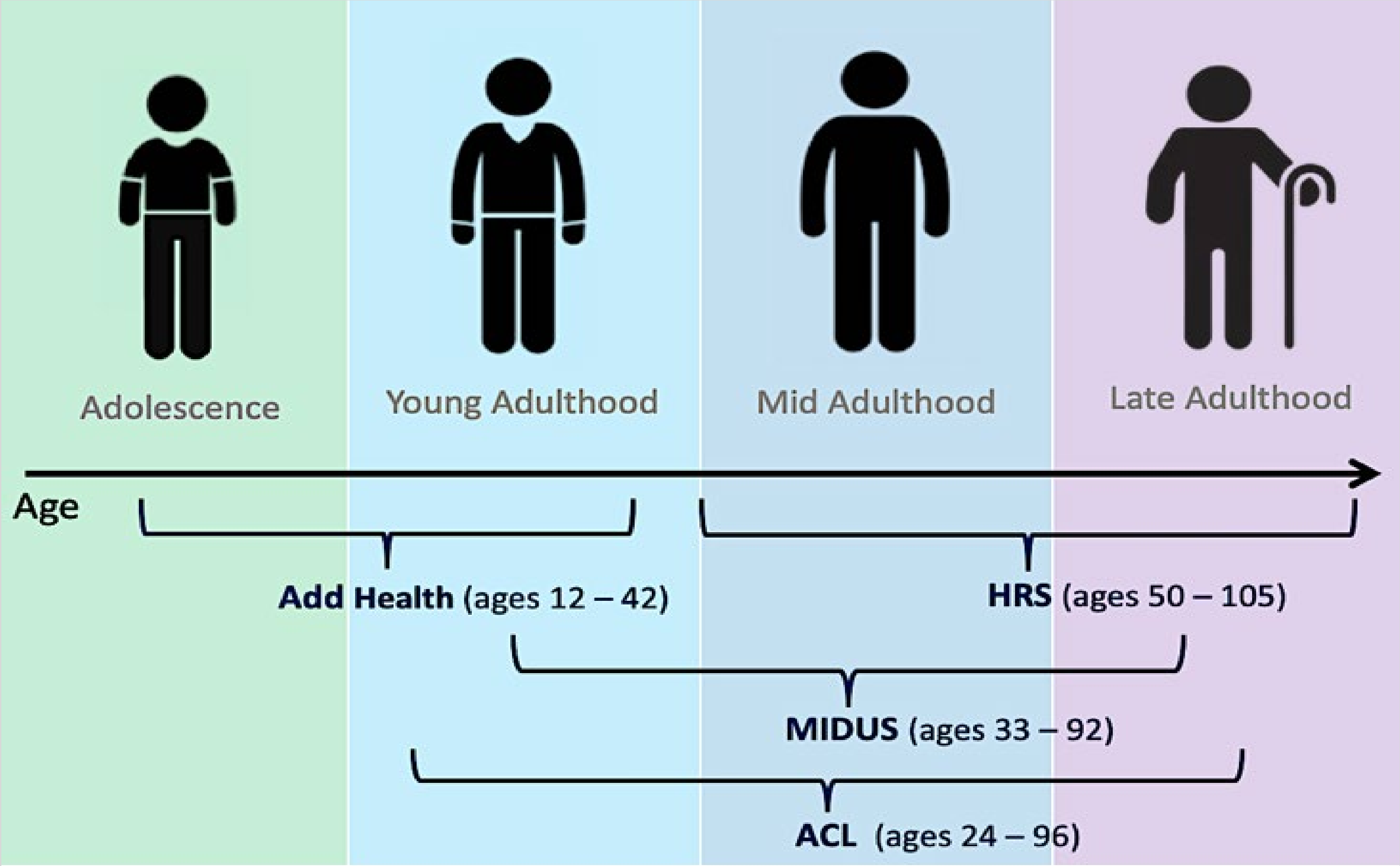


Study 1 + Study 2

Longitudinal Integrative Data Analysis (IDA)

- A novel application of IDA to longitudinal analysis (Yang et al., *PNAS* 2016; 2021)
  - *Coordinated IDA*: parallel models fit to each separate sample and results compared across studies
  - *Pooled IDA*: combined dataset from separate samples using a *synthesized cohort sequential design*
- Innovative advantages
  - Test of novel life course hypotheses over far more extended developmental and historical periods
  - Increase power: larger combined sample sizes, greater representation of diverse populations, decreased confounding of age and cohort effects
  - Modeling heterogeneity across studies strengthens internal and external validity about population inferences
  - Support data sharing for a more cumulative science of population health

Life Course Dynamics and Patterns of Cognitive Aging in the U.S. (Yang et al., *JAH* 2023)



- Augmented accelerated longitudinal panels: synthesized cohort sequential design
- Integrated data from 4 national population-based cohort panels
- Multiple birth cohorts with age overlaps from adolescence to old age
- Over 50,000 individuals followed over 25 years across 17 study waves

Public Use Source Code: Creating the Integrated Dataset (https://www.cpc.unc.edu/projects/public-use-source-code-creating-the-integrated-dataset/)

