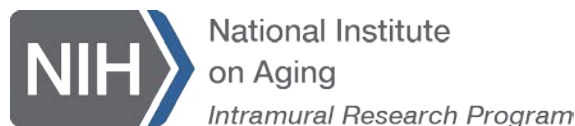


Investigating the Biology of Cognitive Resilience in WHIMS “APOE ϵ 4 Escapees”

Women’s Health Initiative Memory Study (WHIMS)

Susan M. Resnick, Ph.D.
Chief, Laboratory of Behavioral Neuroscience
for the NIA-IRP and WHIMS Team



Investigators

NIA

- Josephine Egan - LCI
- Luigi Ferrucci - TGB
Ruin Moaddel
- Ranjan Sen - LMBI
- Madhav Thambisetty – LBN
- Dimitrios Kapogiannis - LNS
- Peter Rapp - LBN

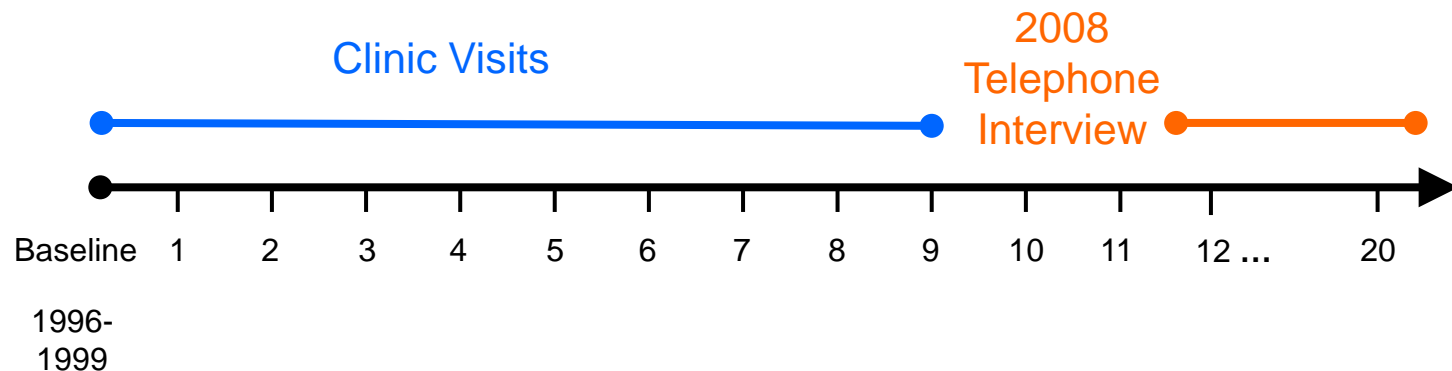
Wake Forest

- Mark Espeland
- Steve Rapp
- Sally Shumaker
- Kate Hayden
- Mark Brown
- Bev Snively

Vanderbilt

- Tim Hohman

WHIMS 2017



- Unique cohort of ~ 2000 of oldest-old women
- Investigate both cognitive resilience and decline
- 20 years of follow-up with extensive cognitive, psychosocial, and health-related information
- Baseline biospecimens

