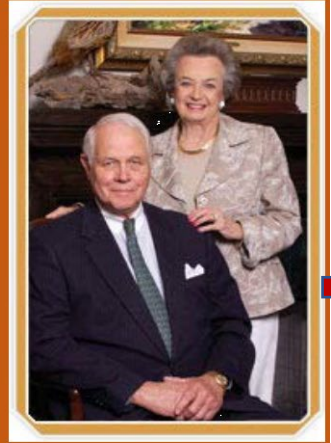
Aging, Resilience, Multimorbidity & Dementia in Oldest-Old

Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases



Mission: *Prevention, Care, Cure for Dementia in South Texas and Beyond*
Core Values: *Caring, Creativity, Collaboration, Humility*

https://biggsinstitute.org/

SOUTH TEXAS ALZHEIMER'S DISEASE RESEARCH CENTER

UT Health San Antonio
Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases

UT Health San Antonio
Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases

UTRGV
UT Health Rio Grande Valley

BOSTON UNIVERSITY

Sudha Seshadri, MD

Director, Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases
Senior Investigator, The Framingham Heart Study

NIA: P30AG066546 U01 AG058589, R01 AG066524, AG061872, AG063507, R56 AG074467, U01 AG052409, RF1 AG059421, AG058464
NINDS: UF1 NS125513, R01 AG017950, UH3 NS100605,
NHLBI, NIDDK, Alzheimer Association, ADDF
Consulted for Biogen, Eisai

Molecular Epidemiology and Big Data for Dementia Research

Date: Friday 10 November 2023

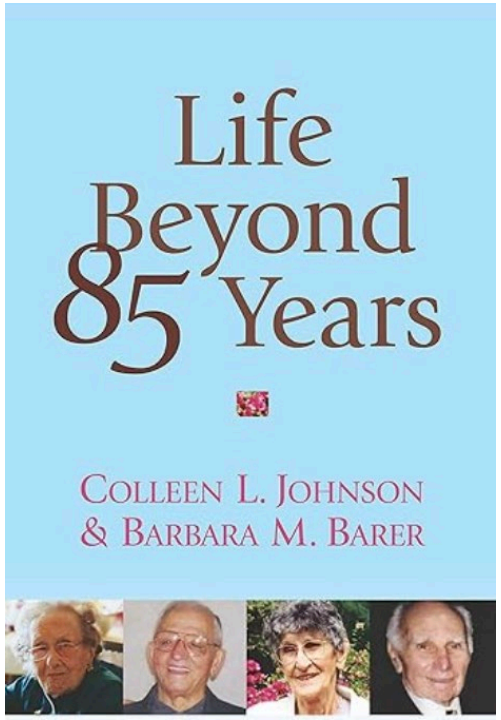
UK Dementia Research Institute
Imperial College London

Founding funders:
UKRI Medical Research Council
Alzheimer's Society
Alzheimer's Research UK

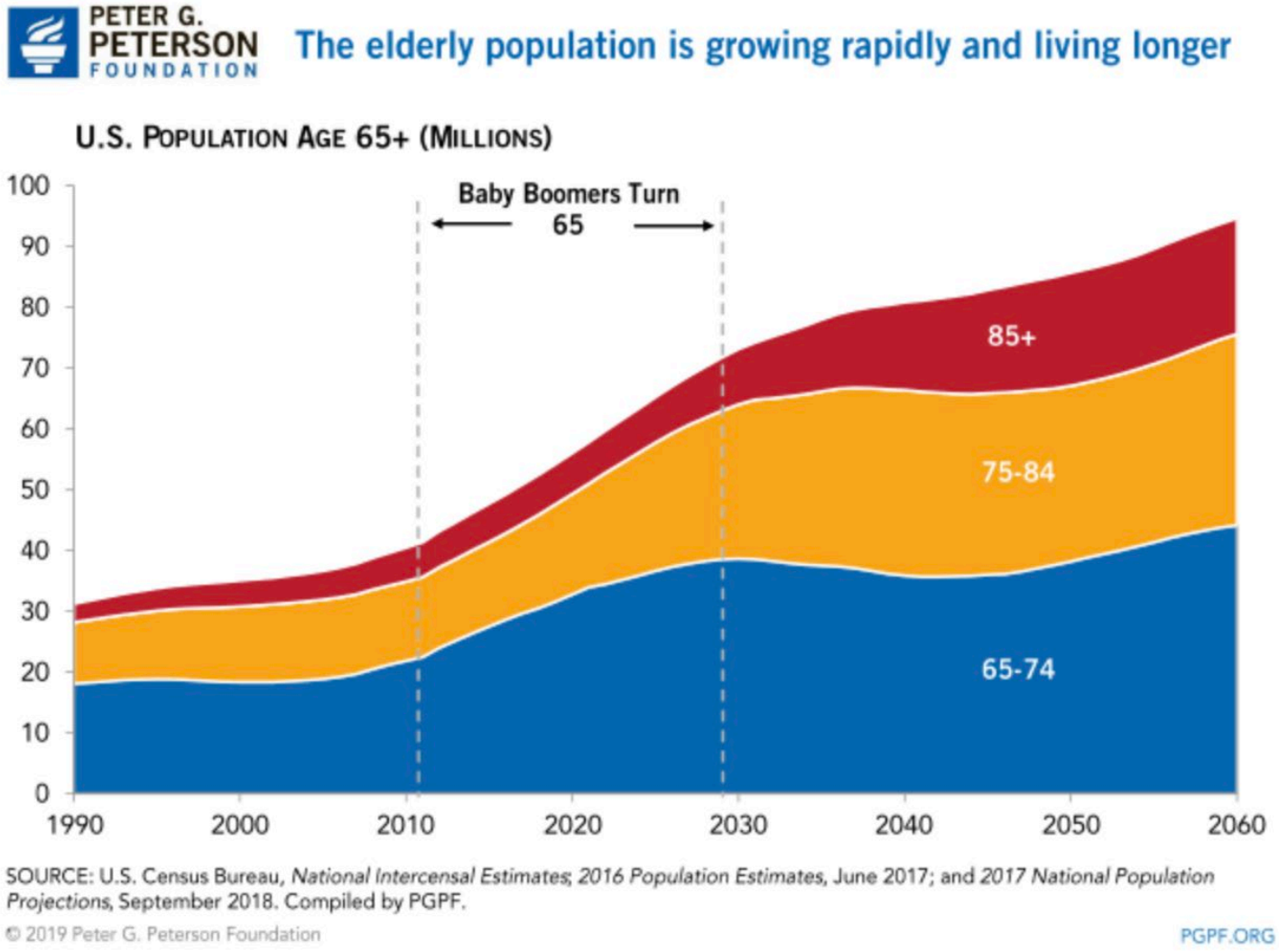
Outline

- Why is **Dementia in the 'Oldest-Old'** Important to Study?
- What do we know about **Biology** of Dementia in Oldest-Old?
- **Prevention:** Life Course Risk Factors, Multimorbidity
- **Promotion of Brain Health:** Biomarkers, Resilience Factors, Genetics

Fastest Growing Demographic



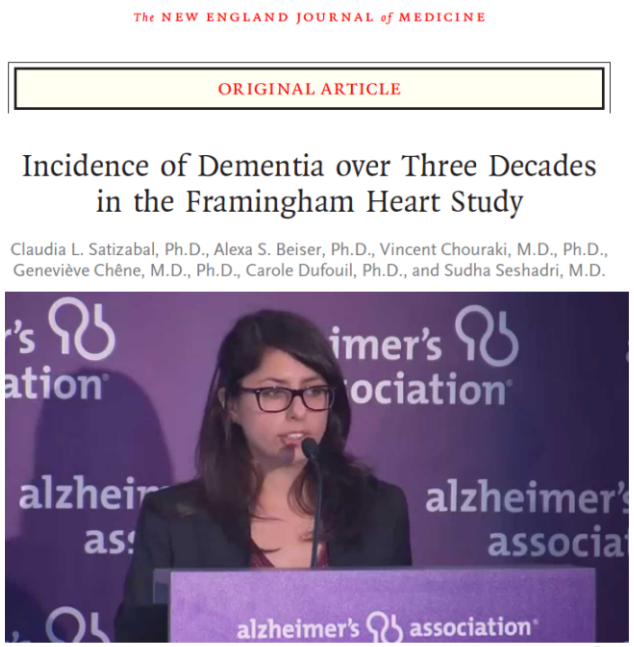
‘Oldest-old’ Persons over age 80, 85 or 90

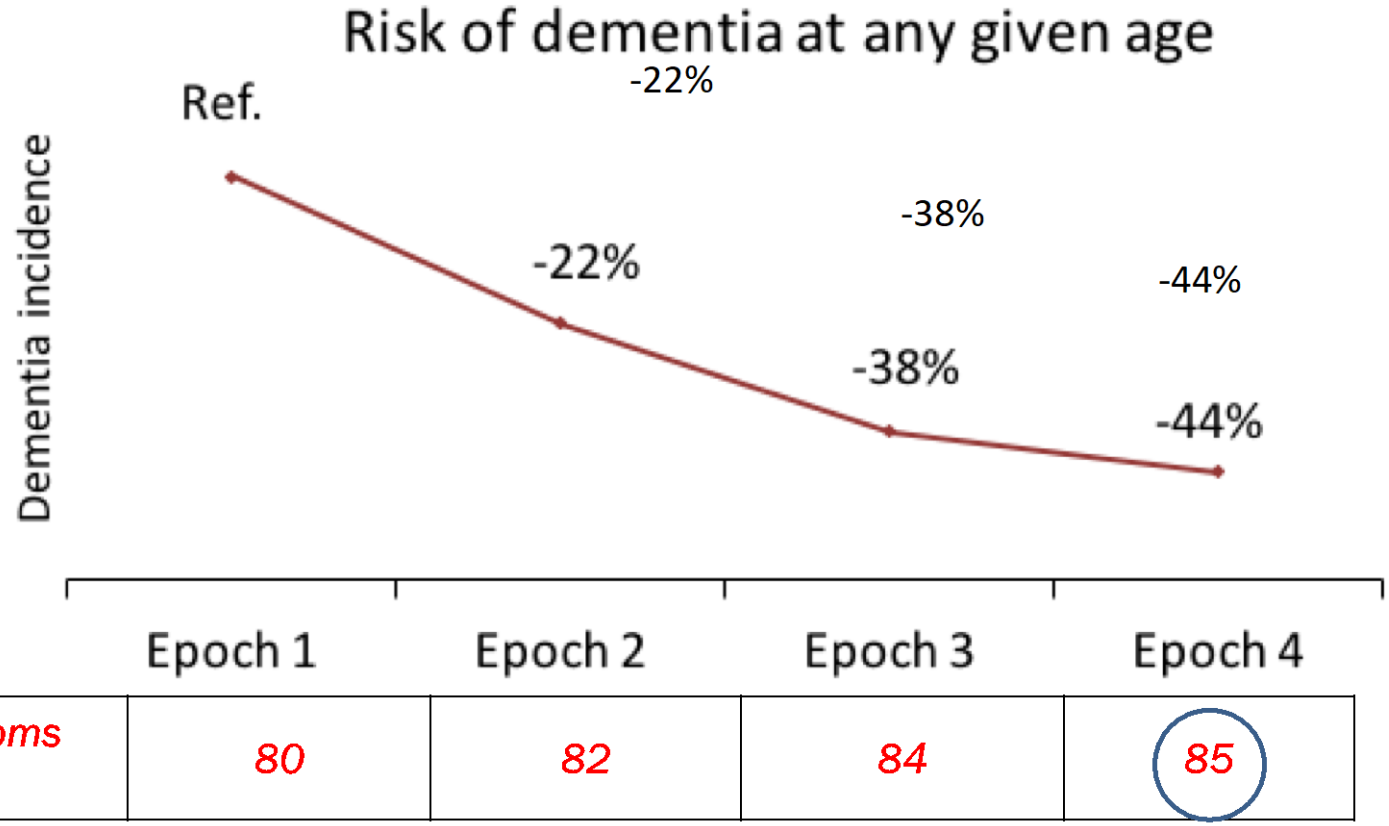


By 2030 one in two persons with dementia will be over age 85 at onset

Clinical Dementia is manifesting at an older age

Average Age at which symptoms of dementia develop has increased from 80 to 85 years





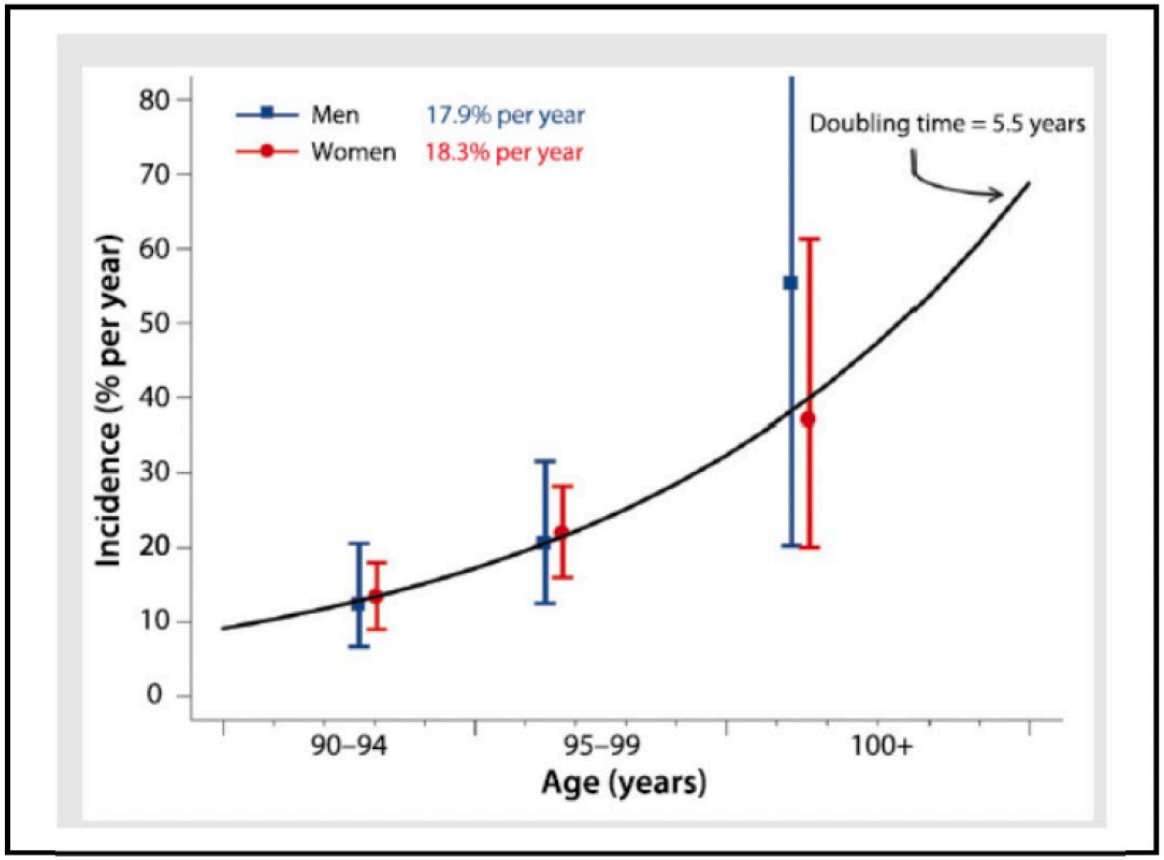
Mean age when symptoms began, in years	*80*	*82*	*84*	*85*

Satizabal et al; NEJM 2016, PMID: 26863354

Why Is Dementia in the Oldest-Old Important to Study?

