THE WOMEN'S HEALTH INITIATIVE

Plenary 2: Dementia risk and cognitive resilience

Chair: Lindsay Reynolds, Wake Forest University of Medicine

Dementia risk and Cognitive Resilience

WHI Annual Investigators Meeting

May 1, 2025

Plenary 2 Chair: Lindsay Reynolds, PhD
Assistant Professor
Department of Epidemiology and Prevention
Wake Forest University School of Medicine

Dementia risk and Cognitive Resilience

- Dr. Michael Duggan (NIA/NIH Intramural Research Program)

  Characterizing biomolecular mechanisms underlying neurodegenerative disease biology

- Dr. Keenan Walker (NIA/NIH Intramural Research Program)

  Identifying biomarkers and therapeutic targets for Alzheimer's disease and related dementias.

- Dr. Mike Bancks (Wake Forest School of Medicine)

  Epidemiology and prevention of type 2 diabetes and cardiovascular disease and their impact on cognitive aging

- Dr. Michelle Mielke (Wake Forest School of Medicine)

  Etiology and epidemiology of neurodegenerative diseases, utility of blood-based biomarkers for diagnosing Alzheimer's disease and related dementias.

Proteomic Analysis of *APOE*ε4 Carriers Implicates Lipid Metabolism, Complement, and Lymphocyte Signaling in Cognitive Resilience

Presented By: Keenan Walker, PhD

Multimodal Imaging of Neurodegenerative Disease (MIND) Unit

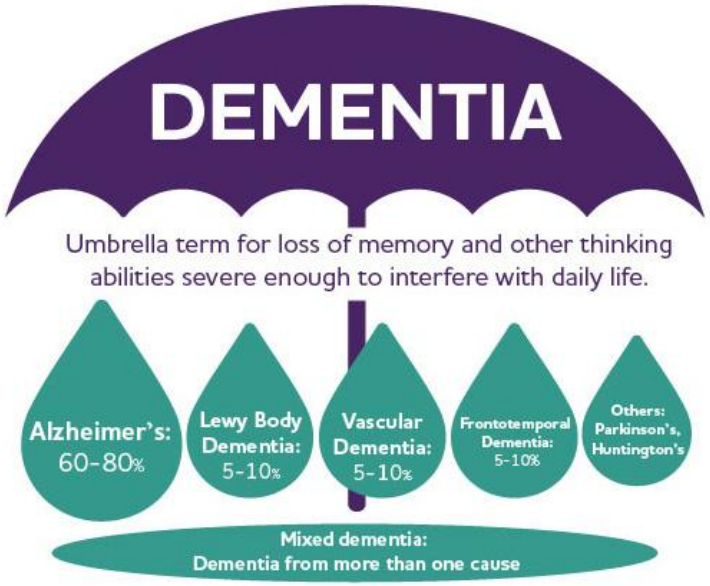
Disclosures & Conflicts of Interest

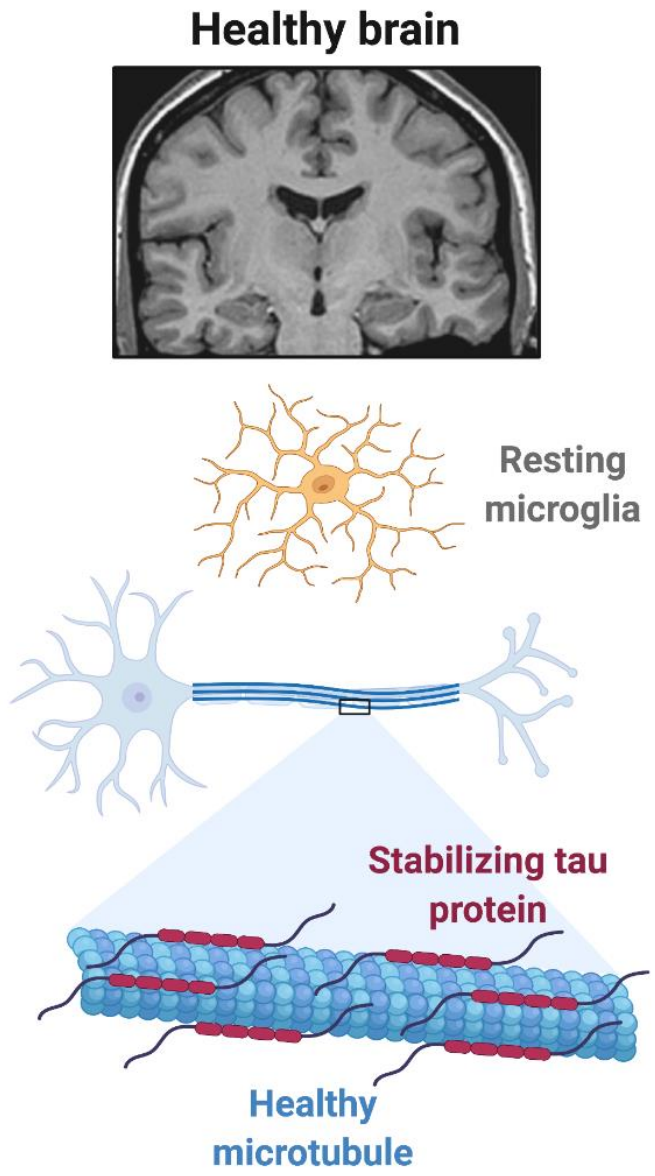
1. Research support from the National Institute on Aging's Intramural Research Program
2. Board of Directors, National Academy of Neuropsychology
3. Associate Editor, Alzheimer's & Dementia
4. Associate Editor, Alzheimer's & Dementia: Translational Research & Clinical Interventions
5. Editorial Board, Annals of Clinical and Translational Neuropsychology

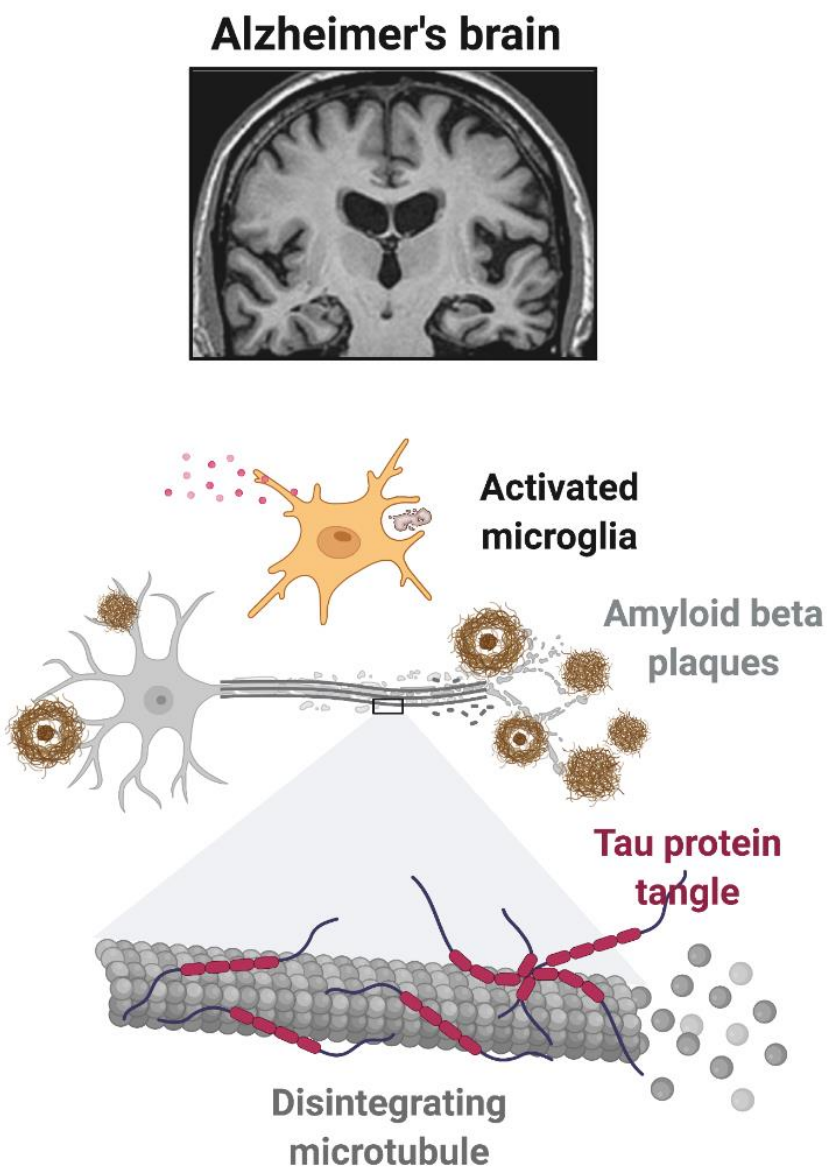
Alzheimer’s Disease

6.2 million Americans (11%) age 65 and older have Alzheimer’s disease

Most common form of dementia (60% to 80%)