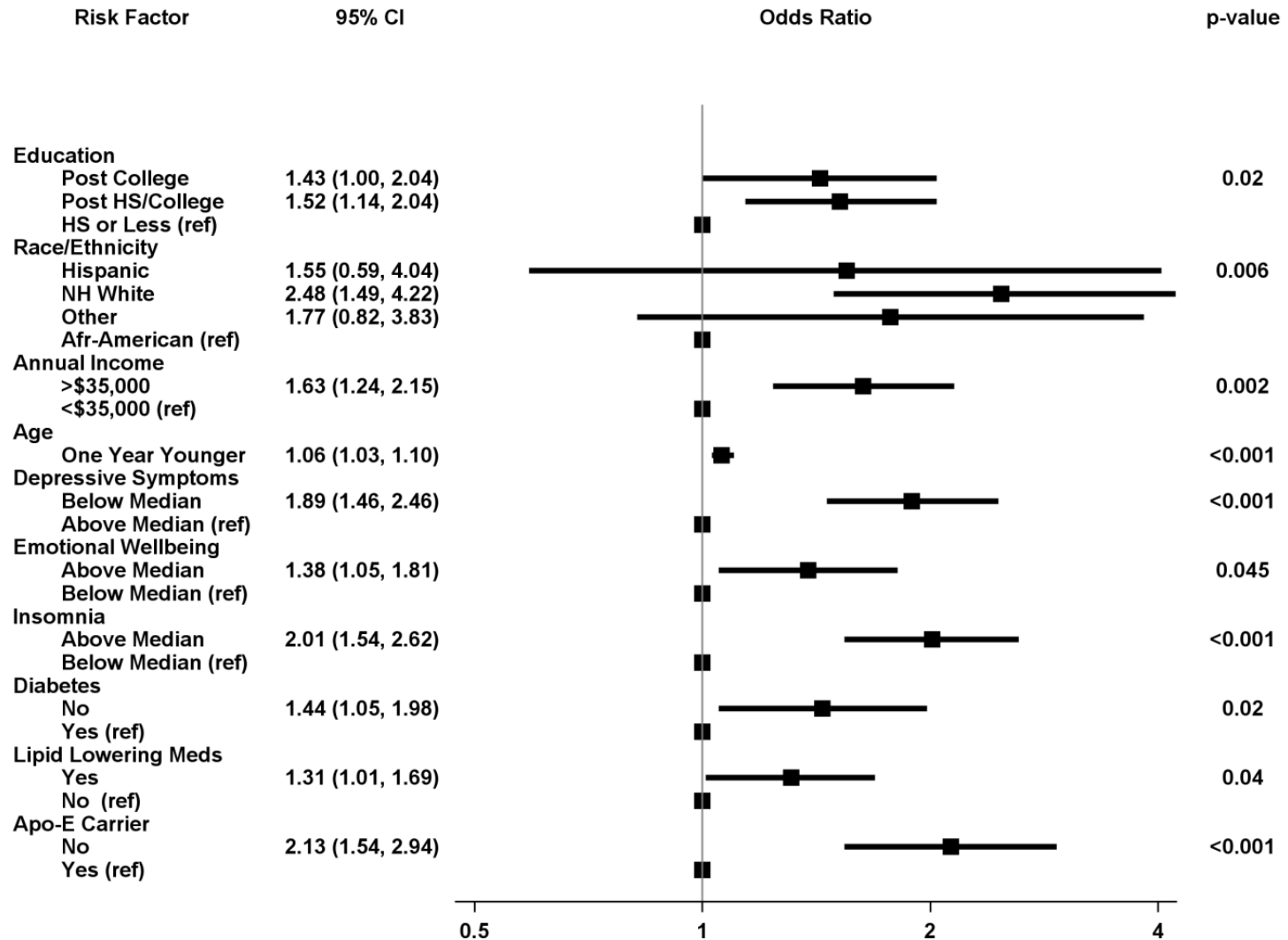
Predictors of Optimal Cognitive Aging in 80+ Women: The Women's Health Initiative Memory Study

Journals of Gerontology March 2016; 71:S62-S71.

Joseph S. Goveas, Stephen Rapp, Patricia Hogan, Ira Driscoll, Hilary Tindle, J. Carson Smith, Shelli Kesler, Oleg Zaslavsky, Rebecca Rossom, Judith Ockene, Kristine Yaffe, JoAnn E. Manson, Susan M. Resnick, Mark A. Espeland for the Women's Health Initiative Memory Study and the 80+ Cognition Work Group



WHIMS 80+: Predictors of Preserved Cognition



Investigation of Baseline Characteristics that Distinguish Subsequently Resilient Women

- Kate Hayden – Ongoing analysis of demographic, health and lifestyle characteristics associated with cognitive resilience in APOE ϵ 4 carriers
- Emerging results - APOE ϵ 4 “escapees” at baseline have:
 - Better general health
 - Higher 3MSE scores
- Does not address physiologic differences that may lead to a greater mechanistic understanding of resilience