- 5-year incidence of dementia rises exponentially, doubling every 5 years till age 90

- **Data from the 90+ suggests that risk continues to increase thereafter**

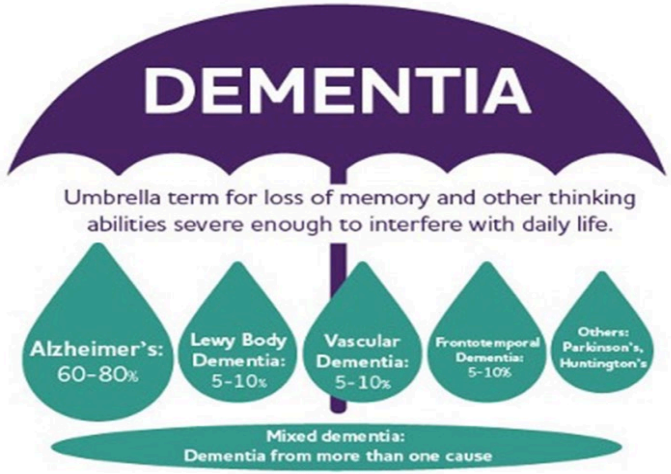


Oldest old are group with the least informal supports, and highest costs per patient

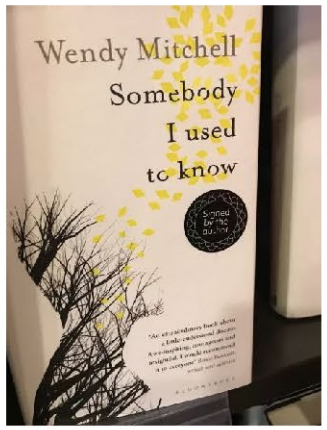
Outline

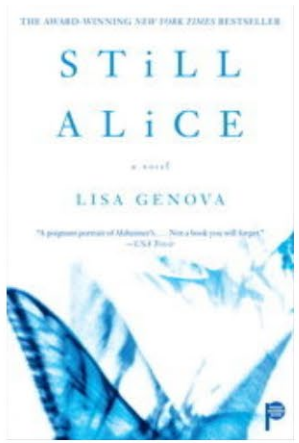
- Why is Dementia in the ‘Oldest-Old’ Important to Study?
- What do we know about Biology of Dementia in Oldest-Old?
- Prevention: Life Course Risk Factors, Multimorbidity
- Promotion of Brain Health: Biomarkers, Resilience Factors, Genetics

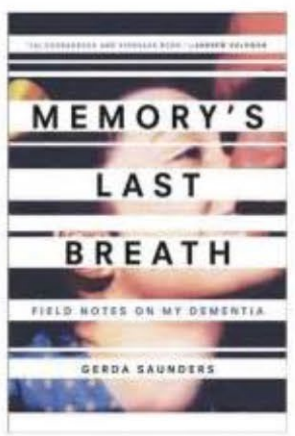
What is Dementia?



- A syndrome
- Loss of memory and thinking abilities or changes in behavior
- Affects the person's ability to function as they used to and wish to







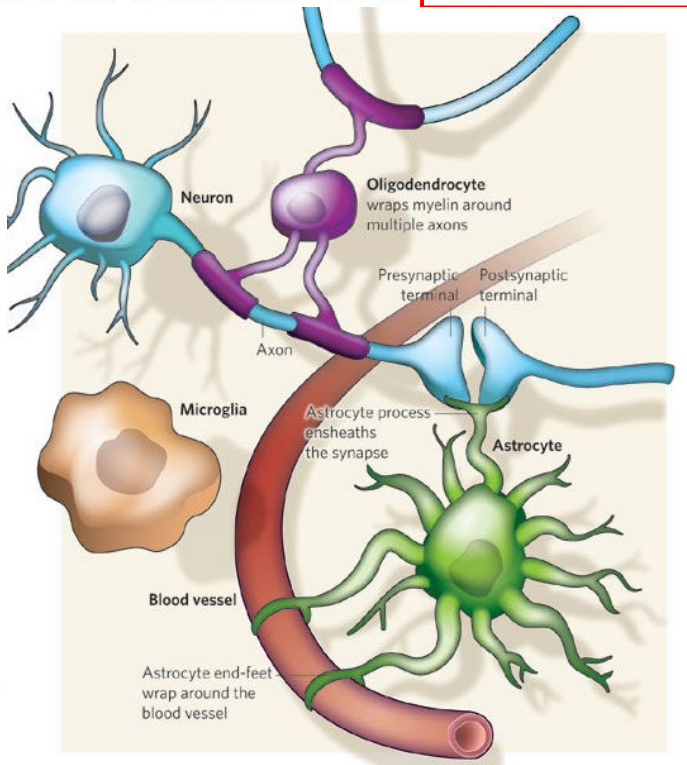
William Utermohlen:

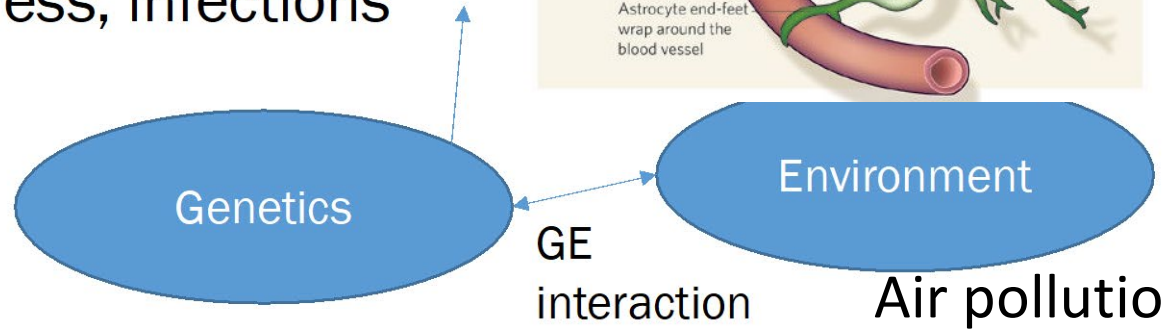
Self potraits; dementia diagnosis at age 61, 1995

What Causes Dementia?

Lifelong

- Things that injure the brain overcome it's resilience/reserve
  - Neurodegenerative Diseases
  - Vascular Brain Injury
  - Age, inflammation
  - Trauma, stress, infections

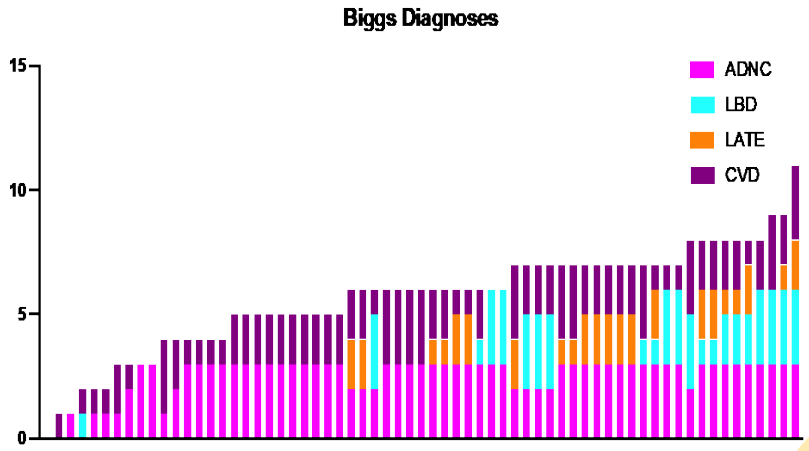




Alzheimer Disease
Dementia with Lewy Bodies
Frontotemporal Dementia
CTE, TBI, Epilepsy, Drugs
TDP-43/LATE
PART, AGD
Vascular VCID/Stroke

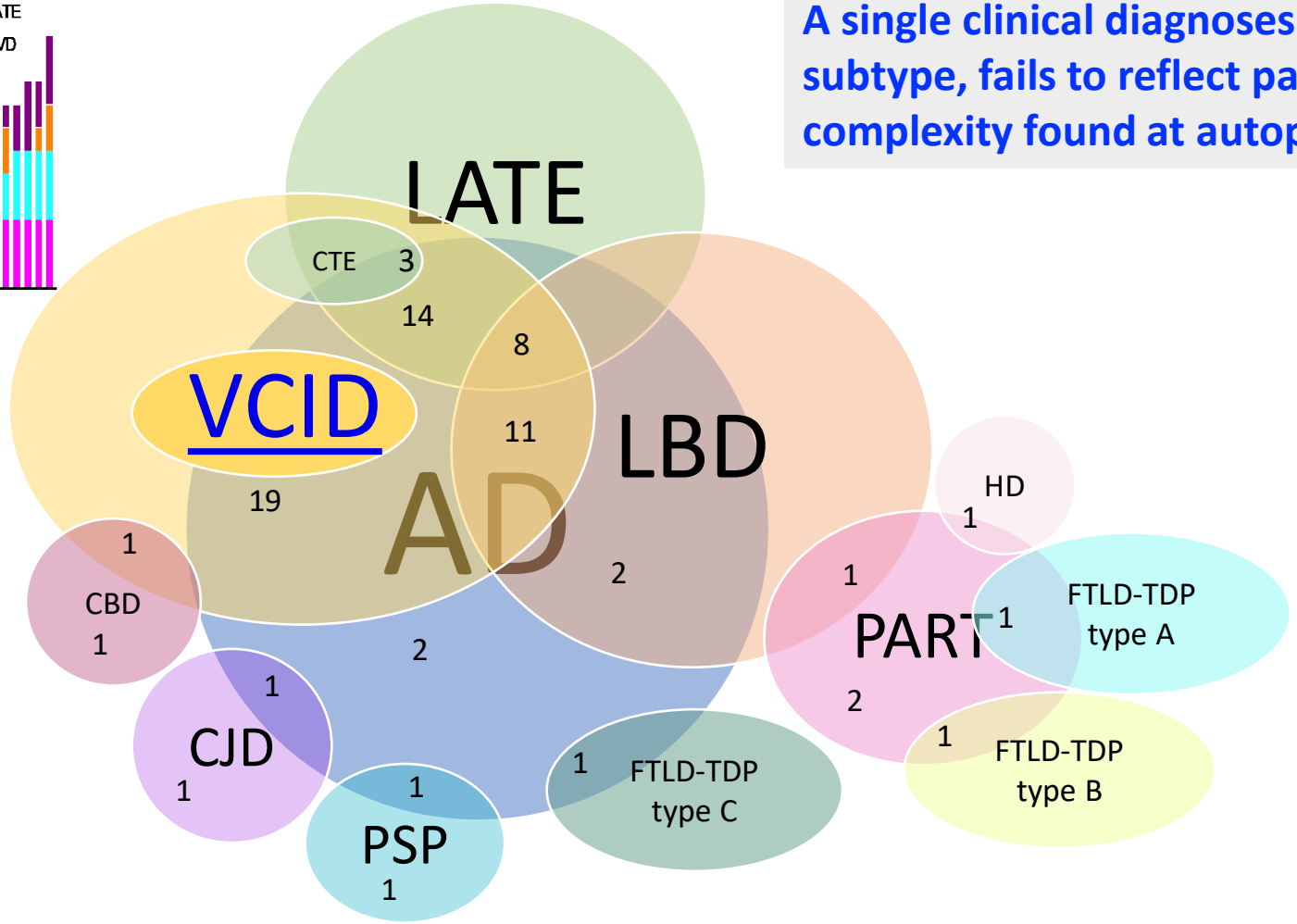
Parkinson's disease
PSP, CBD
Huntington's
MSA, Ataxias
ALS/FTD
COVID
Adult Presentations of NDD
Immuno-inflammatory

AD, VCID (>90%)
DLB, LATE (30%)



Biggs Institute/South Texas ADRC Brain Bank

A single clinical diagnoses of dementia subtype, fails to reflect pathologic complexity found at autopsy



Need biomarkers of various types of dementia

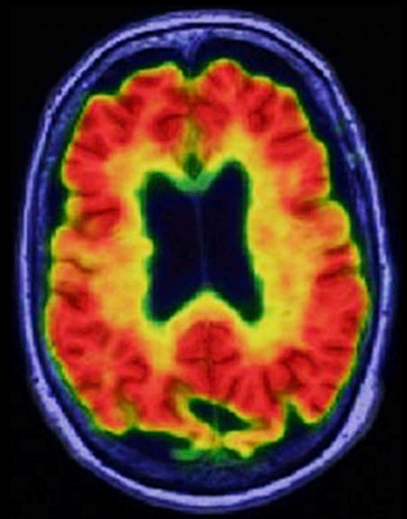
First 141 cases

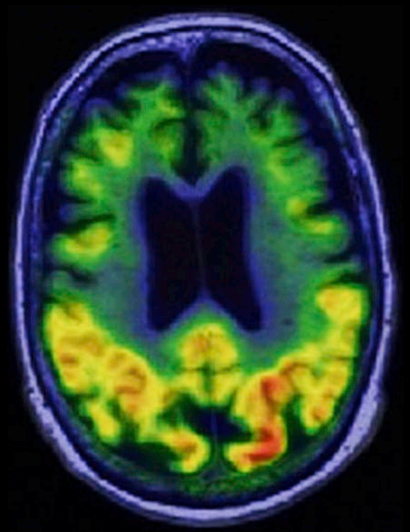
Multiple Etiology Dementia is the Most Common Type

2018 ATN Alzheimer Disease Criteria

Amyloid+

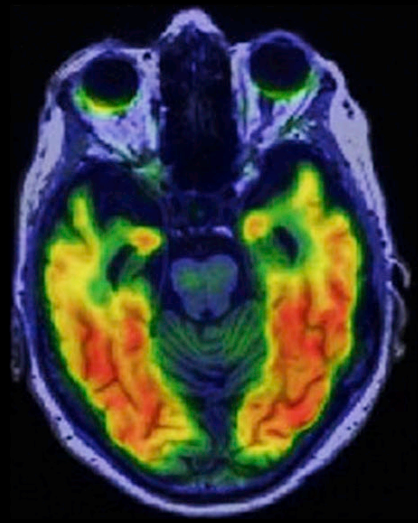
A+ (amyloidosis) = preclinical, prodromal or clinical Alzheimer

