Cognitive Reserve and Brain Health in Older Women: Implications for Future Research in WHI Sciences

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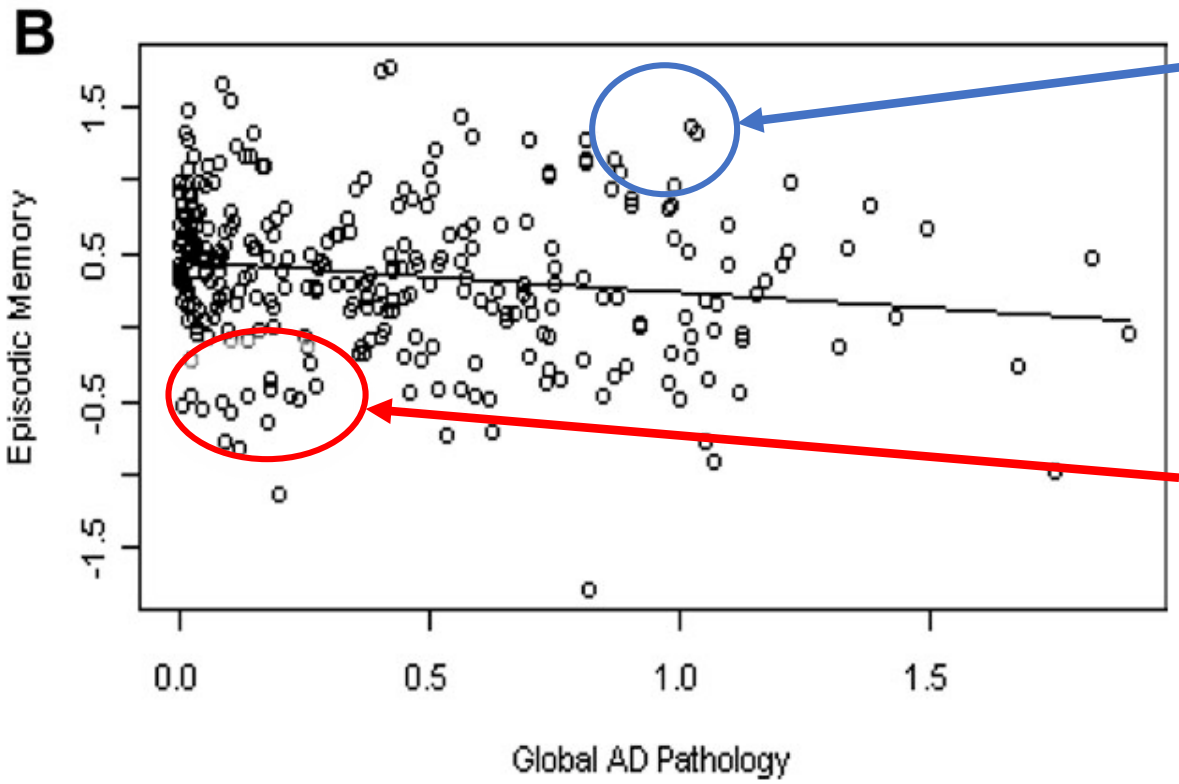
Outline

- What is cognitive reserve (CR) and why is it important?
- How is CR measured?
  - Methodological challenges
  - Conceptual issues
- Estimating CR in WHIMS participants
  - Analytic approaches
  - Construct validity
- Implications for future studies (including WHI follow-up)

What is cognitive reserve?



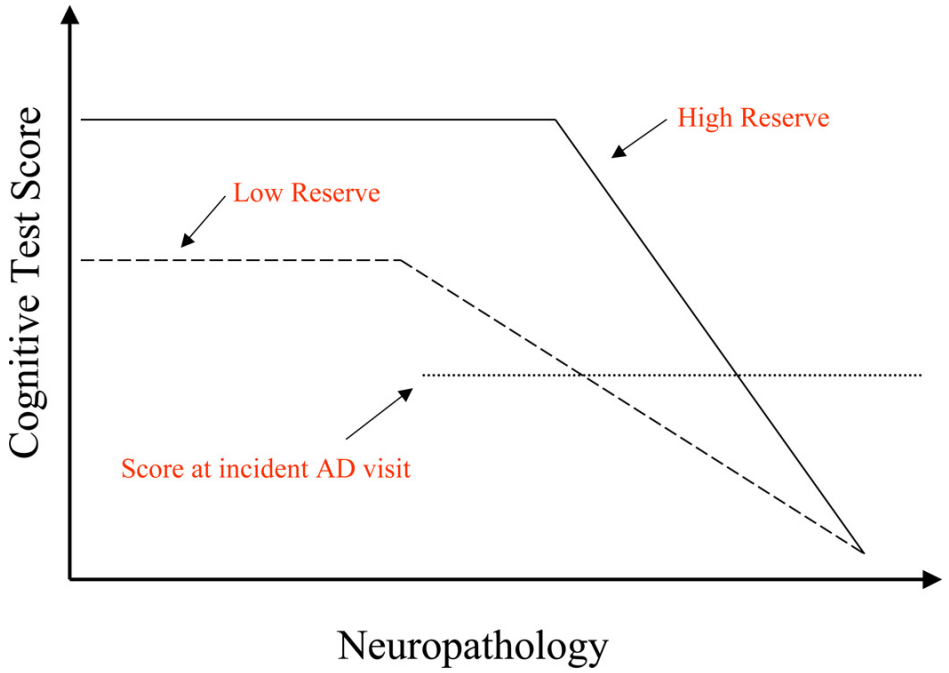
High reserve:
Lots of neuropathology
Good cognitive performance

