Investigating Age Related Cognitive Decline: Mayo Clinic Study of Aging

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Framework

Cognitive performance in an individual

- Age
- Sex
- Genes
- Pathologies
  - Alzheimer's disease pathophysiology
  - Cerebrovascular disease
- Cognitive Reserve
  - Intellectual Lifestyle

Mayo Clinic Study of Aging

Population based sample of >2000 non-demented elderly between 50-90 ages (sampled from the population of Olmsted County, Rochester) with extensive longitudinal clinical and imaging follow-up.

Questions and Studies to investigate age-related cognitive decline

- How much do the two primary pathologies (amyloid and vascular disease) influence age-related cognitive decline ?
- How does a better intellectual lifestyle protect against age-related cognitive decline?
- Does a better intellectual lifestyle also help with slowing down pathological processes ?

Question 1

How much do the two primary pathologies (amyloid and vascular disease) influence age-related cognitive decline ?

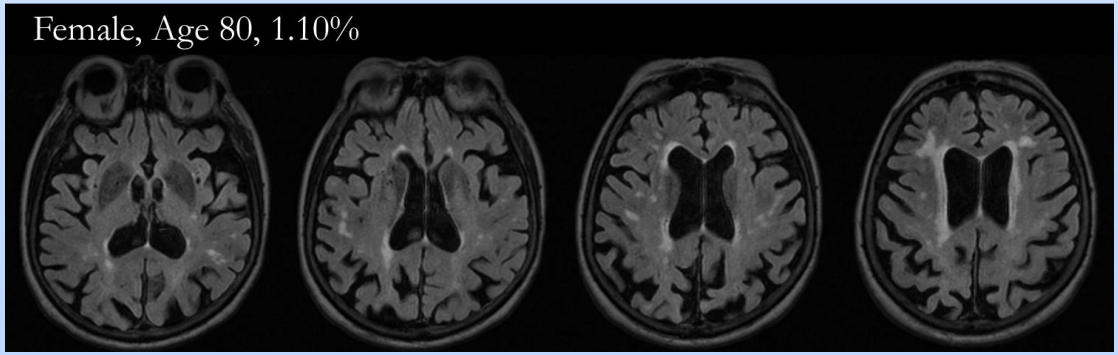
Study 1: Interrelationships between Vascular and Amyloid Pathologies and Longitudinal Cognitive Decline in MCSA