What do we know about the biology
of cognitive resilience: *not much!*

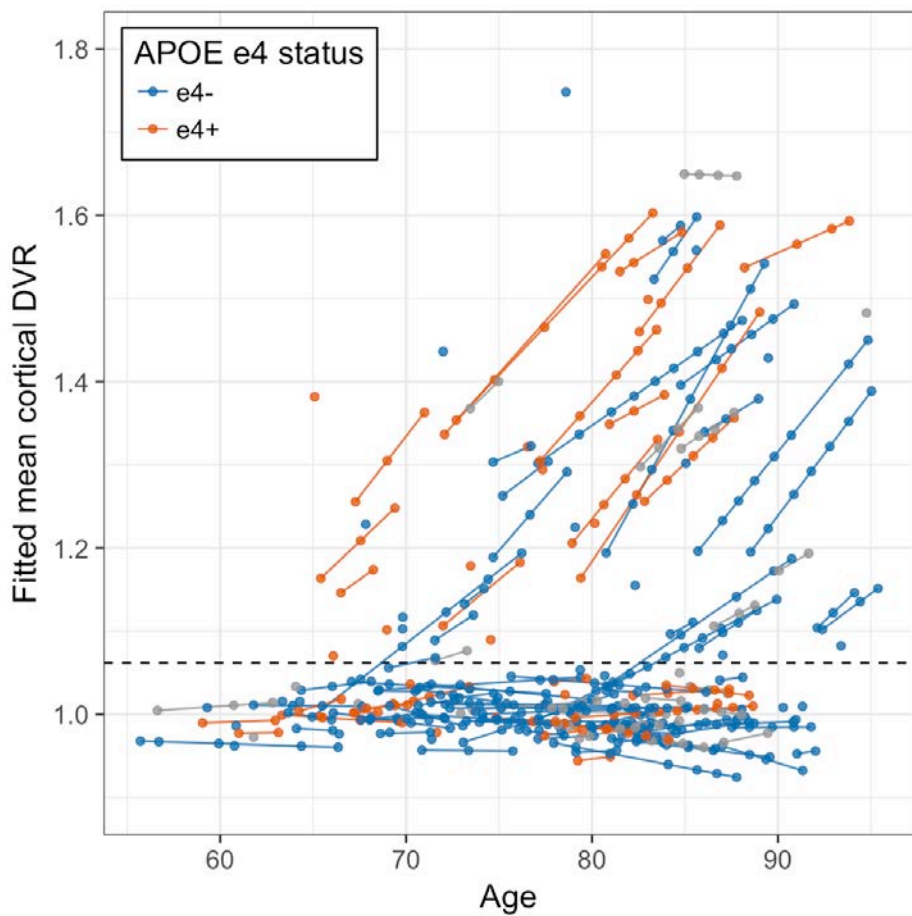
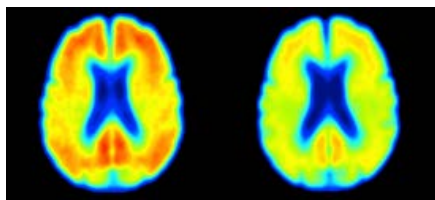
Investigation of Baseline Characteristics that Distinguish Subsequently Resilient Women