Low reserve:
Little neuropathology
Poor cognitive performance

Bennett et al., (2012) *Annals of Neurology*

Why is cognitive reserve important?

- Higher reserve = tolerate more neuropathology
- CR is fluid and changes across entire lifespan
- Potential targets for interventions



Stern (2012) *Lancet Neurology*

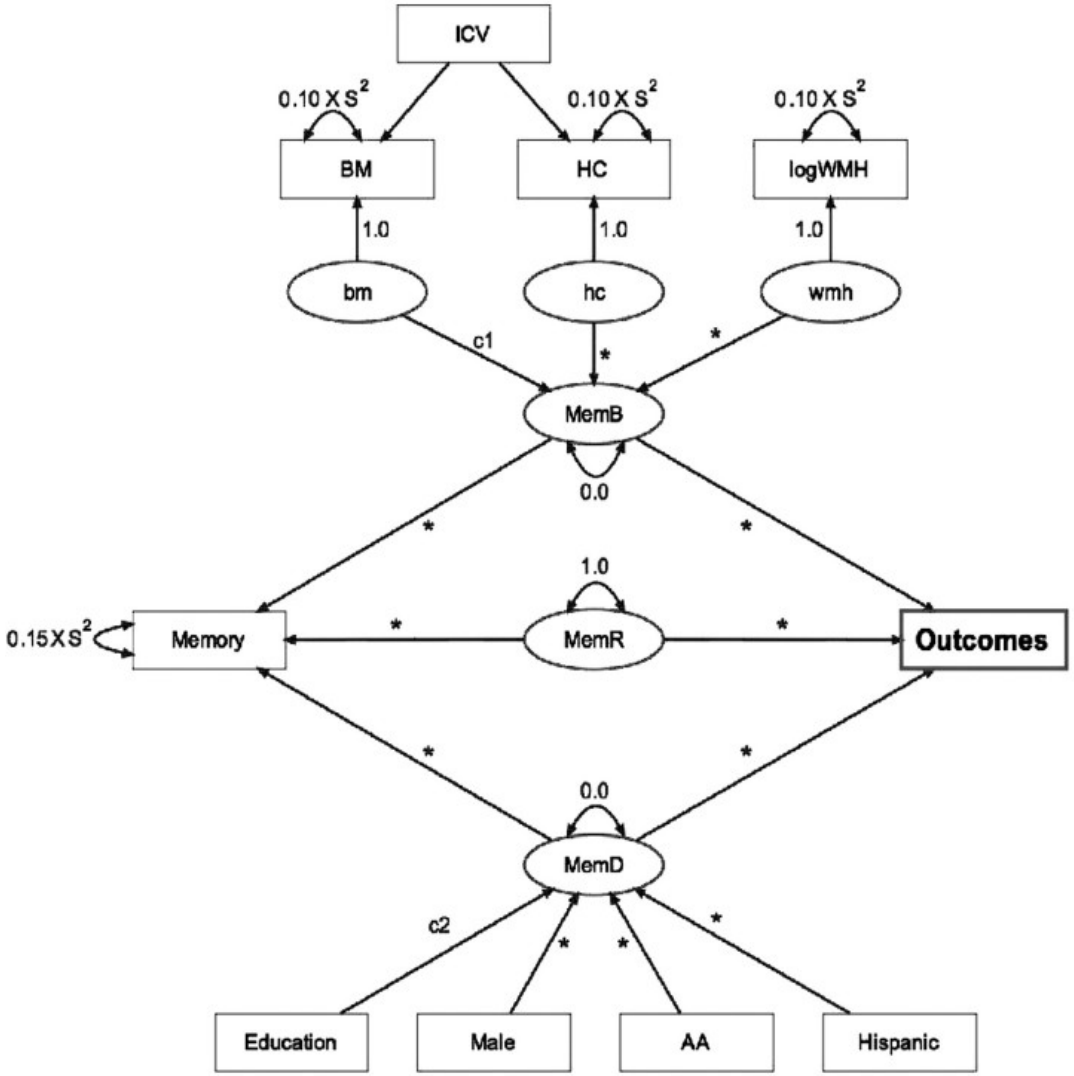
Measuring cognitive reserve is challenging