Vemuri et al. In Press Brain

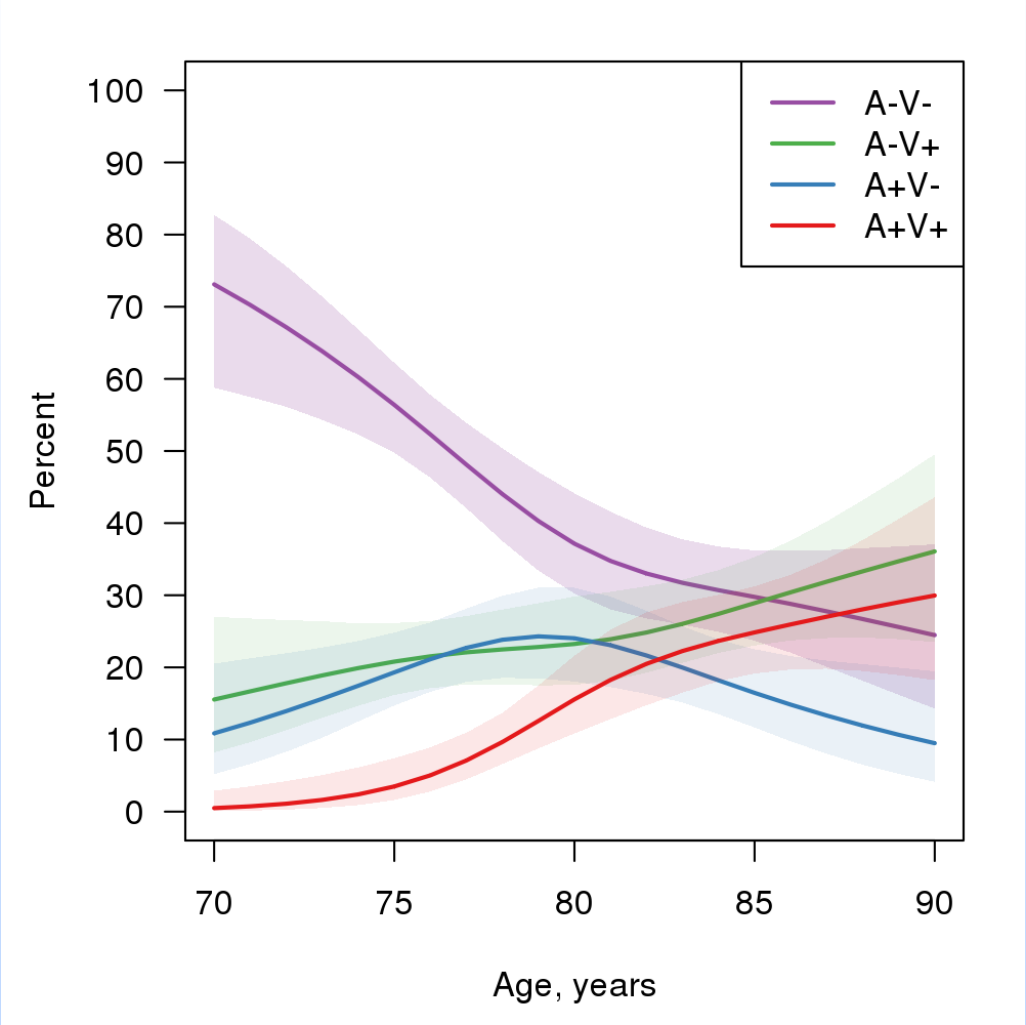
- 393 CN elderly participants in the MCSA (ages 70-89) who had
  - 3T FLAIR-MRI assessment (Vascular gradings –WMH, subcortical infarcts, large cortical infarcts),
  - Amyloid PET scan (Amyloid pathology)
  - Complete neuropsych assessments and Clinical follow-up

Classifying subjects as ADP or VaD

- Amyloid pathway (A+ or ADP) if global cortical PIB-PET value was greater than or equal to 1.5.
- Vascular Pathway (V+ or VaD)
  - Brain infarct and/or
  - WMH/TIV% ≥ 1.11
    - Independent sample of 1082 non-demented elderly
    - Assuming 33% of the population has VaD (Longstreth *et al.* , 2009, Petrovitch *et al.* , 2005, Schneider *et al.* , 2003)



Population Frequencies



A-V- 45%
A-V+ 23%
A+V- 21%
A+V+ 11%

Number and Proportion of Subjects in each pathway	Normal aging n = 178 A-V-[45%]	Vascular n = 89 A-V+[23%]	Both vascular and amyloid n = 45 A+V+[11%]	Amyloid n = 81 A+V- [21%]	P-value
No. of females (%)	85 (48)	41 (46)	19 (42)	33 (41)	0.73
Age (yrs.)	76 (73, 81)	78 (75, 83)	82 (79, 83)	78 (75, 81)	**<0.001**
No. of ε4 carriers (%)	34 (19)	17 (19)	15 (33)	40 (49)	**<0.001**
Education (yrs.)	13.5 (12, 16)	14 (12, 16)	13 (12, 16)	14 (12, 16)	0.48
Short Test of mental status	35.5 (34, 37)	35 (34, 37)	34 (32, 36)	35 (33, 36)	0.17
Global z-score	0.80 (0.19, 1.34)	0.71 (0.24, 1.07)	0.08 (-0.36, 0.59)	0.64 (0.13, 1.26)	**0.002**
Job Score	4 (3, 6)	4 (3, 6)	4 (3, 6)	4 (3, 6)	0.97
Global cortical PIB	1.33 (1.29, 1.38)	1.34 (1.30, 1.38)	1.93 (1.64, 2.22)	1.86 (1.68, 2.11)	---
Mid-life intellectual score	21 (15.5, 27.5)	20 (14.5, 28)	21 (15.5, 27)	21 (14, 24.5)	0.84
Late-life intellectual score	23.5 (17.5, 30.5)	23 (15, 30.5)	23 (17.5, 30.5)	21 (16, 28)	0.35
WMH/TIV %	0.48 (0.36, 0.67)	1.12 (0.59, 1.58)	1.19 (0.87, 1.73)	0.46 (0.35, 0.68)	---
No. with cortical infarctions (%)	0	11 (12)	9 (20)	0	
No. with subcortical infarctions (%)	0	55 (62)	21 (47)	0	
Follow-up (yrs.)	2.7 (1.0, 7.7)	2.8 (1.2, 6.7)	2.7 (1.2, 6.9)	2.7 (1.2, 6.6)	0.49