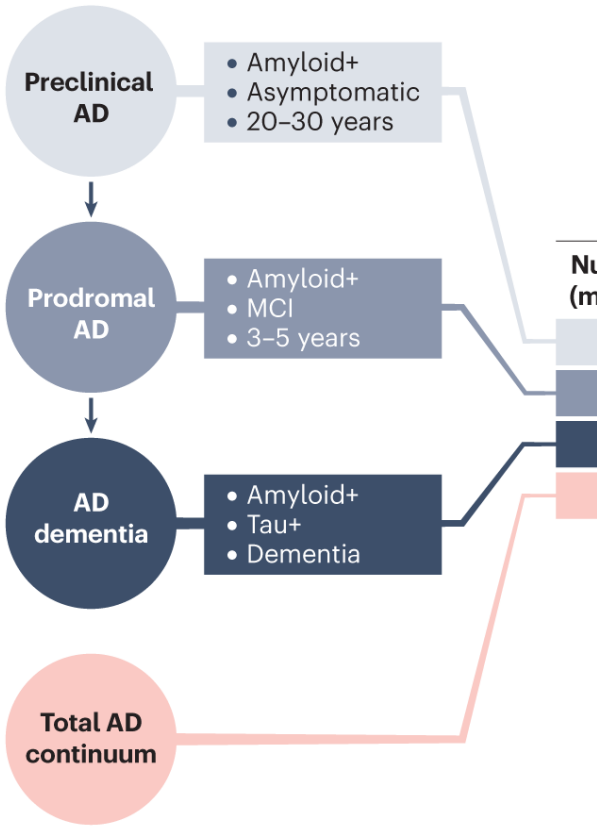






*APOE*ε4 is the Strongest Genetic Risk Factor for Late-Onset Alzheimer's Disease

Alzheimer disease continuum and APOE4

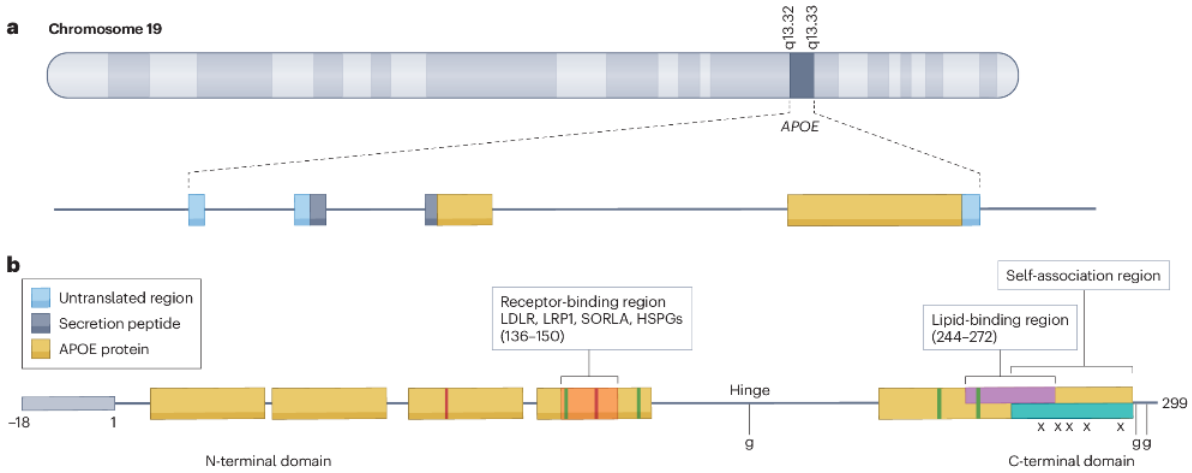


Worldwide estimates

Number (million)	% of people aged >50 years	% *APOE ε4* carriers
315	17.0	55
69	3.7	57
32	1.7	55–75
416	22.4	59

*APOE*ε4 allele possession is associated with:

- Greater Alzheimer's disease risk
- Younger age of symptom onset
- Higher burden of amyloid-β pathology

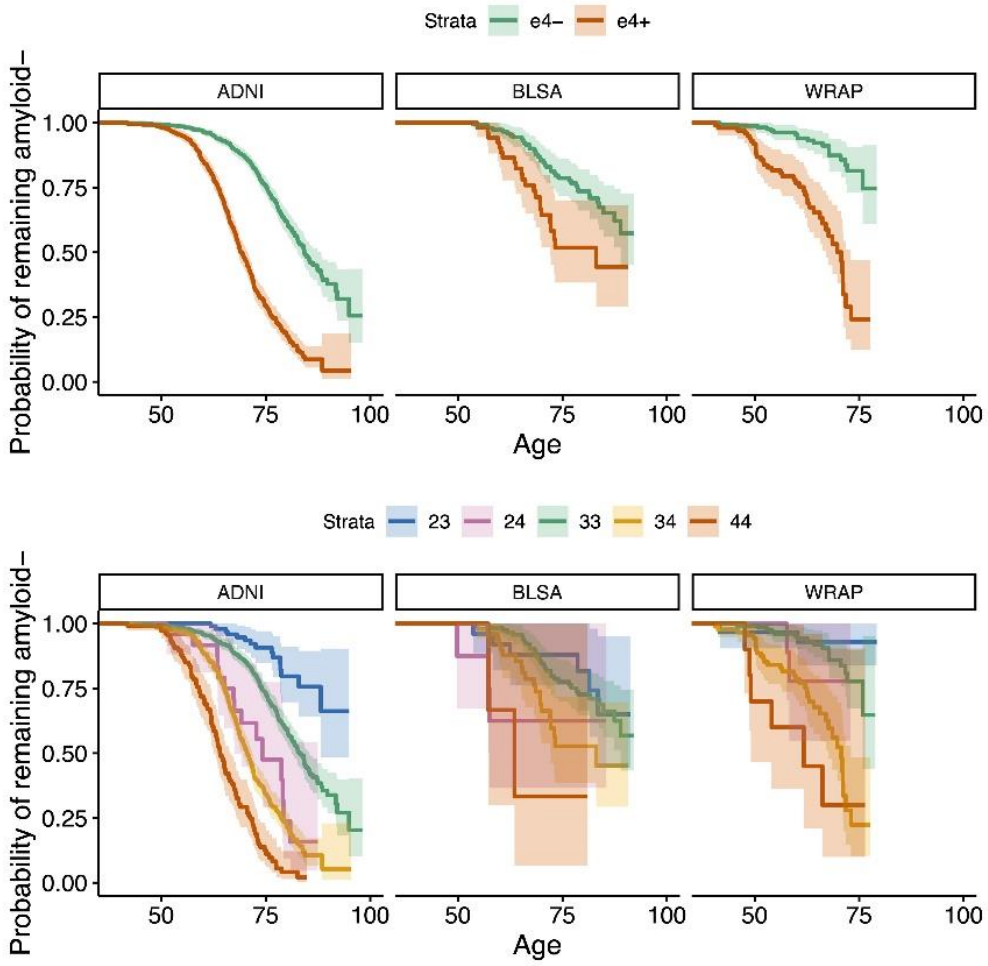


c

		112	136	145	158	236	251
Common variants	*APOE2*	C	R	R	**C**	V	R
	APOE3	C	R	R	R	V	R
	APOE4	**R**	R	R	R	V	R
Rare variants	*APOE3–Christchurch*	C	**S**	R	C	V	R
	APOE3–R145C	C	R	**C**	R	V	R
	APOE3–Jacksonville	C	R	R	R	**E**	R
	APOE4–R251G	**R**	R	R	R	V	**G**

Blumenfeld et al. (2024). *Nature Reviews Neuroscience*
Jackson et al. (2024). *Nature Reviews Neurology*

*APOE*ε4 is the Strongest Genetic Risk Factor for Late-Onset Alzheimer's Disease



*APOE*ε4 allele possession is associated with:

- Greater Alzheimer's disease risk
- Younger age of symptom onset
- Higher burden of amyloid-β pathology

Not all *APOE*ε4 carriers will develop cognitive impairment.

Question: What biological processes allow *APOE*ε4 carriers to maintain cognitive health during late life?

Betthauser et al. (2022). *Brain*

Proteomic Characterization of Cognitive Resilience Among *APOE*ε4 Carriers

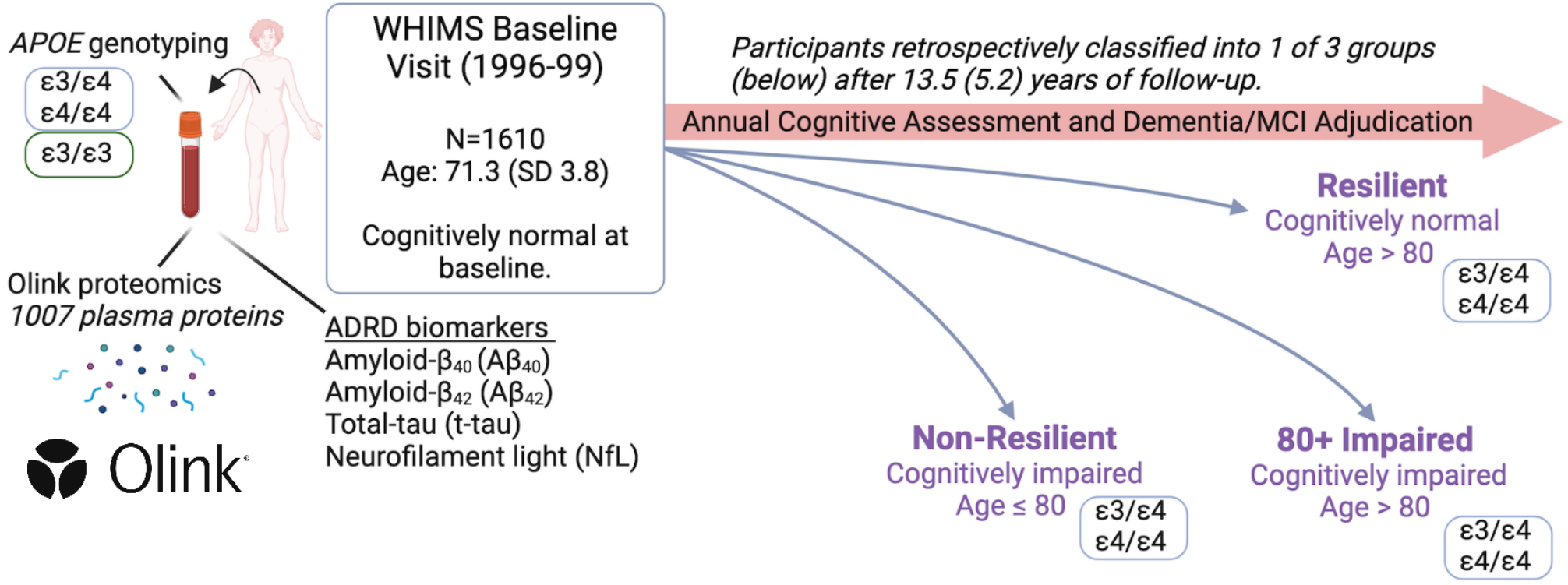
Objective. Use plasma proteomics to identify the biological processes that allow older adults to remain cognitively resilient in the context of high genetic risk for Alzheimer's disease.