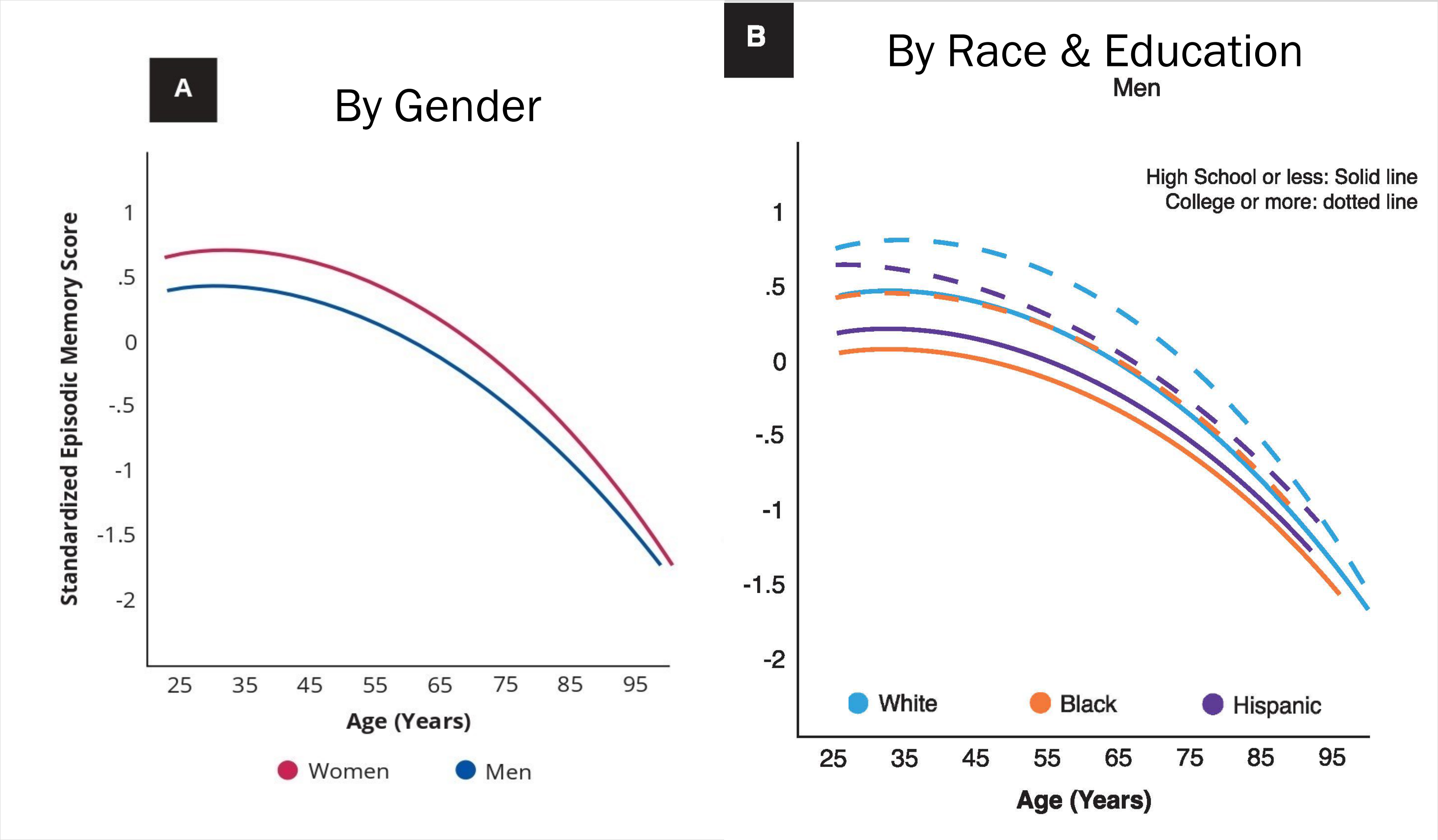
Study Aims

- Model age trajectories of cognitive function from early to late life in the general U.S. population aged 12 and older
- Test main demographic and socioeconomic differentials in these trajectories
  - Gender, race/ethnicity, and education disparities
  - Cohort variation across 20^{th}-century birth cohorts

Analytic Methods

- Linear Mixed-effects Growth Curve Models
  - Pooled IDA of *Episodic Memory*
  - Coordinated IDA of *Overall Cognitive Ability*
- IDA accounts for study heterogeneity due to
  - <u>Measures</u>: constructing harmonized and commensurate variables
  - <u>Sampling design</u>: modeling *Study Membership* as fixed effect with test of study-by-covariate interactions
  - <u>Historical time</u>: accounting for confounding of cohort and period differences with age-by-cohort interactions, fixed effects of *study membership*, and cohort-by-study interactions

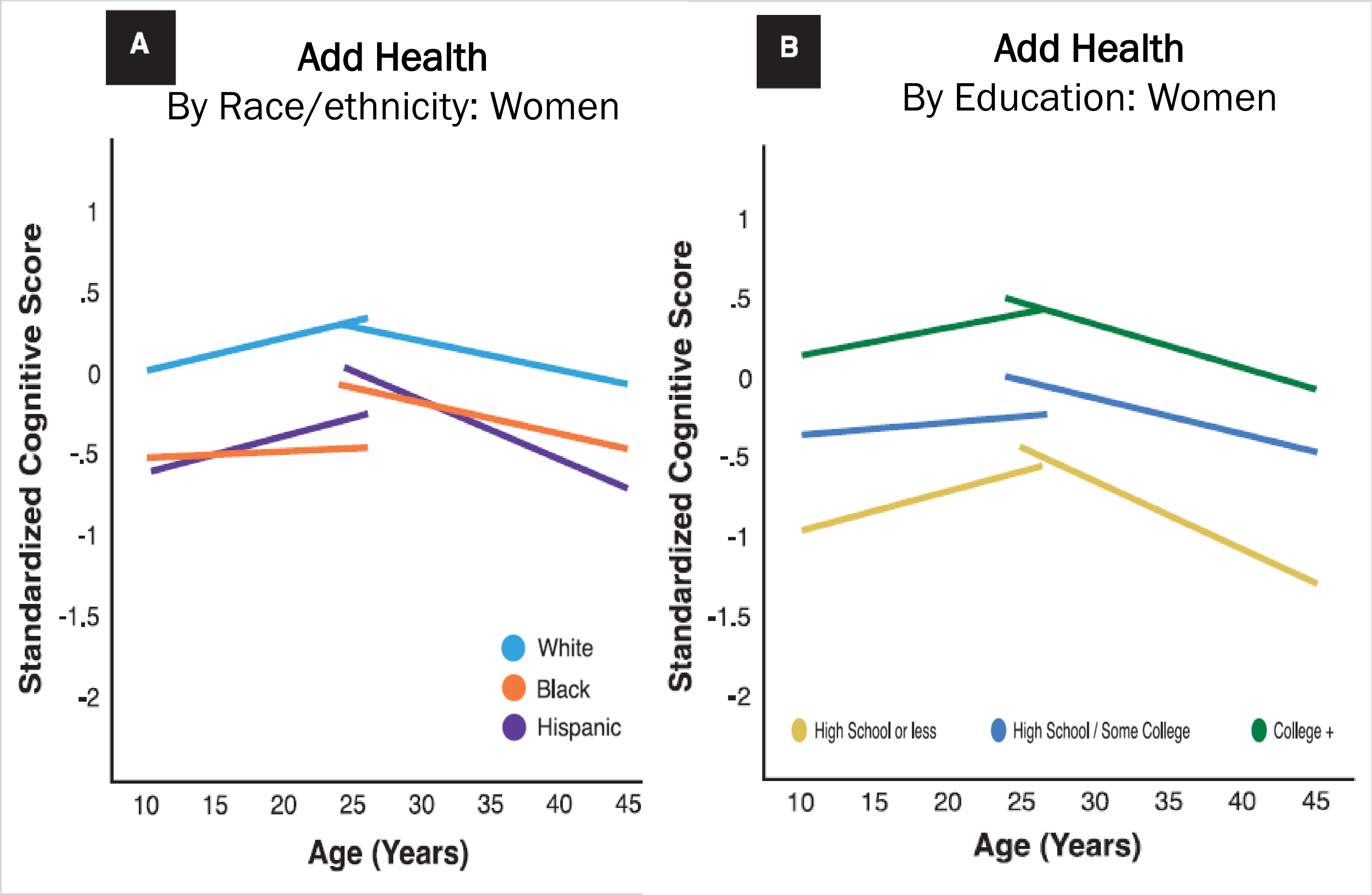
Figure 2. Predicted Age Trajectories of Episodic Memory in Adulthood



- **A curvilinear life-course pattern of memory**: declining with age at 1 SD per decade of life
- **(A) gender difference**: women had better memory on average but a steeper slope of decline than men
- **(B) race and education intersection**: widest gap between the lowest educated NH Blacks and the highest educated NH Whites persisted in old age; fewer cognitive returns from higher education in racial/ethnic minorities

Note: Models estimated from the pooled sample of Add Health, MIDUS, and HRS (N = 51,280 individuals and 217,139 person-years) adjusting for age, age^2, gender, race, education, birth cohort, immigration status, attrition status, study membership and significant interactions. Gender differences (A) are statistically significant (*p*<.001; two-tailed test). Race/ethnicity, education, and race x education effects (B) are statistically significant (*p*<.05; two-tailed test).