Influence of ADP and VaD on cognitive decline

Linear mixed models

Demographic variables, intellectual lifestyle variables and the presence or absence of ADP and VaD as predictors

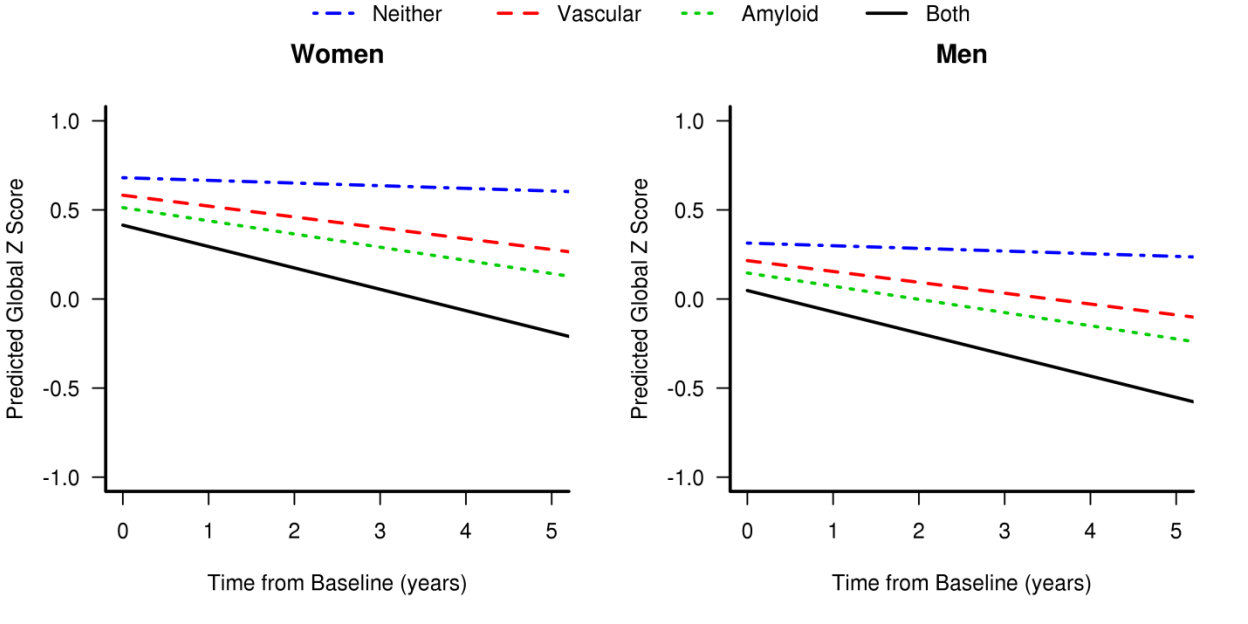
Longitudinal global cognitive z-scores [tested interactions]