Proteomic Characterization of Cognitive Resilience Among *APOE*ε4 Carriers

RESEARCH ARTICLE Open Access

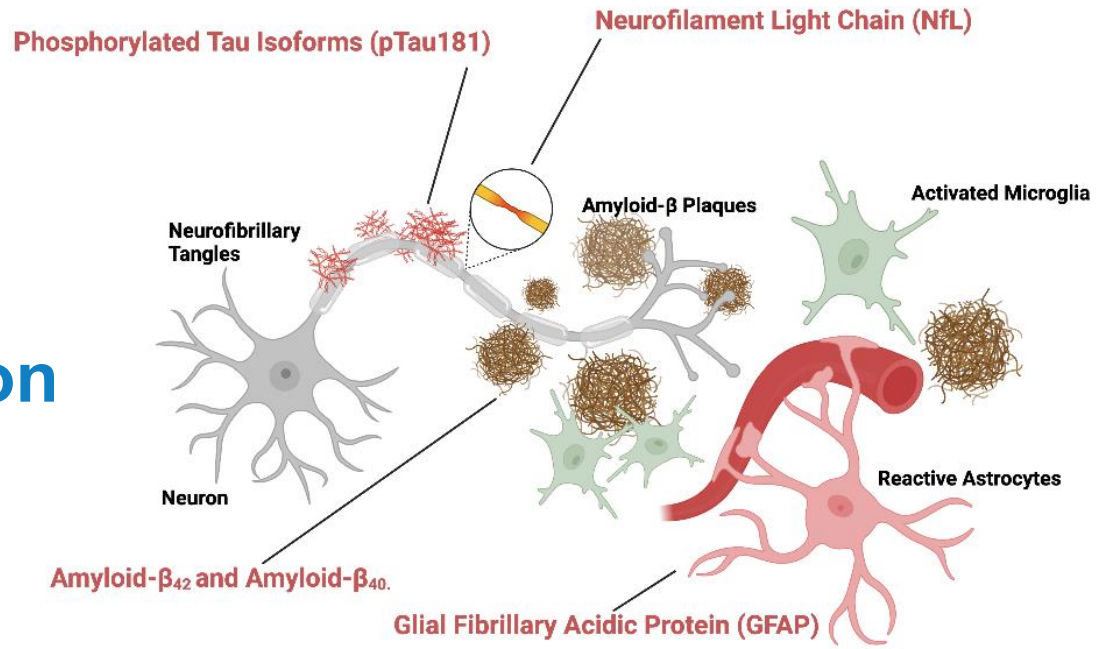
Proteomic analysis of *APOE*ε4 carriers implicates lipid metabolism, complement and lymphocyte signaling in cognitive resilience

Keenan A. Walker[1*], Yang An[1], Abhay Moghekar[2], Ruin Moaddel[3], Michael R. Duggan[1], Zhongsheng Peng[1], Qu Tian[3], Luke C. Pilling[4], Shannon M. Drouin[1], Mark A. Espeland[5,6], Stephen R Rapp[7,8], Kathleen M Hayden[8], Aladdin H. Shadyab[9], Ramon Casanova[6], Madhav Thambisetty[1], Peter R. Rapp[1], Dimitrios Kapogiannis[10], Luigi Ferrucci[3] and Susan M. Resnick[1]



Walker et al. (2024). *Molecular Neurodegeneration*

Targeted Alzheimer's Disease and Neurodegeneration Biomarkers



Alzheimer's disease
Amyloid-β42 (Aβ40)
Amyloid-β40 (Aβ40)

Neurodegeneration
Tau (total)
Neurofilament light (NfL)

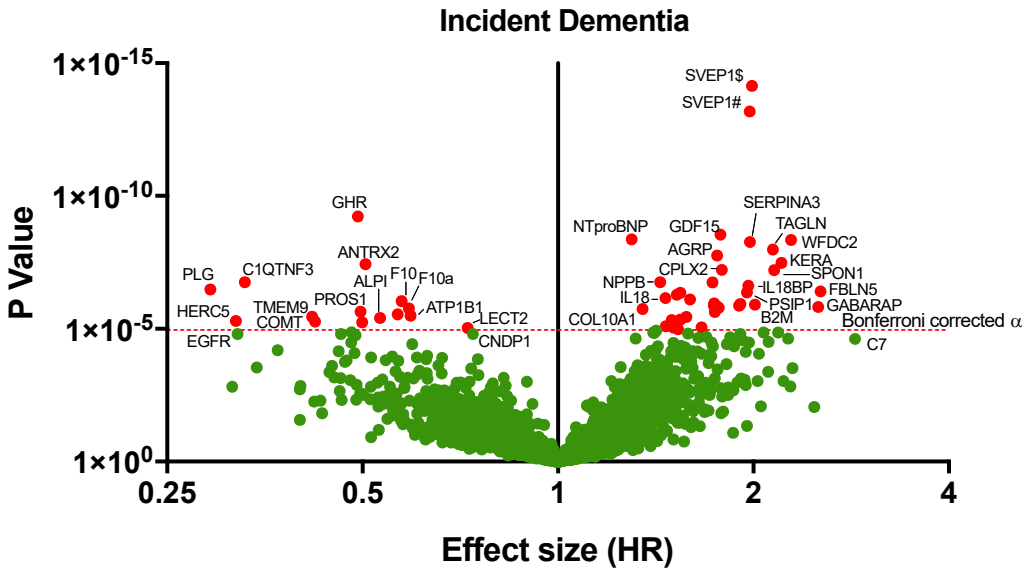
Dark et al. (2023). *Arch. Clin. Neuropsych.*

Untargeted Proteomics

1000+ proteins

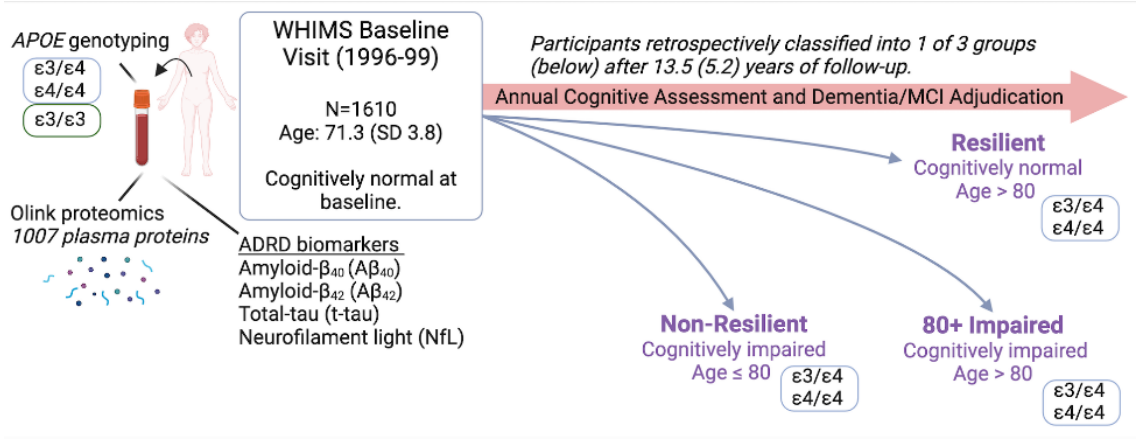
Olink®

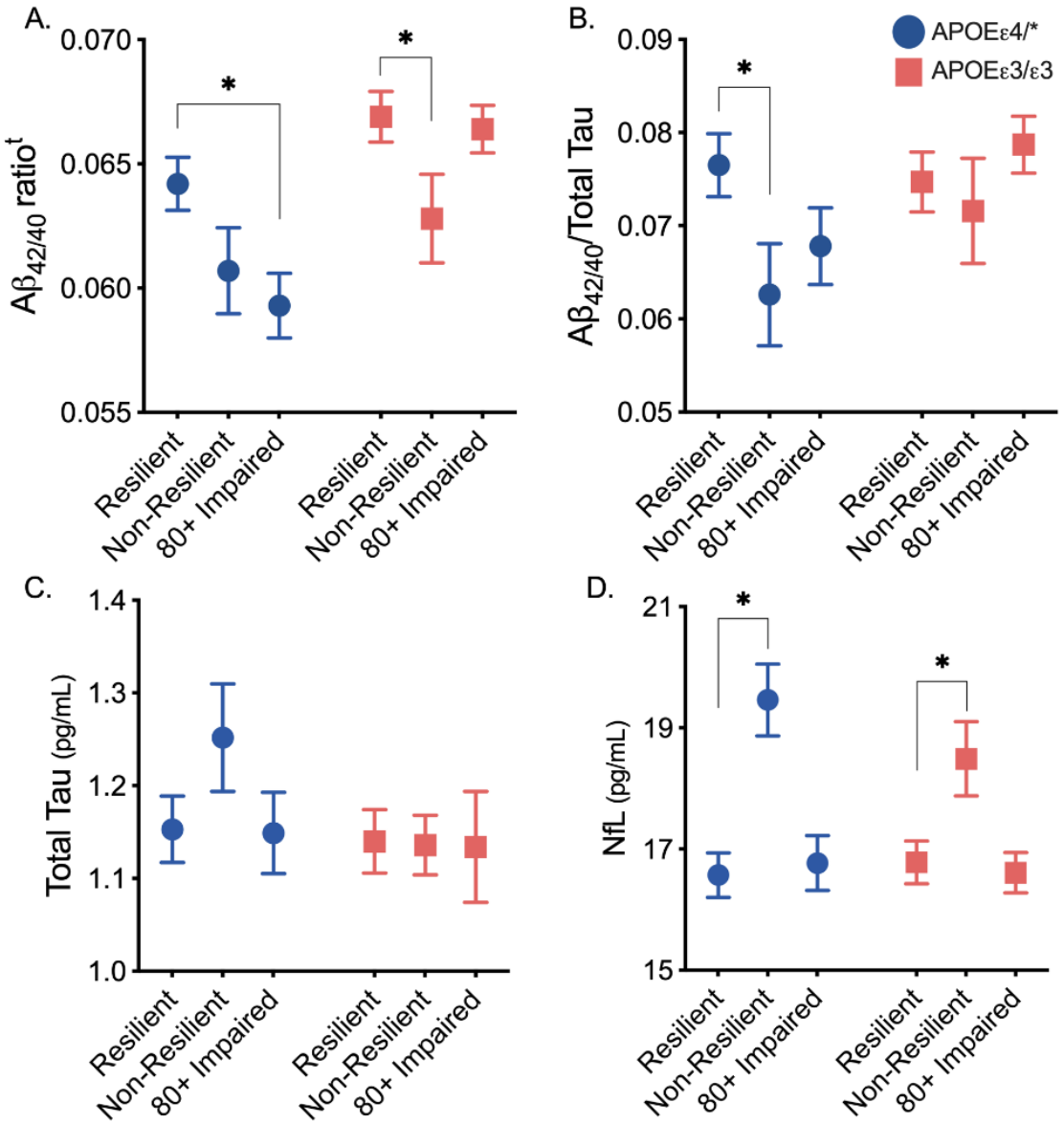
- Developmental
- Cardiovascular II
- Cardiovascular III
- Immune Response
- Inflammation
- Neuro Exploratory
- Organ Damage
- Cell Regulation
- Oncology II