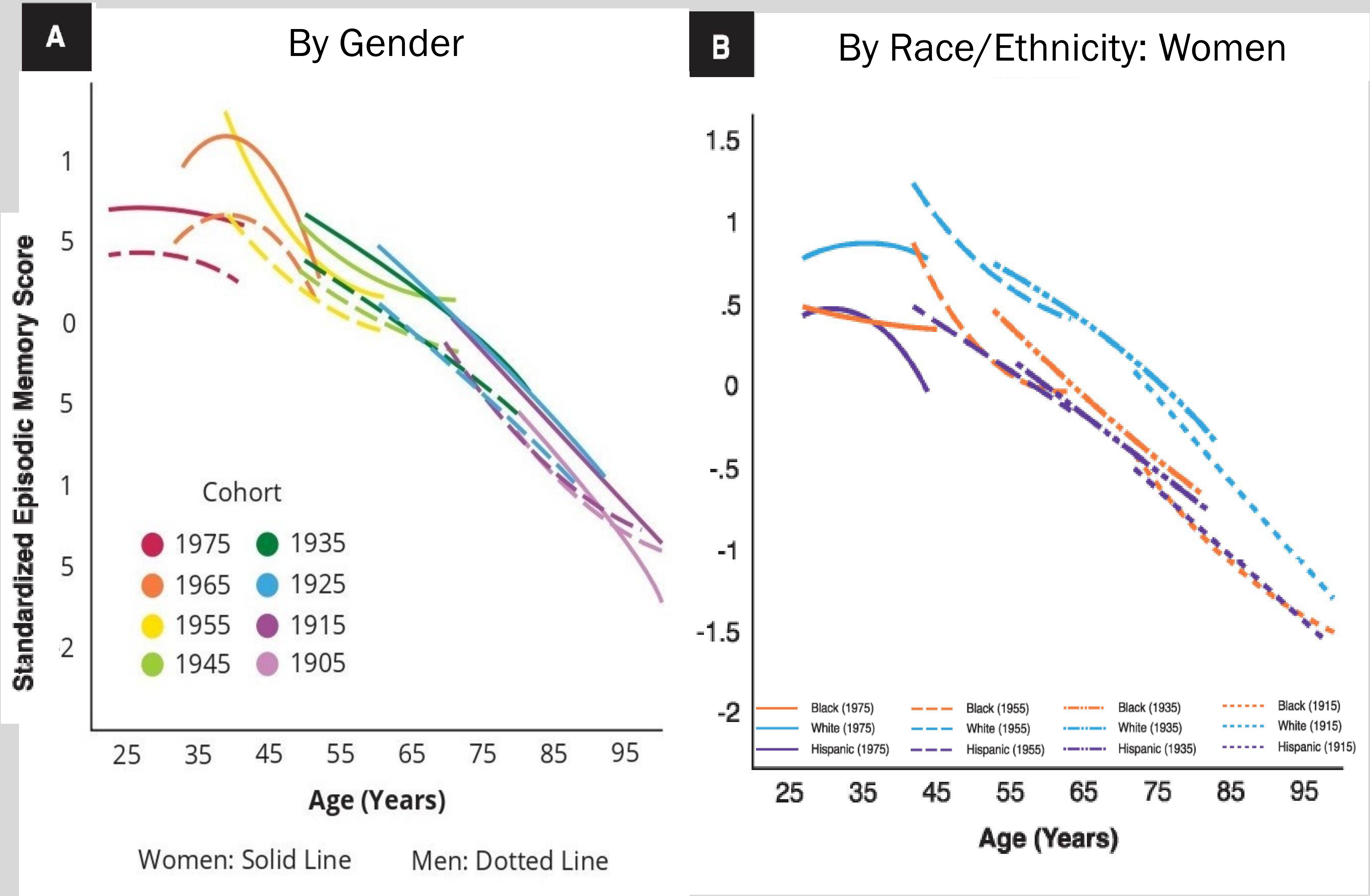
Figure 3. Predicted Age Trajectories of Overall Cognitive Ability in Early Life



- **Social disparities in cognitive aging originated early in life**
- **(A) Racial/ethnic difference**: substantial disadvantages for minorities started in adolescence
- **(B) Educational difference**: clear gradient by level of educational attainment started in adolescence and continued into mid life

Note: Estimates from the best fitting model to each study sample in the Coordinated IDA. For Add Health: PVT scores were used for Waves I-III; cognitive test scores were used for Waves IV-V. Racial/ethnic and educational differences are statistically significant, adjusting for other covariates (p<.001; two-tailed test).

Figure 4. Predicted Age Trajectories of Episodic Memory: Cohort Variation



- **Cross-cohort improvement:** later born cohorts had higher average memory and slower rates of decline
- **(A) within-cohort gender gap**: increased in later than earlier born cohorts
- **(B) within-cohort racial gaps**: increased in later than earlier born cohorts

Note: Models estimated from the pooled sample of Add Health, MIDUS, and HRS (N = 51,280 individuals and 217,139 person-years) adjusting for age, age^2, gender, race, education, birth cohort, immigration status, attrition status, study membership and significant interactions. Birth cohort differences and cohort x gender interactions (A) are statistically significant (*p*<.001, two-tailed test. Birth cohort differences and cohort x race interactions (B) are statistically significant (*p*<.05, two-tailed test).

Summary

- The first longitudinal IDA provides direct evidence on the timing, course, and social patterning of cognition change over the life course in the general U.S. population
- Aging-related cognitive decline onset in the 4th decade and accelerate in the 7th decade
- Social disparities in cognitive aging originate early in life and show persistent influences of compounding social structural exposures and cultural bias that inequitably impact people of color and those poorly educated
- Cohort improvement and divergence suggest positive sociocultural influences on cognitive health and length of productive life on one hand, and the need to reduce inequalities in recent post-baby boomer cohorts on the other

PART 2. DATA LINKAGES AND METHODOLOGIES

2.2 Joint Models of Longitudinal Trajectory and Time-to-Event Data

Background and Significance
(Walsh, Yang, et al., *JGSS* 2022)

- Empirical studies are needed to understand
  - Whether and how are age-related cognitive decline and later-life onset of dementia linked?
  - Is there population heterogeneity in the interlinked processes?
  - How does informative attrition due to dementia and mortality affect population estimates of cognitive decline?
- New knowledge from longitudinal studies of prototypic patterns of cognitive decline can help
  - Better predict dementia risk based on cognitive trajectory (intercept vs. slope)
  - Advance etiological research into the natural history and pathogenesis of dementia
  - Identify optimal time windows and vulnerable subgroups for targeted interventions
  - <u>**Address data limitation for mid life**</u>: available early life cognitive measures can be used to **predict** future dementia risk in later life using the estimates from existing data from older adults as benchmarks

Study Aims

- To investigate the temporal dynamics of progression of cognitive decline and estimate association between longitudinal cognitive trajectory and time-to-dementia incidence in a diverse population-based longitudinal sample of older adults in the U.S.
- To identify distinct age profiles of cognitive trajectories associated with dementia onset within the population
- To account for the competing risk of mortality