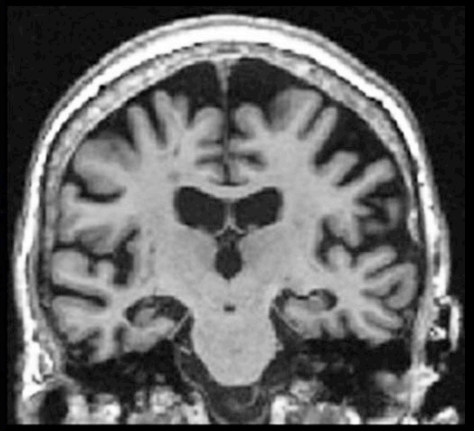




Tau +

Tau +





Neurodegeneration+

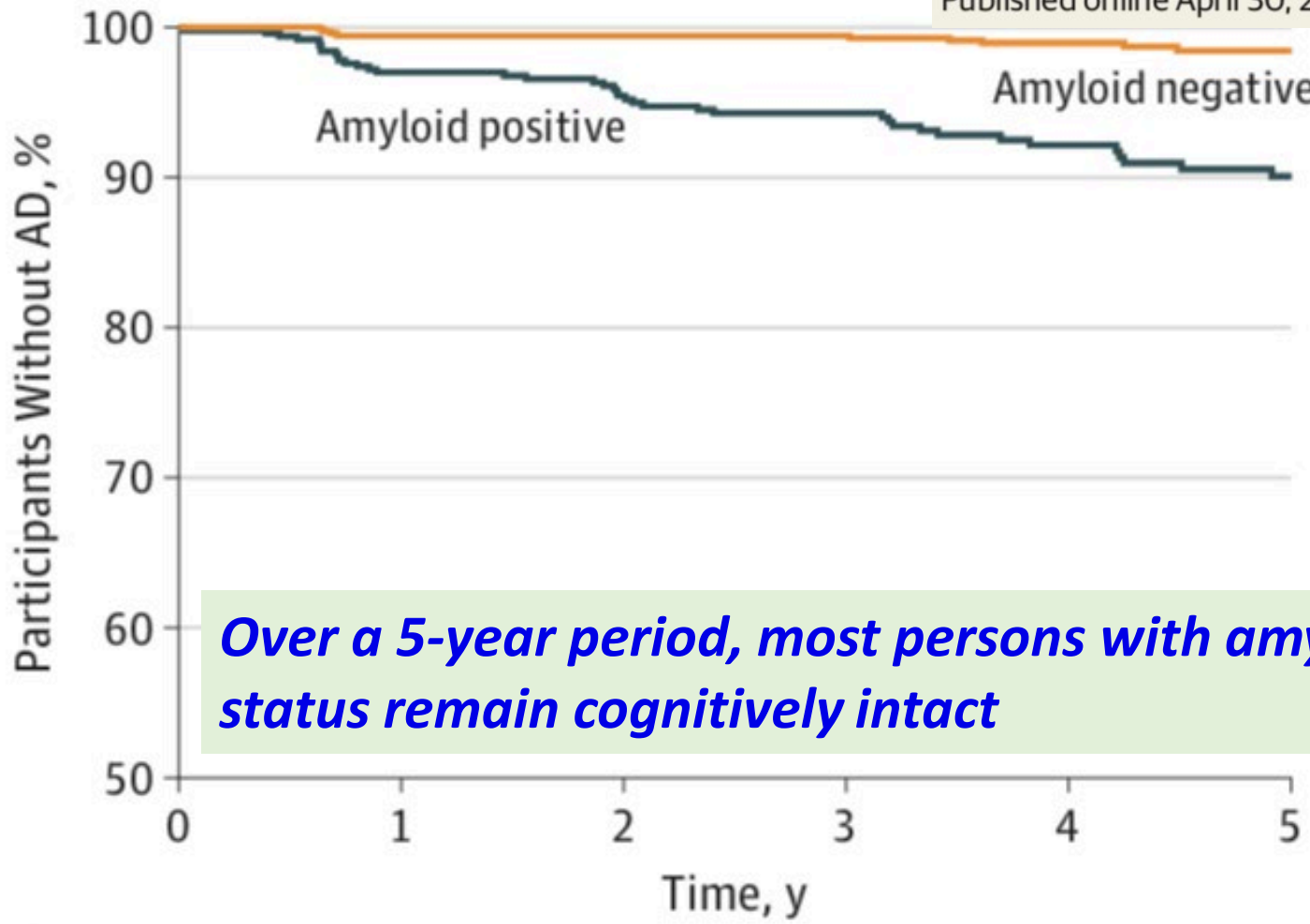
Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2018 14, 535-562DOI: (10.1016/j.jalz.2018.02.018)

Draft 2023 'AD' Criteria; adds V, I and S

Biomarker category	fluid	imaging
Core Biomarkers		
A (Ab proteinopathy)	Ab42/40	Amyloid PET
T (AD tau proteinopathy)	ptau 181, 217	Tau PET
Non - specific biomarkers of tissue reaction involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MR, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD co-pathology		
V vascular brain injury		Anatomic infarction, WMH, abundant dilated perivascular spaces
S α-synuclein	αSyn-SAA*	

Percentage of participants with no cognitive impairment or aMCI without AD dementia over time

JAMA Neurol. 2018;75(8):970-979. doi:10.1001/jamaneurol.2018.0629
Published online April 30, 2018.



No. at risk (events)

Amyloid positive	520 (0)	481 (15)	420 (22)	334 (27)	248 (34)	193 (39)
Amyloid negative	1110 (0)	1048 (6)	903 (6)	669 (6)	418 (9)	294 (11)

Population prevalence of amyloid +ve status in Rochester, MN:

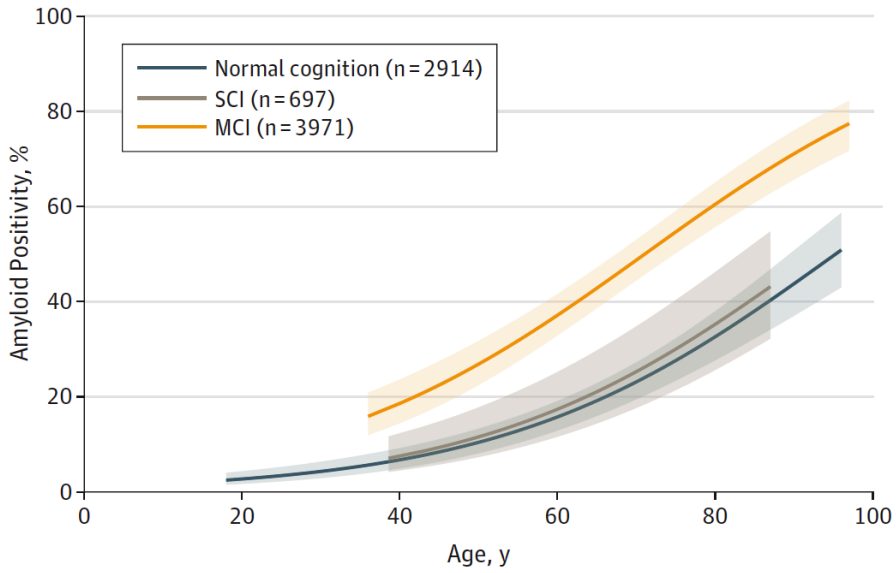
3% at 50-59
41% at 80-89

Over a 5-year period, most persons with amyloid positive status remain cognitively intact

Prevalence of Cerebral Amyloid Pathology in Persons Without Dementia
A Meta-analysis

Willemijn J. Jansen, MSc; Rik Ossenkoppele, PhD; Dirk L. Knol, PhD; Betty M. Tijms, PhD; Philip Scheltens, MD, PhD; Frans R. J. Verhey, MD, PhD; Pieter Jelle Visser, MD, PhD; and the Amyloid Biomarker Study Group

Figure 2. Association of Age With Prevalence Estimates of Amyloid Positivity According to Cognitive Status



The prevalence estimates were generated from generalized estimating equations. The model included age and cognitive status as predictors. Shading indicates 95% CIs; SCI, subjective cognitive impairment; MCI, mild cognitive impairment.

Cerebral amyloidosis is a strong predictor but not sufficient for dementia

Opinion

EDITORIAL

Prevention of Dementia—Thinking Beyond the Age and Amyloid Boxes

Sudha Seshadri, MD

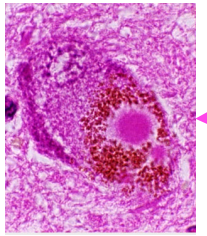
44% of 95-year-olds with normal cognition are amyloid positive

Dementia in Oldest-Old has

Additive or Synergistic Impact of Multiple Pathologies

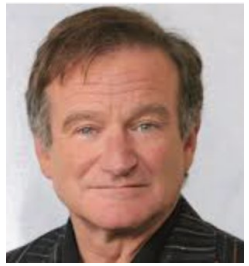
Which Pathologies are most common?

Dementia with Lewy Bodies (DLB)



Lewy body in neurons

- Attention, Executive Function
- Visuospatial Changes, Navigating



- Parkinsonism, falls
- Visual hallucinations
- Fluctuating Cognition, syncope

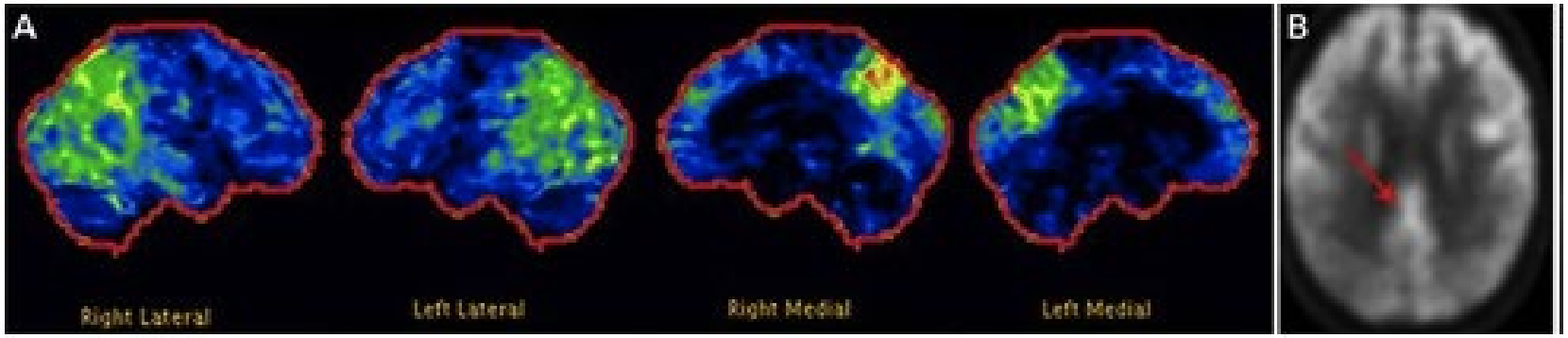
REM Sleep Behavior Disorder

Autonomic System Dysfunction

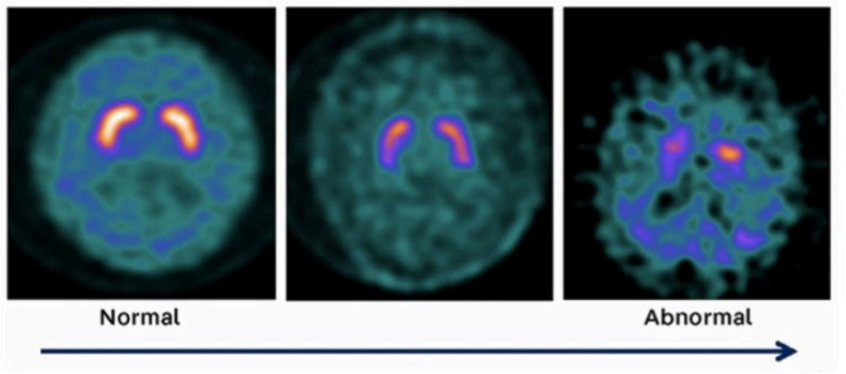
Anxiety and Mood Changes

Oversensitive to both Parkinson's and behavior medications

FDG-PET

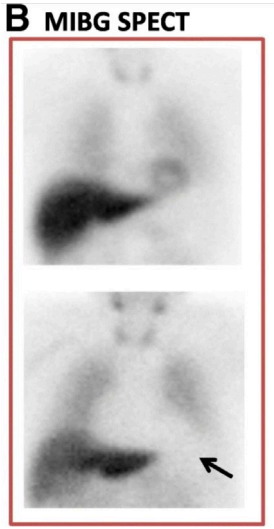


DAT Scans



Additional DLB Preclinical and Predictive Tests

- Cardiac MIBG
- Seed Amplification and RT-QuIC/PRMA tests in CSF



R. Kurapova et al. Experimental Gerontology 165 (2022) 111842

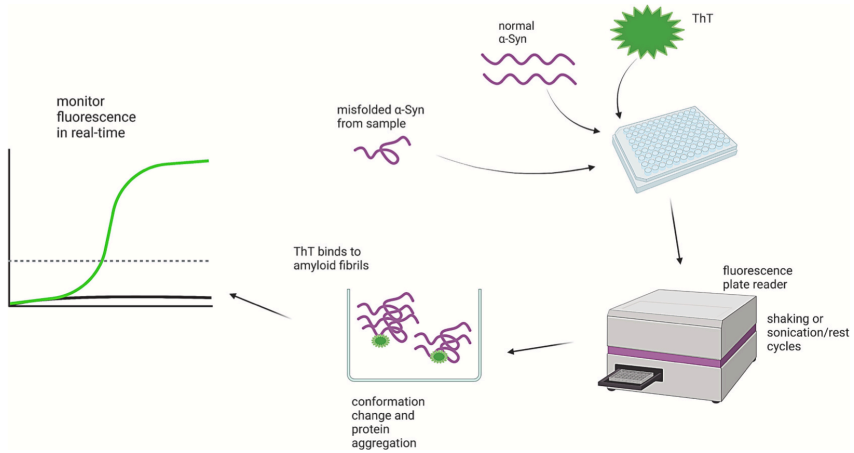
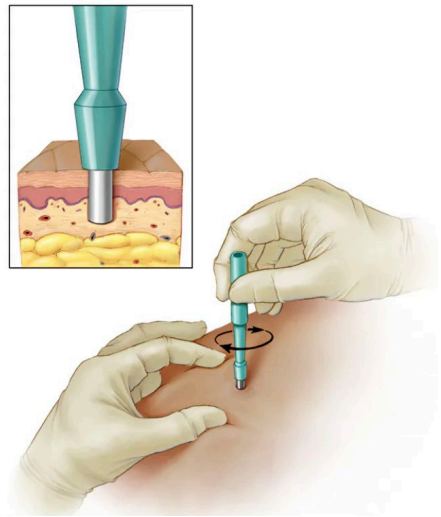
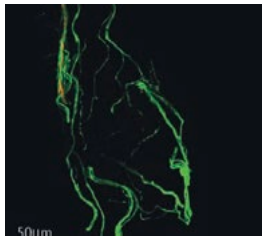


Fig. 1. The PMCA/RT-QuIC process: pathogenic (misfolded) α-syn protein is combined with normal α-syn protein and ThT. Shaking (RT-QuIC) or sonication/rest (PMCA) cycles induce prion-like propagation and amyloid fibril formation, which is measured in real-time with ThT fluorescence.

