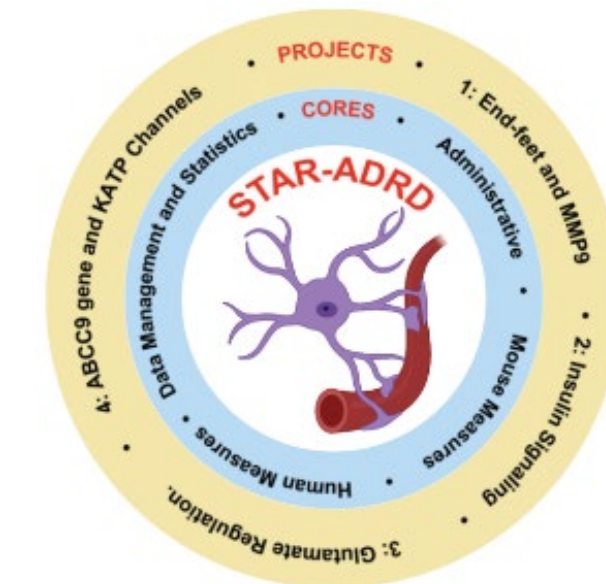


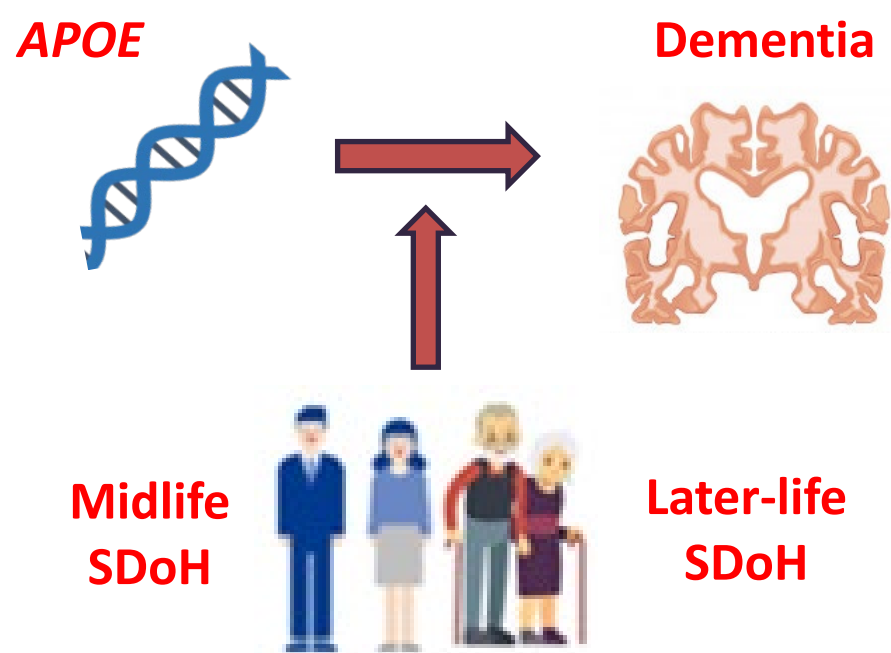


Background

- Genetic risk in Alzheimer's disease related dementia (ADRD), such as the most influential gene *APOE*, may be modified by social determinants of health (SDoH).
- Previous studies have commonly constructed SDoH scores by summing item scores, whereas item response theory (IRT) can estimate more precise composite scores by modeling observable variables.
- Health disparity in ADRD requires our attention to diverse populations.

Aims: 1) Extending our previous work on perceived neighborhood disorder, this study incorporated comprehensive SDoH assessments to construct composite SDoH scores; 2) Investigated whether the SDoH scores modify the effects of *APOE* $\epsilon 4$ status on dementia risk across the lifespan and in diverse populations.