BRC Meeting – June 26, 2017

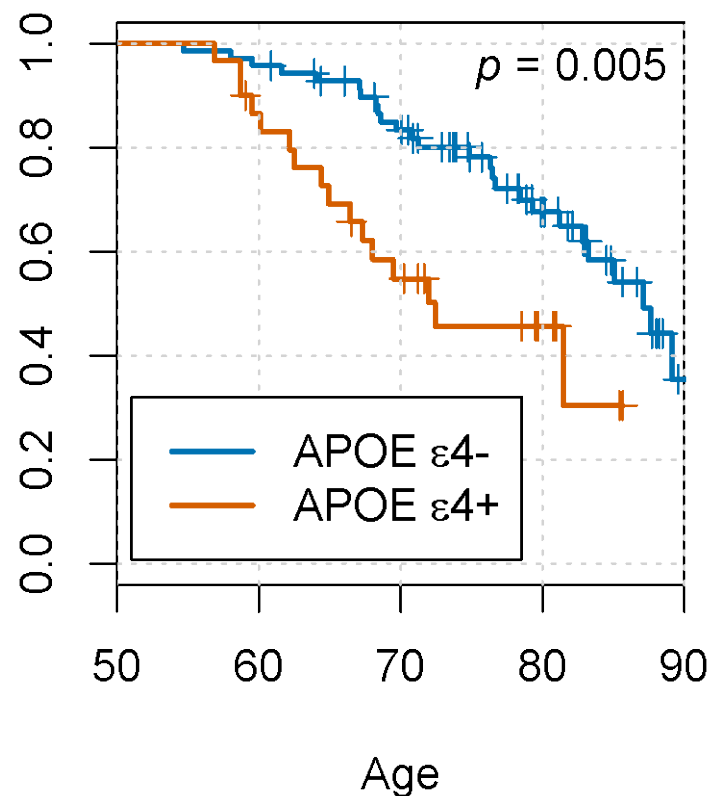
- Why do some women who carry an APOE ϵ 4 allele remain free of cognitive impairment after age 80?
- Are the factors that distinguish these resilient women the same as those in resilient women without an ϵ 4 allele (ϵ 3/ ϵ 3)?

APOE $\epsilon 4$ is Associated with Earlier Age of Onset of Amyloid Accumulation

Bilgel et al. Alz & Dementia 2016



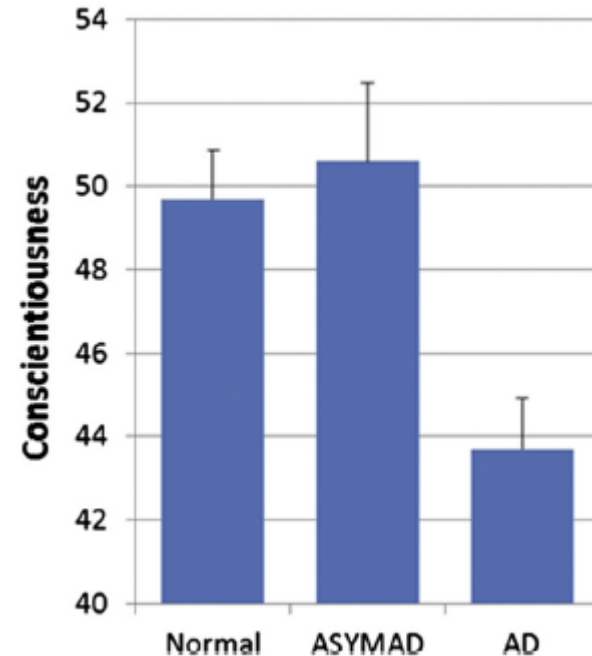
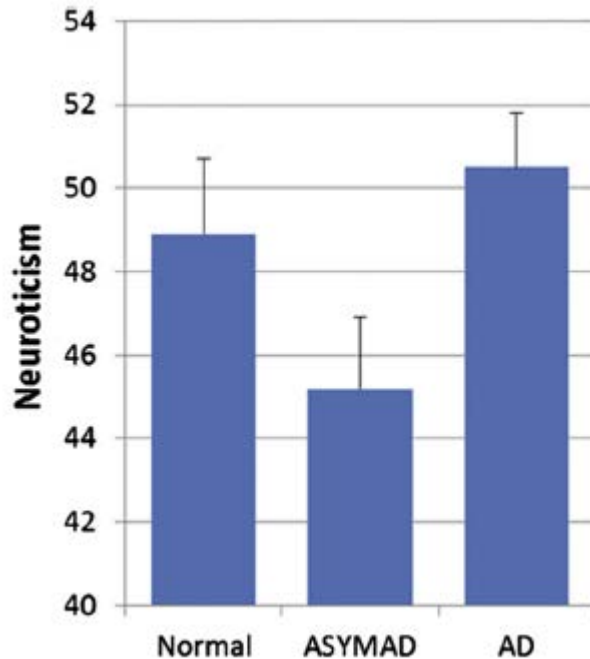
Probability of not having reached the onset of amyloid accumulation