- Skin biopsy (lower sensitivity)



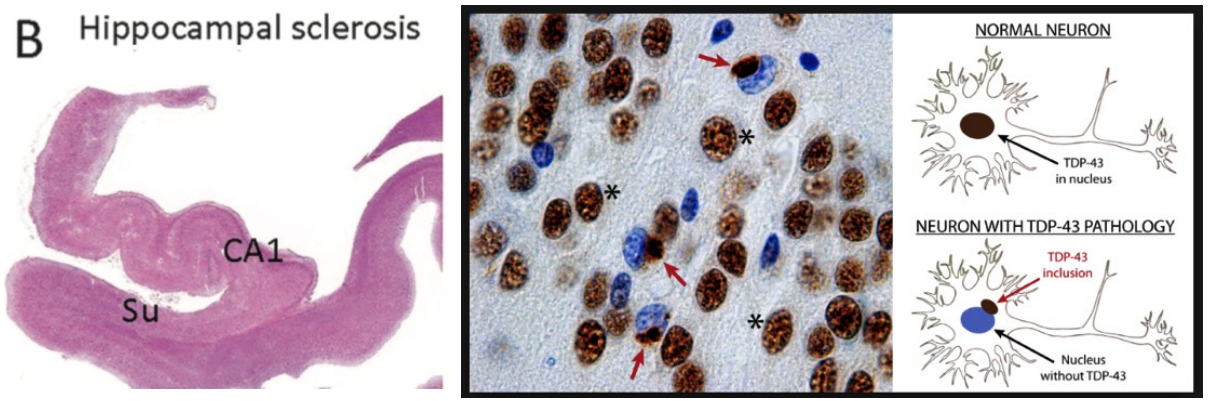


- REM (muscle) atonia on Sleep Study

Limbic Predominant, Age-Related, TDP-43 Encephalopathy

TDP-43 proteinopathy **LATE**

Limbic Predominant, **A**ge-Related, **T**DP-43 **E**ncephalopathy



Ann Neurol. 2007 May; 61(5): 435–445; Lancet Neurol, 2018; Brain 2019,

Older patients, slower decline, 30%

5 genes altering risk for LATE-NC:

- GRN, TMEM106B, ABCC9, KCNMB2, and APOE

TAR DNA-binding protein 43 is normally in nuclei

Under stress conditions moves to cytoplasm and forms stress granules

No good in vivo biomarker, but

In CHS at exam 5, plasma TDP-43 levels were higher in African-Americans

? possibly linked to higher stress

doi:10.1093/brain/awz099 BRAIN 2019: 142; 1503–1527 | 1503

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW

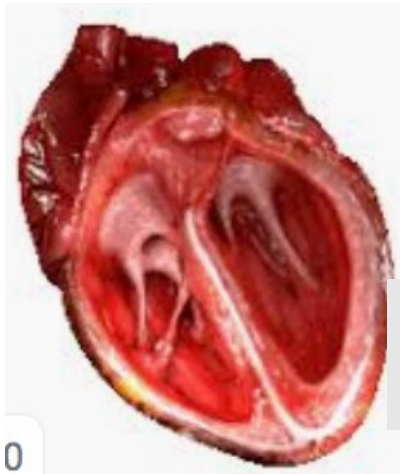
Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

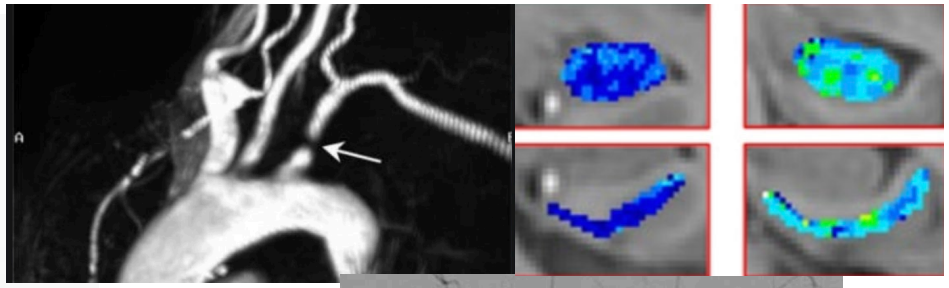
Peter T. Nelson,[1] Dennis W. Dickson,[2] John Q. Trojanowski,[3] Clifford R. Jack Jr.,[4] Patricia A. Boyle,[5] Konstantinos Arfanakis,[5,6] Rosa Rademakers,[2] Irina Alafuzoff,[7] Johannes Attems,[8] Carol Brayne,[9] Ian T.S. Coyle-Gilchrist,[9] Helena C. Chui,[10] David W. Fardo,[1] Margaret E. Flanagan,[11] Glenda Halliday,[12] Suvi R.K. Hokkanen,[9] Sally Hunter,[9] Gregory A. Jicha,[1] Yuriko Katsumata,[1] Claudia H. Kawas,[13] C. Dirk Keene,[14] Gabor G. Kovacs,[15] Walter A. Kukull,[14] Allan I. Levey,[16] Nazanin Makkinejad,[6] Thomas J. Montine,[17] Shigeo Murayama,[18] Melissa E. Murray,[2] Sukriti Nag,[5] Robert A. Rissman,[19] William W. Seeley,[20] Reisa A. Sperling,[21] Charles L. White III,[22] Lei Yu[5] and Julie A. Schneider[5]

Vascular Cognitive Impairment and Dementia

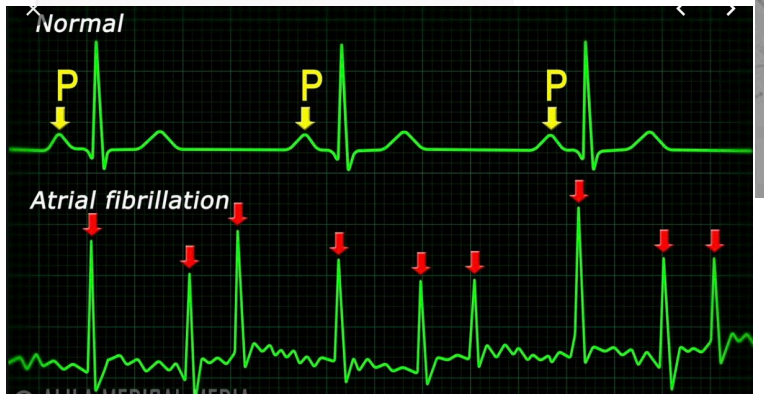
Heart or Blood Vessels, Blood & Blood Brain Barrier

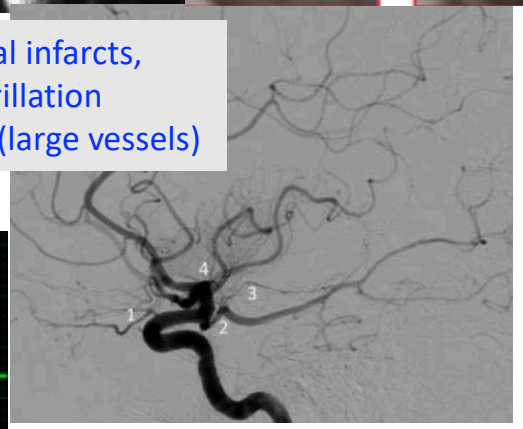
Vascular Risk Factors:
Hypertension, Diabetes, Smoking





Heart failure, Myocardial infarcts,
Valve disease, Atrial fibrillation
Carotid atherosclerosis (large vessels)

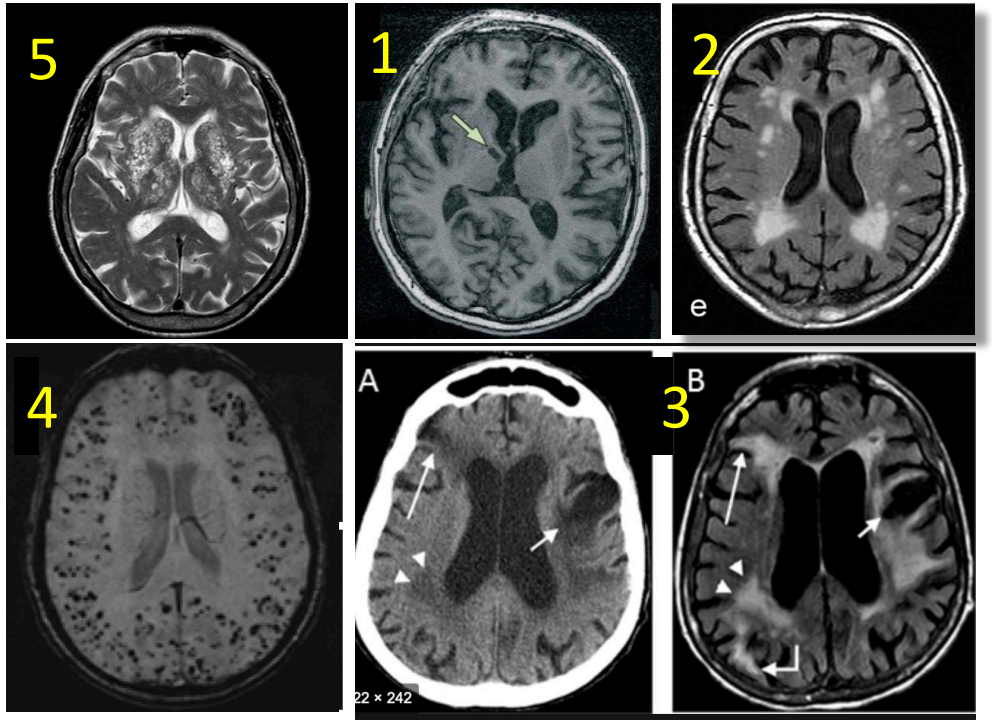




Arterial Stiff

Small arteries (arteriolosclerosis) and capillaries

Vascular Brain Injury



On CT or MRI seen as
(1) lacunes, (2) white matter hyperintensities,
(3) multiple strokes, (4) microbleeds (cerebral amyloid angiopathy (amyloid in small vessels)
(5) enlarged perivascular spaces

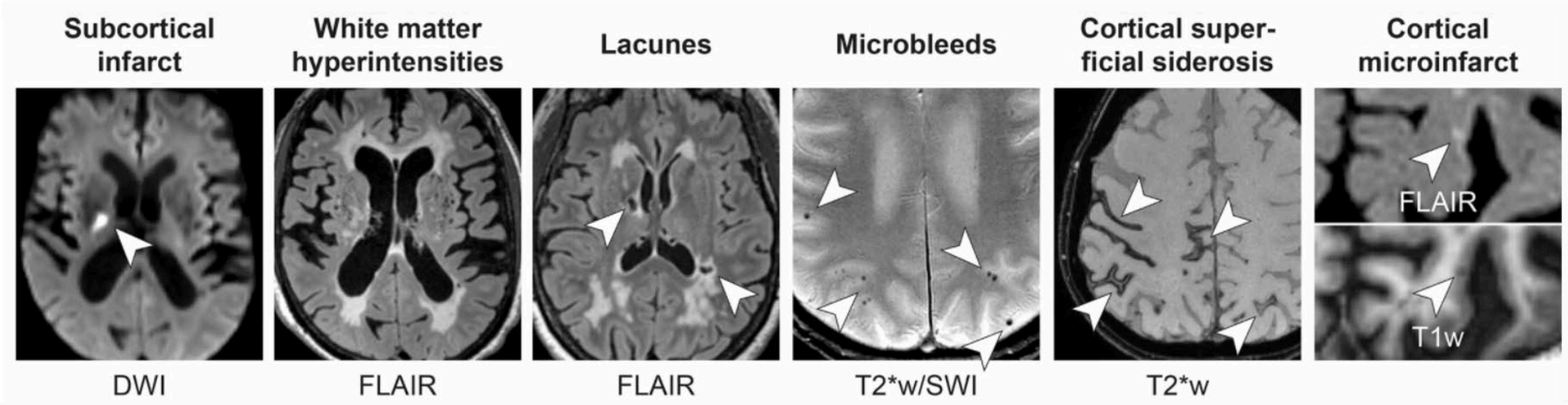
Vascular Cognitive Impairment (VCI)

Today's Inclusive Definition

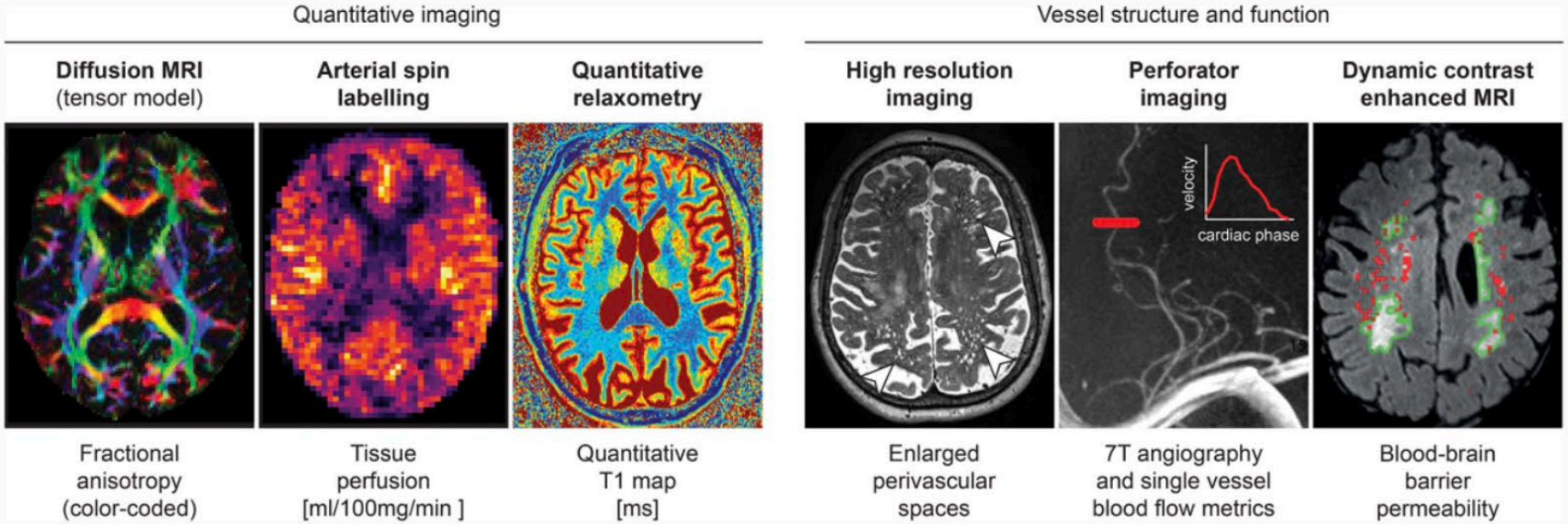
- Cognitive or behavioral problems
- Disease affecting blood vessels or blood flow to part or all of the brain
- Evidence of damage to part or all of brain due to vascular factors

Brain (MRI) Imaging
Others under development

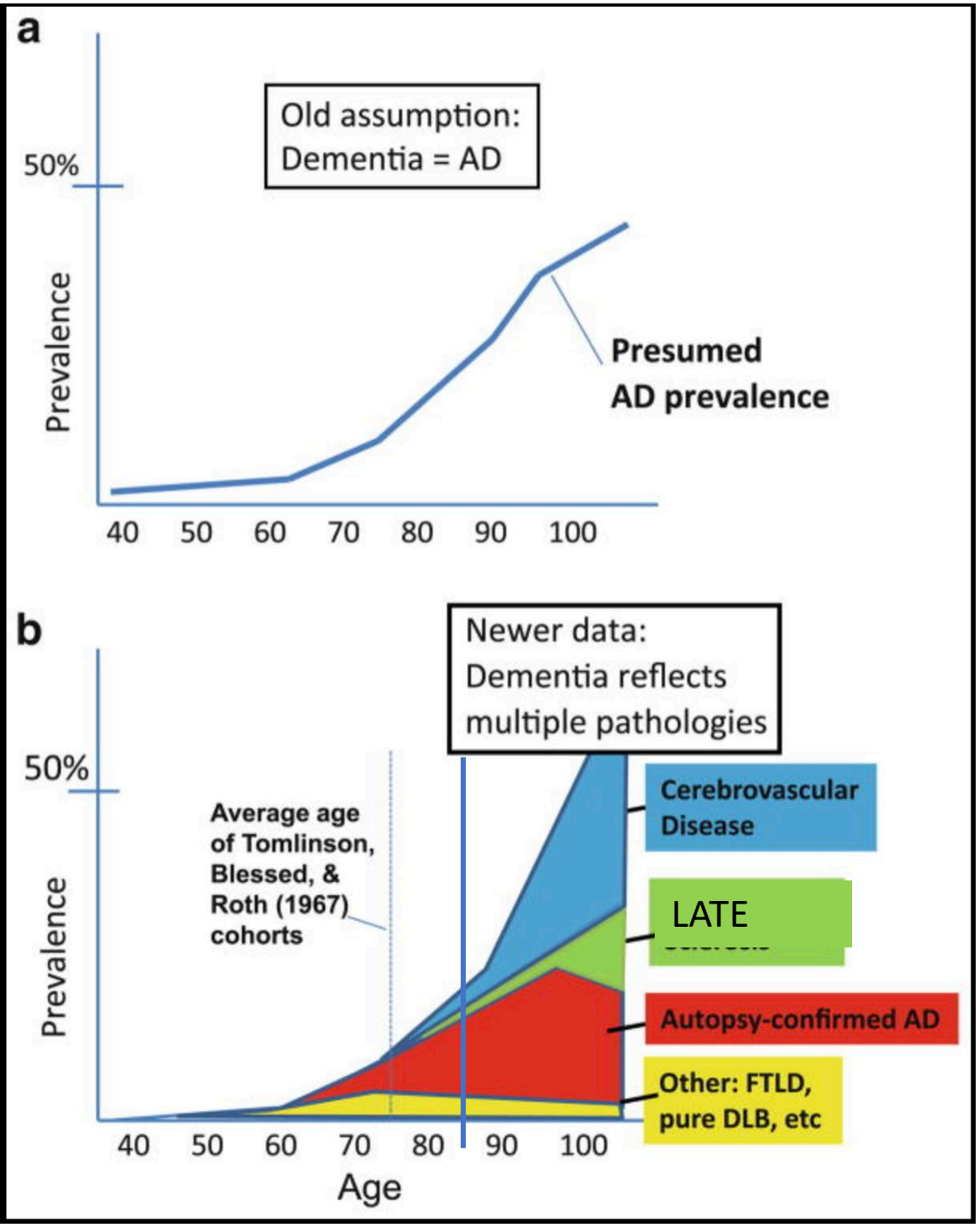
Imaging Markers of VCID



As Imaging Modalities become more sensitive proportion with vascular brain injury grows



Imaging Markers of Vascular Brain Health: Quantification, Clinical Implications, and Future Directions; Stroke: 2022;53:416–426.



