Does education modify the association between an Alzheimer's disease polygenic risk score and memory decline?

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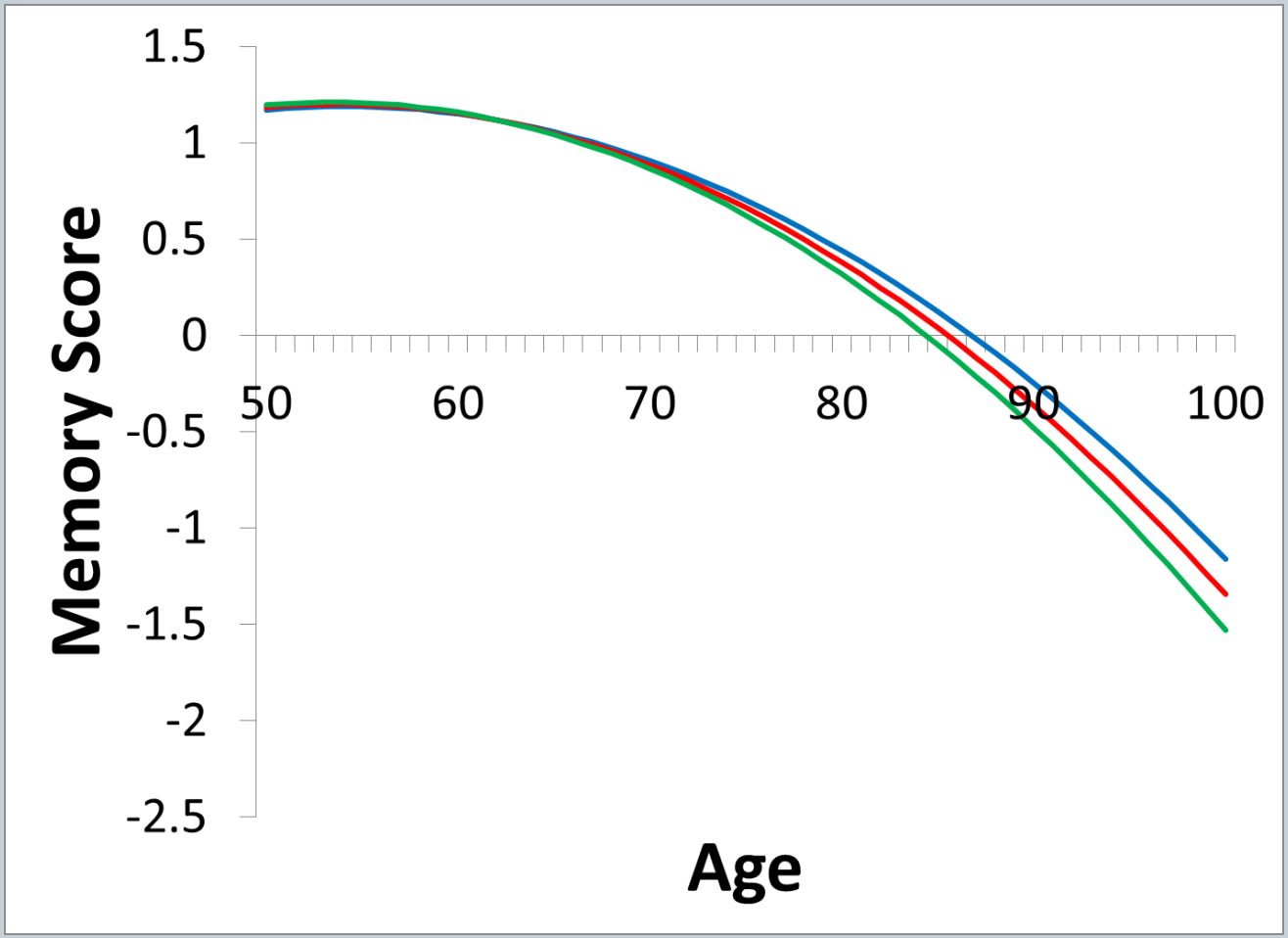
Summary