Personality and resilience to Alzheimer's disease neuropathology: a prospective autopsy study

Antonio Terracciano^{a,b,*,1}, Diego Iacono^{c,d,1}, Richard J. O'Brien^e, Juan C. Troncoso^{d,e}, Yang An^a, Angelina R. Sutin^{a,b}, Luigi Ferrucci^a, Alan B. Zonderman^a, Susan M. Resnick^a

Neurobiology of Aging 34 (2013) 1045–1050



- ❖ Lower Neuroticism and Higher Conscientiousness in ASYMAD vs AD
- ❖ Conversely, high N and low C predict AD (Alz & Dementia 2013)
- ❖ High N and low C are associated with increased IL-6 (Psychol Med 2010)

Target Sample Characteristics

	Age \leq 80 ϵ 4+ Impaired	Age > 80 ϵ 4+ Not Impaired	Age > 80 ϵ 4+ Impaired	Age \leq 80 ϵ 3/ ϵ 3 Impaired	Age > 80 ϵ 3/ ϵ 3 Not Impaired	Age > 80 ϵ 3/ ϵ 3 Impaired
	N = 122	N = 386	N = 261	N = 105	N = 1226	N=461
Age at Enrollment	70.6 (3.4)	70.6 (3.7)	72.7 (3.8)	71.1 (3.6)	70.8 (3.7)	72.2 (3.8)
APOE N (%)*						
ϵ 3/ ϵ 4	99 (81.2)	332 (86.0)	223 (85.4)			
ϵ 4/ ϵ 4	16 (13.1)	18 (4.7)	21 (8.1)			
ϵ 3/ ϵ 3				105 (100)	1226 (100)	461 (100)

* excludes ϵ 2/ ϵ 4

Measures Proposed

- Egan – Insulin Resistance, IGF-1 and its binding proteins
- Ferrucci/Moaddel – SomaLogic proteomics and recent assays for measurement of A β 40, A β 42, t-Tau and p-Tau
- Ranjan Sen – Autoantibody signatures
- Madhav Thambisetty – Targeted metabolomics
- Dimitrios Kapogiannis - Exosomes

Proposed Sample Sizes

Overall

	Age \leq 80 and Cognitive Impairment	Age > 80 and No Cognitive Impairment	Age > 80 and Cognitive Impairment	TOTAL
$\epsilon 4$ carrier	115	350	244	709
$\epsilon 3/\epsilon 3$	105	350	461	916

Exosomes

	Age \leq 80 and Cognitive Impairment	Age > 80 and No Cognitive Impairment	Age > 80 and Cognitive Impairment	TOTAL
$\epsilon 4$ carrier	115	118	150	383
$\epsilon 3/\epsilon 3$	105	100	150	355

Analyses

- Extreme Groups – e4 impaired ≤ 80 vs. resilient > 80 ; e4 impaired ≤ 80 vs all 80+
- Time to onset of impairment
- Age at onset of impairment
- Association with 3MSE

Additional Considerations

- Need for Replication:

WHI: COSMOS-MIND, WHISPER, WHISH

QUESTIONS?

Specific Assays

Egan - Glucose and Insulin Resistance

Insulin

IGF-1

IGF-1 binding proteins

Ferrucci –

SomaLogic 1300 proteins

Quanterix Simoa

IL-6

NF-light

Neurology 3-Plex A, AB40, AB42, Ttau

pTau

Thambisetty - Targeted Metabolomics

AbsoluteIDQ® p400 HR assay - Biocrates

Sen - Antibodies

Autoantibody Profiles

Kapogiannis - Exosomes

SIMOA - p181-tau

SIMOA - A β 42

SIMOA - A β 40

MSD - pSer312-IRS-1

MSD - Py-IRS-1

AKT signaling panel - total and phospho-proteins

3 Synaptic proteins

EV-Associated Clusterin

EV-Associated ApoE

Micro RNAs