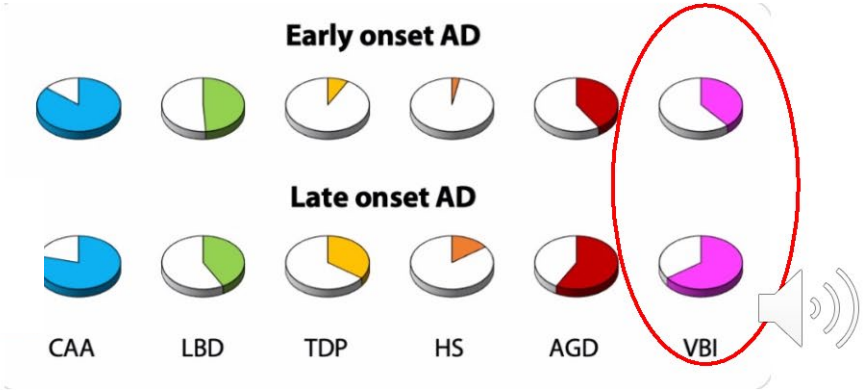
The right question may be 'how much', 'what type' rather than *'if'* someone has VCID

doi:10.1093/brain/awab099 BRAIN 2021: 144; 2186–2198 | 2186

BRAIN
ORIGINAL ARTICLE

Comorbid neuropathological diagnoses in early versus late-onset Alzheimer's disease

Salvatore Spina,[1,†] Renaud La Joie,[1,†] Cathrine Petersen,[1] Amber L. Nolan,[1] Deion Cuevas,[1] Celica Cosme,[1] Mackenzie Hepker,[1] Ji-Hye Hwang,[1] Zachary A. Miller,[1] Eric J. Huang,[2] Anna M. Karydas,[1] Harli Grant,[1] Adam L. Boxer,[1] Maria Luisa Gorno-Tempini,[1] Howard J. Rosen,[1] Joel H. Kramer,[1] Bruce L. Miller,[1] William W. Seeley,[1,2] Gil D. Rabinovici[1,3] and Lea T. Grinberg[1,2]

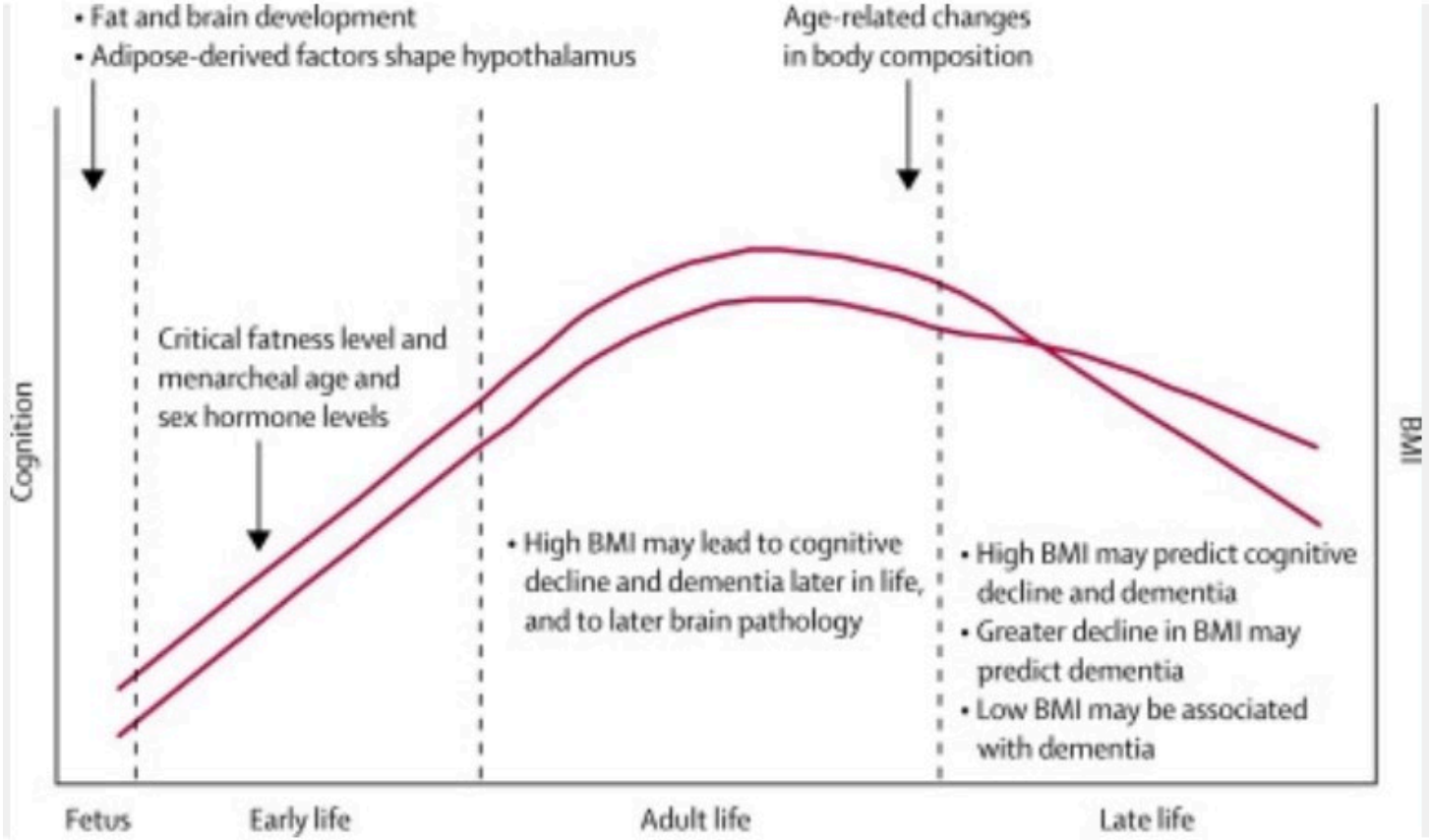


Outline

- Why is Dementia in the ‘Oldest-Old’ Important to Study?
- What do we know about Biology of Dementia in Oldest-Old?
- **Prevention: Life Course Risk Factors, Multimorbidity**
- Promotion of Brain Health: Biomarkers, Resilience Factors, Genetics

Direction of Association Changes in Oldest-old

- Obesity



Emer McGrath, MD, PhD

Contribution of Vascular RFs to Dementia

May Vary ***Across Lifespan*** Mid- to Later-Life

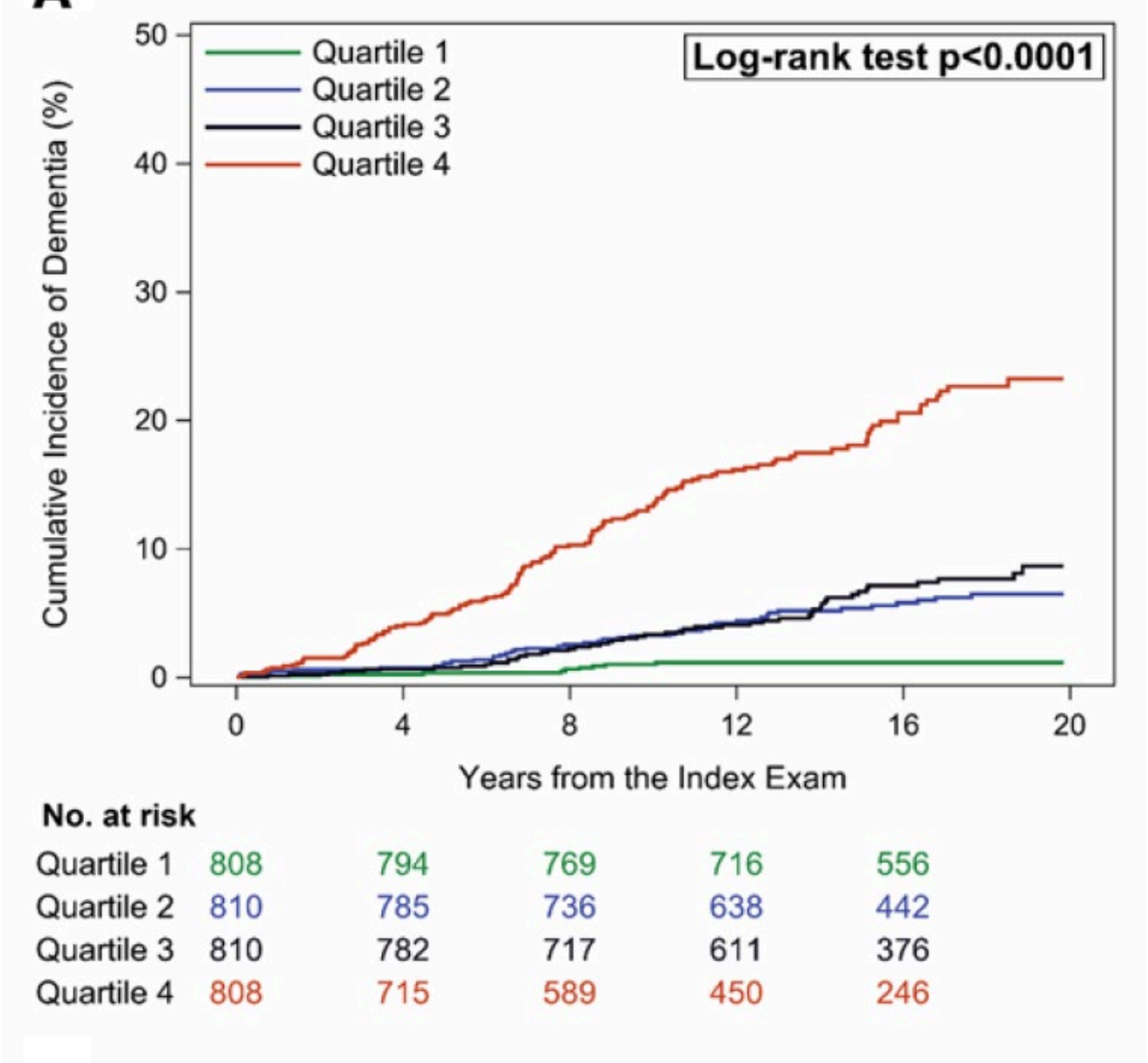
FHS participants 55 (4899, 57%F) to 80 (2386, 62% F)

Stepwise Cox PH models:

Most important RFs for inclusion in age-specific dementia risk scores

In older persons burden of accrued injury matters!

Age 55	Age 65	Age 70	Age 75	Age 80
Systolic BP 1.17 (1.05-1.32)	**All CVD** 2.21 (1.35-3.32)	**Stroke** 2.43 (1.29-4.59)	**Stroke** 1.78 (1.12-2.83)	**Stroke** 1.57 (1.04-2.35)
Diabetes mellitus 3.35 (1.52-7.36)		**Diabetes mellitus** 1.97 (1.37-2.83)	**Diabetes mellitus** 1.56 (1.14-2.15)	**Diabetes mellitus** 1.45 (1.06-1.97)
Insulin, Metformin, Pramlintide, Semaglutide, Dapagliflozin				**Anti-HTN non-use** 1.47 (1.20-1.82)



7283 participants (age 50±9, 53% F); 253 events, ~15 yrs

Arterial Stiffness increased risk of Dementia by 30%

3 million fewer patients if HTN reduced by 25% but

Blood pressure from mid- to late life and risk of incident dementia

Emer R. McGrath, MB, PhD
Alexa S. Beiser, PhD
Charles DeCarli, MD
Kendra L. Plourde, MA
Ramachandran S. Vasan, MD
Steven M. Greenberg, MD, PhD
Sudha Seshadri, MD

Midlife or sustained high SBP increased late life dementia risk

Steep decline in BP from mid to late life in normotensives also increased risk

Neurology® 2017;89:2447-2454

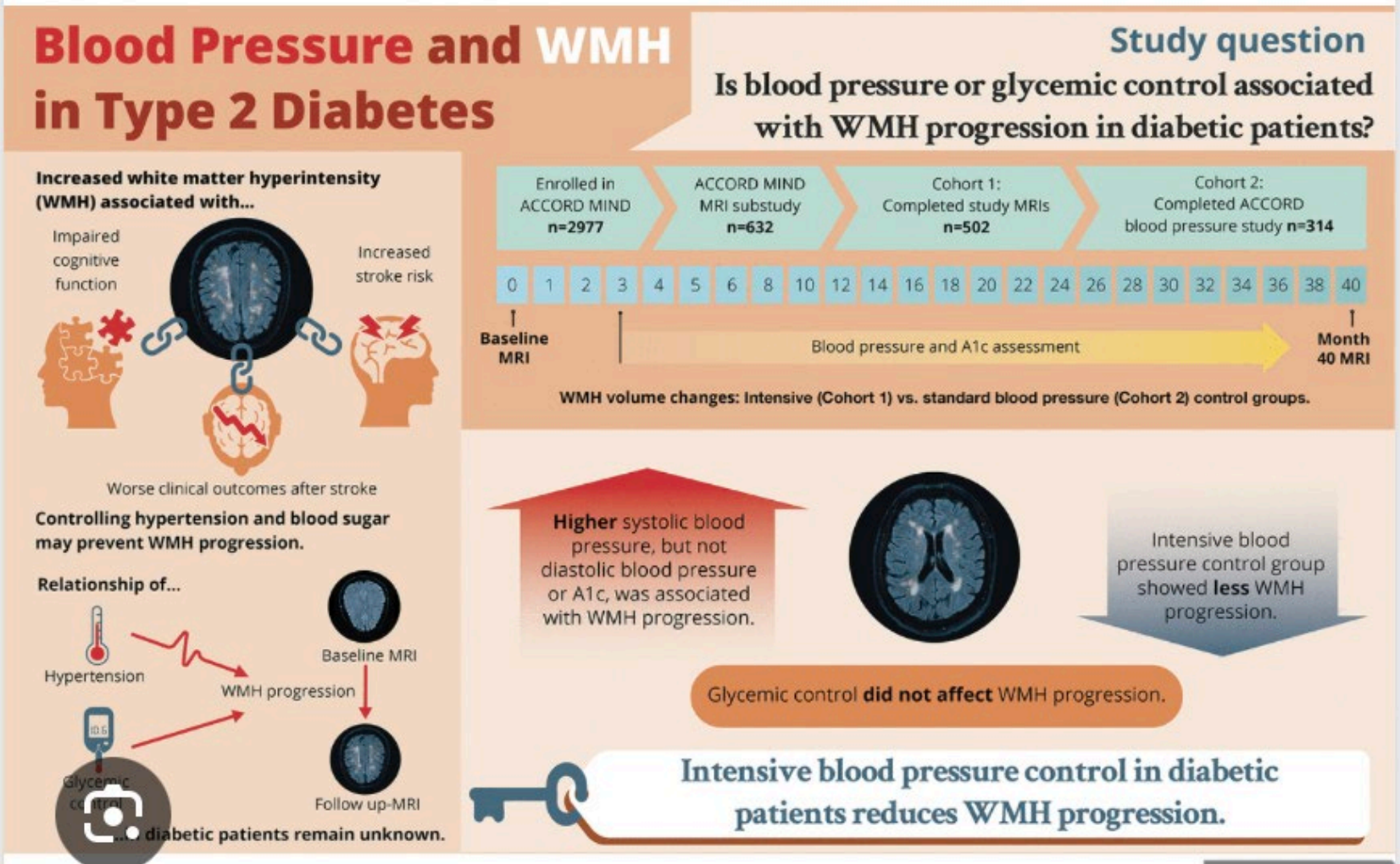
Ramachandran S. Vasan. Hypertension. Arterial Stiffness and Long-Term Risk of Health Outcomes: The Framingham Heart Study, Volume: 79, Issue: 5, Pages: 1045-1056, DOI: (10.1161/HYPERTENSIONAHA.121.18776)

March 12, 2019; 92 (11) ARTICLE

Blood pressure, glycemic control, and white matter hyperintensity progression in type 2 diabetics

Adam de Havenon, Jennifer J. Majersik, David L. Tirschwell, J. Scott McNally, Gregory Stoddard, Natalia S. Rost

First published February 8, 2019, DOI: https://doi.org/10.1212/WNL.0000000000007093



Is BP or BS more impt?