- Reliant on both measure of performance and measure of neuropathology
- Traditional method: Proxy approach
  - e.g. years of education, occupational attainment
- Problems with proxy approach
  - Cohort and geographical differences
  - Static measurement

Jones et al. (2011) *J Int Neuropsychol Soc.*

Quantitative approach to estimate cognitive reserve

- Variance decomposition method (Reed et al., 2009)
- Strengths
  - Quantitative model of CR
  - Individual-specific
- Limitations of prior work
  - Local clinical sample
  - Only quantified "memory reserve"
  - General reserve?



Reed et al. (2009) *Brain*

Estimating cognitive reserve in WHIMS

- Can we identify general and cognitive domain-specific cognitive reserve in WHIMS?
- Can we further establish the construct validity of this approach?

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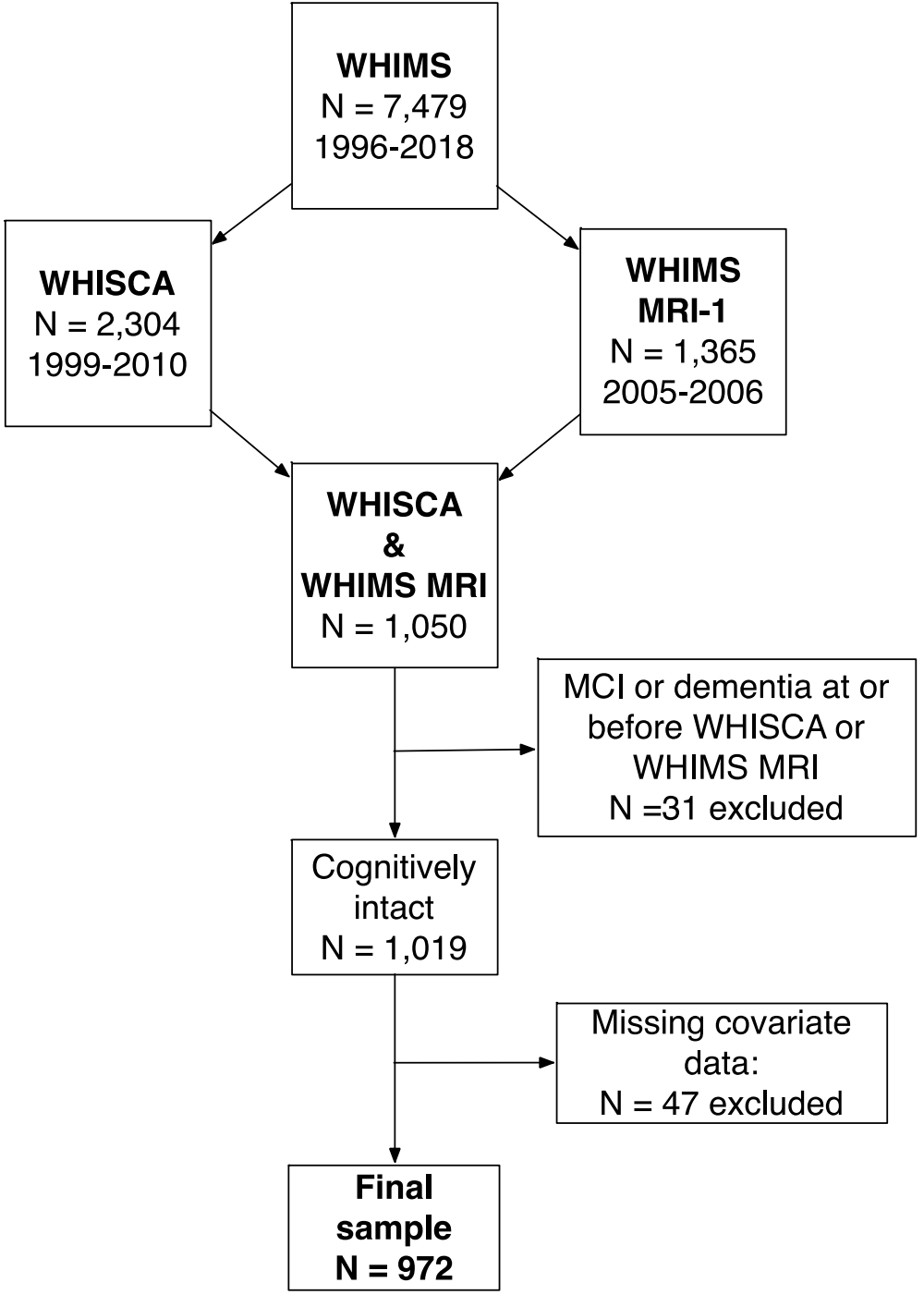
Featured Article