Method



Data source: All of Us V8 data



- Four cohorts (aged 65+ years)
- Non-Hispanic White (NHW)
 - Black/African American (AA)
 - Hispanic
 - Asian

IRT-based SDoH score construction

- Multidimensional generalized partial credit model (GPCM) was applied using R “mirt” package to construct SDoH composite scores within each cohort using 83 items, including 80 SDoH scale items plus three basic survey items (education, annual income, and marriage status).
- Midlife (aged 40-64) and later-later-life (aged ≥ 65) SDoH scores were constructed separately. A higher SDoH composite score represents less favorable SDoH.
- Leave-one-out cross validation was utilized to determine the dimensionality of midlife and later-life SDoH constructs. Better GPCM fit indices, higher comparative fit index (CFI) and standardized root mean square residual (SRMSR), suggest that a more superior model fit in the data.

Downstream interaction analysis

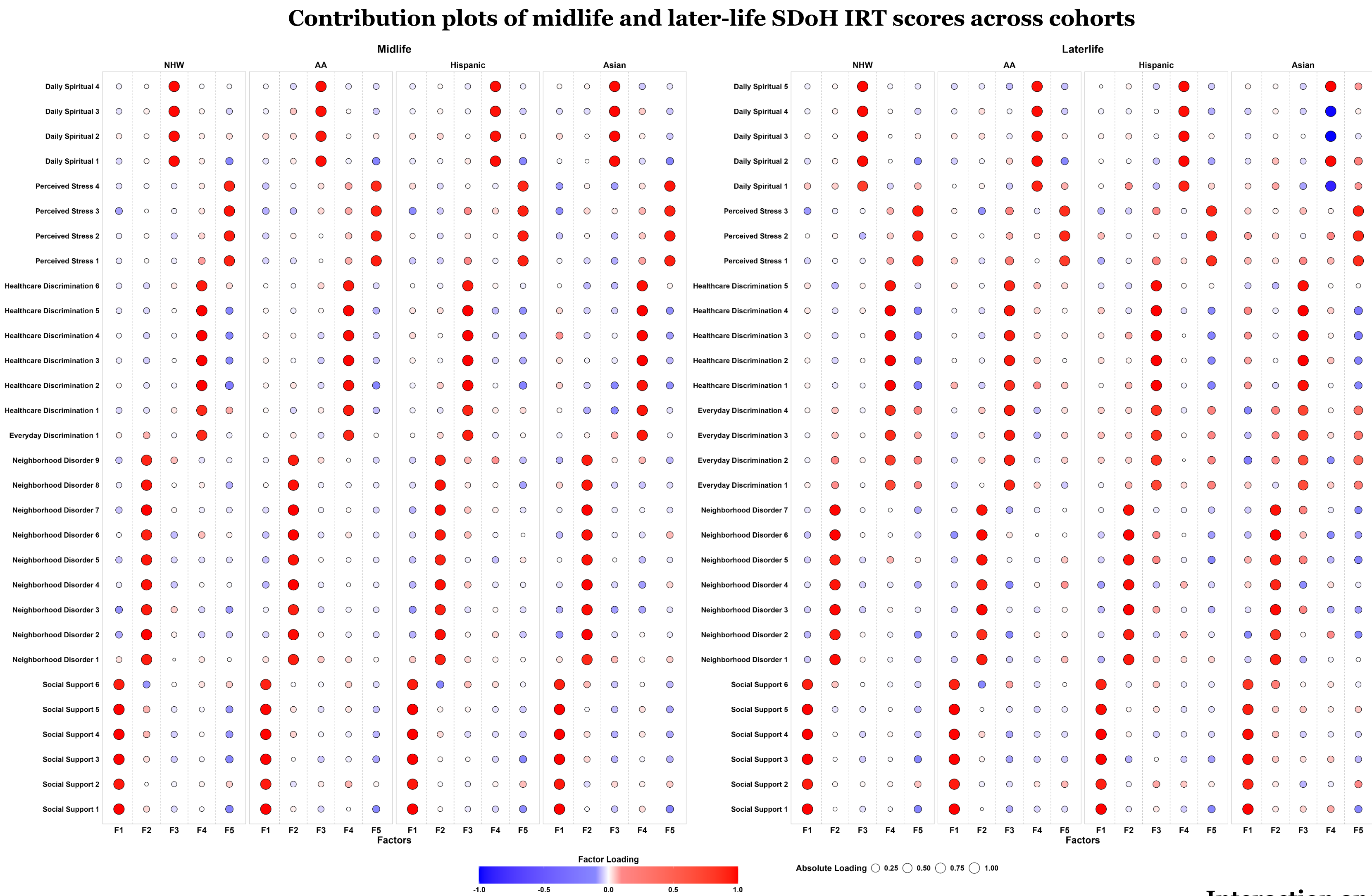
- The phenotype outcome was dementia or memory impairment, which was ICD-based and from participants' Electronic Health Records (EHR).
- Due to low frequency of diagnosed dementia or memory impairment cases in All of Us cohorts, Firth penalized logistic regression was employed, including *APOE* $\epsilon 4$ status (non-carriers vs. carriers) and midlife and later-life SDoH scores, and their interaction terms as predictors, sex and age at the most recent visit as covariates.

