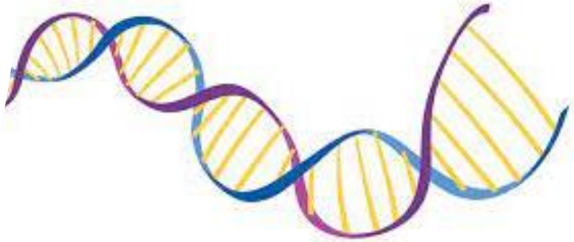
Sanders-Brown Center on Aging

Midlife and Later-life Social Risk Scores (SRSs) Modify the Effects of *APOE* ε4 on Alzheimer's Disease

Xian Wu, PhD
Postdoc Scholar
University of Kentucky
ADRC



Acknowledgment

THE NIA ALZHEIMER'S DISEASE RESEARCH CENTERS PROGRAM

NACC National Alzheimer's Coordinating Center

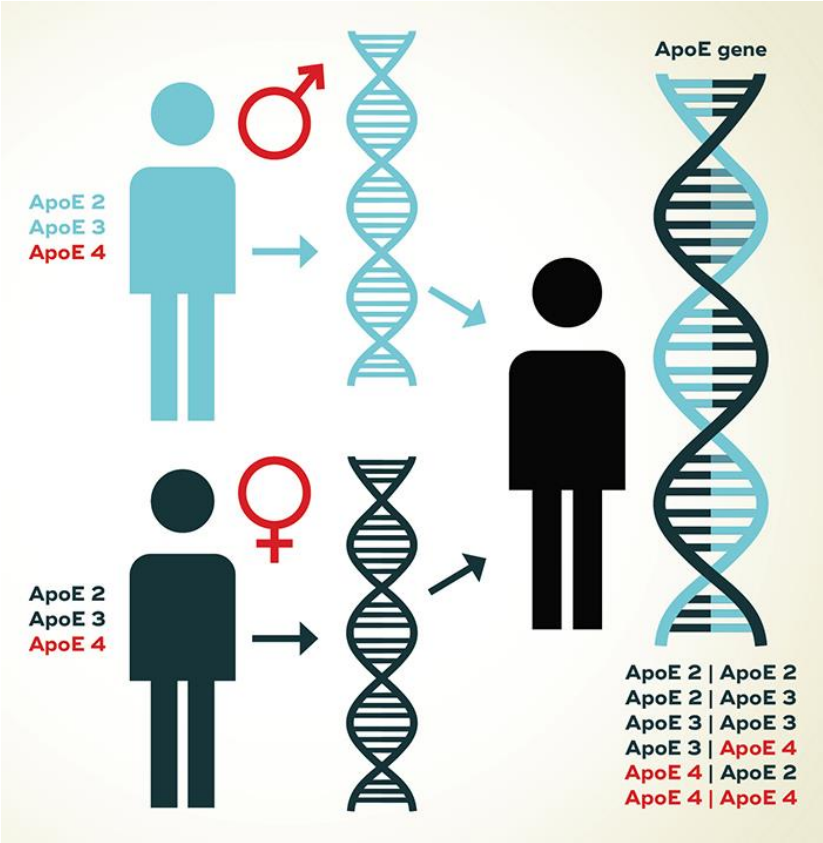
2024-2026 New Investigator Awards

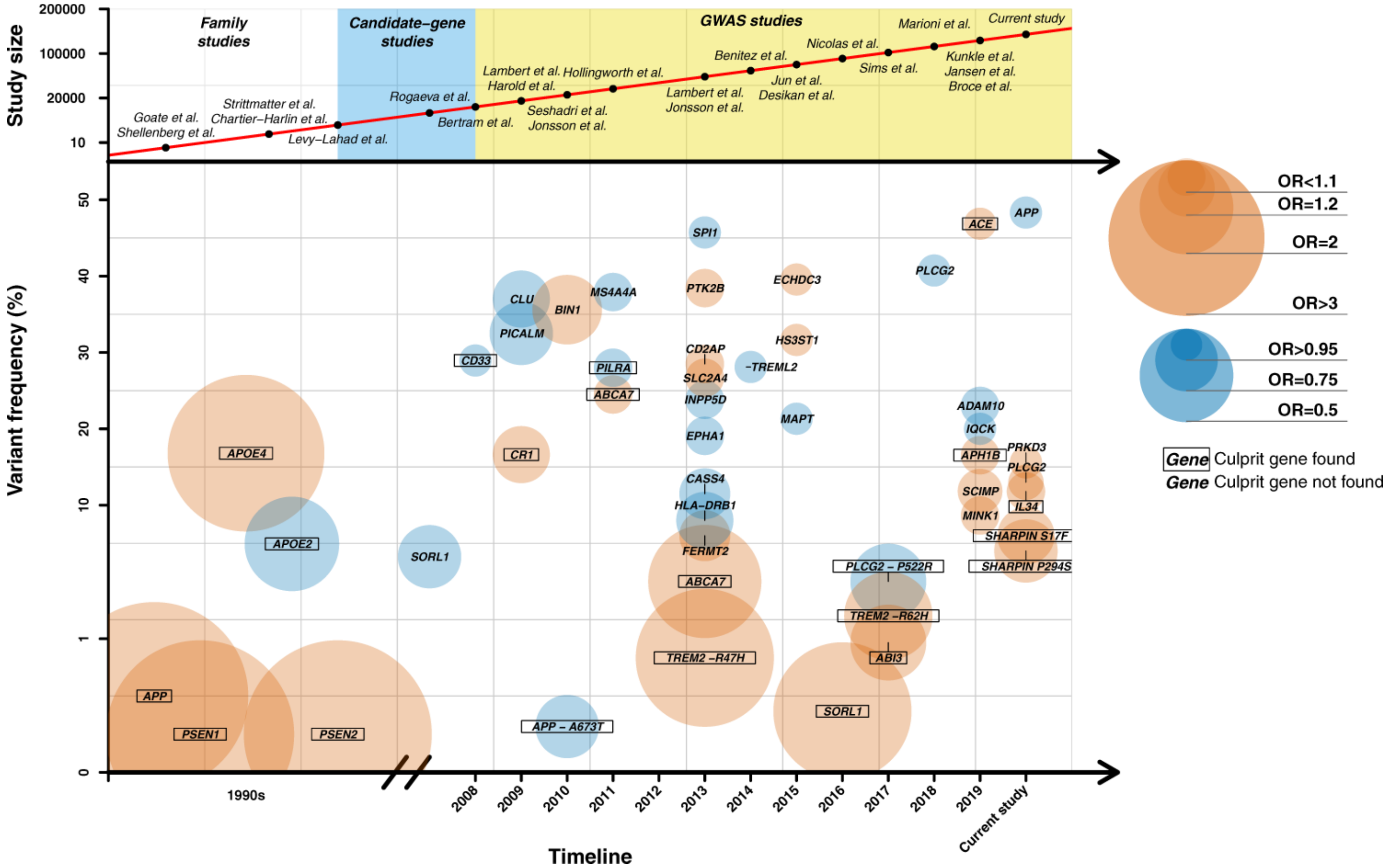
Comprehensive Gene-Environment Interactions in Alzheimer's Disease

Motivation of this project

Late-onset Alzheimer's disease (LOAD): people aged 65 years or older

- 60-80% of LOAD risk heritable
- Multiple genes play a role





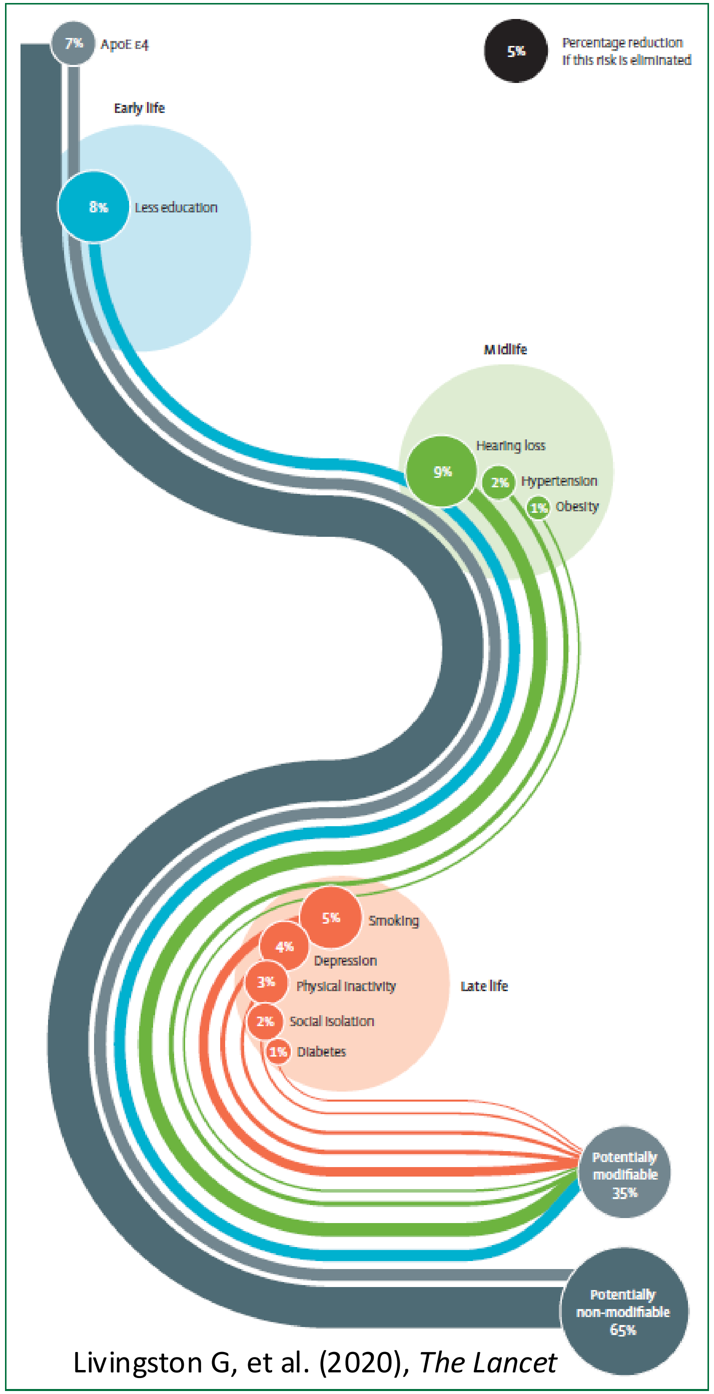
Itziar de Rojas et al. (2021) *Nature communication*