Walker et al. (2021). *Nature Aging*

Targeted Biomarker Characterization of Cognitive Resilience Among *APOEε4* Carriers





Walker et al. (2024). *Molecular Neurodegeneration*

Proteomic Characterizationn of Cognitive Resilience in the Context of High Genetic Risk for Alzheimer's Disease

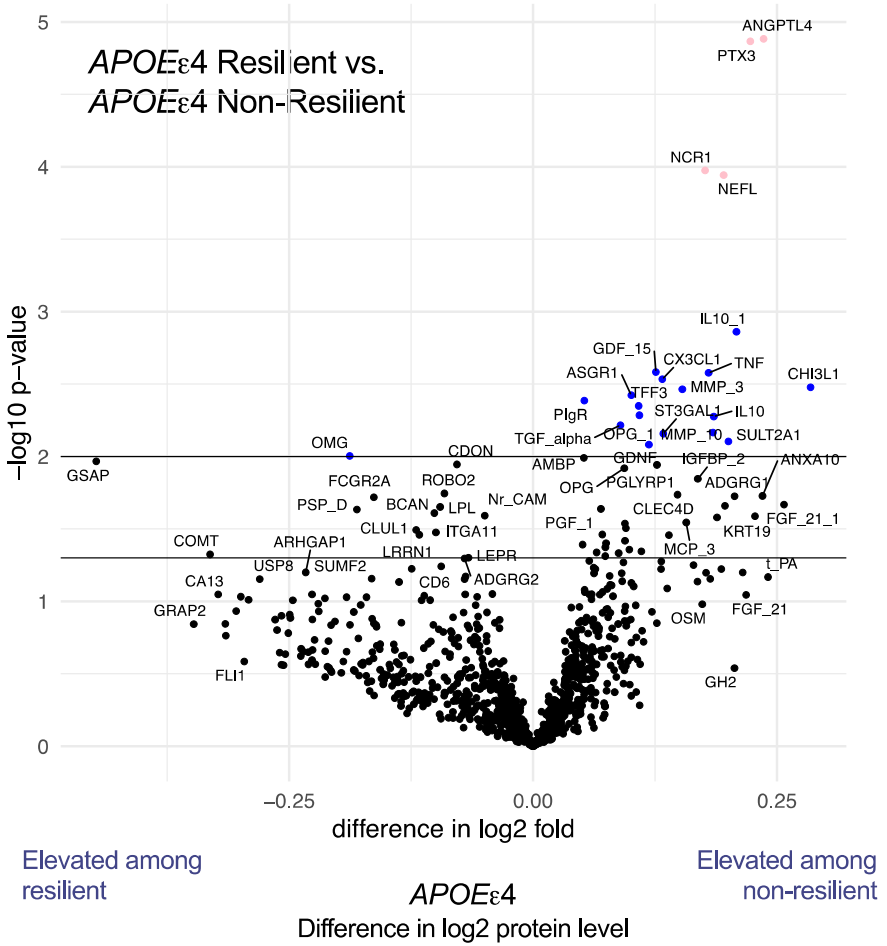
*APOE*ε4 Resilient vs. *APOE*ε4 Non-Resilient

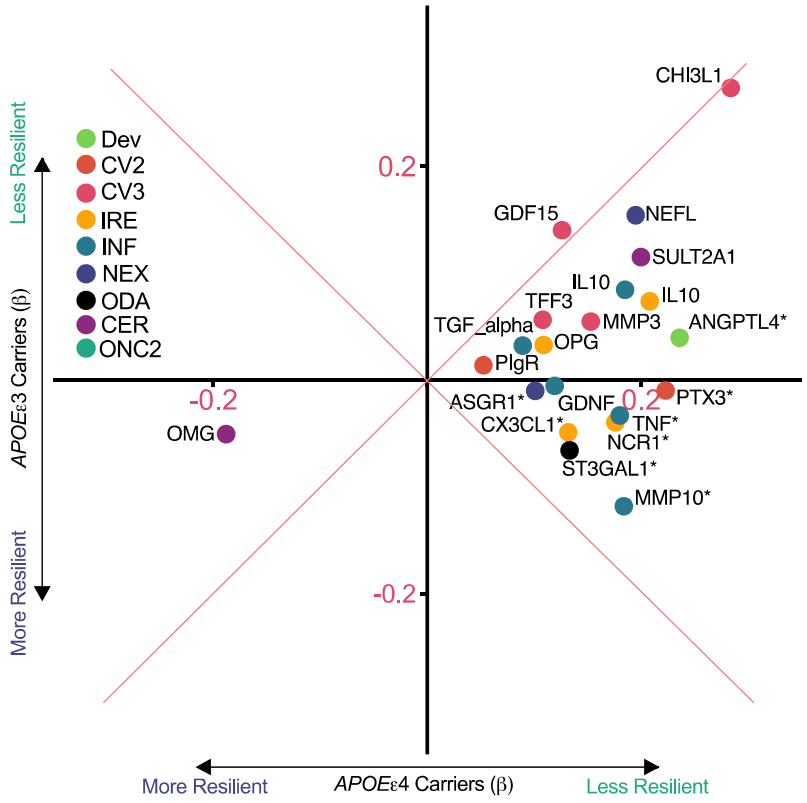
Resilient:
Cognitively Normal 80+
*APOE*ε4 Carriers

Non-Resilient:
Cognitively Impaired
*APOE*ε 4 Carriers <80

Top Proteins (FDR P<0.05)

ANGPTL4
PTX3
NCR1
NEFL





*Candidate proteins (P<0.01) in APOE*ε*4 analysis*
β estimates in among *APOE*ε4 & *APOE*ε3 carriers

Walker et al. (2024). *Molecular Neurodegeneration*

Resilient vs. Non-Resilient *APOE*ε4 Carriers

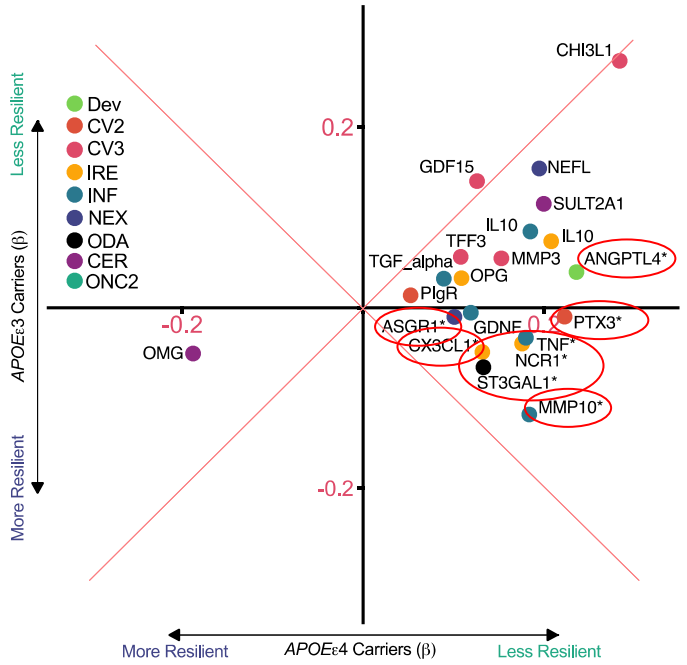
*APOE*ε4 Resilient vs. *APOE*ε4 Non-Resilient

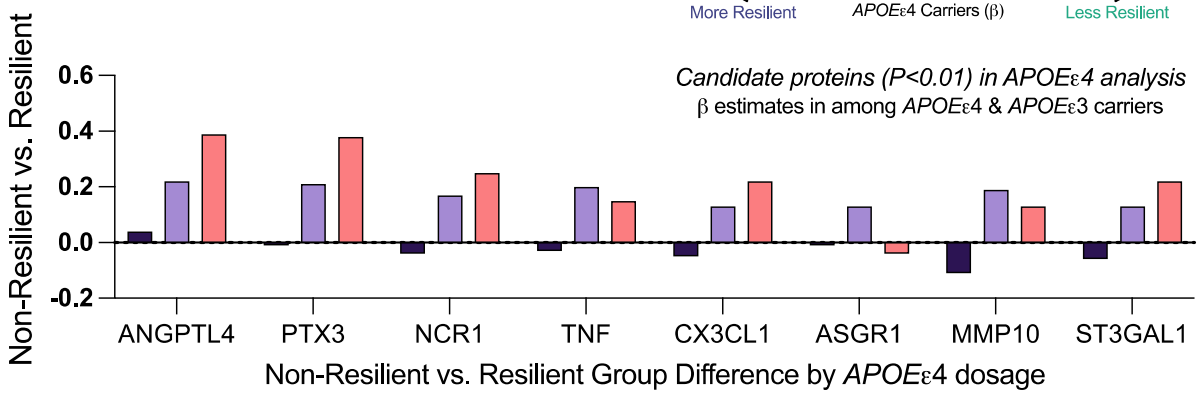
Resilient:
Cognitively Normal 80+
*APOE*ε4 Carriers

Non-Resilient:
Cognitively Impaired
*APOE*ε 4 Carriers <80

APOE Effect Modification

ANGPTL4
PTX3
NCR1
TNF
CXCL1
ASGR1
MMP10
ST3GAL1





Candidate proteins (P<0.01) in APOEε4 analysis
β estimates in among *APOE*ε4 & *APOE*ε3 carriers