Take Home Message

In DM and prediabetic states, prevention of stroke & control of HTN are important to preserve cognition

Central Obesity and Hypertension: A double whammy!!

An 18-year follow-up of Overweight and Risk of Alzheimer's Disease

Gustafson et al., Arch Neurol 2003;163:1524-28

Obesity and Vascular Risk Factors at Midlife and the Risk of Dementia and Alzheimer Disease

Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) *Arch Neurol. 2005;62:1556-1560*

Miia Kivipelto, MD, PhD; Tiia Ngandu, BM; Laura Fratiglioni, MD, PhD; Matti Viitanen, MD, PhD; Ingemar Kåreholt, PhD; Bengt Winblad, MD, PhD; Eeva-Liisa Helkala, PhD; Jaakko Tuomilehto, MD, MPolSci, PhD; Hilkka Soininen, MD, PhD; Aulikki Nissinen, MD, PhD

ELSEVIER

Neurobiology of Aging 26S (2005) S11–S16

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Obesity, diabetes and cognitive deficit: The Framingham Heart Study

Merrill F. Elias[a,b,*], Penelope K. Elias[a,b], Lisa M. Sullivan[a,c], Philip A. Wolf[d], Ralph B. D'Agostino[a]

[*] *Boston University, Department of Mathematics and Statistics, Statistics and Consulting Unit, 111 Cummington Street, Boston, MA 02215, USA*
[b] *The University of Maine, Department of Psychology, 5742 Little Hall, Orono, ME 04469-5742, USA*
[c] *The Boston University School of Public Health, Department of Biostatistics, Boston, MA 02118, USA*
[d] *The Boston University School of Medicine, Department of Neurology, 715 Albany Street, Room B608, Boston, MA 02118, USA*

Original Cohort

18 year follow-up

Adverse effects of obesity seen only in men

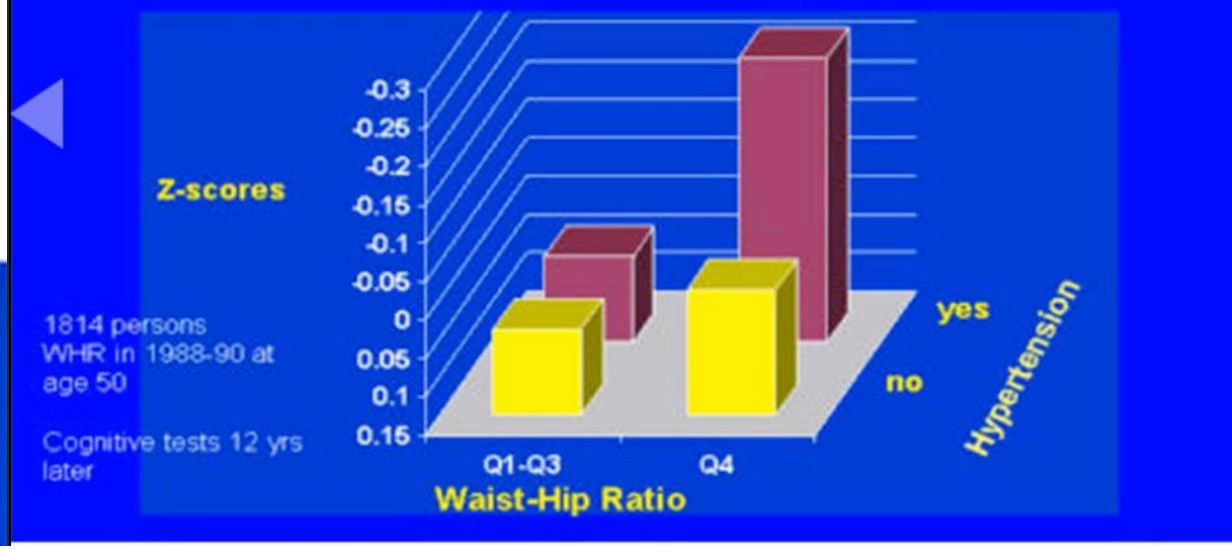
No DM/Obesity interactions observed

Current Alzheimer Research, 2007, 4, 000-000 1

Relation of Obesity to Cognitive Function: Importance of Central Obesity and Synergistic Influence of Concomitant Hypertension. The Framingham Heart Study

P.A. Wolf*, A. Beiser, M.F. Elias, R. Au, R.S. Vasan and S. Seshadri

Combined Impact of Waist-Hip Ratio & HTN on Visual Reproductions – Delayed Recall



Heart and Mind: 'What is Good for the Heart is Good for the Brain'

Increasing Risk With Increasing Intake

Risk of both dementia & of milder memory loss increased

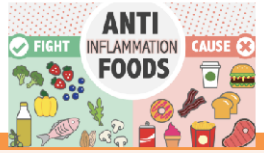
alzheimer's association | Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Higher Dietary Inflammatory Index scores are associated with brain MRI markers of brain aging: Results from the Framingham Heart Study Offspring cohort*

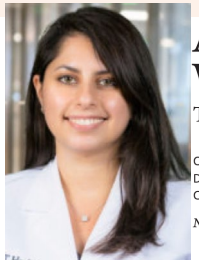
Debora Melo Van Lent, Hannah Gokingco, Meghan I. Short, Changzheng Yuan, Paul F. Jacques, José R. Romero, Charles S. DeCarli, Alexa S. Beiser, Sudha Seshadri, Jayandra J. Himali, Mini E. Jacob

First published: 06 May 2022 | https://doi.org/10.1002/alz.12685



Original Contribution

Sugar- and Artificially Sweetened Beverages and the Risks of Incident Stroke and Dementia
A Prospective Cohort Study



Association of Red Blood Cell Omega-3 Fatty Acids With MRI Markers and Cognitive Function in Midlife
The Framingham Heart Study

Claudia L. Satizabal, PhD,* Jayandra Jung Himali, PhD,* Alexa S. Beiser, PhD, Vasan Ramachandran, MD, Debora Melo van Lent, PhD, Dibya Himali, MS, Hugo J. Aparicio, MD, MPH, Pauline Maillard, PhD, Charles S. DeCarli, MD, William S. Harris, PhD, and Sudha Seshadri, MD

Correspondence
Dr. Satizabal
satizabal@uthscsa.edu

Neurology® 2022;99:e2572-e2582. doi:10.1212/WNL.0000000000201296

DHA: an omega-3 fatty acid found in fish
If level in top fifth, *5 more years AD free*

UT Health San Antonio Physicians

Journals of Gerontology: Medical Sciences
cite as: J Gerontol A Biol Sci Med Sci, 2016, Vol. 00, No. 00, 1–7
doi:10.1093/gerona/glw130
Advance Access publication July 15, 2016

THE GERONTOLOGICAL SOCIETY OF AMERICA®

OXFORD

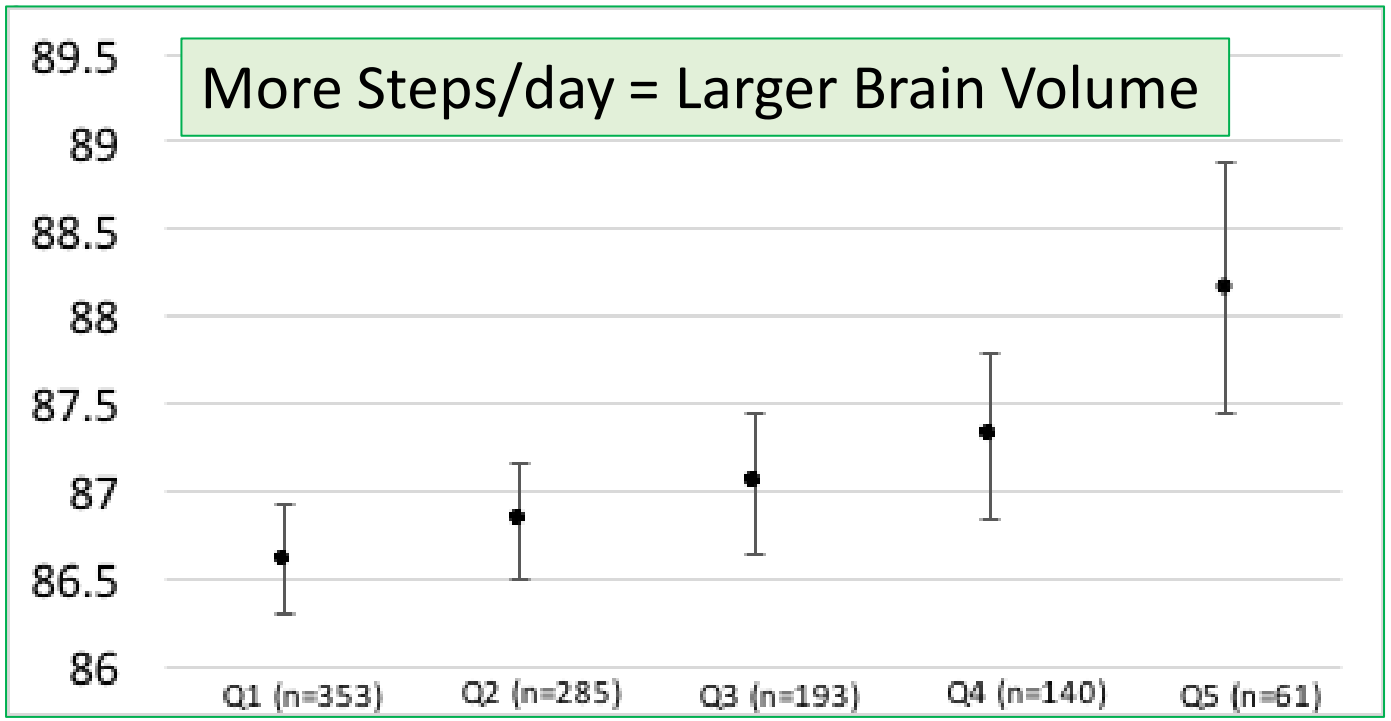
Research Article

Physical Activity, Brain Volume, and Dementia Risk: The Framingham Study

Zaldy S. Tan,[1,2,*] Nicole L. Spartano,[2,3,*] Alexa S. Beiser,[2,4,5] Charles DeCarli,[6] Sanford H. Auerbach,[2,4] Ramachandran S. Vasan,[2,3] and Sudha Seshadri[2]

Nicole L. Spartano, PhD

Zaldy . Tan, MD, MPH



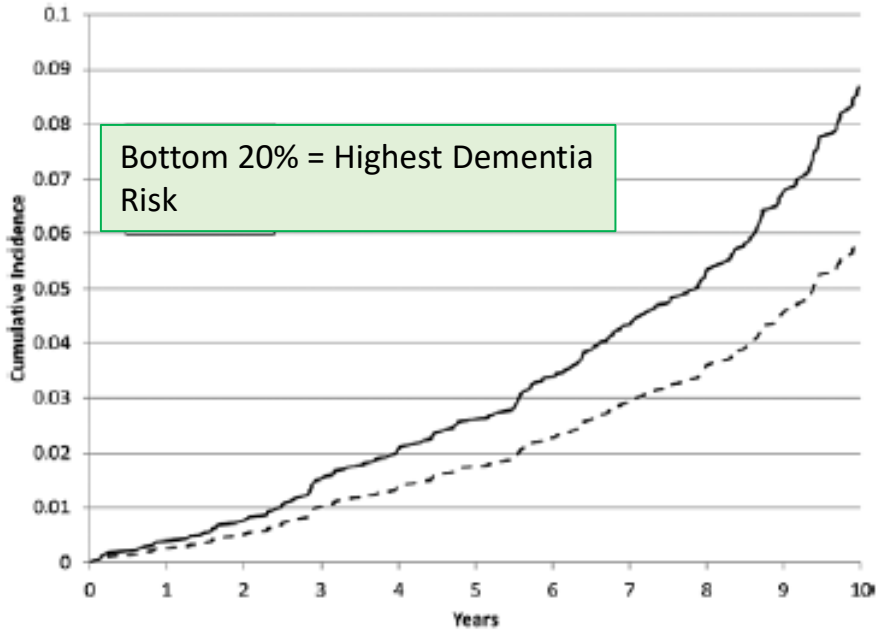


Figure 1. Ten-year cumulative incidence of dementia: Lowest quintile (Q1) of physical activity index (PAI) versus upper four quintiles (Q2–Q5), adjusted for age and sex.