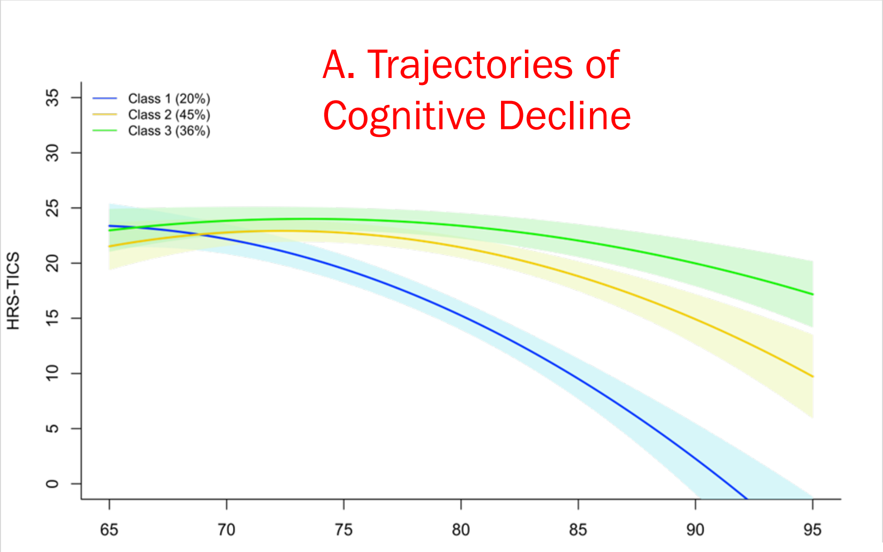
Data, Sample, and Measures

Data and Sample	Outcome	Covariates
Aging, Demographic and Memory Study (ADAMS) 2001 – 2009 (N = 856)	Incidence	
- Stratified random sample from HRS 2000/2002 (Langa et al., 2005; Plassman et al., 2007, 2011)	• Age at diagnosis of dementia • Age at non-dementia mortality	• APOE-4 Status
Health and Retirement Study (HRS) 1996 – 2009	Longitudinal trajectory	
- Linked with ADAMS - Up to 12 years of follow up (7 repeated measures)	• Cognitive function (TICS)	• Sex • Race/ethnicity • Education
Final Analytic Sample: N = 531 - Excludes baseline dementia and missing data		• Population sample weight

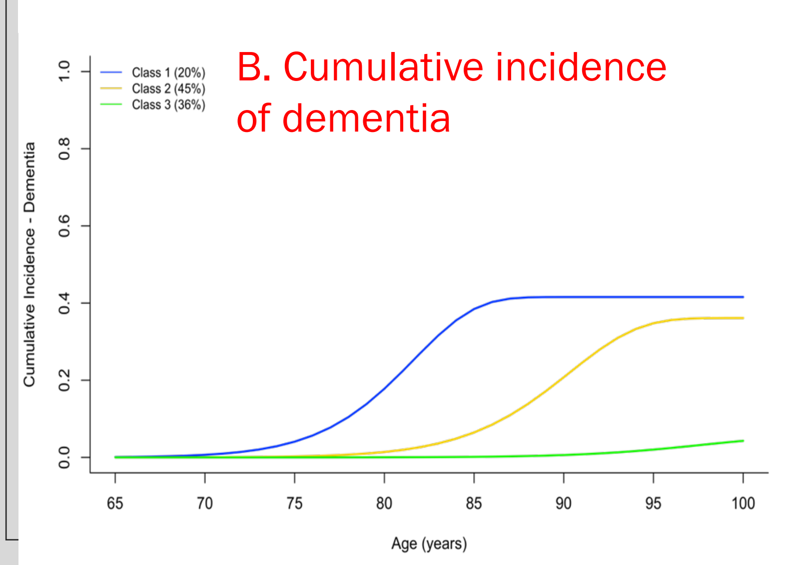
Joint Latent Class Mixed Modeling

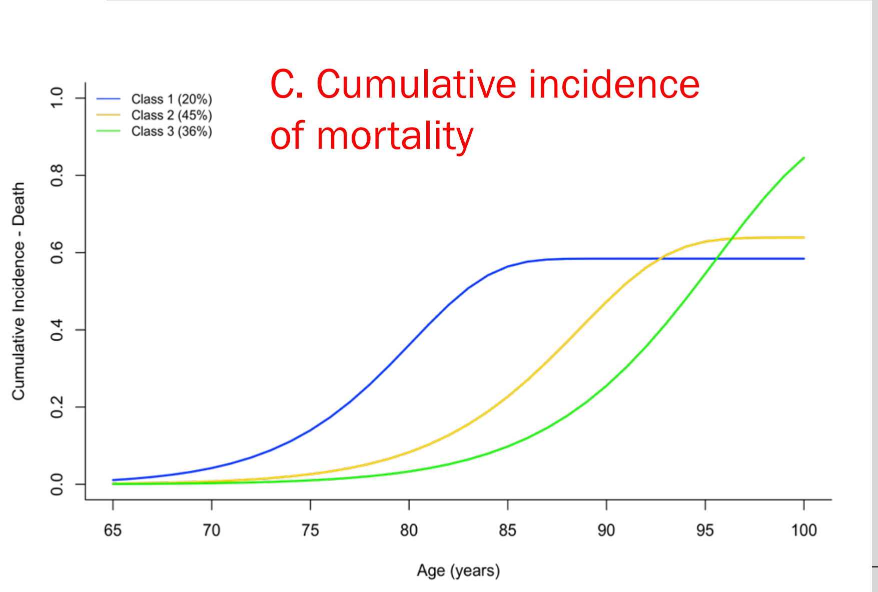
- Generalized modeling framework that integrates:
  - **Joint Modeling** for simultaneous analysis of **a)** longitudinal changes in a marker or health variable and **b)** the time to an event of interest to quantify their association or dependency
  - **Latent Class Mixture Modeling** for detecting heterogeneity and identifying underlying classes with distinct characteristics of longitudinal change
- Accounts for the heterogeneity in dependency between temporal components of longitudinal data (trajectories of change and the risk of the event) related by a common underlying process

Figure 5. Latent Class Profiles of Cognitive Decline and Incidence of Dementia/Death



Three Age Profiles
Class 1: Rapid Cognitive Decline
Class 2: Moderate Progression
Class 3: Optimal Cognitive Aging





- **Distinct classes of cognitive trajectories:** precipitous (Class 1), modest (Class 2), little (Class 3) decline
- **Class-specific cognitive decline associated with dementia and mortality risks:**

  - Class 1: highest incidence and earliest onset

  - Class 3: dementia-free survivors; lowest death rate

  - Class 2: medium risk characteristic of natural aging

Summary

- Our finding that distinct age patterns of cognitive change differentially predict dementia incidence highlights the importance of the rate of change in cognitive trajectories, especially a more rapid decline, above and beyond the initial cognitive level
- The covariate associations with longitudinal change and with dementia risk may be biased in standard mixed models and survival models:
  - Greater cognitive declines for NH Blacks and better educated in the joint models adjusting for informative attrition
  - Greater APOE-4 effect and smaller gender and education effects on dementia incidence in the joint models adjusting for longitudinal cognitive change and competing risks
- It is important for future research to formally account for the strong dependency between various age-related processes: cognitive decline, the occurrence of dementia, and death for unbiased estimates