Motivation of this project

- 1/3 LOAD are modifiable by environmental factors
- Many environmental factors potentially affect LOAD
- Environmental effects on LOAD vary in midlife and later-life

1. Air pollution
2. Depression
3. Diabetes
4. Excessive alcohol use
5. Head injury
6. Hearing loss
7. High cholesterol
8. Hypertension
9. Lower education level
10. Obesity
11. Physical inactivity
12. Smoking
13. Social isolation
14. Vision loss

How to comprehensively examine gene-environment interactions in LOAD from a life-course perspective?



Livingston G, et al. (2020), *The Lancet*

Motivation of this project

One possible solution: G × E interactions in LOAD

- Construct a comprehensive score for genetic risks (G)
- Construct a comprehensive score for environmental risks (E)

Dimensionality reduction

Item Response Theory (IRT)

- Math ability = not directly observed

➡ **Latent variable**

- Test score = directly observed

Item Response Theory (IRT)

Difficulty ↓

Problem	Correct = 1 incorrect = 0	
	Student 1	Student 2
Item 1	1	1
Item 2	0	0
Item 3	1	0
Item 4	1	1
Item 5	0	**1**
Total	3	3

- ❑ Environmental risk = not directly observed

➡ **Latent variable**

Item Response Theory (IRT)

- ❑ Environmental variables = directly observed

Less common ↓

Environmental Variable	Yes = 1 No = 0	
	Participant 1	Participant 2
Alcohol Use	1	1
Smoking	0	0
HNT	1	0
Diabetes	1	1
Hearing Loss	0	**1**
Total	3	3

Model can be extended

Binary 0, 1 → Ordered 0, 1, 2, 3,….

Unidimensional → Multidimensional

One parameter → Two or more parameters

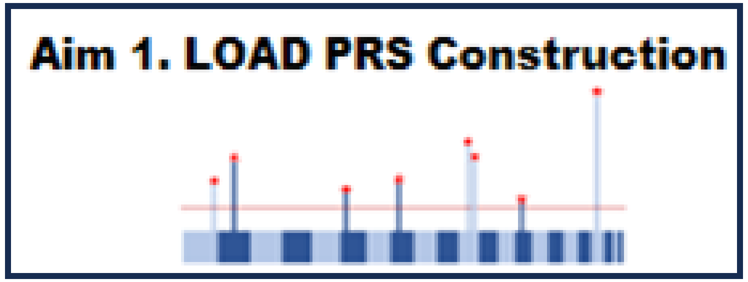
Merits of IRT-based models

- Allow different response patterns
- Fit environment risk structure
- Provide information of variables

Multidimensional Generalized Partial Credit Model (GPCM) implemented by the “mirt” R package

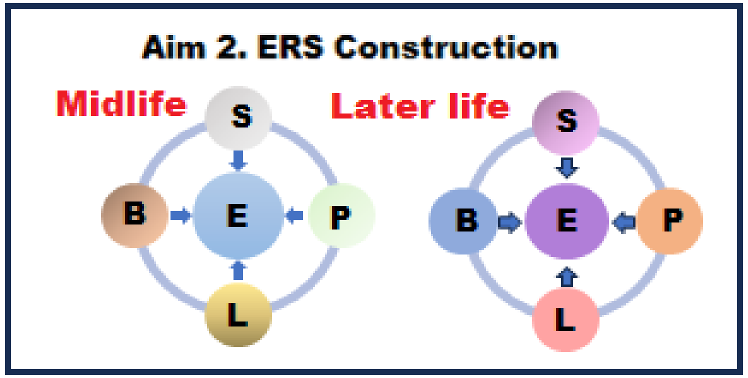
https://cran.r-project.org/web/packages/mirt/mirt.pdf

Aims of this project

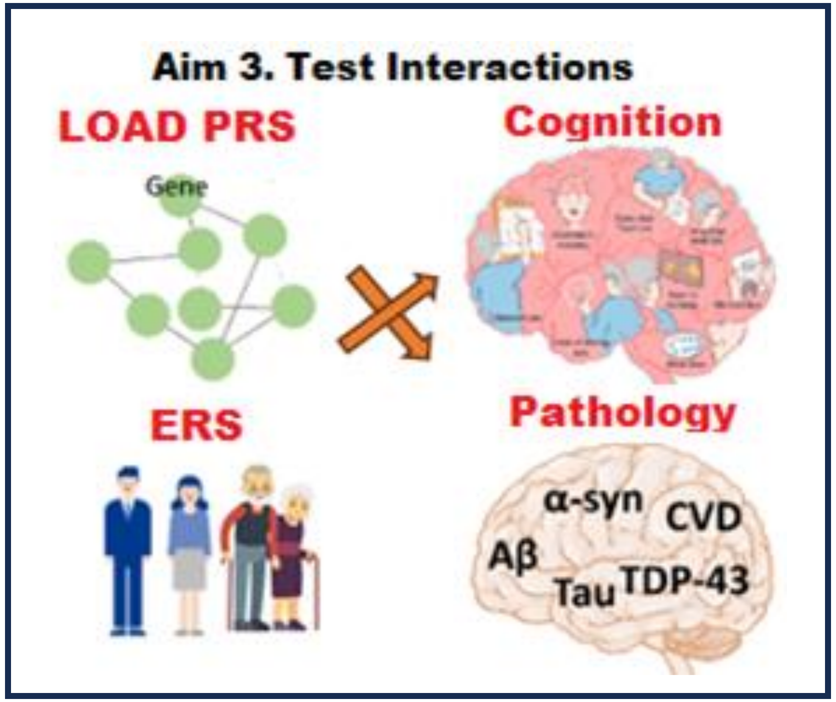


Polygenic risk score (PRS)

An estimate of an individual's genetic liability to LOAD by aggregating the genetic effects of single-nucleotide variants (SNVs)



Environmental risk score (ERS)



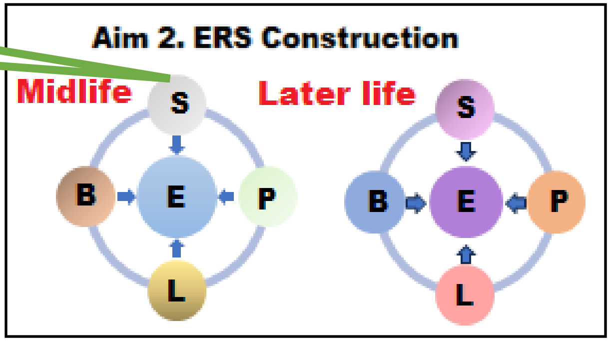
PRS × ERS interactions

Preliminary analyses: social variables in NACC UDS v3

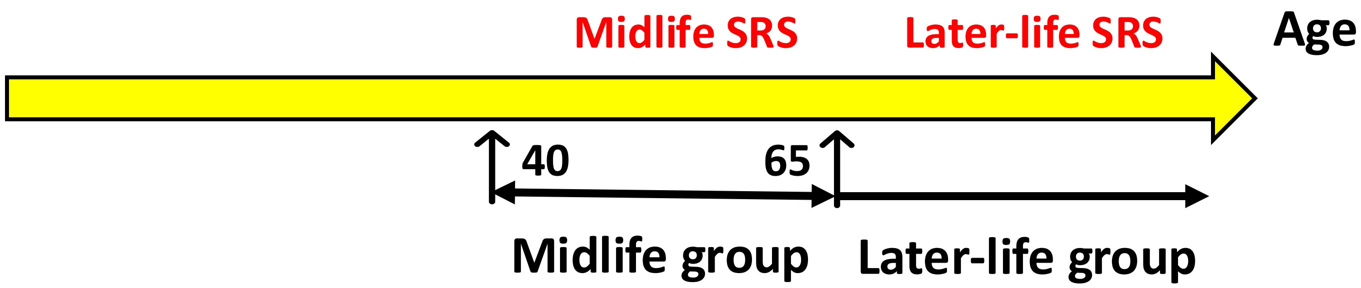
Social risk score (SRS)