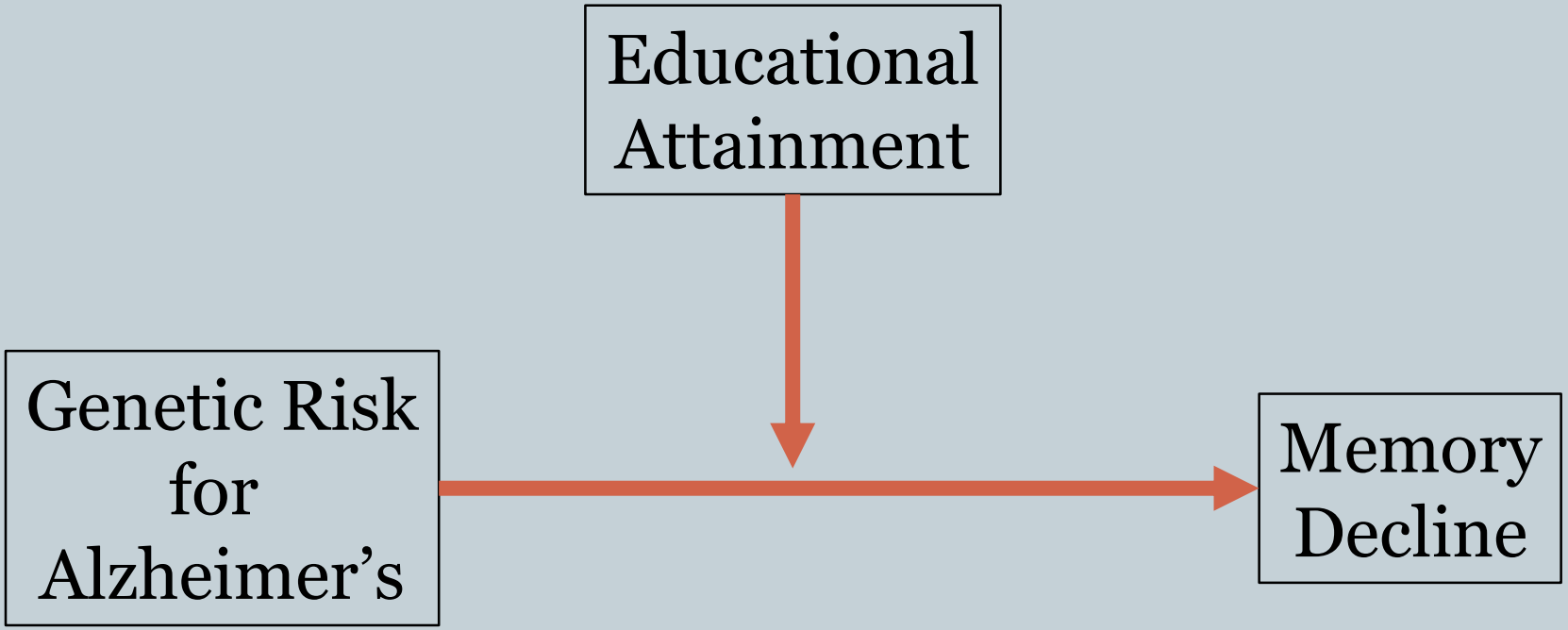
AD-GRS and Memory Decline



Legend

Blue: High Genetic Risk
Red: Average Genetic Risk
Green: Low Genetic Risk

Summary


Educational Attainment
Genetic Risk for Alzheimer's
Memory Decline

Hypothesis

- The harmful effect of high genetic risk for Alzheimer's on memory decline will be magnified by low educational attainment and attenuated by high education.

Gene-Environment Interaction Theory

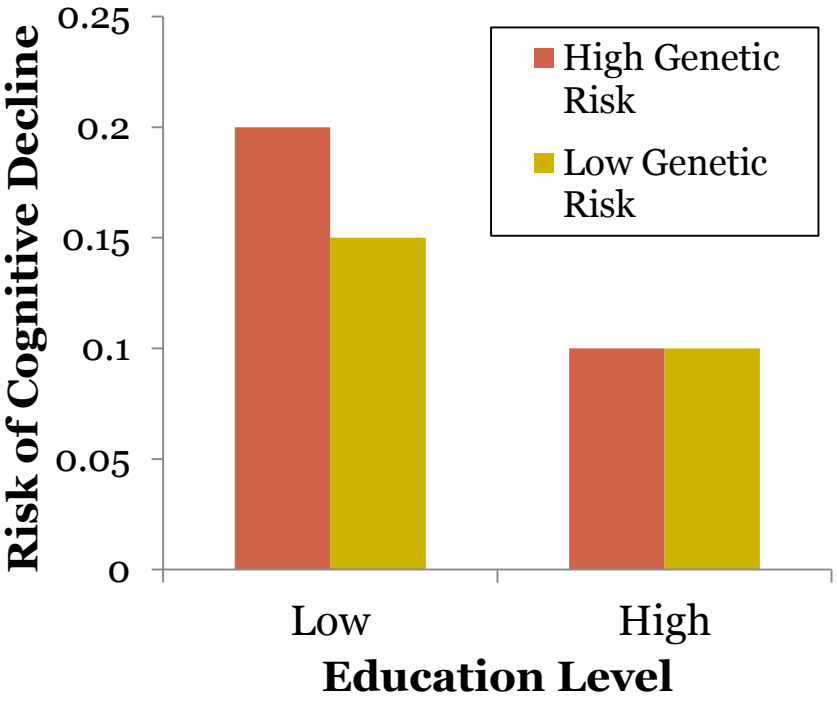
Social Causation	Social Push
• Compounding of risk, i.e. individuals with low education will be most susceptible to the detrimental effects of a high genetic risk profile • Example: APOE, stress, and memory (Peavy 2007), other social epi (e.g. SSBs and obesity)	• Social disadvantage overwhelms, i.e. those most susceptible to the harmful effects of high genetic risk are those with higher educational attainment • Example: Neighborhood disorder, APOE, and cognitive change (Boardman 2012)