PART 2. DATA LINKAGES AND METHODOLOGIES

2.3 Survey Data Linked to Validated External Data for Enhanced Measures of Midlife SES

Background & Significance

- Early life SES and adult education are both linked to cognition at older ages in previous research, but the mechanisms underlying these links over the life course are less clear
- Occupational characteristics can be an independent dimension of adult SES that link early life SES with cognition in mid to late life
  - Occupations act as meso-level work environments and structural contexts that can promote or inhibit cognitive stimulation through the complexity and degree of control over one's work
- Young to mid adulthood is a developmental period where population research on the occupational impact on cognition is scant (Stebbins, et al., *SS&M* 2022)
- Better understanding of social institutional factors such as work organizations that promote cognitive engagement for all workers can inform targeted workplace interventions

Study Aims

- Construct occupational-level measures of cognitive stimulation in mid life in a national representative longitudinal sample of adult respondents with life course information on SES and cognition
  - Integrating survey and external measures of job complexity, precarity and freedom
- Explore the pathways between early life SES, adult education, occupation, and cognition in mid life

Data, Sample, and Measures

- **National Longitudinal Study of Adolescent to Adult Health (Add Health)**
  - A U.S.-representative sample of adolescents in 1994-5 (Wave I) followed until age 42 in 2018 (Wave V)

	Variable	Operationalization
Wave I	Early-life SES	Social Origin Score (parental education, occupation, income, receipt of public assistance)
	Early Cognitive Ability	Picture Vocabulary Test Score (PVT)
Wave IV	Adult Education	< high school, high school, some college, college or higher
Wave V	Occupation	Standard Occupational Classification System 2010 codes of current or most recent paid job
	Memory	Standardized score of immediate word recall, delayed word recall, digits backward
	Covariates: Sex, race, age. Sample Weights	

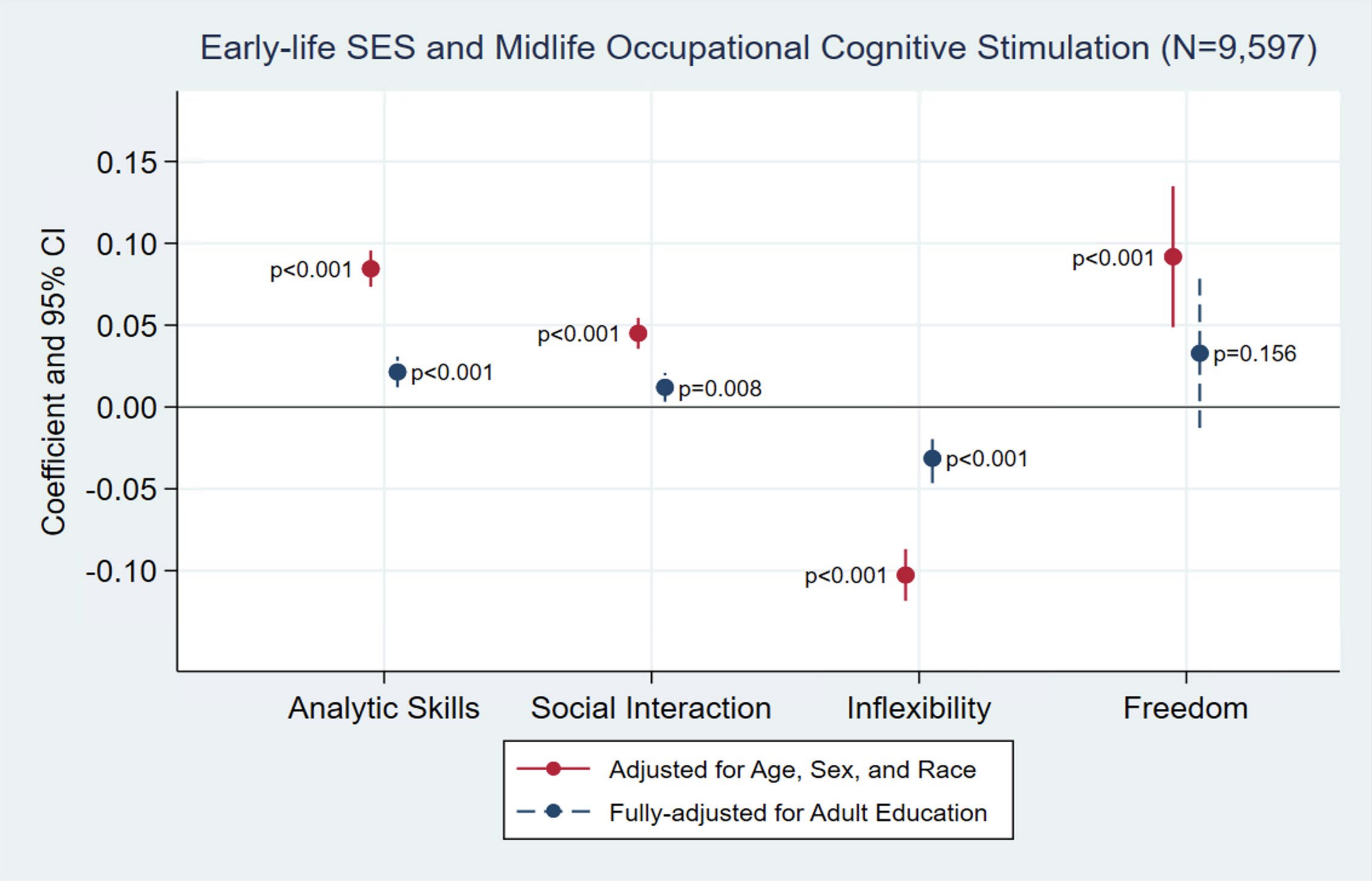
- **Occupational Information Network (O*NET)** (Development, 2018)
  - Linked to occupations in Add Health Wave V
  - Classifications of occupations used to measure job complexity and job inflexibility
  - Mean scores of job-task items across conceptual constructs provided by a content model

Table 3. Occupational Measures

Variable	O*NET Construct & Individual Item	Scale	Mean (SE)	Range
Analytic Skills	***Process:*** Critical Thinking, Active Learning, Learning Strategies, Monitoring ***Complex Problem Solving:*** Develop and implement solutions ***Practical Intelligence:*** Innovation, Analytical Thinking	5-point Likert scale, Mean of constructs	3.28 (0.02)	2.31-4.10
Social Interaction	***Interpersonal Orientation:*** Cooperation, Concern for Others, Social Orientation ***Communicating and Interacting:*** Interpreting Meaning, Communication with Coworkers, and Outside Persons, Establishing and Maintaining Relations, etc.	5-point Likert scale, Mean of constructs	3.49 (0.02)	2.53-4.33
Job (In)flexibility	Schedule, Location, Duration, Autonomy	5- or 3-point, standardized	0.04 (0.03)	-1.29-1.38
	Add Health Item	**Scale**	**Mean (SE)**	**Range**
Job Freedom	Self-reported control over decision making about the tasks performed at work	4-point Likert scale	3.01 (0.04)	1-4