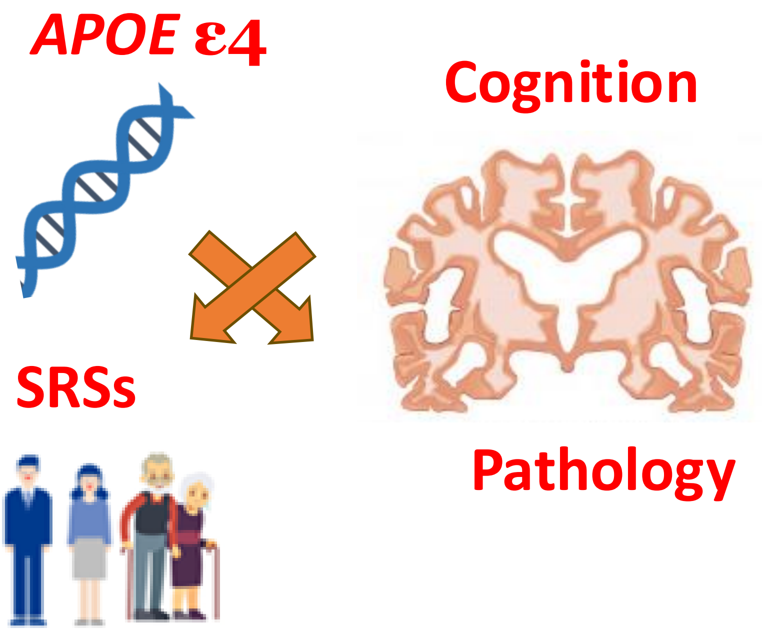
Social variables in NACC UDS
Primary language
Education
Marital status
Living situation
Level of independence
Type of residence