	Non-Resilient (N)	Resilient (N)
ε3ε3	104	405
ε3ε4	98	325
ε4ε4	16	17

Walker et al. (2024). *Molecular Neurodegeneration*

Proteomic Characterizationn of Cognitive Resilience in the Context of Low Genetic Risk for Alzheimer's Disease

*APOE*ε3 Resilient vs. *APOE*ε3 Non-Resilient

Resilient:
Cognitively Normal 80+
*APOE*ε3 Carriers

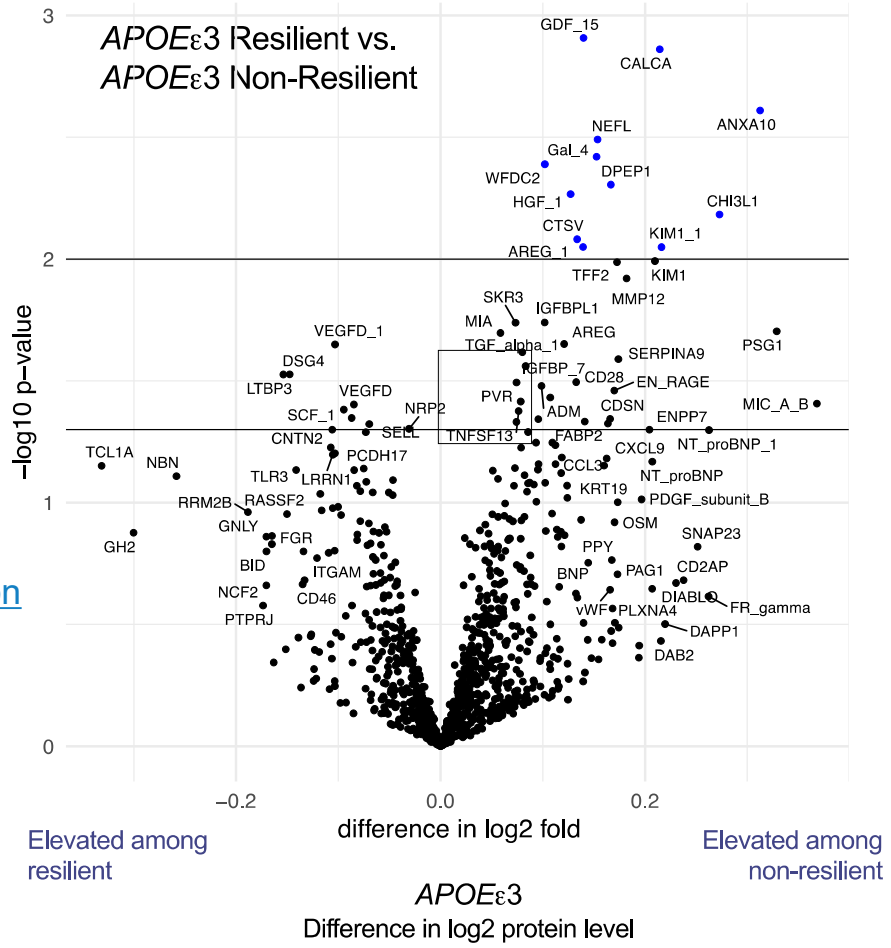
Non-Resilient:
Cognitively Impaired
*APOE*ε3 Carriers <80

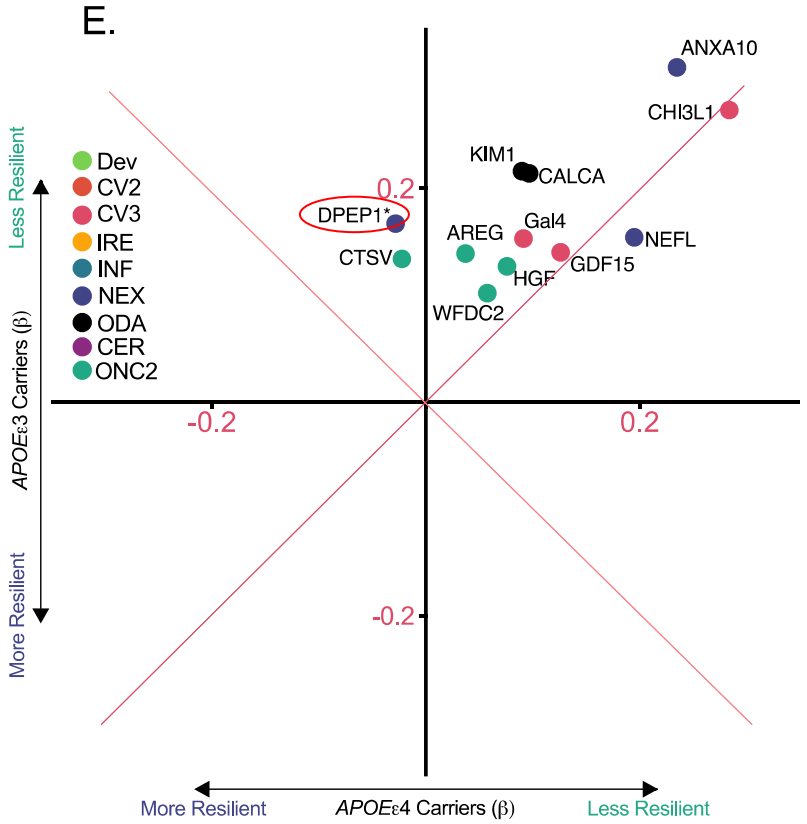
Top Proteins (P<0.01)

GDF15
CALCA
ANXA10
NEFL
GAL4
WFDC2
DPEP1
HGF
CHI3L1

APOE Effect Modification

DPEP1





*Candidate proteins (P<0.01) in APOE*ε*3 analyses*
β estimates in among *APOE*ε4 & *APOE*ε3 carriers

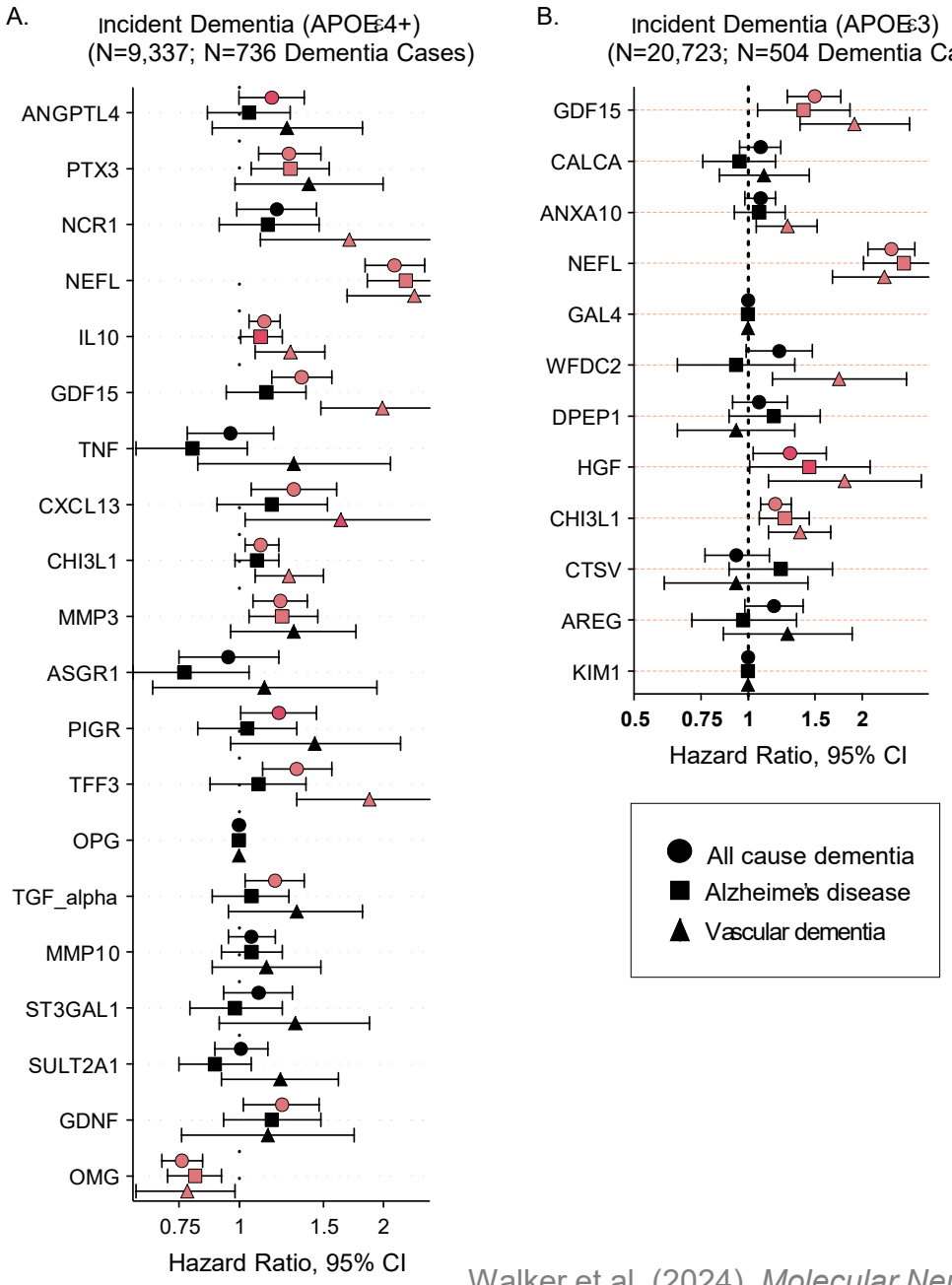
Walker et al. (2024). *Molecular Neurodegeneration*

Replication of Protein Associations in the UK Biobank

13 of the 19 (68%) *APOE*ε4 proteins replicated for all-cause dementia.

Several of these proteins showed specificity for vascular dementia over Alzheimer's disease.