Stebbins et al., (2022: *SS&M*); Zhang and Yang (2024: *PAA Annual Meetings*)

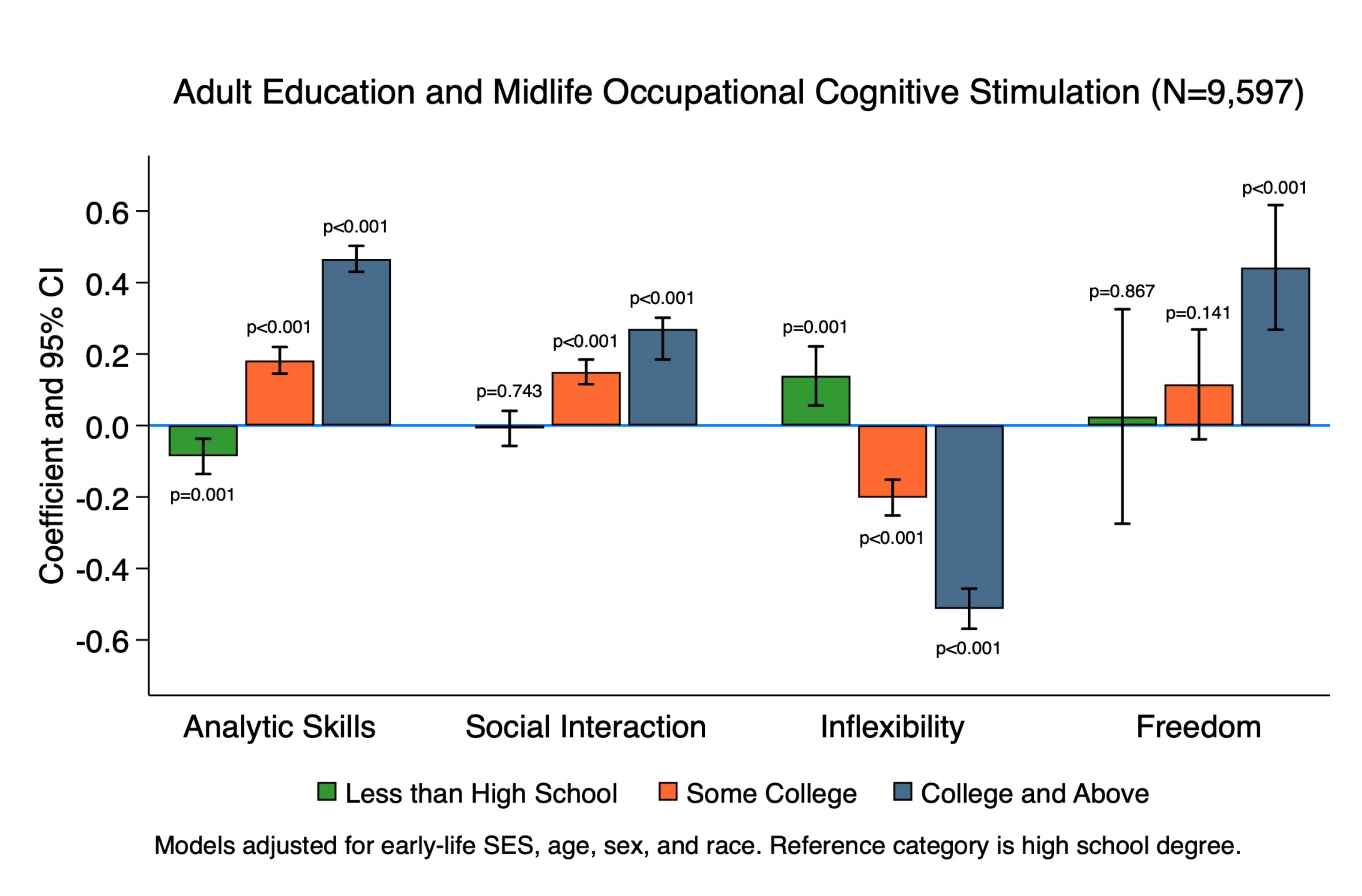
Figure 6. Higher Early-life SES Means Better Midlife Jobs



Note: Sample weights and cluster robust standard errors were used to adjust for complex survey designs.

- ***Higher early SES*** is significantly associated with more ***analytic skills***, ***social interaction***, less ***job inflexibility***, and more ***job freedom***
- Adjusting for adult education mediated these associations, but the effects remain significant for all job characteristics but job freedom

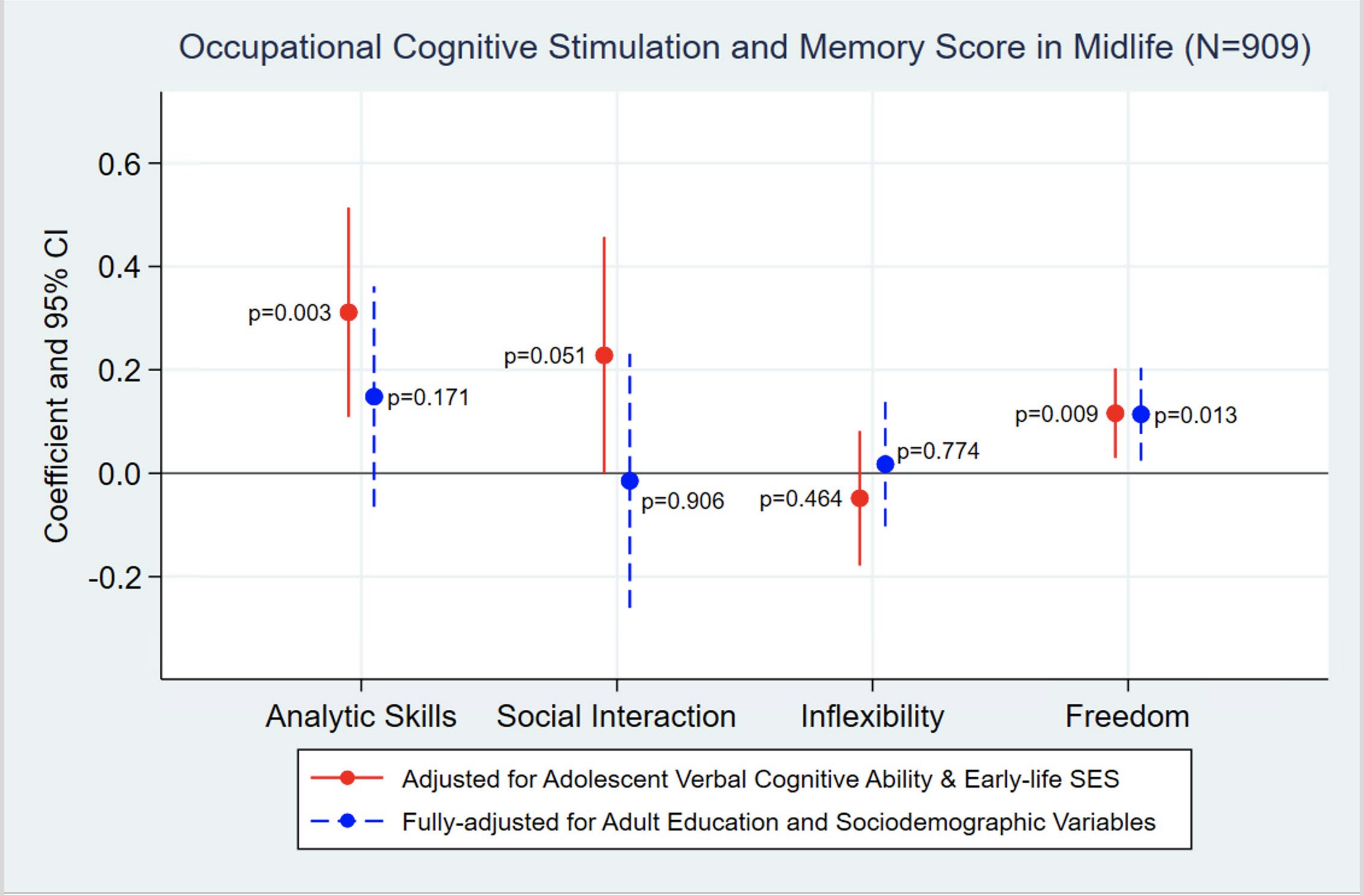
Figure 7. Higher Adult Education Means Better Midlife Jobs