(Raine 2002)

Social Processes

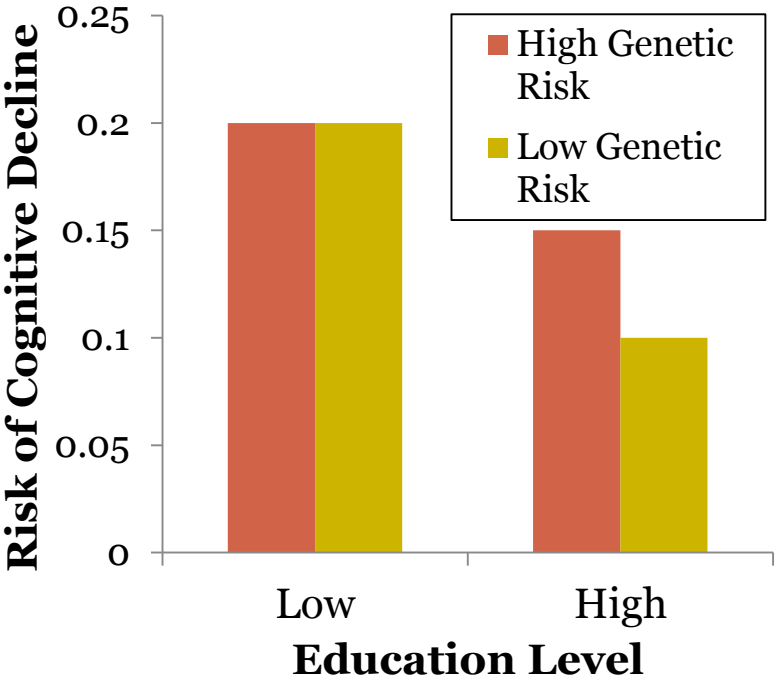
- When examining gene*education interactions, we do not posit molecular level interactions, but rather *social processes* that modify biological development of manifestation of memory disorder, either attenuating or magnifying risk.

Social Causation



People with high levels of education are able to use the resources of education to offset genetic risk regardless of the molecular mechanism of that risk

Social Push



Low education is so harmful that other sources of risk are "overwhelmed," (i.e. the other mechanisms the individual SNPs might trigger have already been triggered by low education)

(Adapted from Boardman 2012)

Methods

Dataset: Health and Retirement Study

- National sample of US adults aged 50+ years
  - Salivary DNA samples collected in either 2006 or 2008 for a subsample
- 7,172 non-Hispanic white participants from 1998-2012 with interviews every two years
- Average follow-up: 12.3 years
- Average memory assessments: 7.2

Measures: Memory Score

- Cognitive Function and Decline (1998-2012)
  - Memory was assessed by immediate and delayed recall tests of a 10-word list
    - For impaired individuals: proxy informants, typically spouses, were asked to assess the participants' memory on a 5-item Likert scale and completed a 16-item version of the IQCODE
  - The HRS working group previously developed a composite memory score combining proxy and direct memory assessments for longitudinal analyses (using ADMS)
  - The composite memory score was standardized by dividing each score by the baseline (1998) standard deviation so that every unit change in composite memory score corresponds to a change of one standard deviation at baseline (Wu et al. 2012)