General and domain-specific cognitive reserve, mild cognitive impairment, and dementia risk in older women

Andrew J. Petkus[a,*], Susan M. Resnick[b], Stephen R. Rapp[c,d], Mark A. Espeland[e], Margaret Gatz[f], Keith F. Widaman[g], Xinhui Wang[a], Diana Younan[h], Ramon Casanova[e], Helena Chui[a], Ryan T. Barnard[e], Sarah Gaussoin[e], Joseph S. Goveas[i], Kathleen M. Hayden[d], Victor W. Henderson[j,k], Bonnie C. Sachs[d,l], Santiago Saldana[d], Aladdin H. Shadyab[m], Sally A. Shumaker[l], Jiu-Chiuan Chen[a,h]

Sample:

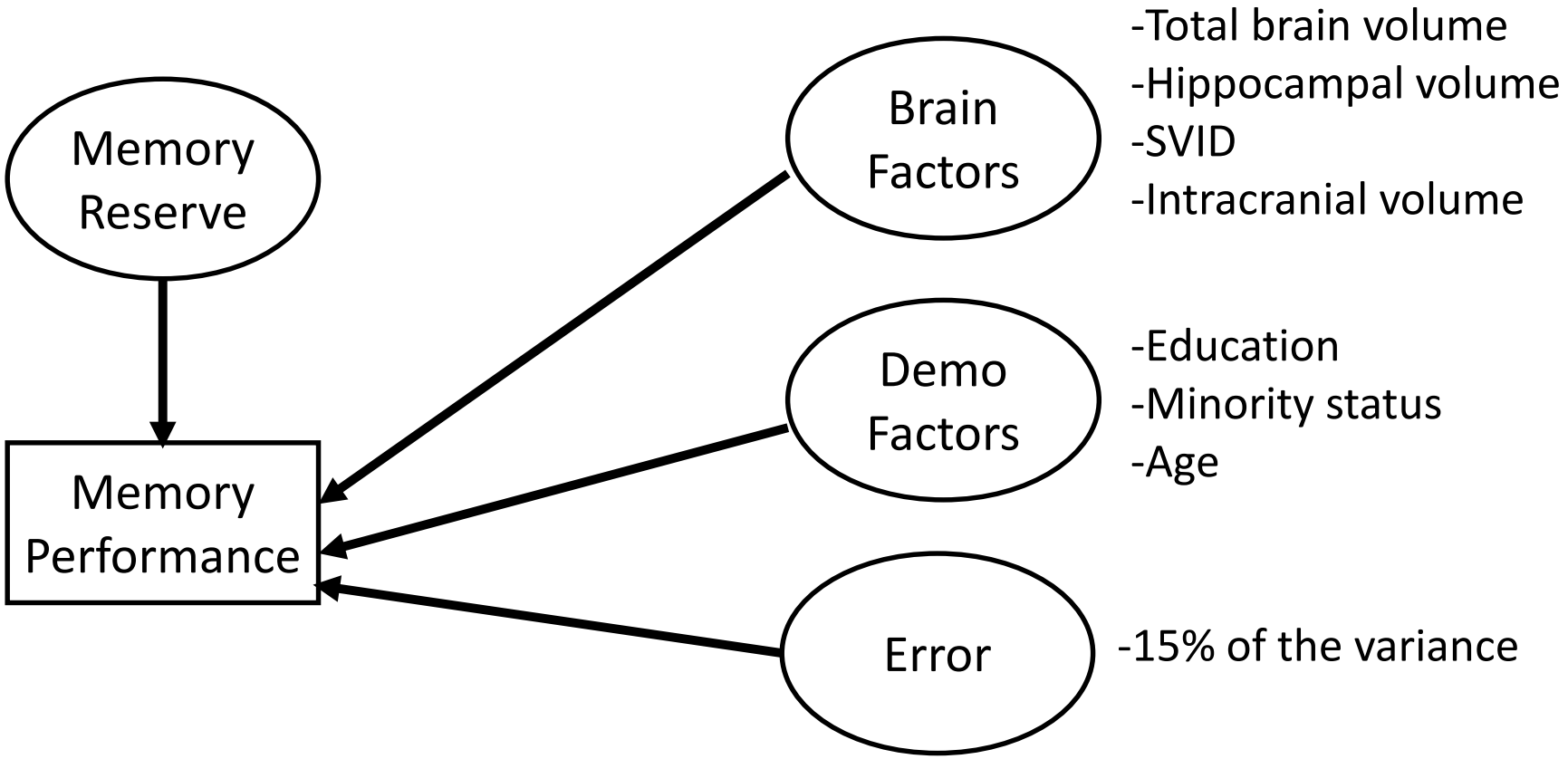
- N = 972 women from WHISCA and WHIMS MRI-1
- 78.1 years old at the time of the cognitive assessment
- Cognitively intact at time of MRI and cognitive assessment
- All-cause MCI and dementia status via WHIMS participation
  - Data available through June 2018