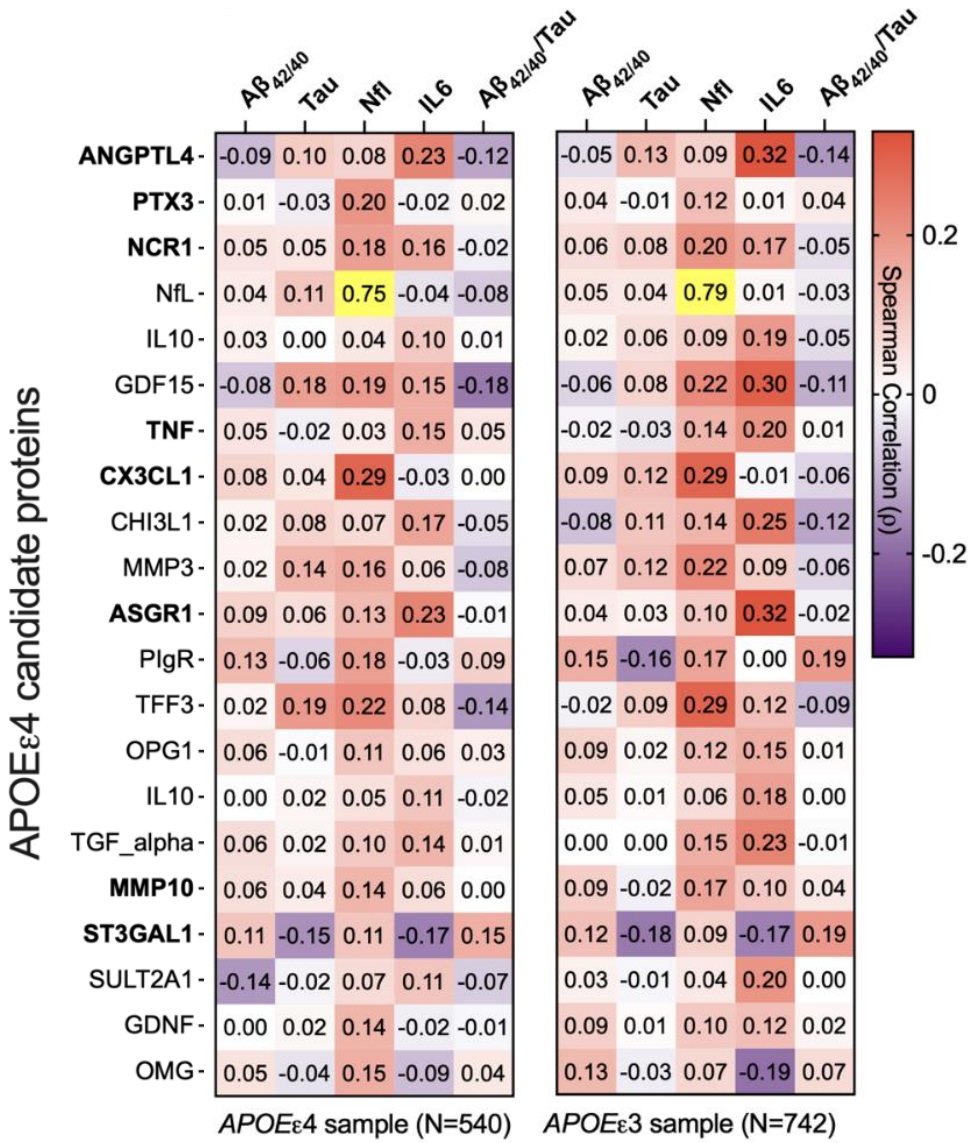
Vascular Dementia Proteins
NCR1
GDF15
CHI3L1
TFF3

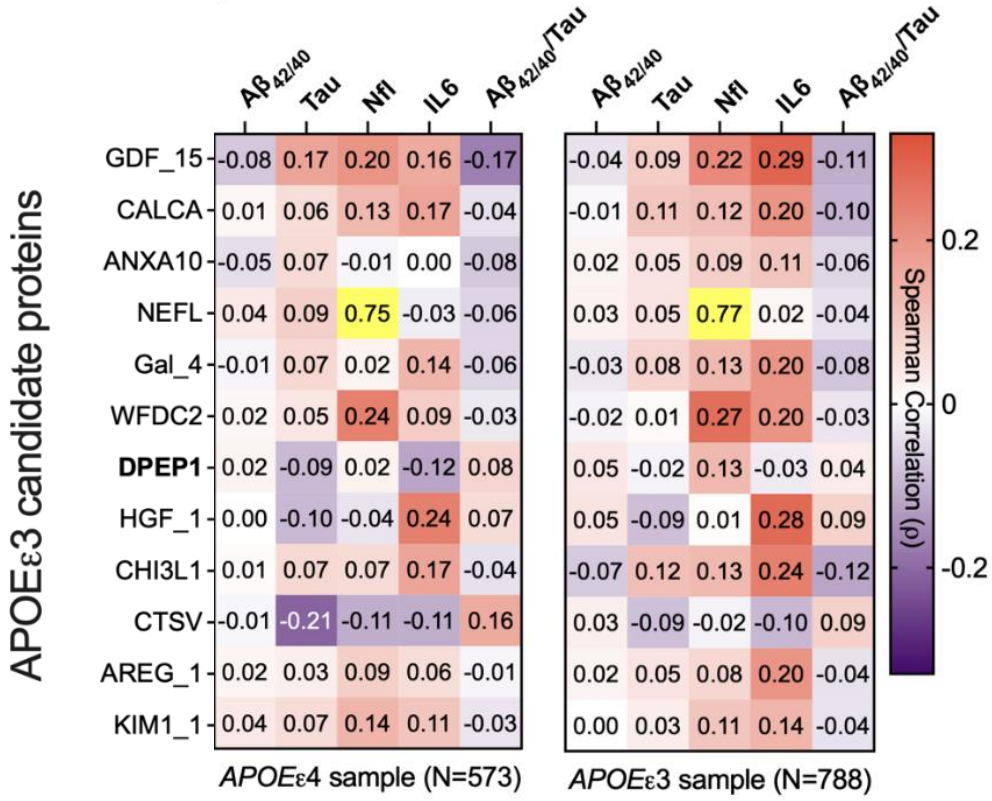


Walker et al. (2024). *Molecular Neurodegeneration*

The Association of Resiliency Proteins with Targeted Dementia Biomarkers

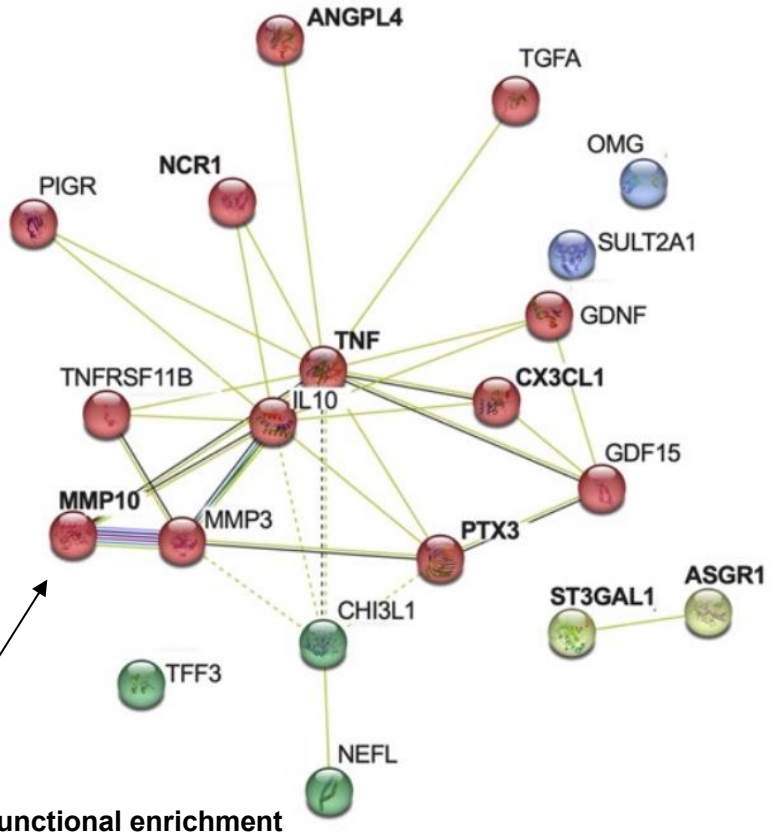
APOE genotype influences the correlation between candidate proteins and IL6.