	Coefficient	Std.Error	p-value
(Intercept)		0.68	<0.0001
Baseline age (years)	-0.05	0.01	<0.0001
Male	-0.37	0.08	<0.0001
Time (years)	0.56	0.12	<0.0001
Education/Occupation-score	0.26	0.04	<0.0001
Previous psych tests	0.10	0.02	<0.0001
Amyloid pathway	-0.17	0.08	0.0386
Vascular pathv		8	0.2223
Baseline age x time	-0.0073	0.0016	<0.0001
Amyloid pathway x time	-0.06	0.02	0.0003
Vascular pathway x time	-0.05	0.02	0.0037

Predictors of Baseline Cognition

Predictors of Longitudinal Cognitive Decline

Decrease in predicted cognitive scores with pathway



For a 79-year-old subject, the predicted annual rate of global z-score decline: A-V- = -0.02, A-V+ = -0.07 [0.02+0.05], A+V- = -0.08 [0.02+0.06], and A+V+ = -0.13 [0.02+0.05+0.06].

The effect of ADP and VaD on cognitive trajectories appears to be additive (and not synergistic) on longitudinal cognitive decline

Conclusions from Study 1

Amyloid and vascular pathologies appear to be independent processes that both affect longitudinal cognitive trajectories adversely and are major drivers of cognitive decline in the elderly

Question 2

- How does a better intellectual lifestyle protect against age-related cognitive decline?

Study 2: Influence of Intellectual Lifestyle on Cognitive Decline

Vemuri et al. JAMA Neurology 2014

Lifetime intellectual enrichment can be grouped into two major components –

- Early and mid-life non-cognitive activities - education and the major occupation/job;
- Mid/late-life cognitive activities.

To examine the effect of each component on baseline cognition and the subsequent rate of cognitive decline in MCSA

Study 2: Influence of Intellectual Lifestyle on Cognitive Decline

Vemuri et al. JAMA Neurology 2014

1995 baseline non-demented (1718 cognitively normal, 277 MCI) subjects with complete neuropsychological assessments, and at least one additional clinical follow-up with complete neuropsychological assessments.

	Coefficient	Std.Error	p-value
(Intercept)		0.29	<0.0001
Baseline age (years)	-0.07	0.004	<0.0001
Men	-0.18	0.04	<0.0001
Time (years)	0.70	0.06	<0.0001
Education/occupation-score	0.33	0.03	<0.0001
Mid/late-life cognitive activity	0.17	0.02	<0.0001
APOE4 carrier		.04	<0.0001
Baseline visit number	0.05	0.01	<0.0001
Baseline age x time	-0.01	0.001	<0.0001
Mid/late-life cognitive activity x time	0.01	0.003	0.0445
APOE4 x time	-0.04	0.01	<0.0001
Baseline visit number x time	-0.01	0.002	0.0157
Baseline visit number x Education/occupation	-0.02	0.01	0.0411