Item Response Theory



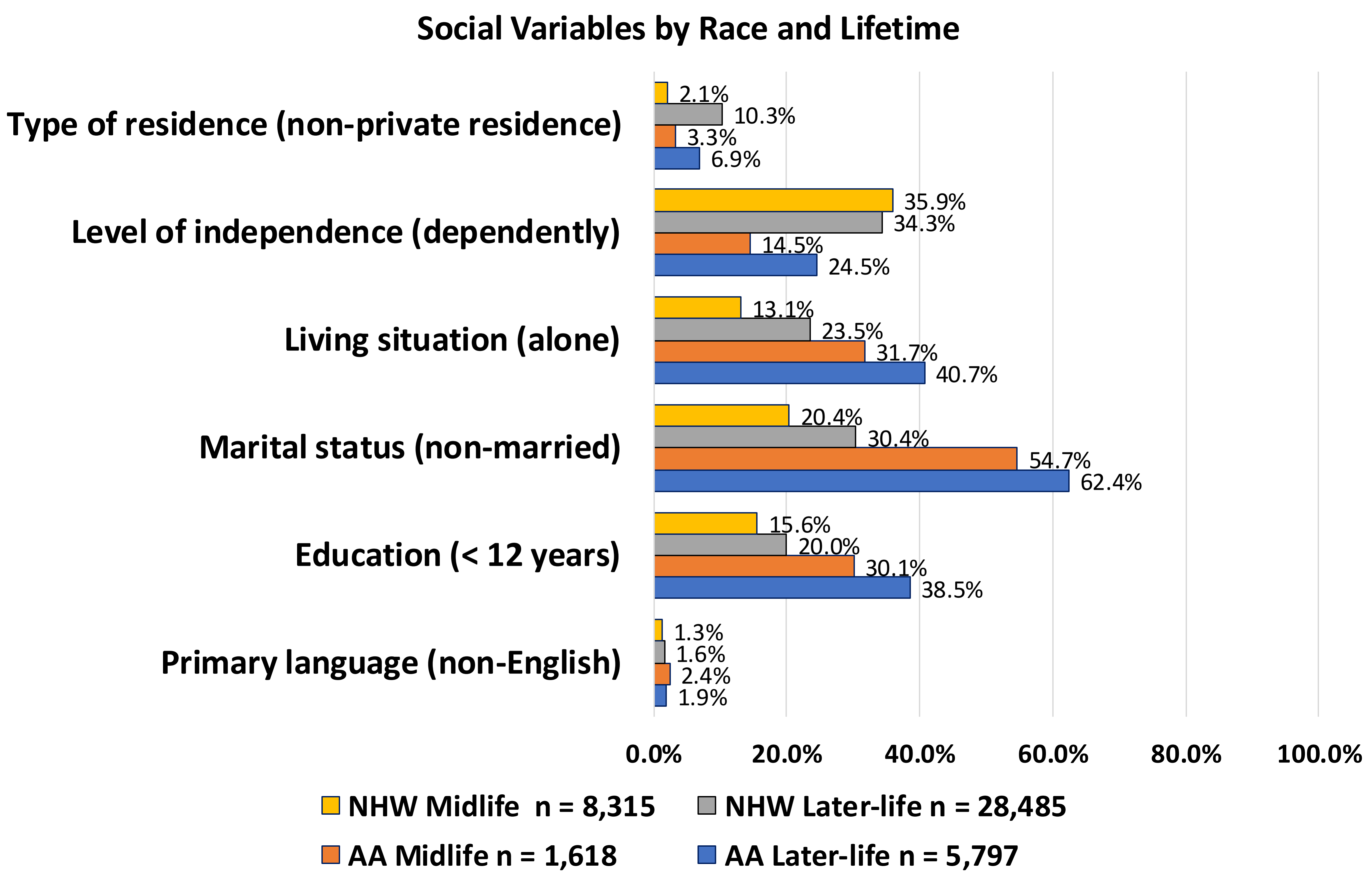
Participants' records at the age range



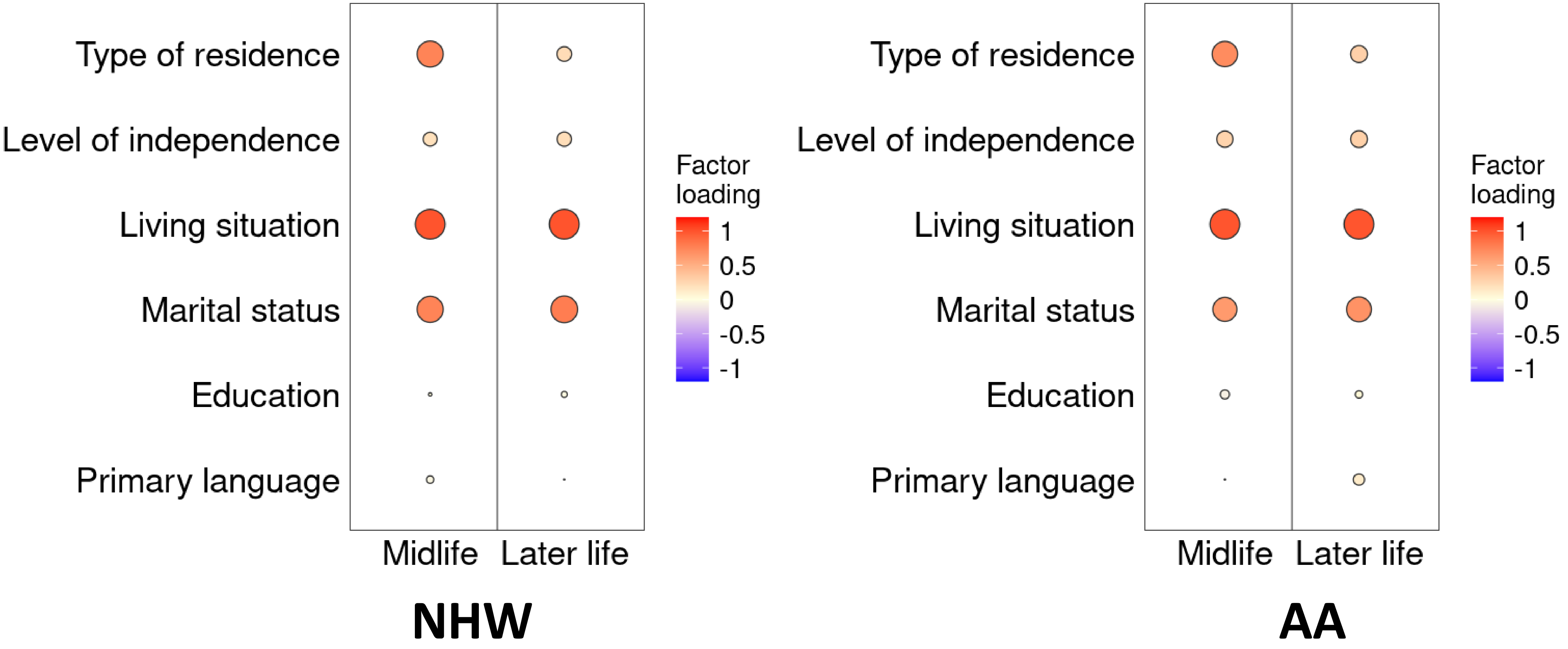


Recoded social variables for GPCM

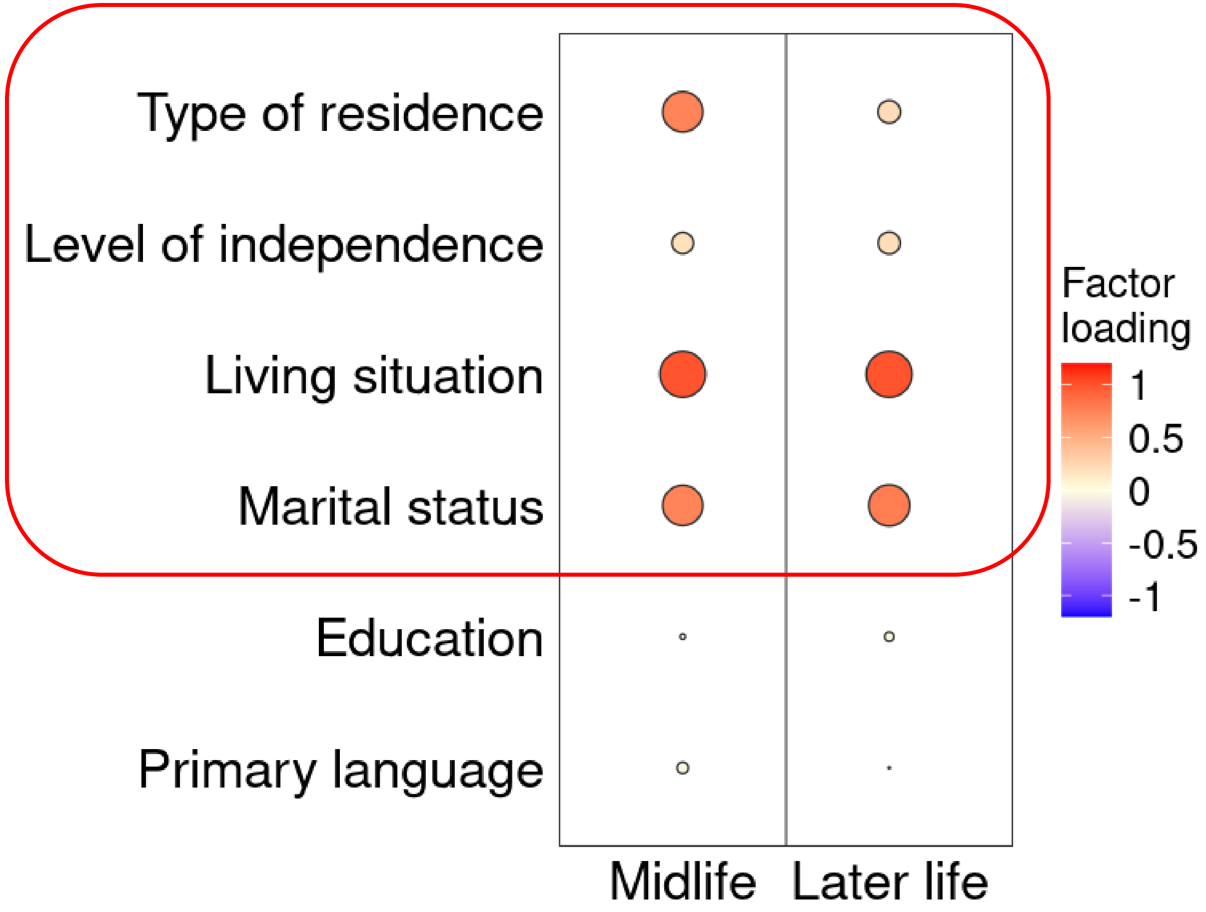
Social factors	NACC variable	0	1	2	3
Primary language	PRIMLANG	English	Non-English		
Education	EDUC	12 years +	9-12 years	6-8 years	0-5 years
Marital status	MARISTAT	Non-married	Married		
Living situation	NACCLIVS	Alone	With spouse	With group	
Level of independence	INDEPEND	Independent	Some assistance	Dependent	
Type of residence	RESIDENC	Private residence	Assisted living home	Hospital	


Social Variables by Race and Lifetime
Type of residence (non-private residence)
2.1%
10.3%
3.3%
6.9%
Level of independence (dependently)
35.9%
34.3%
14.5%
24.5%
Living situation (alone)
13.1%
23.5%
31.7%
40.7%
Marital status (non-married)
20.4%
30.4%
54.7%
62.4%
Education (< 12 years)
15.6%
20.0%
30.1%
38.5%
Primary language (non-English)
1.3%
1.6%
2.4%
1.9%
0.0%
20.0%
40.0%
60.0%
80.0%
100.0%
NHW Midlife n = 8,315
NHW Later-life n = 28,485
AA Midlife n = 1,618
AA Later-life n = 5,797

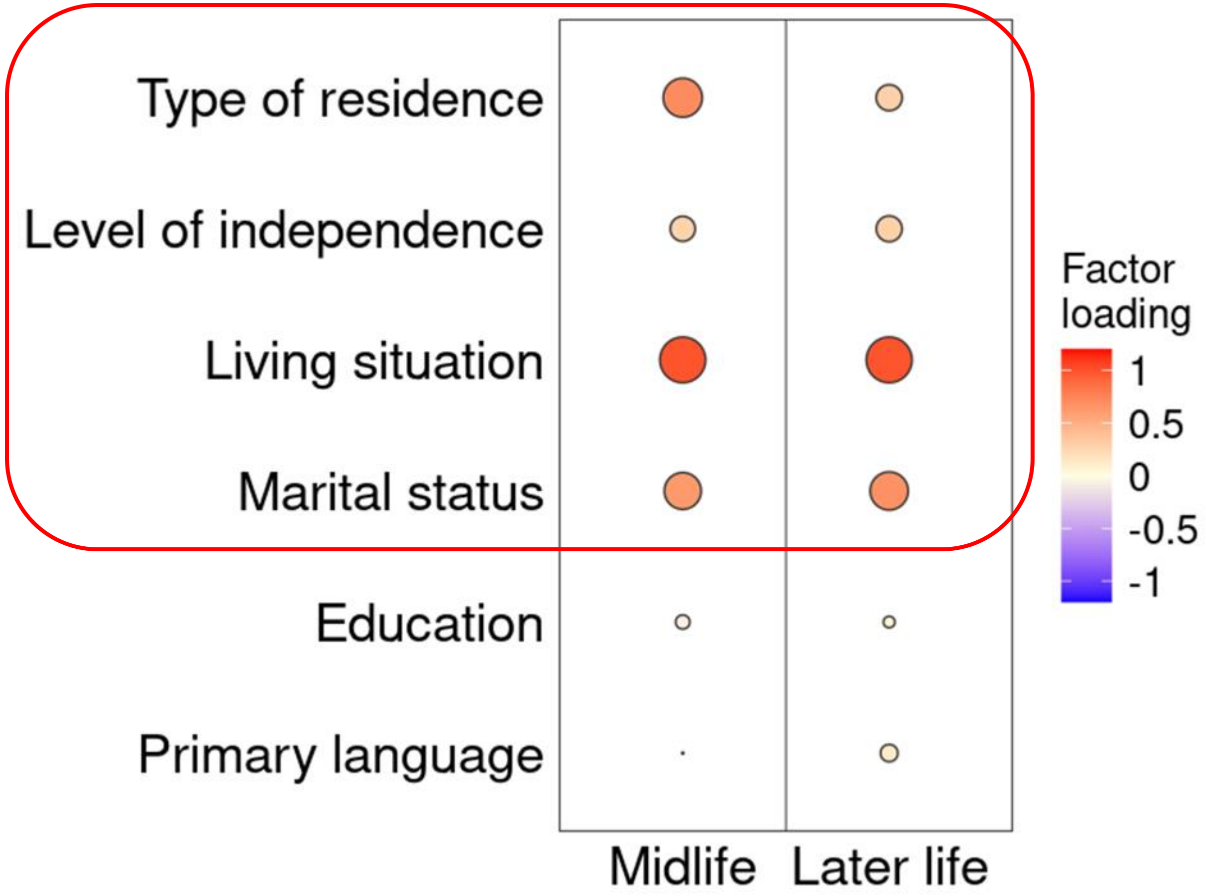
Contributions to SRS for each variable from GPCM