Table 1. Descriptive statistics across cohorts and the lifespan & SDoH survey constructs scales

Demographics	NHW		AA		Hispanic		Asian	
	Midlife	Later life	Midlife	Later life	Midlife	Later life	Midlife	Later life
Sample size (n)	15,371	15,030	2,142	1,149	2,845	1,052	643	273
Sex (female), n (%)	10,494 (69.3)	7,929 (53.0)	1,584 (73.9)	751 (65.4)	1,958 (68.8)	613 (58.3)	383 (59.6)	150 (54.9)
Age (at the last visit), mean (SD)	49.9 (7.6)	71.0 (6.1)	50.7 (7.3)	68.7 (5.5)	48.4 (7.4)	69.1 (5.9)	47.9 (7.4)	69.1 (5.5)
Education ($\leq$ college), n (%)	5,480 (35.7)	4,265 (28.4)	1,195 (55.8)	614 (53.4)	1,454 (51.1)	593 (56.4)	397 (61.1)	121 (43.6)
Annual income ($\leq$ \$10k), n (%)	6,459 (42.0)	7,949 (52.9)	879 (41)	531 (46.2)	1,286 (45.2)	440 (41.8)	231 (39)	121 (44.3)
Marital status (yes), n (%)	9,947 (64.7)	10,247 (68.2)	712 (33.2)	414 (36)	1,630 (57.3)	637 (60.6)	426 (66.3)	189 (69.2)
<i>APOE</i> ($\epsilon 4$), n (%)	4,017 (26.1)	3,672 (24.0)	846 (39.5)	431 (37.5)	626 (22.0)	208 (19.8)	105 (16.3)	37 (13.6)
Diagnosed cases, n (%)	563 (3.7)	833 (5.5)	60 (2.8)	62 (5.4)	71 (2.5)	67 (6.4)	13 (2.0)	9 (3.3)
SDoH surveys, mean (SD)								
<i>Social and community context</i>								
Social cohesion among neighbors (4 items)	1.20 (0.72)	1.01 (0.65)	1.48 (0.76)	1.32 (0.75)	1.40 (0.72)	1.26 (0.68)	1.21 (0.64)	1.12 (0.64)
Social Support (8 items)	1.05 (0.99)	1.01 (0.88)	1.28 (1.12)	1.19 (1.06)	1.13 (1.07)	1.22 (1.09)	1.32 (1.02)	1.32 (1.08)
Loneliness (8 items)	1.02 (0.67)	0.81 (0.61)	0.59 (0.69)	0.82 (0.62)	0.89 (0.68)	0.72 (0.62)	0.96 (0.58)	0.86 (0.58)
Perceived everyday discrimination (10 items)	0.92 (0.53)	0.81 (0.53)	1.33 (0.99)	1.00 (0.82)	0.91 (0.89)	0.54 (0.72)	0.95 (0.96)	0.75 (0.72)
Perceived stress (10 items)	1.55 (0.77)	1.03 (0.67)	1.57 (0.78)	1.12 (0.74)	1.52 (0.77)	1.13 (0.69)	1.43 (0.69)	1.11 (0.70)
Daily spiritual experiences (6 items)	2.90 (1.48)	2.37 (1.48)	1.45 (1.23)	1.26 (1.13)	2.19 (1.44)	1.76 (1.37)	2.83 (1.50)	2.68 (1.56)
Religious service attendance (1 item)	3.31 (1.53)	3.13 (1.70)	2.44 (1.60)	1.96 (1.61)	3.13 (1.59)	2.66 (1.60)	3.39 (1.71)	3.38 (1.71)
English proficiency (1 item)	0.08 (0.26)	0.04 (0.21)	0.10 (0.30)	0.05 (0.22)	0.06 (0.47)	0.63 (0.48)	0.61 (0.49)	0.53 (0.50)
<i>Economic stability</i>								
Food insecurity (2 items)	0.17 (0.44)	0.04 (0.22)	0.41 (0.63)	0.19 (0.43)	0.27 (0.52)	0.13 (0.35)	0.09 (0.31)	0.04 (0.21)
Housing insecurity (1 item)	0.17 (0.51)	0.11 (0.38)	0.28 (0.71)	0.18 (0.59)	0.22 (0.61)	0.15 (0.51)	0.18 (0.50)	0.14 (0.35)
Housing quality (1 item)	0.22 (0.41)	0.13 (0.34)	0.30 (0.46)	0.25 (0.44)	0.25 (0.51)	0.17 (0.43)	0.21 (0.41)	0.12 (0.33)
<i>Neighborhood and built environment</i>								
Neighborhood Disorder (13 items)	0.60 (0.49)	0.49 (0.43)	0.89 (0.61)	0.82 (0.52)	0.79 (0.55)	0.73 (0.52)	0.62 (0.50)	0.51 (0.46)
Neighborhood Environment (8 items)	0.95 (0.56)	0.91 (0.55)	0.95 (0.53)	0.96 (0.54)	0.78 (0.51)	0.68 (0.51)	0.68 (0.48)	0.75 (0.50)
<i>Health and healthcare</i>								
Perceived discrimination in medical settings (7 items)	0.64 (0.64)	0.44 (0.53)	0.77 (0.74)	0.66 (0.67)	0.59 (0.66)	0.40 (0.59)	0.58 (0.59)	0.50 (0.57)