Measures: Genetic Risk

- Polygenic Risk Score for Dementia (AD-GRS)
  - Using top 10 genes associated with dementia risk in AlzGene
    - ApoE, BIN1, CLU, ABCA7, CR1, PICALM, MS4A6A, CD33, MS4A4E, and CD2AP
  - Ranges from 0 to 1
  - Can be interpreted as the genetic probability of dementia
  - ApoE was the most important contributor, but the genetic risk score was significantly associated with dementia risk even without ApoE

1) $$genetic\ odds\ ratio\ for\ dementia = \left(\sum_{k=1}^{\#\ loci} \beta_k \cdot allele\ count_{i,k}\right)$$

2) $$odds\ of\ dementia = 0.1 \cdot e^{(log\ odds\ ratio - mean[log\ odds\ ratio])}$$

3) $$probability\ of\ dementia = \frac{odds\ of\ dementia}{1 + odds\ of\ dementia}$$

Measure: Education

- Self-report of years of education: “What is the highest grade of school or year of college you completed?”
- Continuous, with a ceiling of 17 years
- We also include an education^2 term to allow the relationship between education and memory to be non-linear

Statistical Analysis

- Linear regression models with robust standard errors to account for repeated measures
  - Modeled via a quadratic growth curve
    - i.e. the change in the memory score from wave to wave until death or loss to follow-up
    - Interaction terms with both age and age^2 with the AD-GRS and education (non-sig terms close to 0 were removed to save power)
  - All models were adjusted for baseline age (centered at age 70), sex, an indicator for first interview, and six eigenvectors to control for residual population stratification
- This model was replicated using:
  - 1) the alternative AD-GRSexAPOE
  - 2) a dichotomous indicator for any APOE4 allele

Results

Results using the AD-GRS

	AD-GRS β (95% CI)
Genetic Risk (per 0.1 unit difference)	-0.05 (-0.07, -0.04)**
Current Age (in decades, centered at age 70)	-0.32 (-0.34, -0.3)**
Current Age^2	-0.10 (-0.11, -0.08)**
Education (in years, centered at 12)	0.03 (0.02, 0.03)**
Education^2	-0.0005 (-0.00099, 0.00003)
Genetic Risk *Current Age	-0.08 (-0.101, -0.058)**
Education*Current Age	0.019 (0.012, 0.026)**
Genetic Risk *Current Age^2	-0.020 (-0.040, -0.010)*
Education*Genetic Risk *Current Age	-0.007 (-0.015, 0.001)
Education*Genetic Risk *Current Age^2	-0.003 (-0.005, -0.001)*