Contributions to SRS for each variable from GPCM

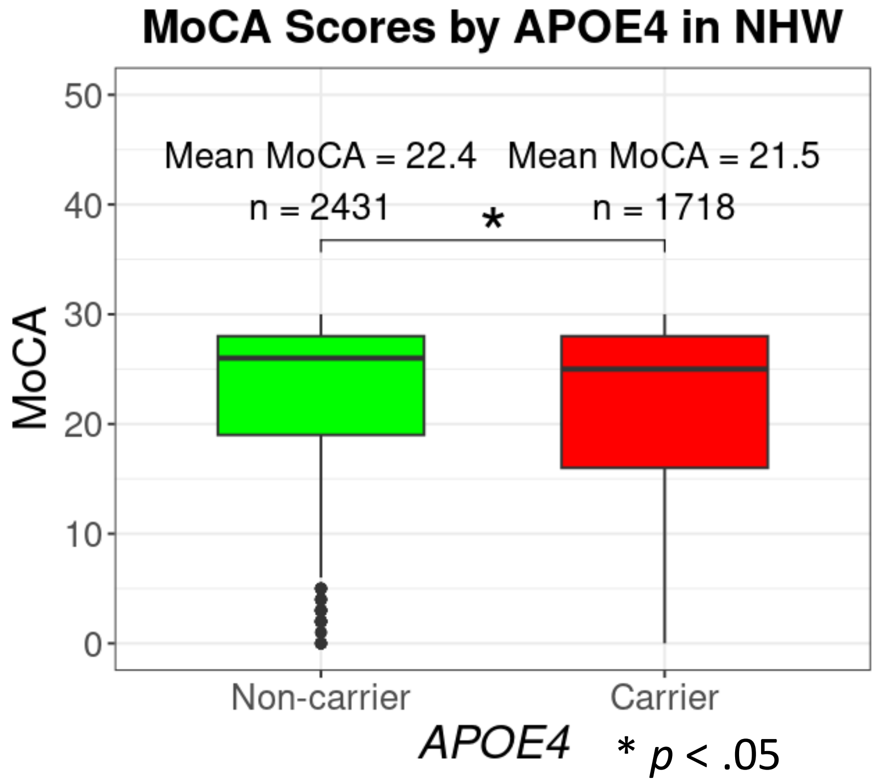


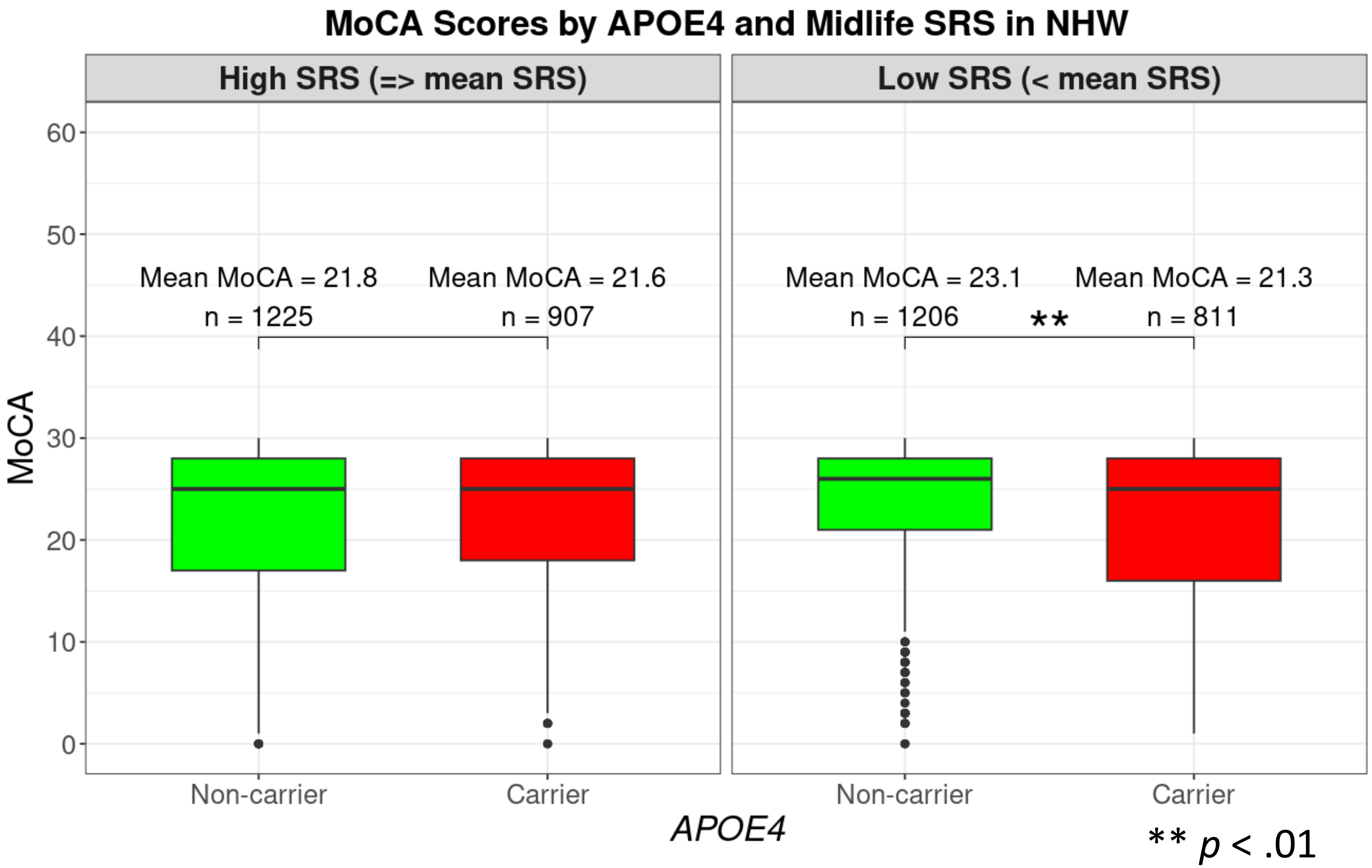
NHW



AA

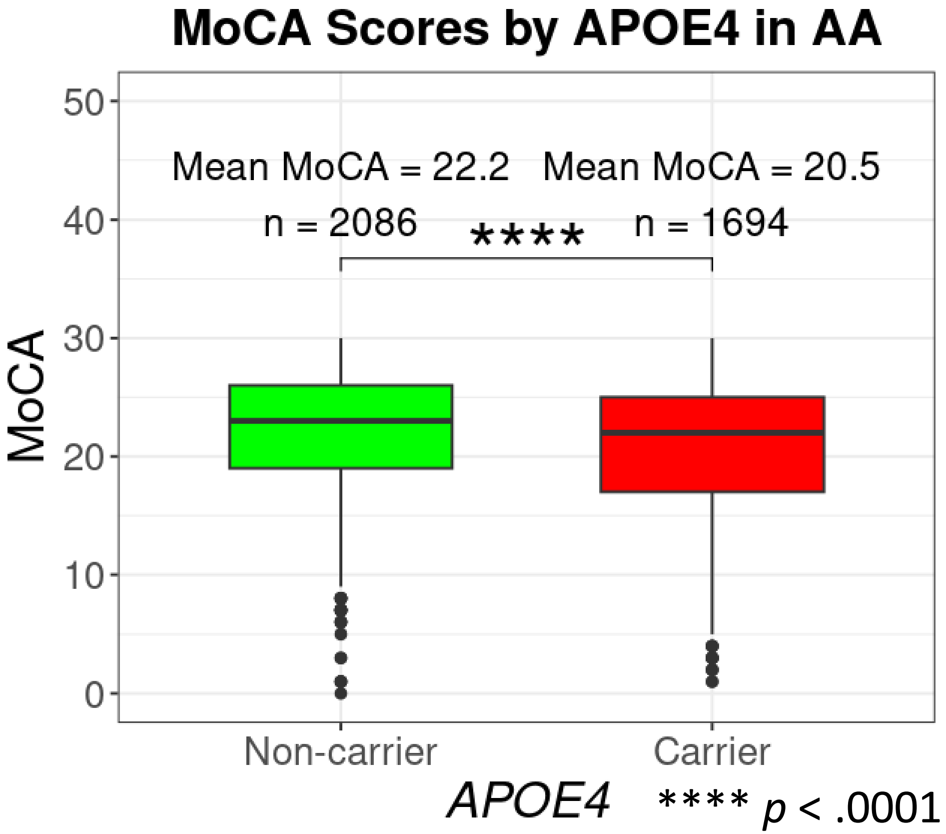
In NHW, *APOE* ε_4 carriers had lower MoCA scores on average