- ***Adult educational attainment*** is significantly associated with all occupational characteristics, adjusting for early SES
- ***Less than high school*** is associated with jobs involving ***less analytic skills*** and ***more job inflexibility***
- ***College*** education is associated with better jobs in all regard

Note: Sample weights and cluster robust standard errors were used to adjust for complex survey designs.

Figure 8. Better Midlife Jobs Promote Memory Function



Note: Sample weights and cluster robust standard errors were used to adjust for complex survey designs.

- Job with ***more analytic skills, social interaction, and freedom*** are significantly associated with ***higher memory scores***, adjusting for prior cognitive ability and early SES
- The association of job freedom with memory remains significant after adjusting for adult education and other covariates

Summary

- The study enhanced the SES measure in midlife by the linkage of survey and validated external data and integration of direct and self-reported measures of occupational characteristics
- The new data enabled the empirical test of occupational cognitive stimulation as an independent meso-level dimension of adult SES linking early life disadvantage with poorer memory later in life:
  - Higher early-life SES and adult education sort individuals into cognitively stimulating occupational roles in mid life
  - Cognitively stimulating occupational roles can contribute to improved memory in mid life; the most beneficial forms of stimulation: analytic skills, social interaction, and freedom
- Improvements in cognitive health can be achieved through changes in workplace, regardless of early SES background

PART 3. DATA AND METHODS NEEDS

Long-term Longitudinal Cognitive Data and Multidimensional SES Measures

What We Learned from Example 1: Longitudinal IDA of Cognitive Aging

- Study Limitation 1
  - Heterogeneity in cognitive measures across studies (domain and tests) present challenges for data harmonization using standardizations in a fully integrated study of all cognitive functions
    - Standardization method may lead to bias when the assumption is not met that the construct is the same across measures and datasets
    - Pooled IDA is restricted to the memory measures common to three datasets (word recalls)
    - Coordinated IDA of individual studies provided qualitative comparisons across studies
- Future Research Needed
  - Collect longitudinal cognitive data across all domains
  - Engage more sophisticated methods to harmonize diverse cognitive measures (e.g., latent variable models, item response theory models, etc.)

What We Learned from Example 1: Longitudinal IDA of Cognitive Aging

- Study Limitation 2
  - Individual datasets are limited in age and birth cohort representations and lengths of follow-up
    - Only 2 waves of cognitive data available for the Add Health and MIDUS analyses
    - Pooled IDA improved life course inference but limited to memory measures
- Future Research Needed
  - Additional longitudinal follow-ups from young to mid adulthood
  - Add Health is particularly valuable for providing cognitive data for a life course stage least studied (e.g., Wave VI being collected)

What We Learned from Example 1: Longitudinal IDA of Cognitive Aging

- Study Limitation 3
  - The study is large in scale and complexity and could not examine causal pathways underlying social disparities in cognitive aging
- Future Research Needed
  - Assessments of structural measures of disparities
  - Potential cultural bias in survey-based cognitive measures that may disadvantage minority older adults
  - Other explanatory factors (biological, behavioral, or psychosocial) of individual differences in cognitive decline

What We Learned from Example 2: Age Profiles of Cognitive Decline and Dementia

- Study Limitations
  - ADAMS has the advantage of integrating population-based survey data (HRS) with the gold standard for dementia diagnosis based on neuropsychological assessment, but the study sample is small (particularly for NH Blacks) relative to other population-based studies
  - The data are limited to older adults followed in a few waves with no cognitive or dementia measures earlier in life
- Future Research Needed
  - Larger and younger samples with more years of follow-ups for the examination of a longer lifetime trajectory of cognitive change and the associated risk of dementia
  - A first step is to extend the analysis using the HRS 1996 – 2020 of adults 50+ with TICS and TICS-based dementia measures

What We Learned from Example 3: Occupational Cognitive Stimulation as Midlife SES Pathway

- Study Limitation 1
  - The association between occupational variables and memory is limited to cross-sectional analysis of Add Health Wave V
    - respondents were in early midlife (early 40s) and likely to experience further change in occupations due to job mobility
    - Job inflexibility, while found to have adverse health effects, was not associated with memory, which may indicate that its detrimental cognitive impact does not manifest until later in life
- Future Research Needed
  - Longitudinal data on both employment and cognitive function throughout mid life until retirement
  - Longitudinal analysis of long-term effects of occupational characteristics on cognition

What We Learned from Example 3: Occupational Cognitive Stimulation as Midlife SES Pathway

- Study Limitation 2
  - Occupational measures are limited to those in two previous studies of the same dataset and may not fully capture important (and changing) workplace contextual characteristics and lead to underestimation of the structural effects on individual cognitive function
- Future Research Needed
  - Expand multidimensional meso-level SES measures as an upstream driver of cognitive disadvantage
    - Additional domains of occupational constraint, resources, and demands
    - Increasing prevalence of work precarity
    - Accumulating chronic work-related stress

SUPPLEMENTAL MATERIALS

Table S1. Cognitive Measures across Four Longitudinal Cohort 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	0-15	Digits backward	0-7
			Delayed word recall	0-15	Picture Vocabulary Test	13-146
MIDUS	BTACT	-2.9-3.6	Immediate word recall	0-15	Digits backward	0-8
			Delayed word recall	0-15	Category fluency	0-42
					Stop & Go Accuracy	0-40
					Number Series	0-5
					Backward Counting	-13-100
ACL	SPMSQ	0-5	n/a		Serial 3's subtraction	0-1
					Date naming	0-1
					Day of week	0-1
					Current president	0-1
					Previous president	0-1
HRS	TICS	0-35	Immediate word recall	0-10	Backward counting	0-2
			Delayed word recall	0-10	Serial 7's subtraction	0-5
					Date naming	0-4
					Object naming	0-2
					President/VP	0-2

Source: Yang, et al., *JAH* (2023)