Sedentary time is bad; avoiding that is more important than reaching specific activity levels

JAMA Network Open

Original Investigation | Neurology

Association of Multimorbidity, Disease Clusters, and Modification by Genetic Factors With Risk of Dementia

Catherine M. Calvin, PhD; Megan C. Conroy, MSc; Sarah F. Moore, MB BChir; Elżbieta Kuźma, PhD; Thomas J. Littlejohns, PhD

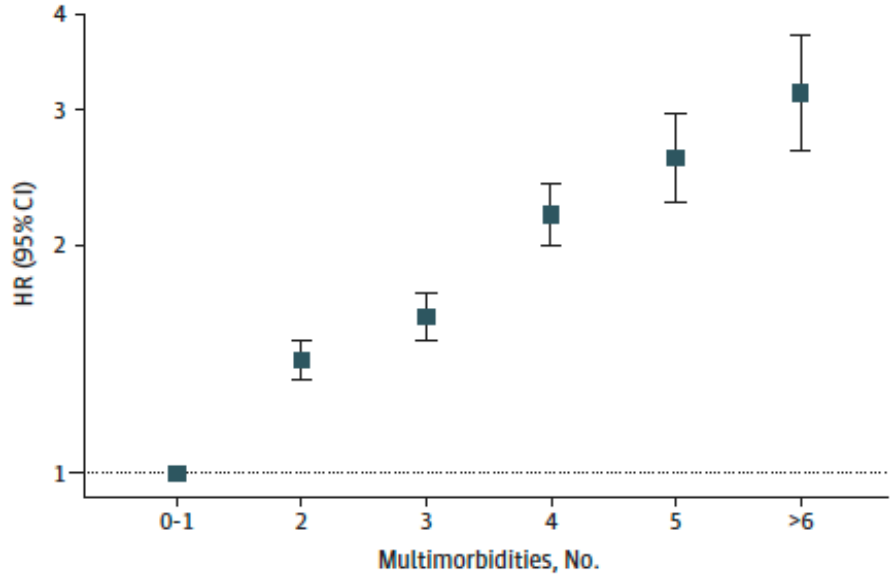
Hospital Records, over 200,000 persons

Doubling of dementia risk in those with low genetic risk

40% in persons with high genetic risk

Not specific to Oldest-old

Figure 2. Cox Proportional Hazards Models for the Association Between Number of Multimorbid Conditions and Incident Dementia

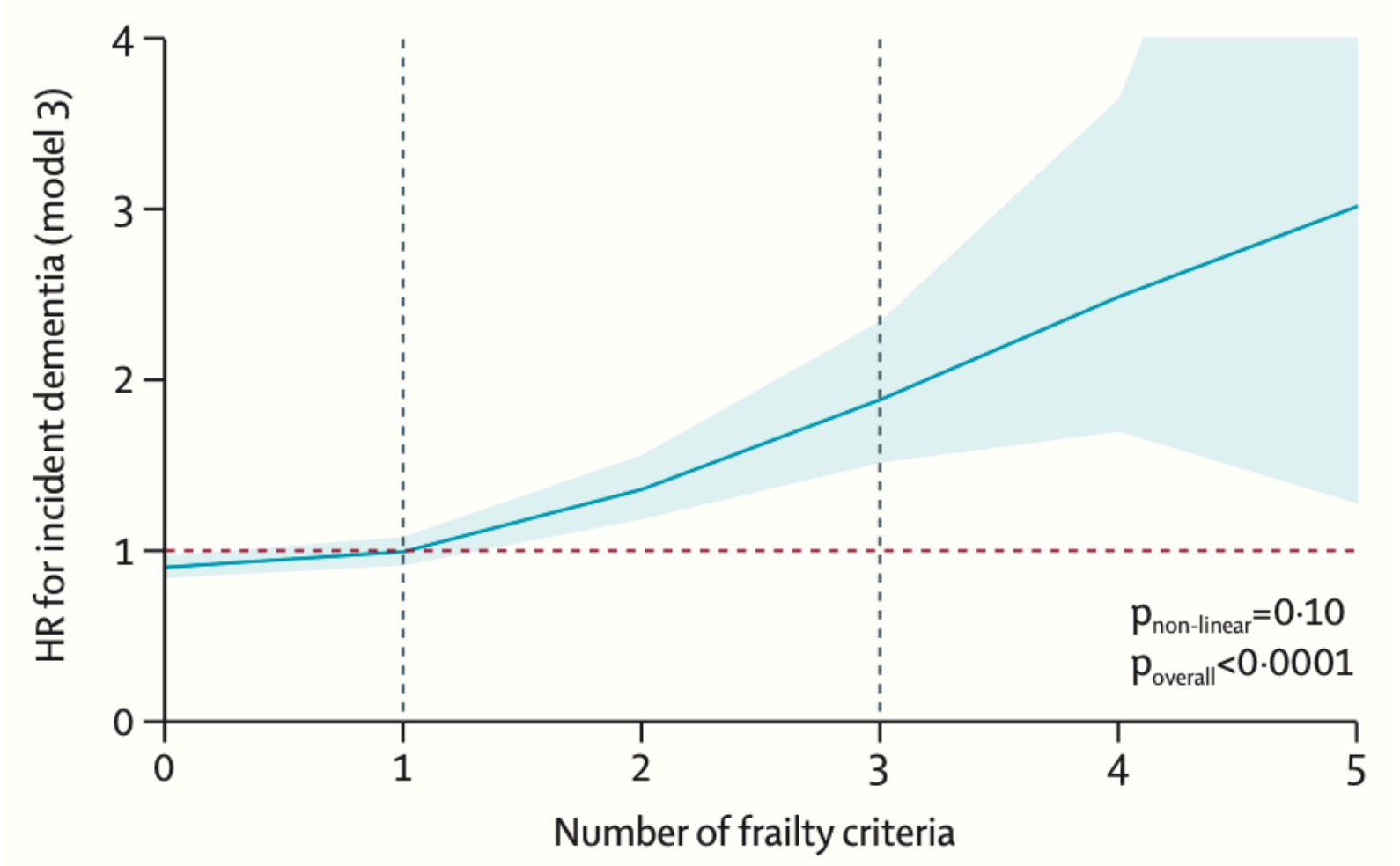


All models adjusted for age, ethnicity, education, socioeconomic status, and APOE-ε4 status. Dementia cases, sample size, hazard ratios, and incidence rates within each number of mulimorbidities group are presented in eTable 5 in the Supplement.

Associations between physical frailty and dementia incidence: a prospective study from UK Biobank

Fanny Petermann-Rocha, Donald M Lyall, Stuart R Gray, Irene Esteban-Cornejo, Terence J Quinn, Frederick K Ho, Jill P Pell*, Carlos Celis-Morales**

(weight loss, tiredness, physical activity, gait speed, and grip strength),



Even in fully adjusted models, frailty was a predictor of dementia risk

Greater number of frailty criteria being positive increased risk

Causal or marker?

Outline

- Why is Dementia in the ‘Oldest-Old’ Important to Study?
- What do we know about Biology of Dementia in Oldest-Old?
- Prevention: Life Course Risk Factors, Multimorbidity
- **Promotion of Brain Health: Biomarkers, Resilience Factors, Genetics**

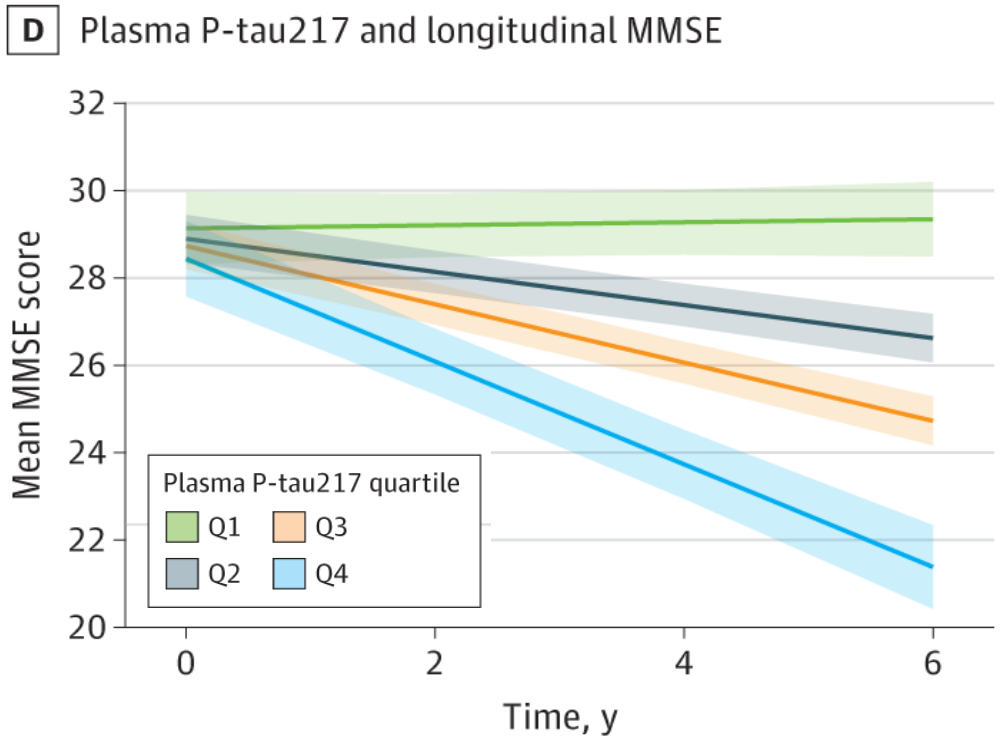
Alzheimer Association International Conference: July 18, 2019, Plenary Lecture

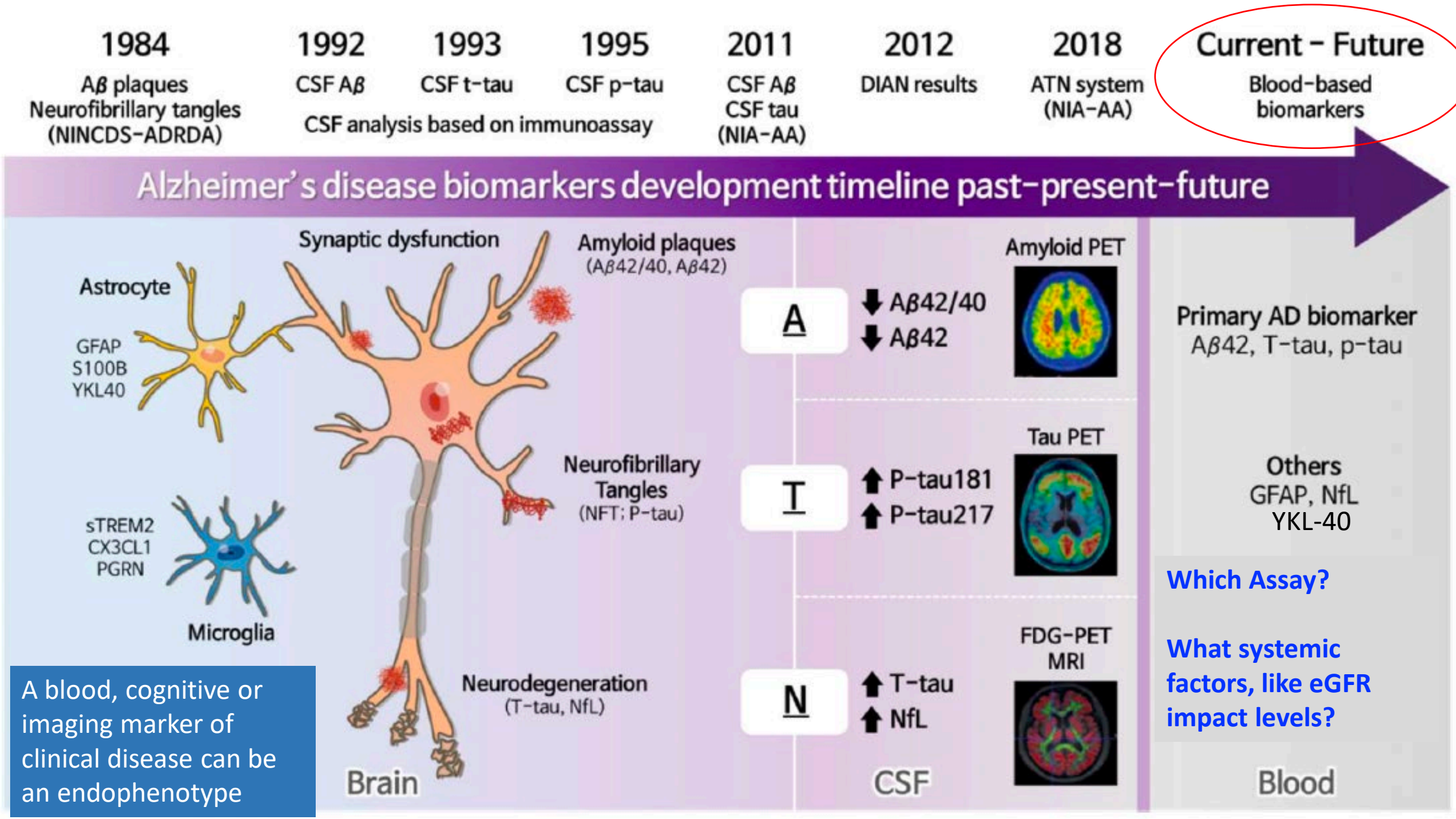
A Precision, Personalized Approach to Dementia Prevention, Diagnosis & Treatment

2021 NIH Alzheimer's Research Summit: Path to Precision Medicine for Treatment and Prevention

Considering all causes of Dementia

- Searching for biomarkers of -
  - **Amyloid and Tau**
  - Inflammatory
  - Synaptic
  - Other genetic, omic, molecular markers
  - Other diseases (VCID, DLB, LATE, PART, AGD)
  - Environmental (built, social, behavioral)
  - Behavioral (sleep, physical activity, diet)



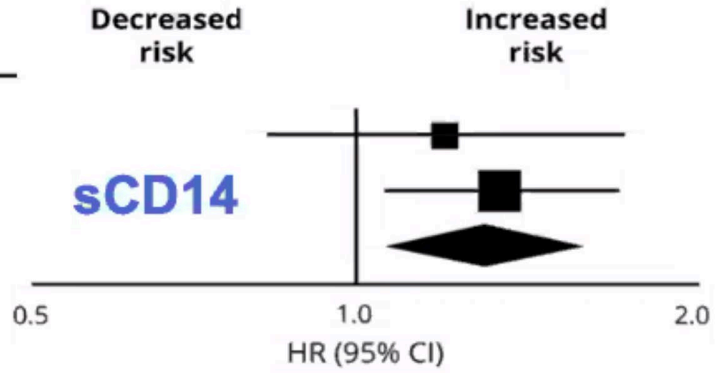

1984
Aβ plaques
Neurofibrillary tangles
(NINCDS-ADRDA)
1992
CSF Aβ
1993
CSF t-tau
1995
CSF p-tau
CSF analysis based on immunoassay
2011
CSF Aβ
CSF tau
(NIA-AA)
2012
DIAN results
2018
ATN system
(NIA-AA)
Current - Future
Blood-based
biomarkers
Alzheimer's disease biomarkers development timeline past-present-future
Synaptic dysfunction
Amyloid plaques
(Aβ42/40, Aβ42)
Astrocyte
GFAP
S100B
YKL40
Neurofibrillary
Tangles
(NFT; P-tau)
sTREM2
CX3CL1
PGRN
Microglia
Neurodegeneration
(T-tau, NfL)
Brain
A
Aβ42/40
Aβ42
T
P-tau181
P-tau217
N
T-tau
NfL
CSF
Amyloid PET
Tau PET
FDG-PET
MRI
Primary AD biomarker
Aβ42, T-tau, p-tau
Others
GFAP, NfL
YKL-40
Which Assay?
What systemic factors, like eGFR impact levels?
Blood
A blood, cognitive or imaging marker of clinical disease can be an endophenotype

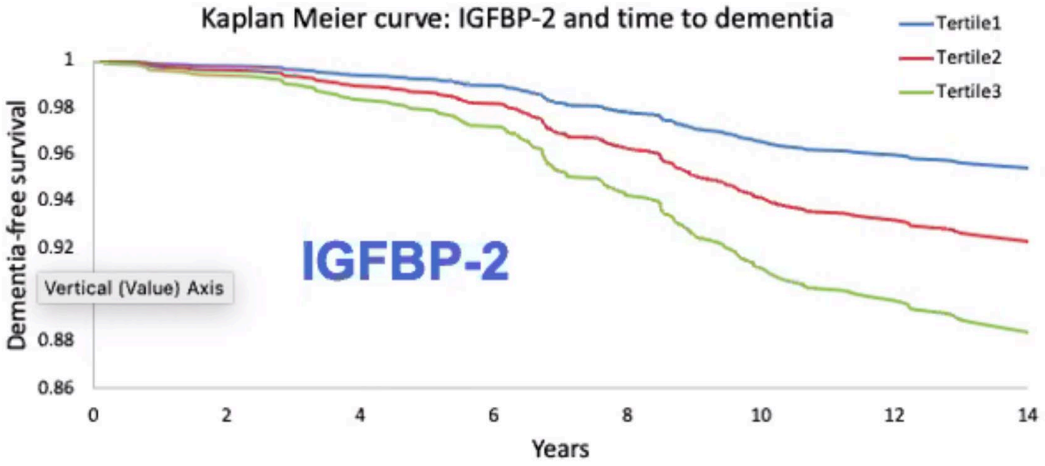
Other potential candidate BMs

Neurodegeneration	Neuronal injury	Inflammation	Vascular/ Thrombosis	Neurotrophic factors	Hormones and metabolic factors
Aß42	GFAP	CRP	Fibrinogen	BDNF	Cortisol
Aß40	NFL	IL-6	D-dimer	VEGF	Estrogen
Tau	NSE	MCP-1	NT-proBNP	B-NGF	FGF-23
P-tau species	MBP	OPG	ST2	IGF-1	HbA1c
NT-1		P-selectin	Trop I	IGFBP-1	Insulin
Clusterin		TNF-α	Homocysteine	IGFBP-2	Adipokines
Aß37		GDF-15	Lipids, ceramides	IGFBP-3	
Aß38		sCD14	PAI-1		
		YKL-40	MMP-9		
		sCD40L	sCD40L		