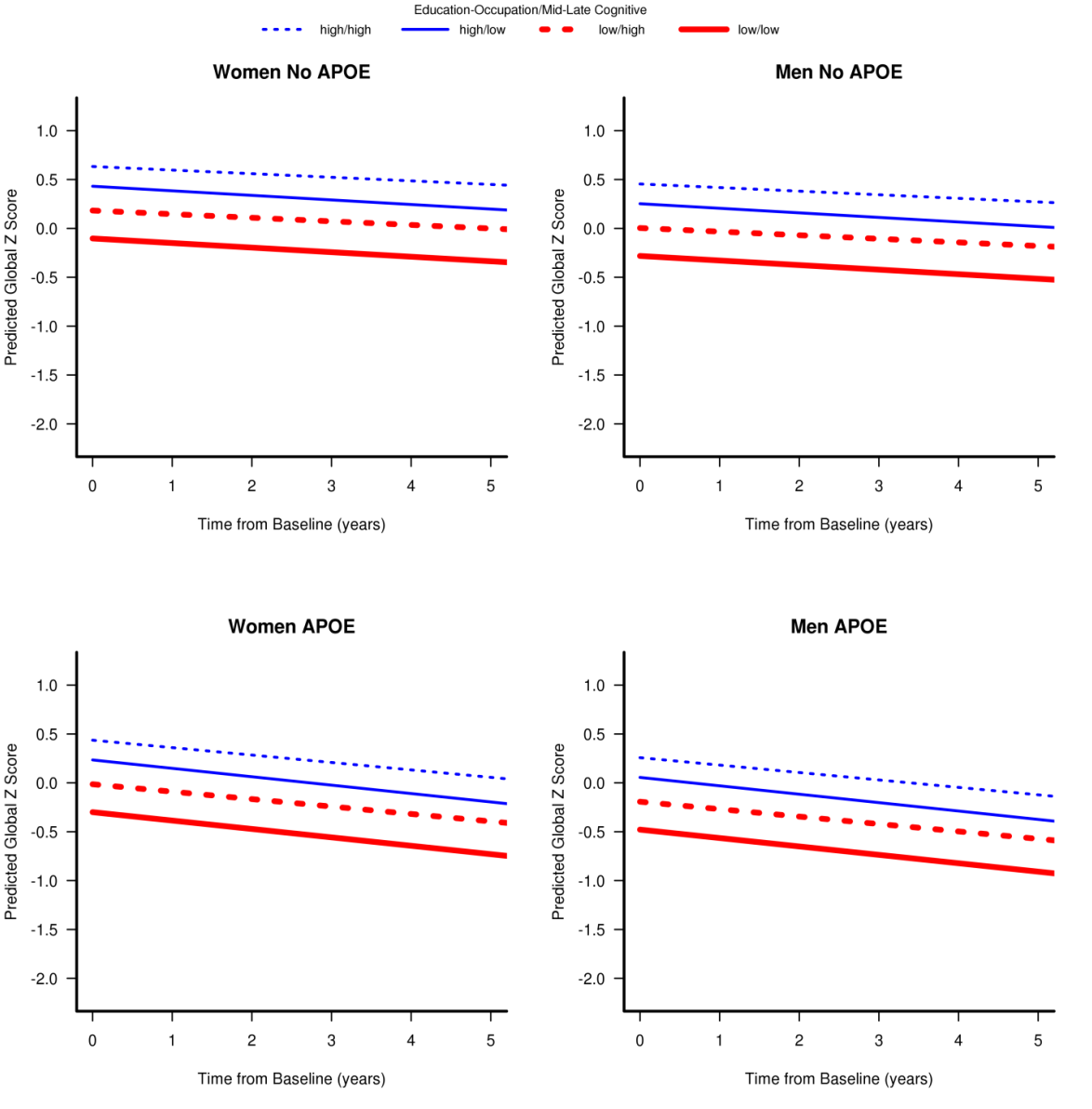
Predictors of Baseline Cognition

Predictors of Longitudinal Cognitive Decline

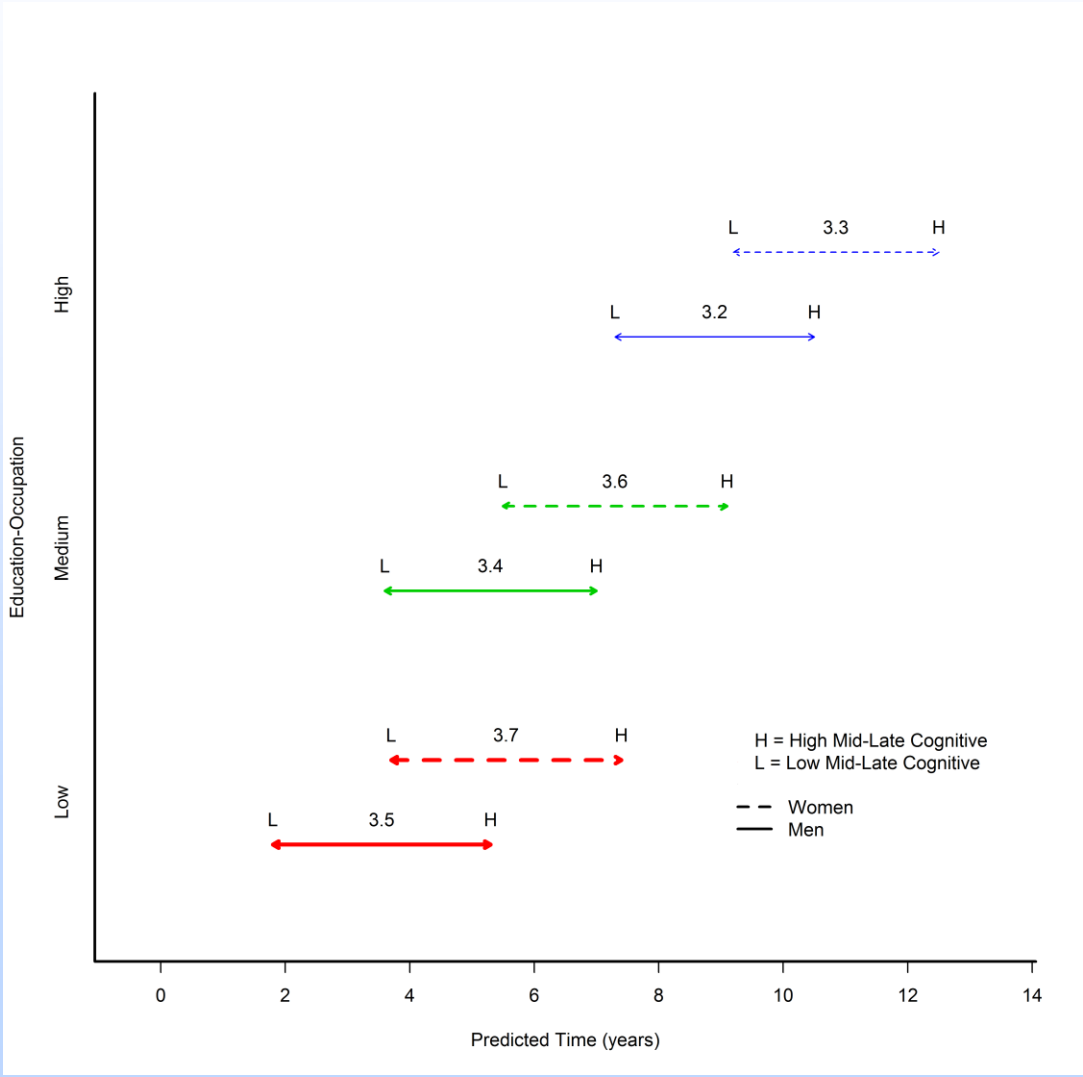
Summarizing the models

- Both better education/occupation and mid/late-life cognitive activity were associated with better cognitive performance.
- Mid/late life cognitive activity also had a significant interaction with time from baseline where the slope of this relationship increased over time.
- There was a significant interaction between the two intellectual enrichment variables ($p = 0.03$). Who does higher mid/late cognitive activity help ?

Decrease in predicted cognitive scores with intellectual lifestyle



Differences in the predicted time to cognitive impairment for an 80 year old APOE4 carrier subject