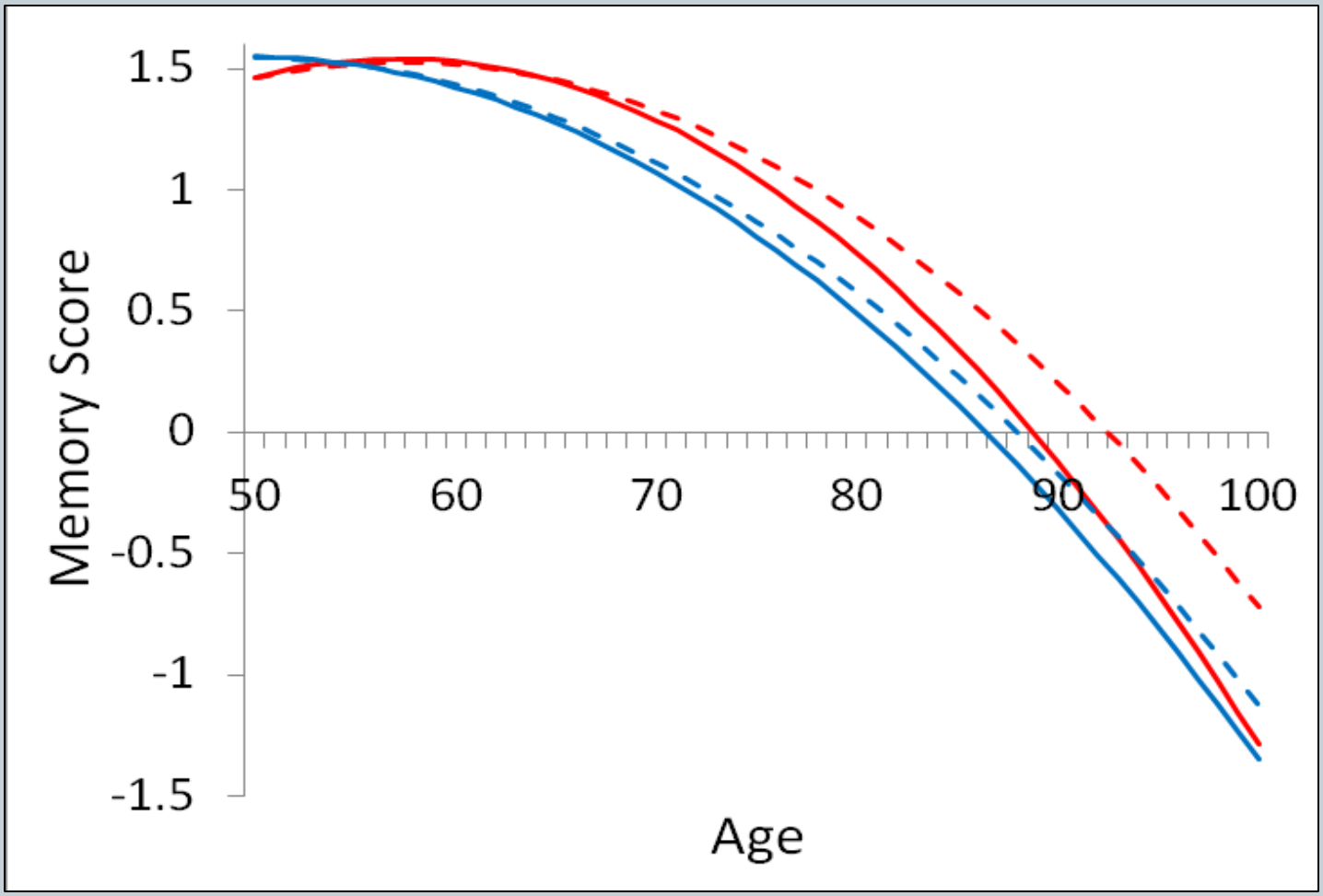
Results using the AD-GRSexAPOE

	AD-GRSexAPOE β (95% CI)
Genetic Risk (per 0.1 unit difference)	-0.04 (-0.07, -0.02)*
Current Age (in decades, centered at age 70)	-0.37 (-0.4, -0.34)**
Current Age^2	-0.11 (-0.133, -0.088)**
Education (in years, centered at 12)	0.03 (0.02, 0.03)**
Education^2	-0.00051 (-0.00102, -0.00001)*
Genetic Risk *Current Age	-0.03 (-0.058, -0.001)*
Education*Current Age	0.026 (0.015, 0.037)**
Genetic Risk *Current Age^2	-0.0049 (-0.0281, 0.0183)
Education*Genetic Risk *Current Age	-0.0149 (-0.0262, -0.0036)*
Education*Genetic Risk *Current Age^2	-0.004 (-0.005, -0.002)**

Results using APOE alone

	APOE only β (95% CI)
APOE4 (at least 1 allele vs none)	-0.04 (-0.05, -0.02)**
Current Age (in decades, centered at age 70)	-0.38 (-0.39, -0.37)**
Current Age^2	-0.114 (-0.12, -0.109)**
Education (in years, centered at 12)	0.02 (0.02, 0.03)**
Education^2	-0.00048 (-0.00099, 0.00003)
APOE4*Current Age	-0.062 (-0.078, -0.046)**
Education*Current Age	0.012 (0.009, 0.015)**
APOE4*Current Age^2	-0.0177 (-0.0316, -0.0037)*
Education*APOE4*Current Age	0.0004 (-0.0055, 0.0063)
Education*APOE4*Current Age^2	-0.002 (-0.006, 0.003)