Table S2. IDA of Cognitive Aging: Data and Measures

Outcome Measures	Covariates
Episodic Memory • Immediate and delayed word recall tests (Add Health, MIDUS, HRS) • Harmonized measure: standardized memory score **Overall Cognitive Function** • Total score of all cognitive tests (different across 4 studies) • Harmonized measures: standardized total scores	• **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

Source: Yang, et al., *JAH* (2023)

Table S3. IDA: Data and Study Samples

- Pooled Analysis of Episodic Memory

Survey	N individuals	N person-years	Survey Years	Length of Follow-Up	# Study Waves
Add Health	12,046	13,134	2008-2018	10 years	2
MIDUS	3,817	6,058	2004-2017	13 years	2
HRS	35,417	197,947	1996-2018	22 years	11
Pooled	**51,280**	**217,139**	**1996-2018**	**22 years**	**15**

- Coordinated Analysis of Overall Cognitive Function

Survey	N individuals	N person-years	Survey Years	Length of Follow-Up	# Study Waves
Add Health	12,039	34,336	1994-2018	24 years	4
MIDUS	3,820	6,185	2004-2017	13 years	2
HRS	33,240	131,817	1996-2018	22 years	11
ACL	3,532	11,623	1986-2011	25 years	5

- Public Use Source Code: Creating the Integrated Dataset (https://cpc.unc.edu/projects)

Source: Yang, et al., *JAH* (2023)

JLCMM Model Specifications

- 1) Class-specific mixed models of latent longitudinal trajectory

$$\mathrm{TICS}_{ij} \mid c_{i=g} = (\gamma_{00(g)} + X'_{ik}\gamma_{0k(g)} + u_{0i(g)}) + (\gamma_{10(g)} + X'_{ik}\gamma_{1k(g)} + u_{1i(g)})*\mathrm{AGE}_{ij} + (\gamma_{20(g)} + X'_{ik}\gamma_{2k(g)} + u_{2i(g)})*\mathrm{AGE}_{ij}^{2} + \varepsilon_{ij} \quad \text{(Eq. 1)}$$

- 2) Class-specific time-to-event models of competing risks of events

$$h_p(t) \mid c_{i=g} = h_{0p(g)}(t)e^{\beta_{1p}SEX+\beta_{2p}RACE+\beta_{3p}EDUC+\beta_{4p}APOE4},\ p = 1, 2 \quad \text{(Eq. 2)}$$

- 3) Multinomial logistic regression model of latent class membership probability

$$P((c_i = g) = \pi_g \text{ for latent class } g = 1, \ldots, G \quad \text{(Eq. 3)}$$

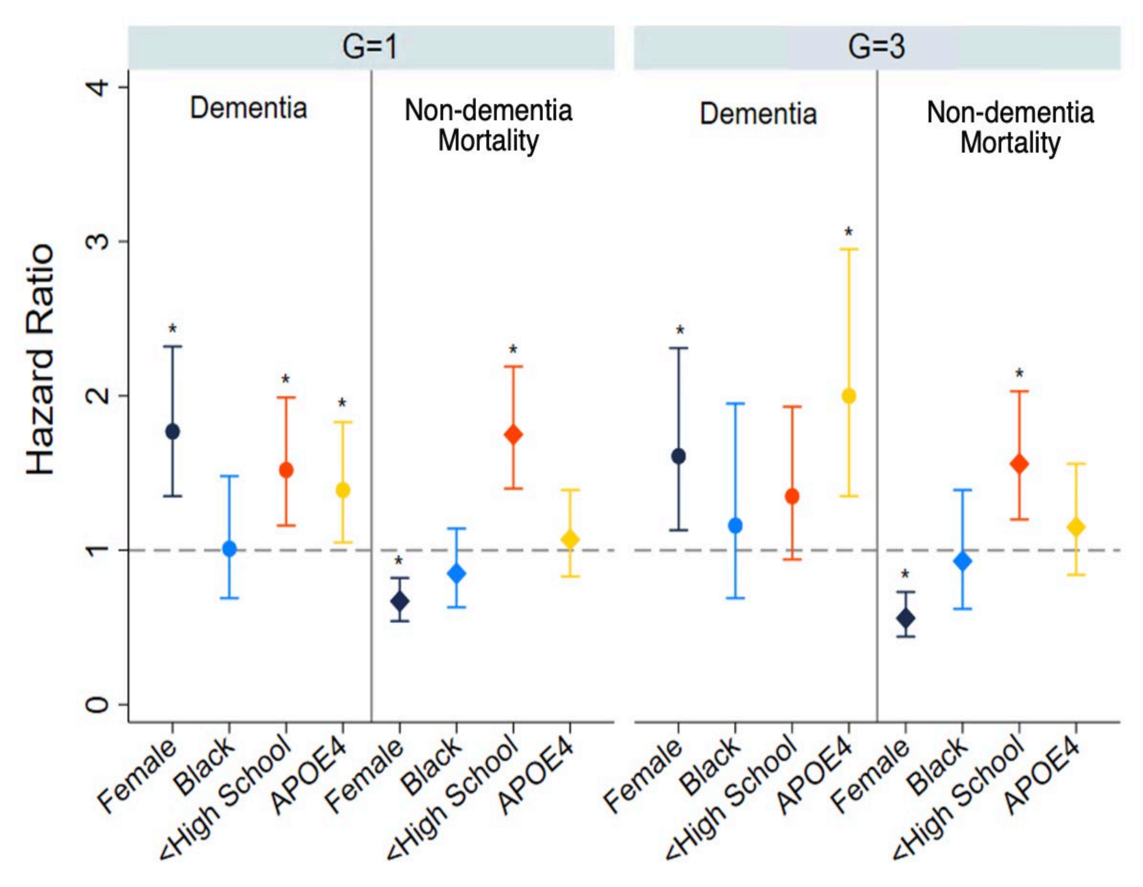
Source: Walsh, Yang, et al., *JGSS* (2022)

Figure S1. JLCMM vs. Standard Mixed and Survival Models

- Fixed Effects Estimates of Cognitive Trajectories

	Model 1: Mixed Model (G = 1)		Model 2: Joint Latent Class Model (G = 3)	
Parameters	Coefficient	SE	Coefficient	SE
Intercept ($\gamma_{0.}$)	22.72***	0.55		
Class 1			22.14***	0.93
Class 2			23.36***	0.74
Class 3			22.94***	1.03
Age at baseline	0.23*	0.09	0.17	0.09
Female	0.87	0.54	1.17*	0.58
Non-Hispanic Black	-2.63**	0.77	-2.28**	0.83
EDUC: < HS degree	-4.54***	0.58	-4.72***	0.64
APOE-4 Carrier	1.47*	0.66	1.56*	0.71
Linear Slope ($\gamma_{1.}$)	-0.14*	0.06		
Class 1			-0.40*	0.20
Class 2			-0.24**	0.09
Class 3			0.04	0.08
Age at baseline	0.00	0.01	-0.02***	0.01
Female	-0.01	0.04	0.00	0.02
Non-Hispanic Black	-0.02	0.05	-0.11*	0.05
EDUC: < HS degree	0.01	0.04	0.08*	0.04
APOE-4 Carrier	-0.09*	0.04	-0.08†	0.04

- Hazard Ratios of Dementia/Mortality & 95% CI



Source: Walsh, Yang, et al., *JGSS* (2022)