Measures

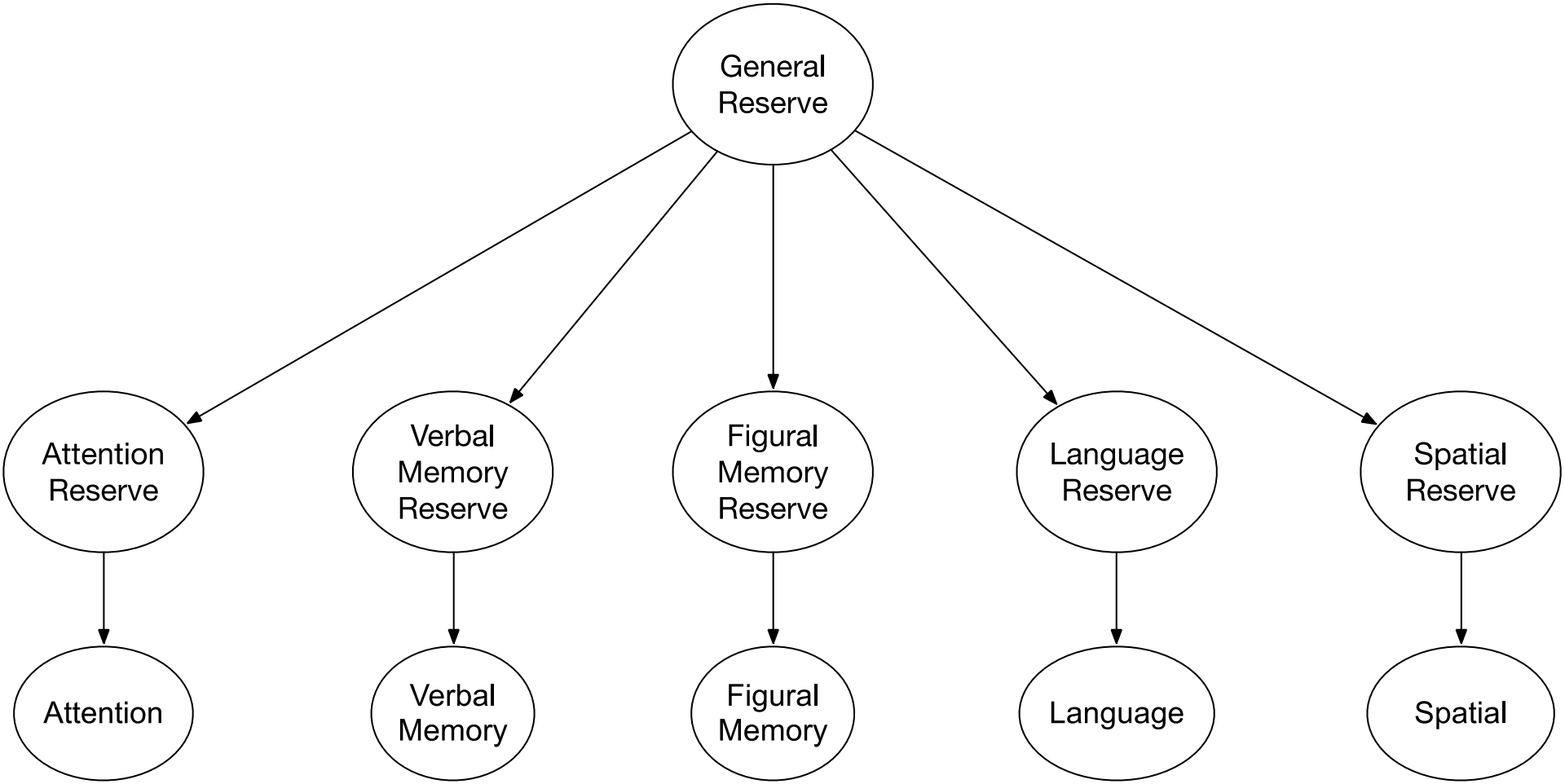
- **Cognitive measures (WHISCA)**
  - Attention
  - Verbal memory
  - Figural memory
  - Visuospatial ability
  - Attention/working memory
- **Structural MRI (WHIMS MRI-1)**
  - Hippocampal volume
  - Total brain volume
  - Small vessel ischemic disease (SVID)
- **Covariates**
  - **Demographics** (baseline age, education, ethnicity, employment, geographic region of residence, income)
  - **Lifestyle** (smoking, alcohol use, exercise, hormone treatment ever)
  - **Clinical** (cholesterol, hypertension, cardiovascular disease, diabetes)