Note: NHW = non-Hispanic White, AA = Black or African American. SD = standard deviation. Diagnosed cases = dementia or memory impairment. A higher value of mean indicates less social favorable or greater disadvantage in the scale. 83 items, including 80 SDoH survey scale items plus 3 basic survey items (education, annual income, and marital status) were utilized to derive midlife (aged 40-64) and later-life (aged ≥ 65) SDoH risk scores.

Results



- GPCM fit indices, comparative fit index (CFI > 0.9) and standardized root mean square residual (SRMSR < 0.6), suggested that a five-dimension SDoH structure provided an acceptable fit (**Figure 1**). These five factors (**Figure 2**) were characterized as social support (F1), neighborhood (F2), spiritual life (F3), discrimination (F4), and stress (F5).

Figure 2. Contribution plots of midlife and later-life SDoH scores by race/ethnicity. Factor loadings were sorted from the largest to the smallest, and the top 30 most contributed items were included to the plots.

Dimension determination of SDoH constructs across cohorts

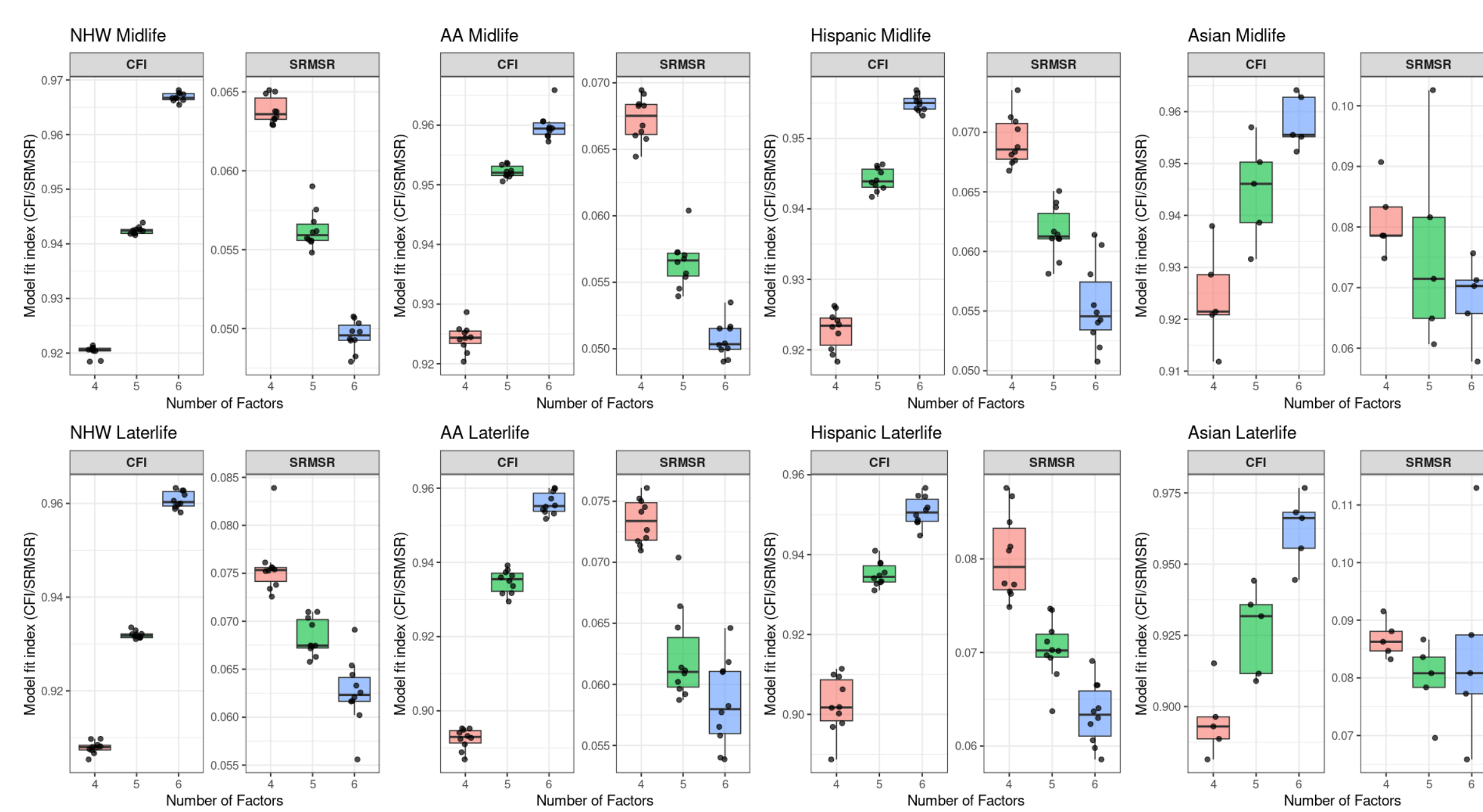


Figure 1. Boxplots of GPCM fit indices across cohorts and the lifespan. CFI = comparative fit index (CFI), SRMSR = standardized root mean square residual.