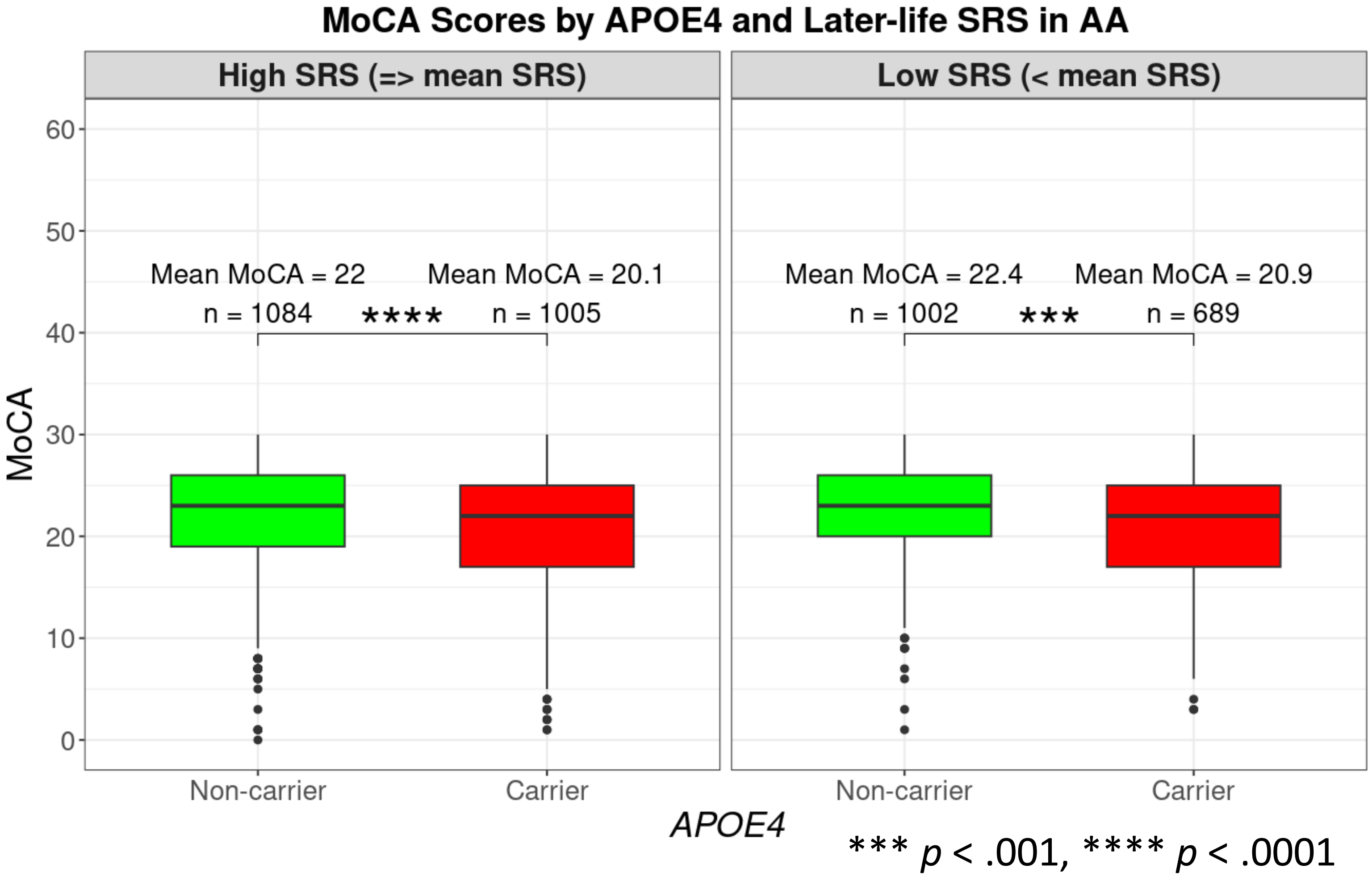




In Low SRS group, *APOE* ε_4 carriers had a lower mean MoCA score, compared to *APOE* ε_4 non-carriers

In AA, *APOE* ε_4 carriers had lower MoCA scores on average

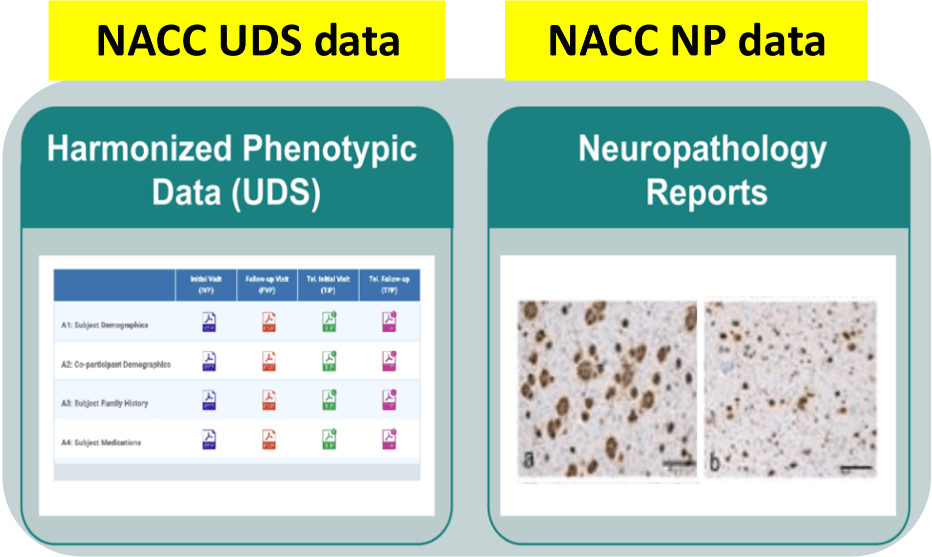




APOE ε_4 carriers who had a higher later-life SRS had the lowest mean MoCA score

Modeling

- *APOE* ε4 genotype: 0 = -/-, 1 = ε4/-, 2 = ε4/ε4.
- Phenotypes: Neurocognition & Neuropathology
  - MMSE (Mini-Mental State Examination)
  - MoCA (Montreal Cognitive Assessment)
  - Aβ (Thal phase ratings for Aβ distribution, A score)
  - Tau (Braak NFT stage categories for tau neurofibrillary degeneration, B score)
- Adjustment: age & sex
- Two racial groups:
  - Non-Hispanic White (NHW) (sample size n = 37,142)
  - African American (AA) (sample size n = 7,422)



Regression Results

Midlife (aged 40 and 65 years)				
	MMSE	MoCA	Aβ	Tau
NHW	$\hat{\beta}$ (SE)	$\hat{\beta}$ (SE)	$\hat{\beta}$ (SE)	$\hat{\beta}$ (SE)
APOE	**-0.5** (0.2)	**-1.0** (0.3)	**1.0** (0.1)	**0.8** (0.1)
SRS	**-0.7** (0.1)	**-0.8** (0.2)	0.2 (0.1)	**0.2** (0.1)
APOE×SRS	0.1 (0.2)	0.2 (0.3)	-0.2 (0.1)	-0.1 (0.1)
AA				
APOE	**-1.9** (0.3)	-0.7 (0.4)	2.0 (1.4)	**1.3** (0.6)
SRS	0.0 (0.3)	-0.1 (0.4)	-0.0 (0.6)	0.8 (0.6)
APOE×SRS	**0.6** (0.3)	-0.1 (0.5)	1.7 (1.5)	-0.3 (0.8)

Significant results in bold (*p* < .05). NHW = non-Hispanic White, AA = African American, MMSE = Mini-mental state examination, MoCA = Montreal cognitive assessment, SRS = social risk score, SE = standard error

Later life (aged 65 years or older)				
	MMSE	**MoCA**	**Aβ**	**Tau**
NHW	$\hat{\beta}$ (SE)	$\hat{\beta}$ (SE)	$\hat{\beta}$ (SE)	$\hat{\beta}$ (SE)
APOE	**-1.9** (0.1)	**-2.1** (0.1)	**1.4** (0.1)	**1.1** (0.1)
SRS	**-0.6** (0.1)	**-0.5** (0.1)	**0.1** (0.1)	**0.1** (0.0)
APOE×SRS	0.0 (0.1)	-0.1 (0.1)	0.0 (0.1)	-0.0 (0.0)
AA				
APOE	**-2.0** (0.2)	**-1.8** (0.3)	**1.6** (0.3)	**1.1** (0.2)
SRS	**-0.6** (0.1)	-0.1 (0.2)	0.1 (0.3)	0.2 (0.2)
APOE×SRS	**-0.4** (0.2)	**-0.7** (0.3)	0.0 (0.3)	0.2 (0.2)

Significant results in bold ($p < .05$). NHW = non-Hispanic White, AA = African American, MMSE = Mini-mental state examination, MoCA = Montreal cognitive assessment, SRS = social risk score, SE = standard error

Summary

- We constructed midlife and later-life SRSs based on six variables primary language, education, marital status, living situation, level of independence, type of residence

- Marital status, living situation, type of residence mainly contributed to midlife and later-life SRSs across NHW and AA, which might indicate "<u>living conditions</u>"

- Midlife and later-life SRSs modified the effects of *APOE* ε4 on neurocognition scores (MMSE and MoCA) in AA

Next steps: we will include more environment variables

Physical variables
Body mass index (BMI)
Hypertension
Diabetes
Hypercholesterolemia
Arthritis
Traumatic brain injury (TBI)
Hyposomnia/insomnia
Bowel Incontinence
Urinary Incontinence
Sleep apnea
Wear corrective lenses
Wear a hearing aid(s)
Depression

Lifestyle variables
Average number of packs smoked per day
At least one drink of any alcoholic beverage
Vitamin B12 deficiency

Behavioral variables
Writing checks
Assembling tax records
Shopping alone
Playing a game of skill
Heating water
Preparing a balanced meal
Keeping track of current events
Paying attention to a TV program
Remembering appointments
Traveling

Next steps:
Look forward to UDS v4 data available
We could include more variables, SDoH

Topic	Project - Activity or deliverable	√	2024 (Q2 Q3 Q4: A M J J A S O N D)	2025 (Q1 Q2 Q3 Q4: J F M A M J J A S O N D)	2026 (Q1 Q2: J F M A M J)	Future
UDSv4 Implementation	Content complete and PDFs shared (initial packet)					
	REDCap forms complete and shared (initial packet)					
	Follow-up packets complete (PDF and REDCap)					
	UDSv4 START – used for all ADRC data collection					
	UDSv3 STOP – backlog submission stop for ADRCs					
	UDSv3 STOP – Spanish and Chinese /Affiliated studies					
Pilots	NACCID Pilot					
	UDSv4 Pilot					
UDSv4 Resource Development	UDSv3 to UDSv4 crosswalk					
	UDSv4 onboarding checklists					
	SOPs on how to leverage REDCap for UDSv4					
	Data element dictionary					
	Coding guidebooks					
	QC rules and codes published					
ADRC Training and Support	Launch Community Forum					
	Clinical Staff Training Session					
	UDSv4 and NACCID Pilot training					
	Bi-Weekly Office Hours					
	UDSv4 Digital Voice Guidelines					
UDSv4 Translations	Chinese Translations (funded by separate R01)					
	Spanish Translations					