Variance decomposition approach to quantify reserve



Higher memory reserve = performance better than what we would expect given the combination of brain and demographic factors

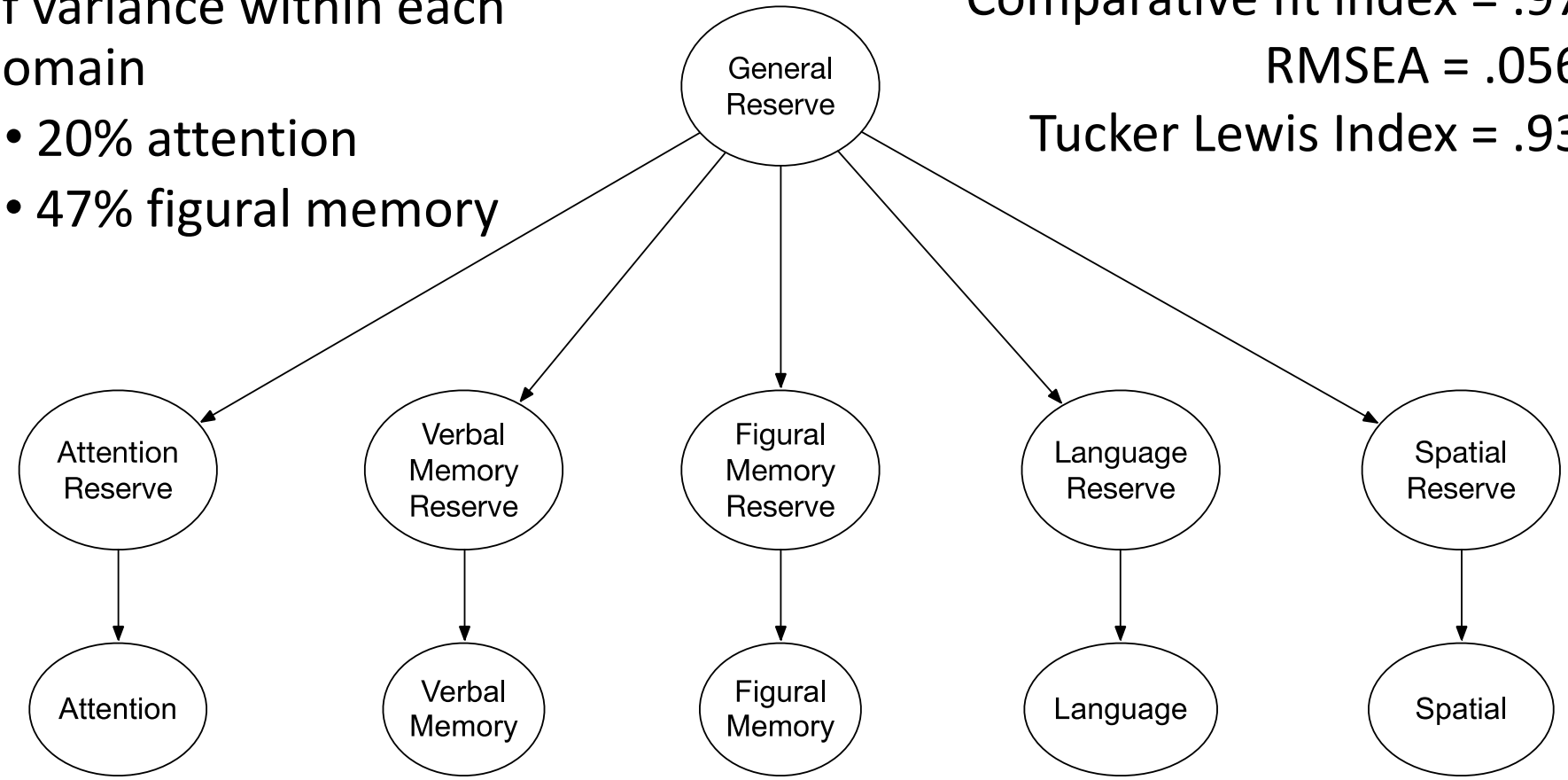
Is there a “g” cognitive reserve factor?