Memory Decline Curves: AD-GRS

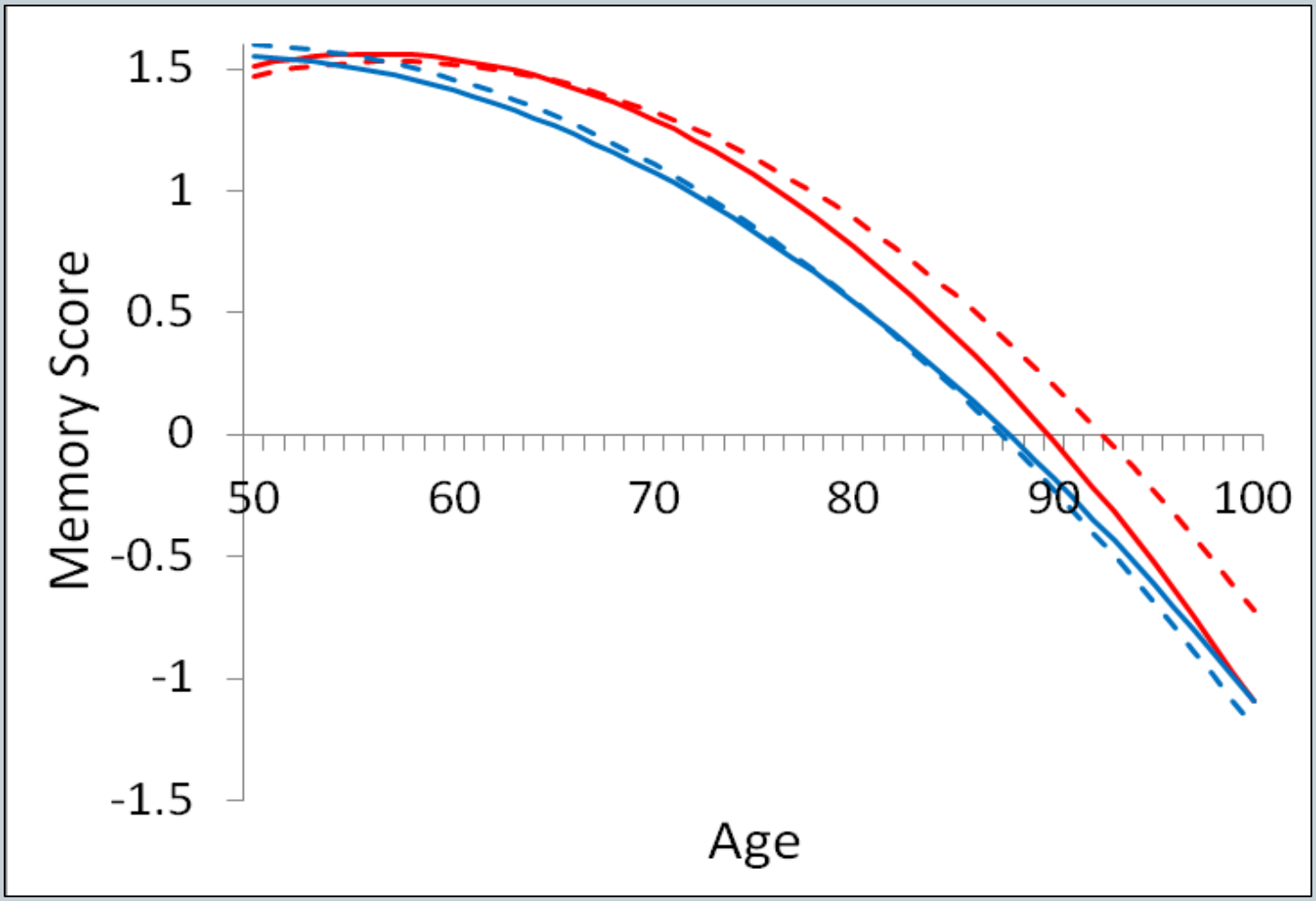


Legend

Red: High Education
Blue: Low Education

Dashed: Low Genetic Risk
Solid: High Genetic Risk

Memory Decline Curves: AD-GRSexAPOE



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Conclusions

Evidence for the "Social Push" GxE theory:

- Lack of schooling may have such a dominant and overwhelming effect on memory decline that it is only when this social disadvantage is minimized that the more subtle effects of genetic predisposition become apparent
- Education may not provide useful resources to offset genetic risk, possibly because there are no known steps to take if one learns he or she is at a high genetic risk for Alzheimer's

Strengths and Limitations

Limitations

- Possible rGE: the AD-GRS could be correlated with educational attainment (but r=0.01)
- We have implicitly imposed the assumption that the interaction between education and each SNP operates in the same direction

Strengths

- Rich characterization of both the "gene" and "environment"
- Long follow-up allowing for quadratic curves

Next Steps

- Extend to other social and psychosocial measures, including neighborhood characteristics
  - Use of neighborhood characteristics would help minimize rGE
  - Use of lifecourse SES measures would more richly characterize exposure to social disadvantage
- Use a new AD-GRS that is based on a new meta-analysis by Lambert et al.
  - Relationships with memory decline are very similar
- Create a genome-wide AD-GRS?
- Extend to non-Hispanic blacks?

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Questions?