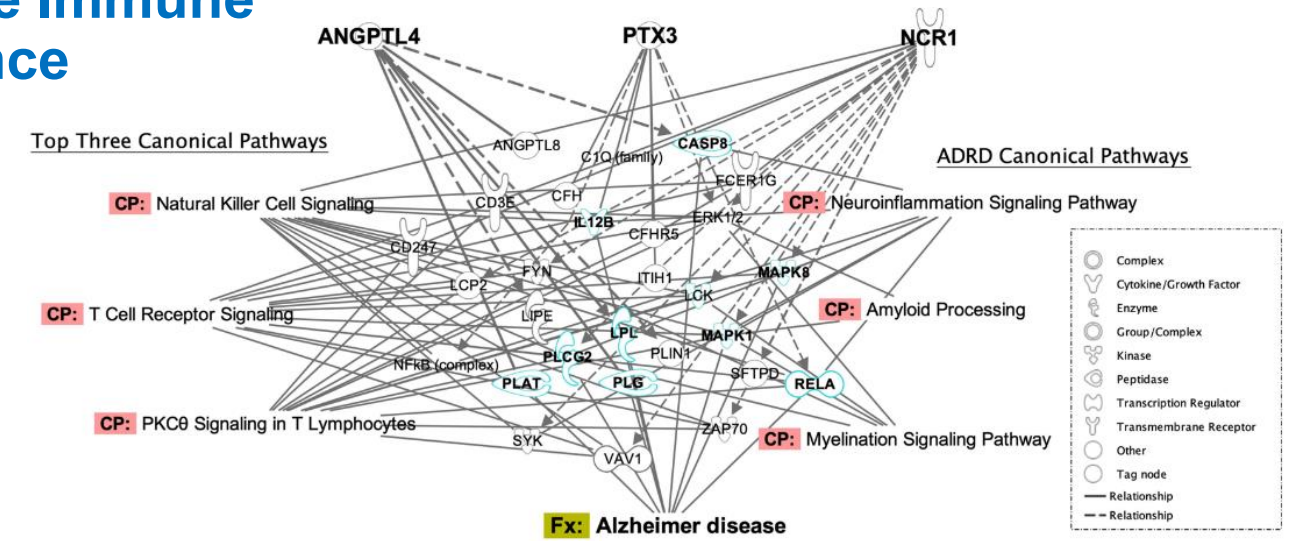


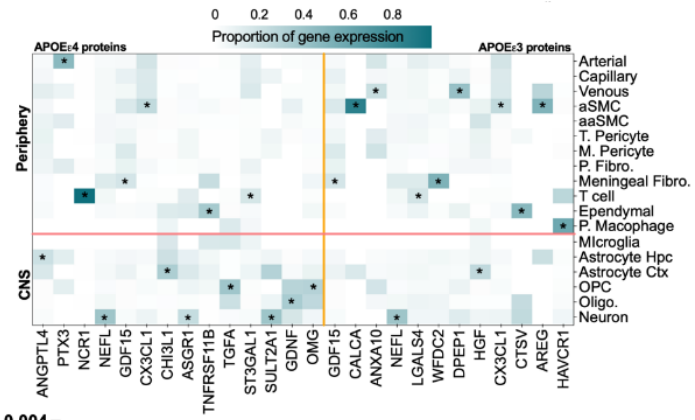
Walker et al. (2024). *Molecular Neurodegeneration*

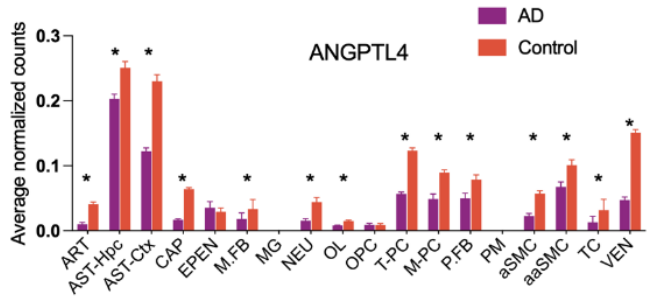
Protein Interaction Networks Implicate Immune Biology in APOEe4 Cognitive Resilience

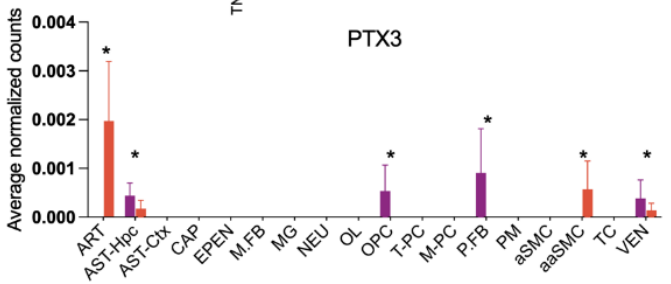


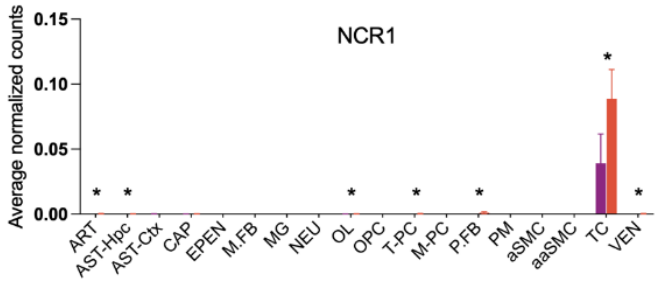
Network functional enrichment
Regulation of chronic inflammatory response (GO-BP)
COVID-19 adverse outcomes pathway (Wikipathways)
Matrix metalloproteinases (Wikipathways)
Cytokine and inflammatory response (Wikipathways)











Walker et al. (2024). *Molecular Neurodegeneration*

Acknowledgements

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75N92021D00005.

Blood-based Alzheimer's biomarker and dementia risk in the Women's Health Initiative

Michelle M. Mielke, PhD
Chair, Department of Epidemiology and Prevention
Director, Real-world Advocate DAta for Research (RADAR)
Professor, Epidemiology and Prevention
Professor, Gerontology and Geriatric Medicine
Women's Health Initiative: May 1, 2025

Wake Forest University
School of Medicine

ADVOCATE
HEALTH

Disclosures

- *Research funding*: NIH/NIA, Department of Defense, Alzheimer's Association, Davos Alzheimer's Consortium

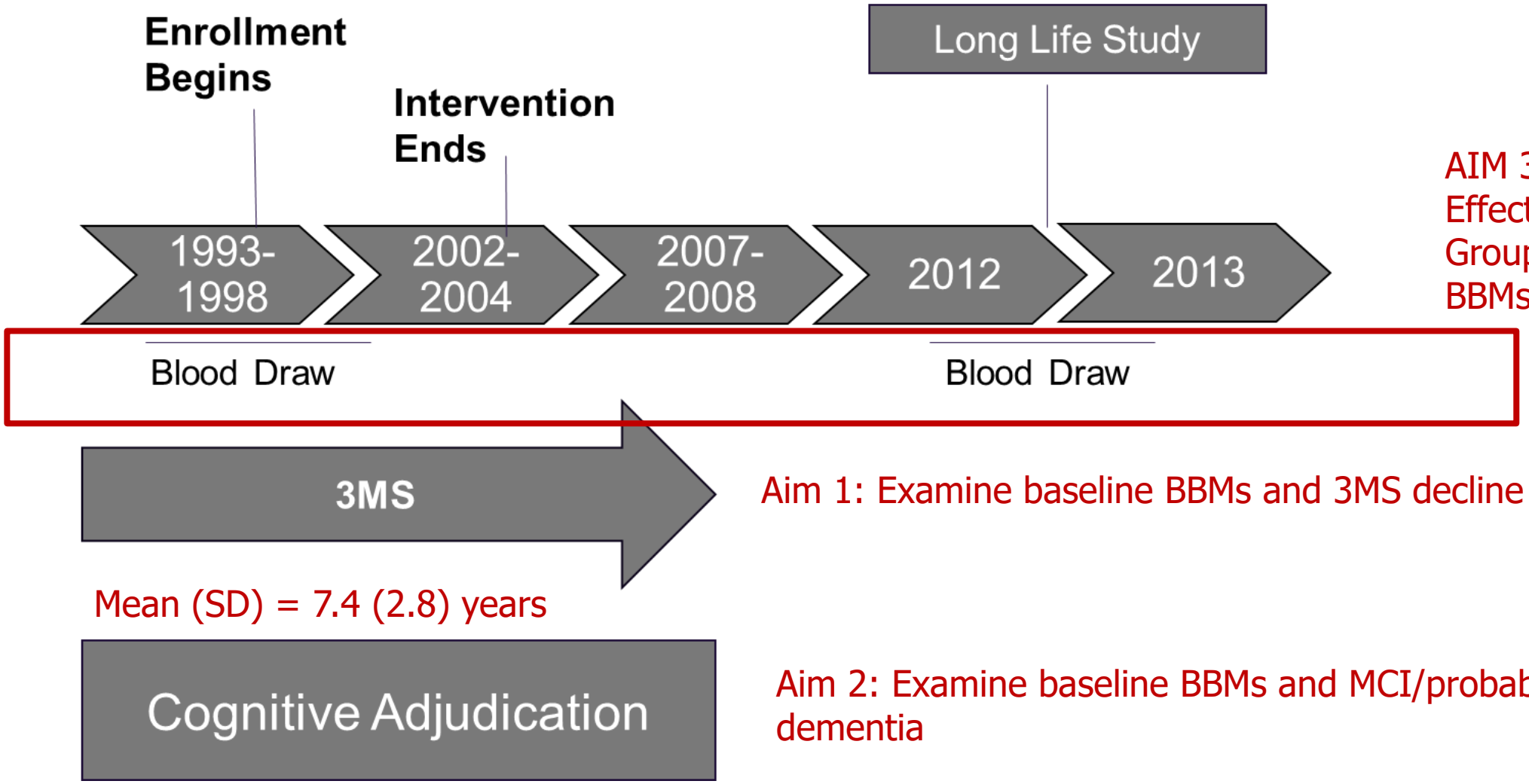
- *Senior Editor*: Alzheimer's Research and Therapy, Alzheimer's & Dementia

- *Consultant/Advisory Board*: Althira, Beckman Coulter, Biogen, Cognito Therapeutics, Eisai, LabCorp, Lilly, Merck, Novo Nordisk, Roche, Siemens Healthineers

Background

- Several studies have suggested that blood-based biomarkers (BBMs) of Alzheimer' disease (AD) and related dementias (ADRD) are indicative of ADRD brain pathology; clinically available to aid in the diagnosis
  - Low Aβ42/40 ratio and high phosphorylated tau 181 (P-tau181) indicators of amyloid pathology
  - Neurofilament light (NfL) is a non-specific biomarker of neurodegeneration
  - Glial fibrillary acidic protein (GFAP) is a marker of astrocyte reactivity and inflammation
- PET/CSF not feasible in large-scale studies so assessment of BBMs provide opportunity of assessing ADRD pathology and risk & protective factors that contribute to pathological changes
  - Additional studies needed on community-based participants with multiple chronic conditions, particularly for women
- Studies of hormone therapy (HT) or menopausal symptoms with cognitive impairment, dementia, and AD pathology are mixed and depend on study design
- Previous studies assessing the effect of HT on ADRD BBMs have small sample sizes
  - Previous studies of HT use and AD Biomarkers have been small

Timeline for current analyses using WHIMS



AIM 3: Effects of HT Group on BBMs

Aim 1: Examine baseline BBMs and 3MS decline

Mean (SD) = 7.4 (2.8) years

Aim 2: Examine baseline BBMs and MCI/probable dementia

Methods

- Linear mixed models to examine associations between baseline BBMs and 3MSE
  - 3 models
  - Excluded those with eGFR<60 in sensitivity analyses
  - Interactions with HT group, *APOE*, age
- Cox Proportional Hazards Models to examine association between baseline BBMs and incident MCI and probable dementia
  - Outcomes assessed together and separate
- LS Mean (95% CI) to examine change in BBMs by baseline HT group
- Used Inverse Probability Weighting (IPW)