Domain-specific and general reserve were estimable

- General reserve explained a modest to moderate amount of variance within each domain
  - 20% attention
  - 47% figural memory

Comparative fit index = .97
RMSEA = .056
Tucker Lewis Index = .93



Higher reserve = lower risk of MCI

	Separate model estimates		Joint model estimates	
Reserve type	HR	P	HR	P
General	**.07**	**<.01**	NA	NA
Verbal memory	**.37**	**<.01**	**.49**	**<.01**
Figural memory	**.42**	**<.01**	**.65**	**<.01**
Language	**.42**	**<.01**	.82	.21
Spatial	**.54**	**<.01**	**.74**	**.02**
Attention	**.61**	**<.01**	.91	.49

- All reserve variables were scaled with mean = 0 and SD = 1
- All models adjust for demographic variables, structural brain neuropathology, lifestyle factors, and clinical variables

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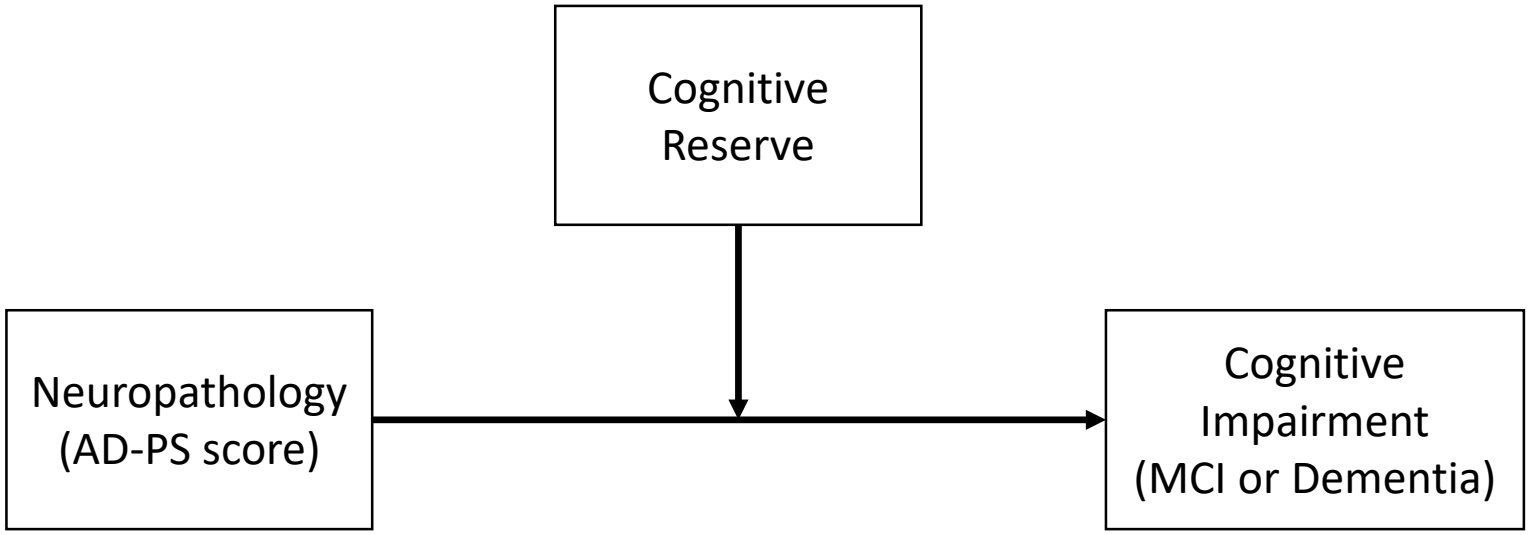
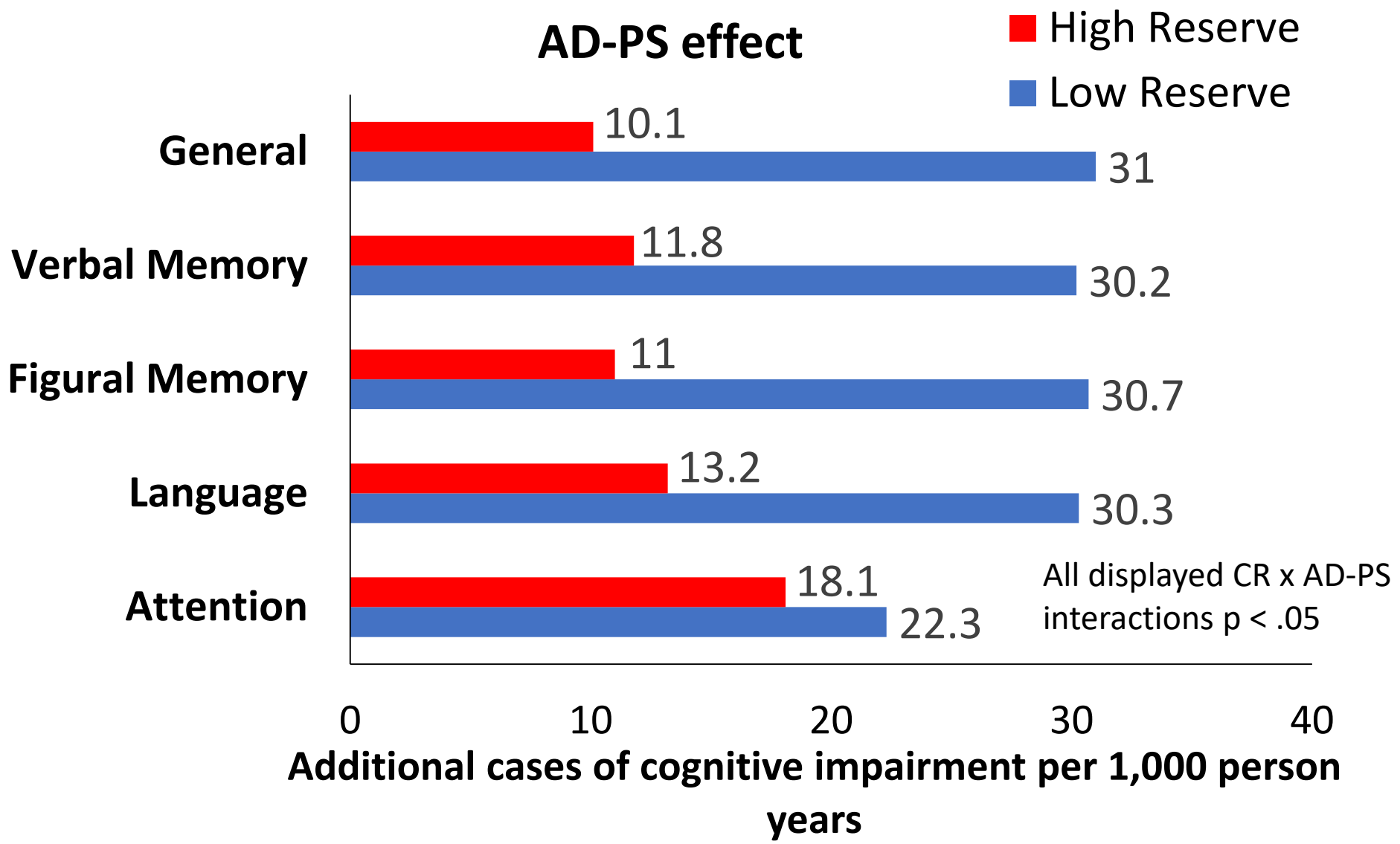
Moderating effect of reserve on neuropathology



- Neuropathology measure: Alzheimer's disease pattern similarity score (AD-PS) (Casanova et al., 2018)
  - Machine learning derived score of capturing AD-related grey matter atrophy
  - Higher score = greater AD-like pattern of brain tissue atrophy
- Aalen additive hazards model to examine the AD-PS x Reserve interaction

Good construct validity of reserve estimates



- AD-PS score and all reserve variables were scaled with mean = 0 and SD = 1
- All models adjust for demographic variables, lifestyle factors, and clinical variables

Summary of findings

- General and domain-specific reserve were identifiable in WHIMS with acceptable model fit
  - General reserve explained a modest amount of variance
- Construct validity of analytic approach
  - Higher reserve was mostly associated with lower risk of MCI and dementia
  - Heterogeneity between domains and across outcomes
  - Reserve moderated the adverse effect of increased neuropathology (AD-PS) on risk of cognitive impairment

What does this mean and implications?

- How do important lifestyle and clinical factors impact reserve?
  - Emotional factors (anxiety and depression)
  - Diet and physical exercise
  - Sleep
- Reserve as an intervention outcome?
- Cognitive reserve in the oldest old?
- Can we apply this approach to study other types of reserve and resilience?
  - Physical functioning reserve
  - Emotional resilience

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