✓ Current Status | Activity Duration | Draft | Complete | Deadline

Social Determinants of Health

Acknowledgment

THE NIA ALZHEIMER'S DISEASE RESEARCH CENTERS PROGRAM

National Alzheimer's Coordinating Center

2024-2026 New Investigator Awards

Comprehensive Gene-Environment Interactions in Alzheimer's Disease

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Dr. Pete Nelson

Dr. Erin Abner

Dr. Bryan James

UK-ADRC Director

Dr. Linda Van Eldik

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University of Kentucky CCTS
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My Lab (Statistical 'Omics Research Center, S'ORCe)

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شكراً جزيلاً
ngiyabonga
рахмат
danke
謝謝
spas
teşekkür ederim
Баярлалаа
mersi
kia ora
barka
welalin
tack
mahalo
tapadh leat
спасибо
faafetai lava
vinaka
спасибі
blagodaram
dank je
misaotra
matondo
paldies
grazzi
kiitos
dankie
nanni
nandri
dhanyavad
thank you
gracias
хвала
asante
manana
obrigada
tenki
bedankt
bayarlalaa
gràcie
hvala
mauruuru
köszönöm
aciu
dankon
akun
djiere dieuf
tau
mochchakkeram
murakoze
enkosi
dziękuję
дякую
mamnun
chnorakaloutioun
gratias ago
gràcies
sulpáy
taiku
go raibh maith agat
chokrane
sobodi
dėkuji
sagolun
sukriya
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obrigado
arigatô
takk
dakujem
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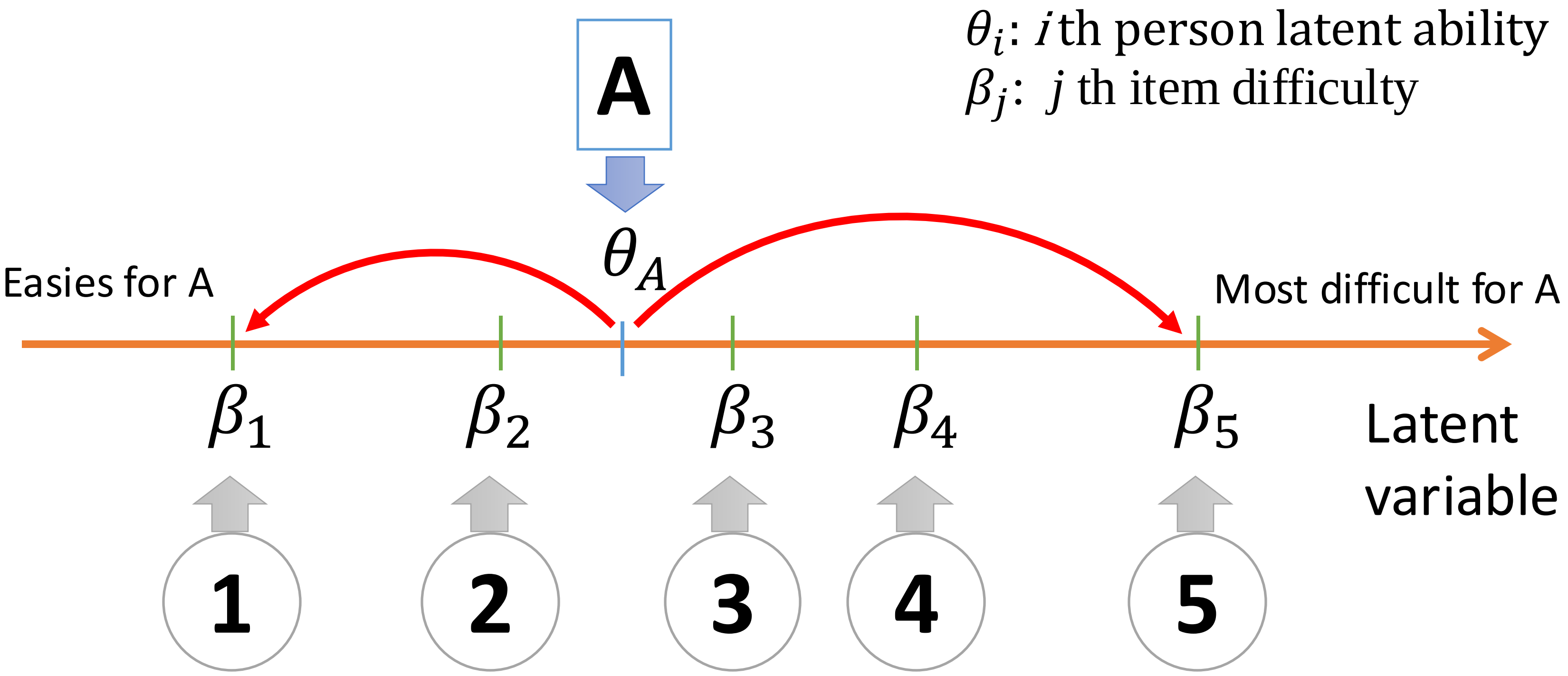
mèsi
didi madloba
najis tuke
ありがとう
tanemirt
grazie
terima kasih
rahmet
kam sah hamnida
rahmat
diolch
dhanyavadagalu
shukriya
mercê
мерси
তোমাকে ধন্যবাদ
감사합니다
xièxie
ευχαριστώ
merci

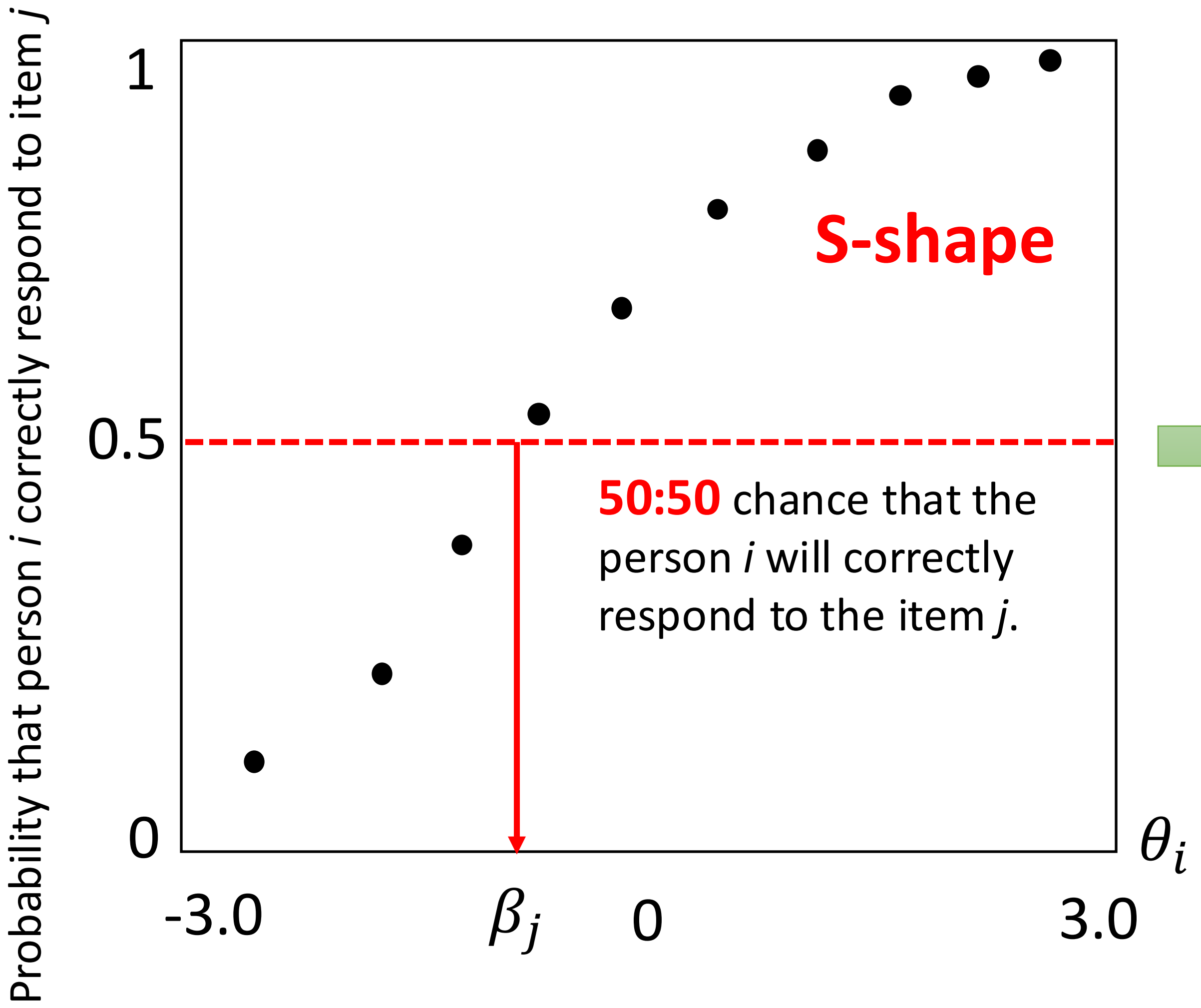
Both items and persons are located on the same latent variable continuum.