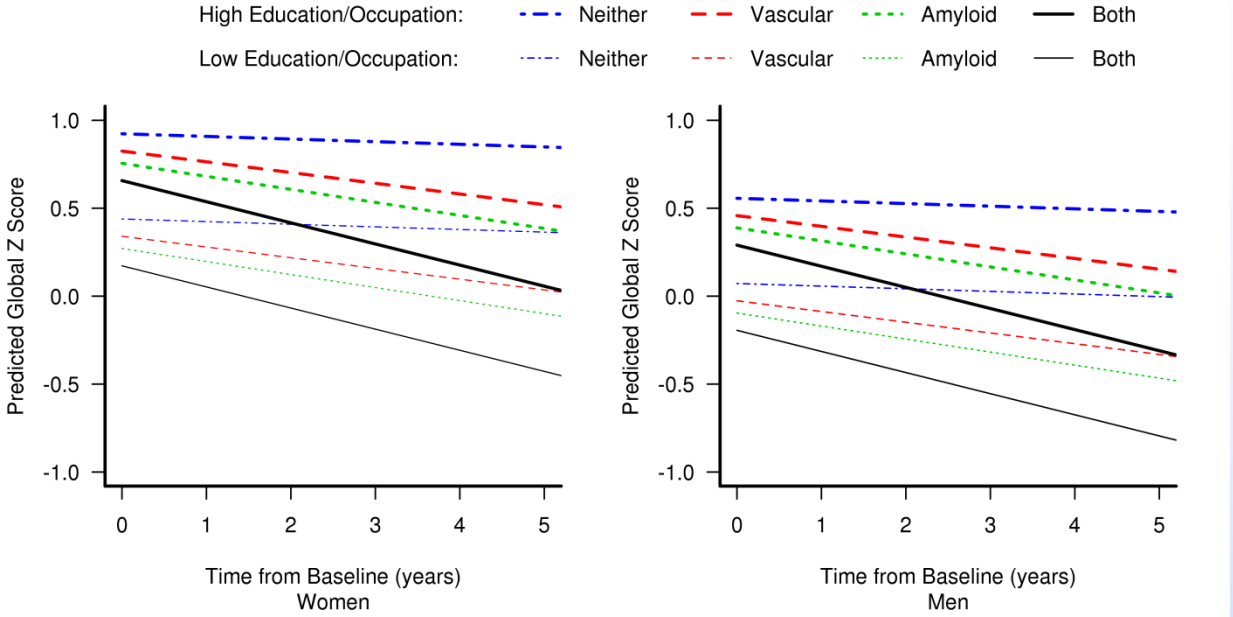


Conclusions from Study 2

Lifetime intellectual enrichment might delay the onset of cognitive impairment.

- Education and Jobs
- Intellectual enrichment to mid/late-life individuals

Protective Effect of Intellectual Lifestyle in those with Amyloid and Vascular Pathologies



CR Shifts the trajectories – [Vemuri et al. Brain 2011; Vemuri et al. Annals of Neurology 2012; Vemuri et al. Under review]

Average person in this population [79 year old] with low CR [light blue line]
Subject on Vascular pathway and high CR would take 7 years,
Subject on Amyloid pathway and high CR would take 5 years, and
Subject on both pathways and high CR would take 2 years to decrease to the same level of baseline cognitive performance.

Study 3: Can intellectual lifestyle alter the biomarker trajectories ?

393 non-demented (340 cognitively normal, 53 MCI) participants who had complete intellectual and physical lifestyle measures available and also had at least two separate AD biomarker (PIB, FDG and MRI) measurements available.

Age, APOE and not lifestyle influence biomarkers

Predictors	Coefficient	Std.Error	p-value
MODEL 1: Amyloid Deposition			
(Intercept)	0.2778	0.1492	0.0632
Time from baseline (years)	-0.000053	0.000003	<0.0001
Baseline age (years)	-0.0084	0.0019	<0.0001
APOE	-0.1179	0.0209	<0.0001
MODEL 2: FDG Hypometabolism			
(Intercept)	2.0109	0.1160	<0.0001
Time from baseline (years)	-0.00003	0.000005	<0.0001
Baseline age (years)	-0.0077	0.0015	<0.0001
APOE	-0.0434	0.0163	0.0079
MODEL 3: Total Hippocampal Volume			
(Intercept)	9.0992	0.7086	<0.0001
TIV	0.0019	0.0002	<0.0001
Time from baseline (years)	0.0003	0.0002	0.1096
Baseline age (years)	-0.0661	0.0083	<0.0001
Baseline age (years) x Time from baseline (years)	-0.000007	0.000003	0.0053

Better lifestyle

Time against cognitive impairment

Significantly improving baseline cognitive but does not appear to alter the underlying pathological processes

Conclusions

- >50% of 70-90 individuals have significant degree of neuropathological changes that are significant drivers of cognitive decline.

- Alzheimer's Association: Delaying the onset of AD by five years means reducing the expected number of AD patients by 2050 by about 43% in the US alone
  - Higher education (sex and APOE)
  - Mid/late-life activities

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