Comparison of baseline characteristics for those with and without Alzheimer's blood-based biomarkers

Characteristic	AD Blood Biomarkers (N=2467)	Missing Blood Biomarkers (N=5012)	Overall (N=7479)	p-value
Age, y	71.10 (3.78)	70.93 (3.87)	70.99 (3.84)	0.065
Race/Ethnicity*				<0.0001
American Indian/Alaskan	2 (0.1)	24 (0.5)	26 (0.3)	
Asian/Pacific Islander	12 (0.5)	115 (2.3)	127 (1.7)	
Black/African American	180 (7.3)	355 (7.1)	535 (7.2)	
Hispanic/Latino	36 (1.5)	143 (2.9)	179 (2.4)	
White	2219 (90.1)	4274 (85.5)	6493 (87.0)	
Other	14 (0.6)	89 (1.8)	103 (1.4)	
Education, y				<0.0001
<13 years	681 (27.6)	1542 (30.9)	2223 (29.8)	
13-16 years	1180 (47.8)	2435 (48.8)	3615 (48.5)	
>16 years	606 (24.6)	1014 (20.3)	1620 (21.7)	
APOE E4 carrier	699/2232 (31.3%)	818/4074 (20.1%)	1517/6306 (24.1%)	<0.0001
BMI, kg/m2	28.3 (5.5)	28.6 (5.8)	28.5 (5.7)	0.061
eGFR	83.7 (12.6)	83.5 (13.5)	83.6 (13.4)	0.444
Hypertension	1177 (47.7)	2551 (50.9)	3728 (49.9)	0.009
Diabetes	172 (7.0)	454 (9.1)	626 (8.4)	0.002
CVD History	137 (5.6%)	345 (6.9%)	482 (6.4%)	0.028
Randomization Arm				0.070
E-alone Active	475 (19.3)	989 (19.7)	1464 (19.6)	
E-alone Placebo	470 (19.1)	1013 (20.2)	1483 (19.8)	
E+P Active	784 (31.8)	1445 (28.8)	2229 (29.8)	
E+P Placebo	738 (29.9)	1565 (31.2)	2303 (30.8)	

Associations of baseline blood biomarker z-scores and change in 3MS

	Model 1		Model 2		Model 3	
	b(95% CI)	*p-value*	*b(95% CI)*	*p-value*	*b(95% CI)*	*p-value*
Aβ42/40	0.20 (0.06, 0.33)	0.0061	0.18 (0.04, 0.32)	0.0118	0.18 (0.04, 0.32)	0.0103
PTau181	-0.27 (-0.39, -0.15)	<.0001	-0.27 (-0.39, -0.15)	<.0001	-0.27 (-0.39, -0.15)	<.0001
GFAP	-0.48 (-0.66, -0.31)	<.0001	-0.52 (-0.70, -0.34)	<.0001	-0.52 (-0.69, -0.34)	<.0001
NfL	-0.36 (-0.53, -0.19)	<.0001	-0.39 (-0.58, -0.21)	<.0001	-0.40 (-0.58, -0.22)	<.0001

Model 1 adjusts for age, education, and APOE

Model 2 adjusts for variables in Model 1 and race/ethnicity, diabetes, hypertension, alcohol use, BMI, and eGFR

Model 3 adjusts for variables in Model 2 and HRT randomization group

Associations of baseline blood biomarker z-scores and incident MCI/probable dementia

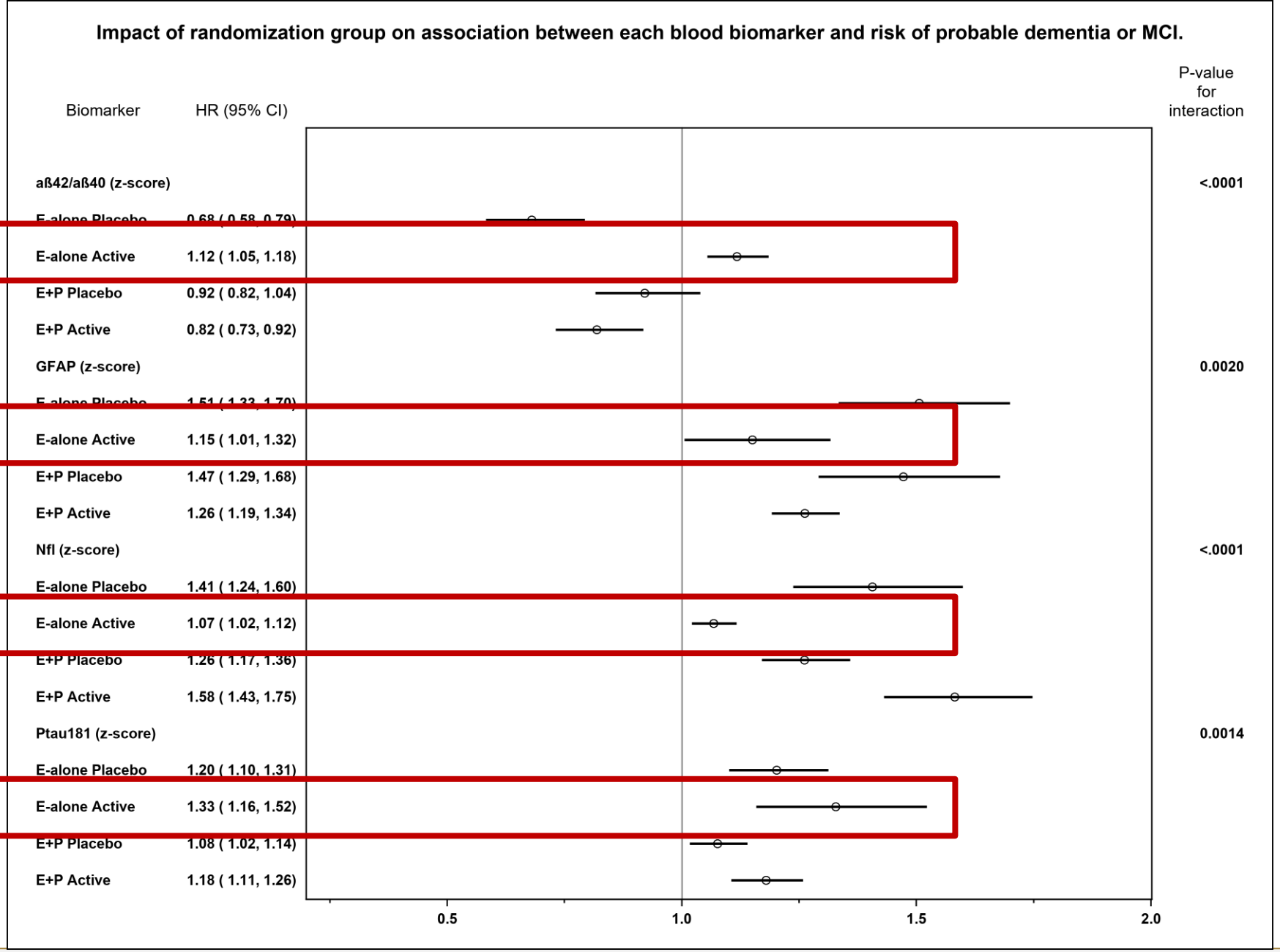
			Model 1		Model 2		Model 3	
	events	person-yrs	*HR (95% CI)*	*p-value*	*HR (95% CI)*	*p-value*	*HR (95% CI)*	*p-value*
Aβ42/40	461	19,792.36	0.94 (0.88, 0.99)	0.0166	0.96 (0.91, 1.01)	0.1257	0.96 (0.91, 1.01)	0.1286
PTau181	467	20,267.68	1.11 (1.08, 1.14)	<0.0001	1.11 (1.08, 1.14)	<0.0001	1.11 (1.08, 1.15)	<0.0001
GFAP	461	19,833.95	1.22 (1.17, 1.26)	<0.0001	1.27 (1.22, 1.32)	<0.0001	1.27 (1.22, 1.32)	<0.0001
NfL	461	19,823.01	1.10 (1.07, 1.12)	<0.0001	1.10 (1.08, 1.12)	<0.0001	1.10 (1.08, 1.12)	<0.0001

Model 1 adjusts for age, education, and APOE

Model 2 adjusts for variables in Model 1 and race/ethnicity, diabetes, hypertension, alcohol use, BMI, and eGFR

Model 3 adjusts for variables in Model 2 and HRT randomization group

Impact of randomization group on association between each blood biomarker and risk of probable dementia or MCI.



Relationship between HT group and change in BBMs

	LS Mean (95% CI)				
	E-alone Active	**E-alone Placebo**	**E+P Active**	**E+P Placebo**	**p-value**
AB42/40 ratio	-0.00 (-0.01, 0.00)	-0.00 (-0.01, -0.00)	-0.00 (-0.01, -0.00)	-0.00 (-0.01, -0.00)	0.602
GFAP	99.26 (78.32, 120.20)	99.51 (79.97, 119.10)	97.73 (77.04, 118.40)	93.46 (73.63, 113.30)	0.795
NfL	17.72 (10.87, 24.57)	19.14 (12.75, 25.53)	17.88 (11.11, 24.64)	19.66 (13.17, 26.15)	0.839
P-tau181	2.30 (1.12, 3.49)	2.52 (1.41, 3.63)	2.09 (0.91, 3.28)	2.26 (1.13, 3.39)	0.792

Models adjust for age, education, APOE, race/ethnicity, diabetes, hypertension, alcohol use, BMI, and eGFR

Discussion

- Among women (mean age of 70) enrolled in WHIMS, increasing GFAP, NfL, and P-tau181 associated with greater 3MSE decline and risk of MCI/probable dementia over ~7.4 year follow-up
  - GFAP was strongest predictor

- Interactions between BBMs and HT group in relation to cognitive outcomes
  - Results not completely clear; potential for differential effects on biomarkers/pathways

- All BBMs increased over time; no effect of HT

Thank you !!

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Aging SIG

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