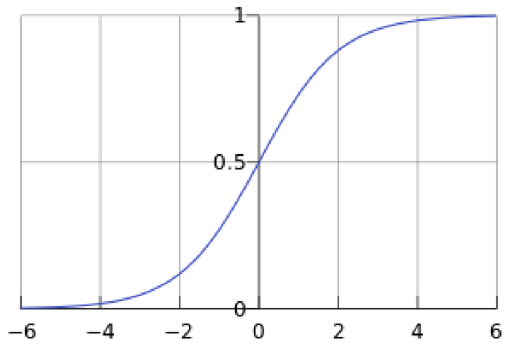


The **distance** between the person and item locations → $\theta_i - \beta_j$

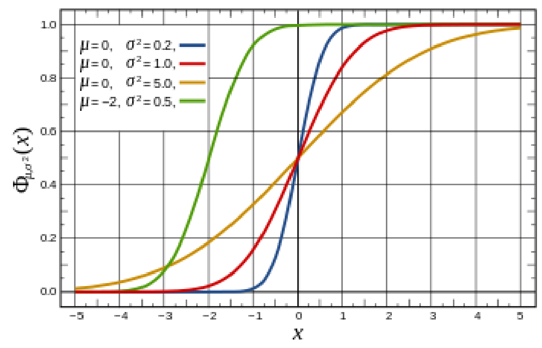
The probability that the person *i* will correctly respond to the item *j* → $f(\theta_i - \beta_j)$

What does $f(\theta_i - \beta_j)$ look like?





Logistic function



CDF of normal distribution

Logistic function $P\left(y_{ij} = 1 \middle| \theta_i, \beta_j\right) = \dfrac{1}{1 + e^{-(\theta_i - \beta_j)}}$ Rasch model

In general, the Rasch model can be written as

$$L(\boldsymbol{\theta}, \boldsymbol{\beta}|\boldsymbol{y}) = \prod_{i=1}^{N}\prod_{j=1}^{J}\frac{e^{y_{ij}(\theta_i-\beta_j)}}{1+e^{(\theta_i-\beta_j)}} = \frac{\exp\left\{\sum_{i=1}^{N}\sum_{j=1}^{J} y_{ij}\left(\theta_i-\beta_j\right)\right\}}{\prod_{i=1}^{N}\prod_{j=1}^{J}\left\{1+e^{(\theta_i-\beta_j)}\right\}}$$

Model can be extended

Binary 0, 1 ⇨ Ordered 0, 1, 2, 3,….

$$y_{ijk} = \begin{cases} 1 & \text{if } u_{ij} = k \\ 0 & \text{otherwise} \end{cases}$$

Unidimensional ⇨ Multidimensional

One parameter ⇨ Two or more parameters

$$\frac{\gamma_j}{1+e^{-\alpha_j(\theta_i-\beta_j)}}$$

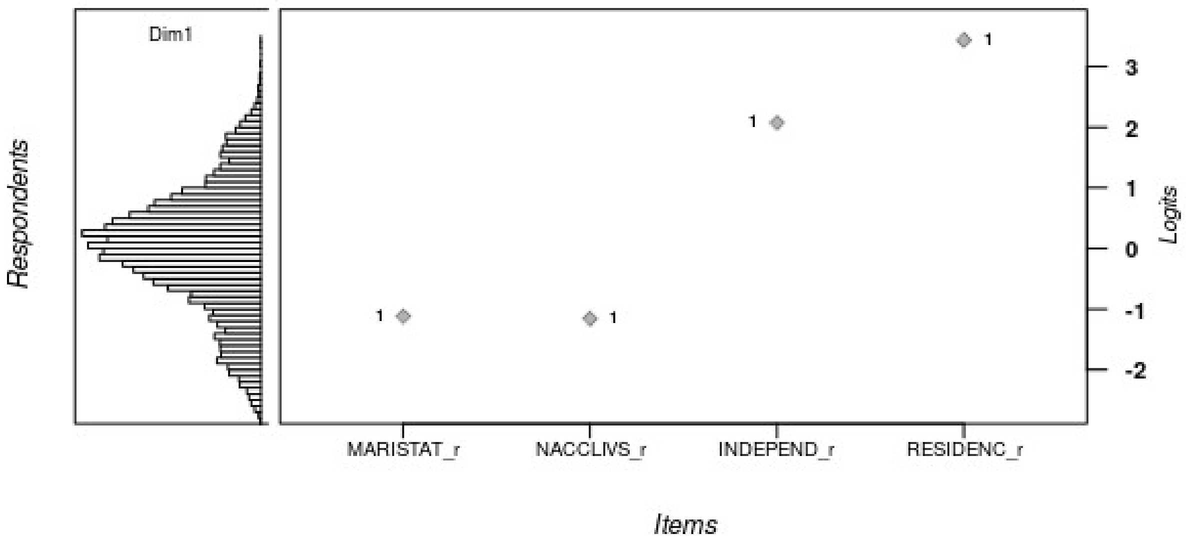
Multidimensional Partial Credit Model

implemented by the “mirt” R package

https://cran.r-project.org/web/packages/mirt/mirt.pdf

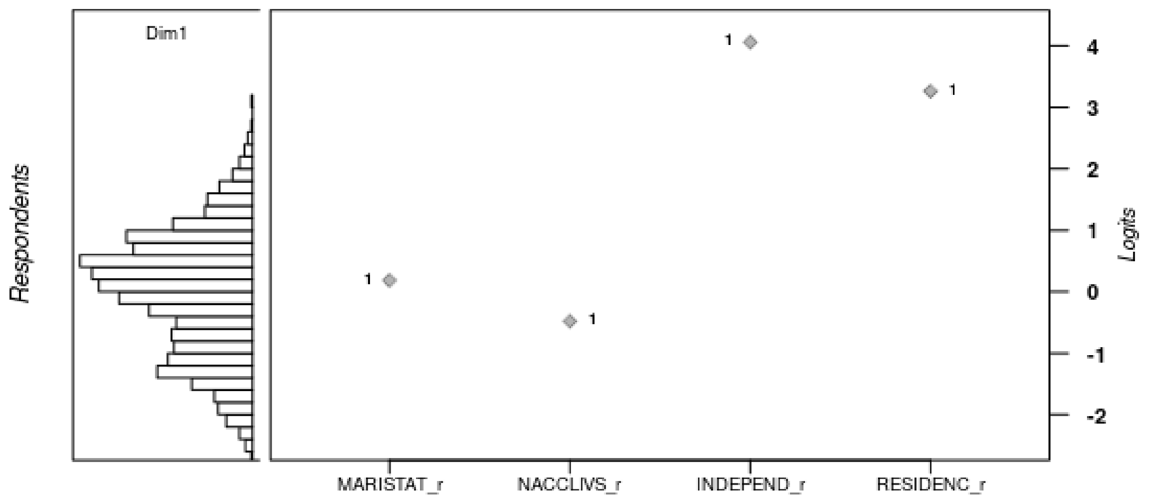
NHW-Midlife

Wright Map



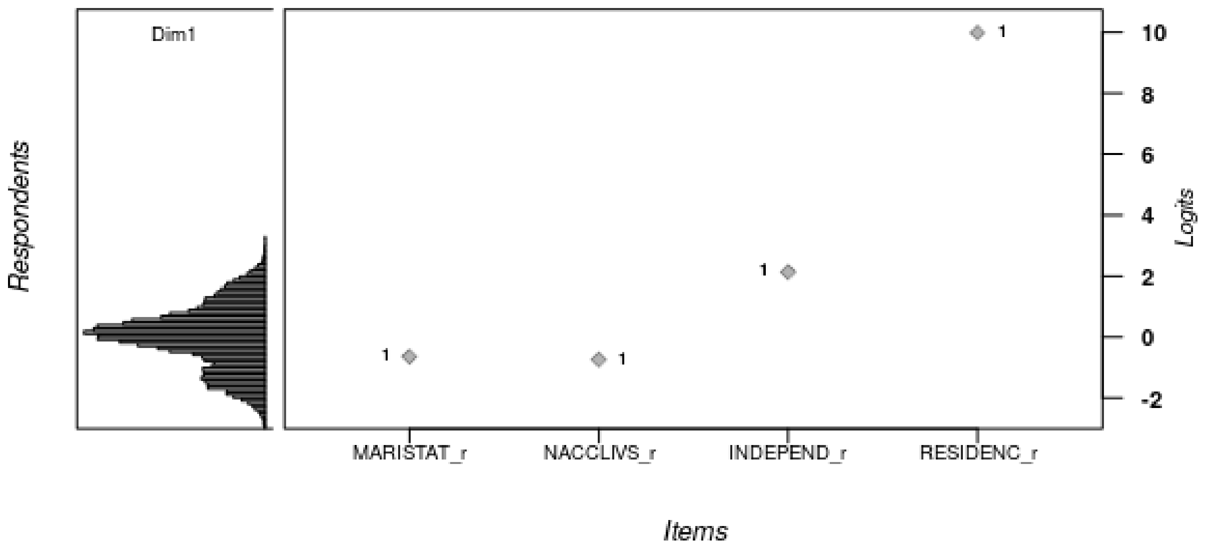
AA-Midlife

Wright Map



NHW-Later life

Wright Map



AA-Later life

Wright Map