Interaction analysis

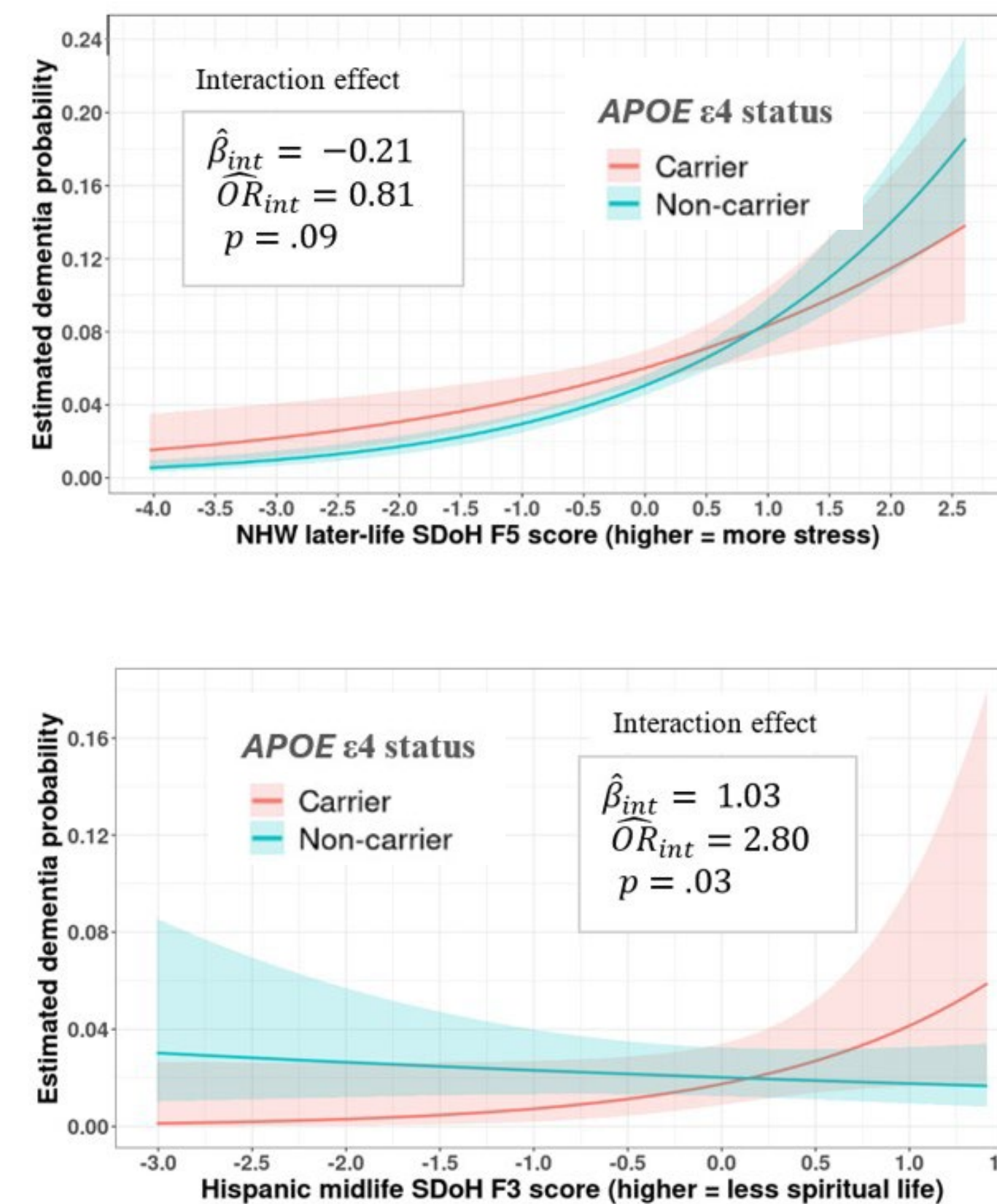


Figure 3. Midlife and later-life SDoH factor scores modified the associations of *APOE* $\epsilon 4$ status with dementia risk. The upper panel: NHW later-life stress scores; the lower panel: Hispanic midlife spiritual life scores.

- The total sample size was 21,001 (**Table 1**).
- The proportions of *APOE* $\epsilon 4$ carriers ranged from 13.6% (later-life Asian cohort) to 39.5% (midlife AA cohort).
- The proportions of diagnosed cases ranged from 2.0% (midlife Asian cohort) to 6.4% (midlife AA cohort).
- Summary statistics of SDoH raw scores for each scale are shown in **Table 1**.

Discussion

- We found two significant interaction effects. In NHW cohorts, later-life stress scores modified the associations of *APOE* $\epsilon 4$ status (non-carriers vs. carriers) with dementia risk ($\hat{\beta}_{int} = -0.21, \bar{OR}_{int} = 0.81, p = .09$; when *APOE* $\epsilon 4$ coded as 0/1/2 copies, $p = .06, \bar{OR}_{int}$ did not change). In Hispanic cohort, the effects of *APOE* $\epsilon 4$ on dementia risk were modified by midlife spiritual life scores ($\hat{\beta}_{int} = 1.03, \bar{OR}_{int} = 2.80, p = .04$). Interaction effects are shown in **Figure 3**.
- Midlife and later-life SDoH scores modified the associations of *APOE* $\epsilon 4$ with dementia. Understanding these complex interactions may help inform targeted prevention strategies. Future research should include more genetic risk factors and consider the timing of SDoH assessments.

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