Figure 2 Association of soluble cluster of differentiation 14 (sCD14) with incident dementia

Cohort	HR (95% CI)	*p*
Top decile of sCD14		
FHS	1.25 (0.80, 1.97)	0.33
CHS	1.44 (1.08, 1.94)	<0.05
Overall I^2 = 0%	1.38 (1.08, 1.77)	0.01





GDF-15
NT-proBNP

Table 3. Association of Plasma Total Tau With Cognition and Hippocampal Volume in the Framingham

T-tau

Outcome	Model 1[b] β (SE)	*P* Value
Episodic memory		
Logical memory, No. correct	−0.12 (0.06)	.049
Paired associate learning, No. correct	−0.05 (0.02)	.04
Verbal reasoning: similarities, No. correct	−0.18 (0.05)	<.001

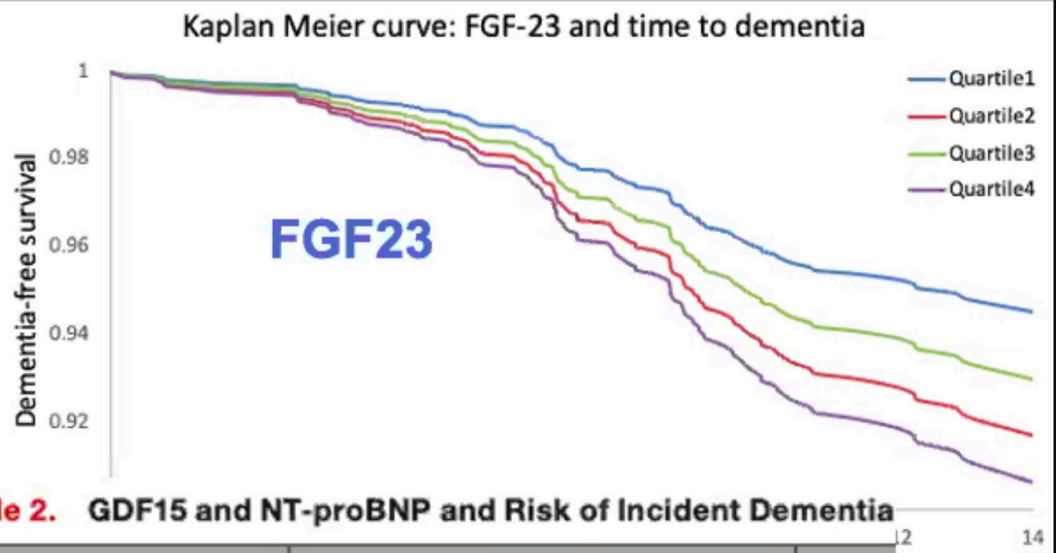


Table 2. GDF15 and NT-proBNP and Risk of Incident Dementia

Biomarker	Model 1 HR (95% CI)	*P* Value	
GDF15			
Per SDU increase	1.57 (1.30–1.90)	<0.0001	1.5
T2 vs T1	1.26 (0.78–2.02)	0.35	1.3
T3 vs T1	2.49 (1.61–3.87)	<0.001	2.3
NT-proBNP			
Per SDU increase	1.40 (1.14–1.71)	0.001	1.3

Table 3. Ceramide ratios and MRI markers of structural brain injury.

Ceramides

	TBV		Hippocampal volume	
	$\beta \pm$ SE	*P*-value	$\beta \pm$ SE	*P*-value
Ceramide 24:0/16:0	0.03 ± 0.05	0.44	−0.001 ± 0.001	0.46
Ceramide 22:0/16:0	0.07 ± 0.05	0.17	−0.0004 ± 0.001	0.74

Machine learning approaches to dementia risk prediction

Biomarker	Inter-assay CV (%)	Intra-assay CV (%)	Biomarker	Inter-assay CV (%)	Intra-assay CV (%)
Aß40 (pg/mL)	10.5	3.2	IGFBP-1 (pg/mL)	5.4	2.5
***Aß42** (pg/mL)	7.6	2.6	***IGFBP-2** (pg/mL)	8.7	6.0
***Aß42/40**	-	-	IGFBP-3 (pg/mL)	18.0	4.4
Adiponectin (ug/mL)	9.6	6.2	IL-6 (pg/mL)	9.0	3.7
Apo A1 (pg/mL)	7.3	11.8	Insulin (pmol/L)	6.1	3.9
ApoB (pg/mL)	13.4	6.6	***Leptin** (pg/mL)	7.0	3.2
BDNF (pg/mL)	7.6	4.8	***MCP-1** (pg/mL)	11.1	3.8
BNP (pg/mL)	7.2	10.3	MMP-9 (pg/mL)	10.0	3.9
CD14 (pg/mL)	14.5	3.6	MPO (ng/mL)	NR	3.2
CD40L (ng/mL)	14.1	4.9	OPG (pmol/L)	NR	3.7
Clusterin (pg/mL)	12.6	9.1	***PAI-1** (pg/mL)	10.8	3.6
CRP mg/L	5.3	3.2	P-selectin (ng/mL)	NR	3.2
***Cystatin C** (mg/L)	3.3	2.4	Resistin (ng/dL)	11.0	4.6
FGF-23 (pg/mL)	13.4	5.5	TC (mg/dL)	1.5	0.7
Fibrinogen (mg/dL)	4.4	1.1	***TNF-α** (pg/dL)	11.3	7.6
GDF-15 (pg/mL)	2.9	2.3	TNFR-2 (pg/mL)	NR	2.3
HbA1c (%)	<2.5	<2.5	VEGF (pg/mL)	14.7	4.3
***HDL-C** (mg/dL)	2.8	0.9	Vitamin B12 (pg/mL)	10.0	8.5
***Homocysteine** (umol/L)	7.0	4.5	Vitamin D (ng/mL)	8.5	NR
ICAM-1 (ng/mL)	6.0	3.9	T-tau (pg/mL)	7.5	4.1
IGF-1 (ng/mL)	4.5	3.4			

1642 Framingham Offspring cohort participants

243 developed dementia (mean f/u 12±5yr)

ML methods (SVM, XGB, ANN), 41 candidate biomarkers for incident dementia

10 most informative BMs identified including **Aß42, Aß42/40, Cystatin C, sCD40L, IGFBP-2, Leptin, MCP-1, PAI-1, TNF- α, HDL-C**

Lin et al, In Press 2022

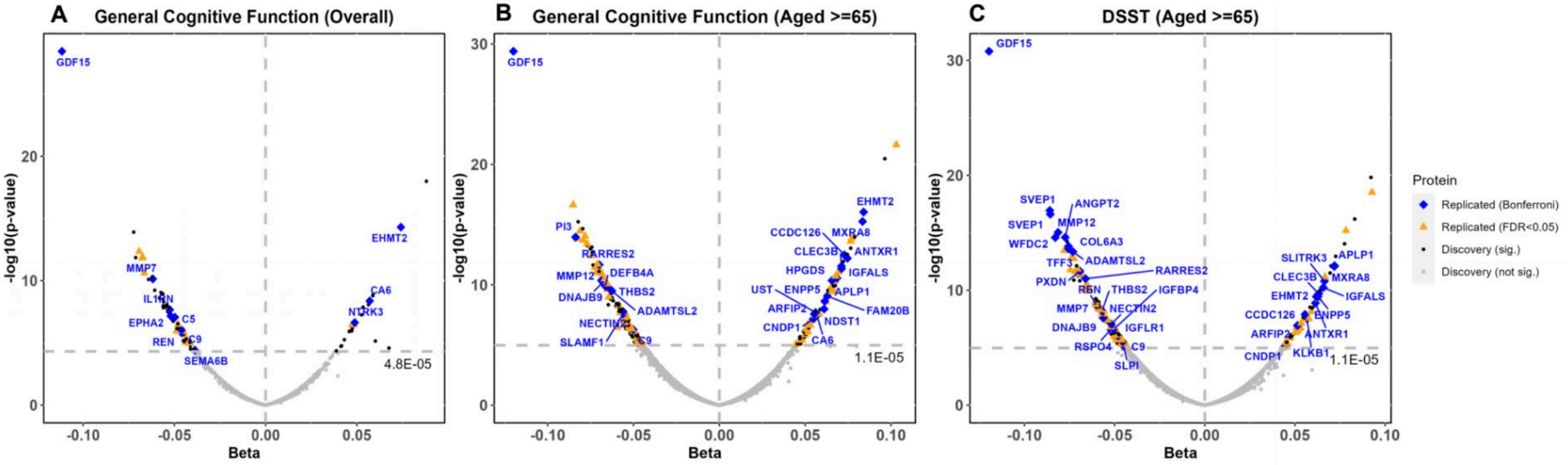


Figure 2. Volcano plots showing the beta coefficients and p-values from the discovery meta-analyses with colors indicating whether a protein was replicated. The three discovery analyses were for general cognitive function among aged ≥ 25 (A) and aged ≥ 65 (B), and Digit Symbol Substitution Test (C).

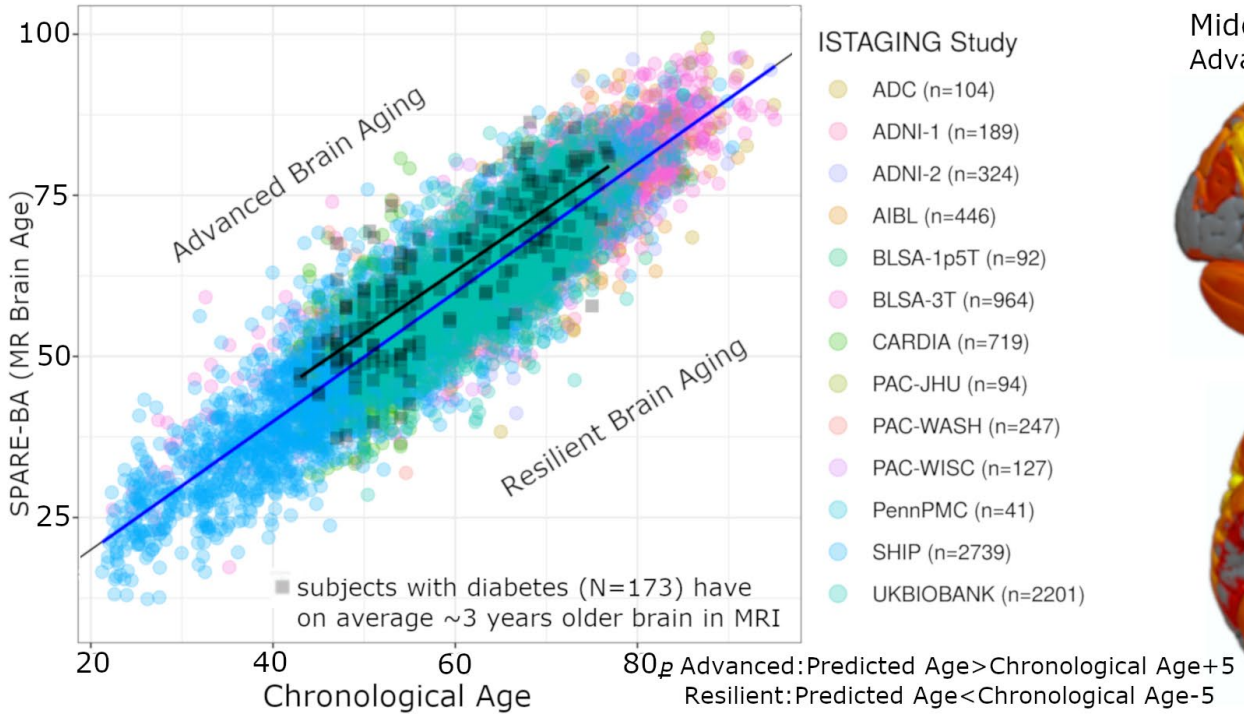
Somascan in ~8000, replication in ~9000
Olink validation in ~3000 persons

Consistent Pattern: NECTIN2, lower CRP, 22 proteins in all

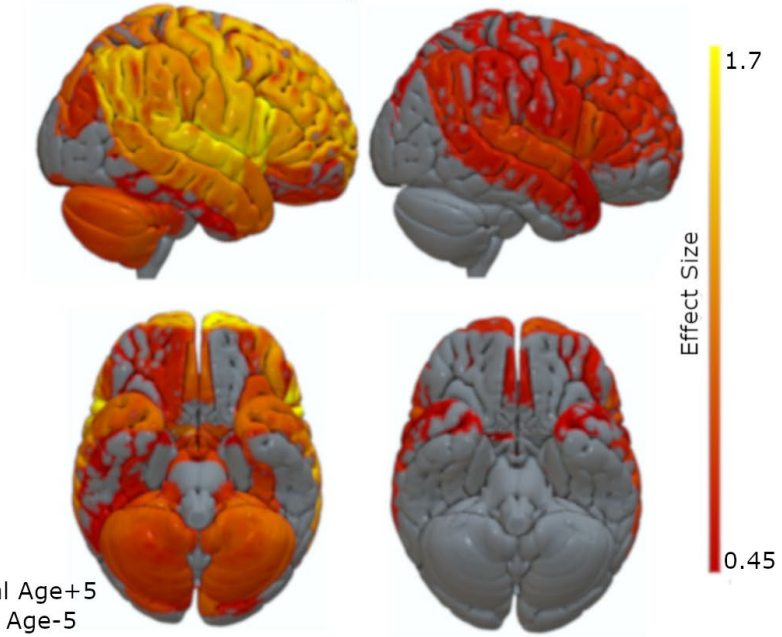
Preclinical AD patterns predicted with AI:
brain age for 8287 healthy subjects from 10 cohorts

Coming Soon to a Radiologist's Office Near You!

Patterns of Advanced Brain Aging



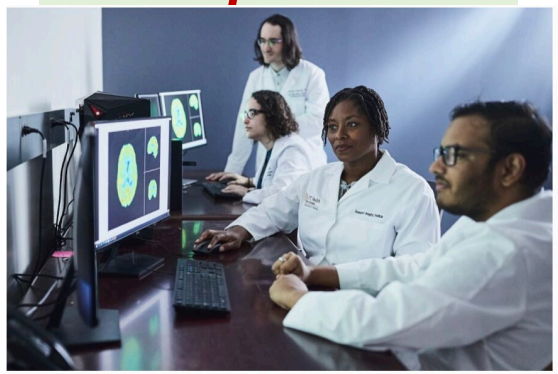
B. Pattern of Reduced Grey Matter in Advanced BA



* Advanced:Predicted Age>Chronological Age+5
Resilient:Predicted Age<Chronological Age-5

Habes *et al. AD&D 2021*

Artificial Intelligence (AI) based tools can permit *measurements & comparisons*



Neuroimaging researchers, UT Health San Antonio

Phongpreecha *et al.*
Alzheimer's Research & Therapy (2023) 15:192
https://doi.org/10.1186/s13195-023-01329-z

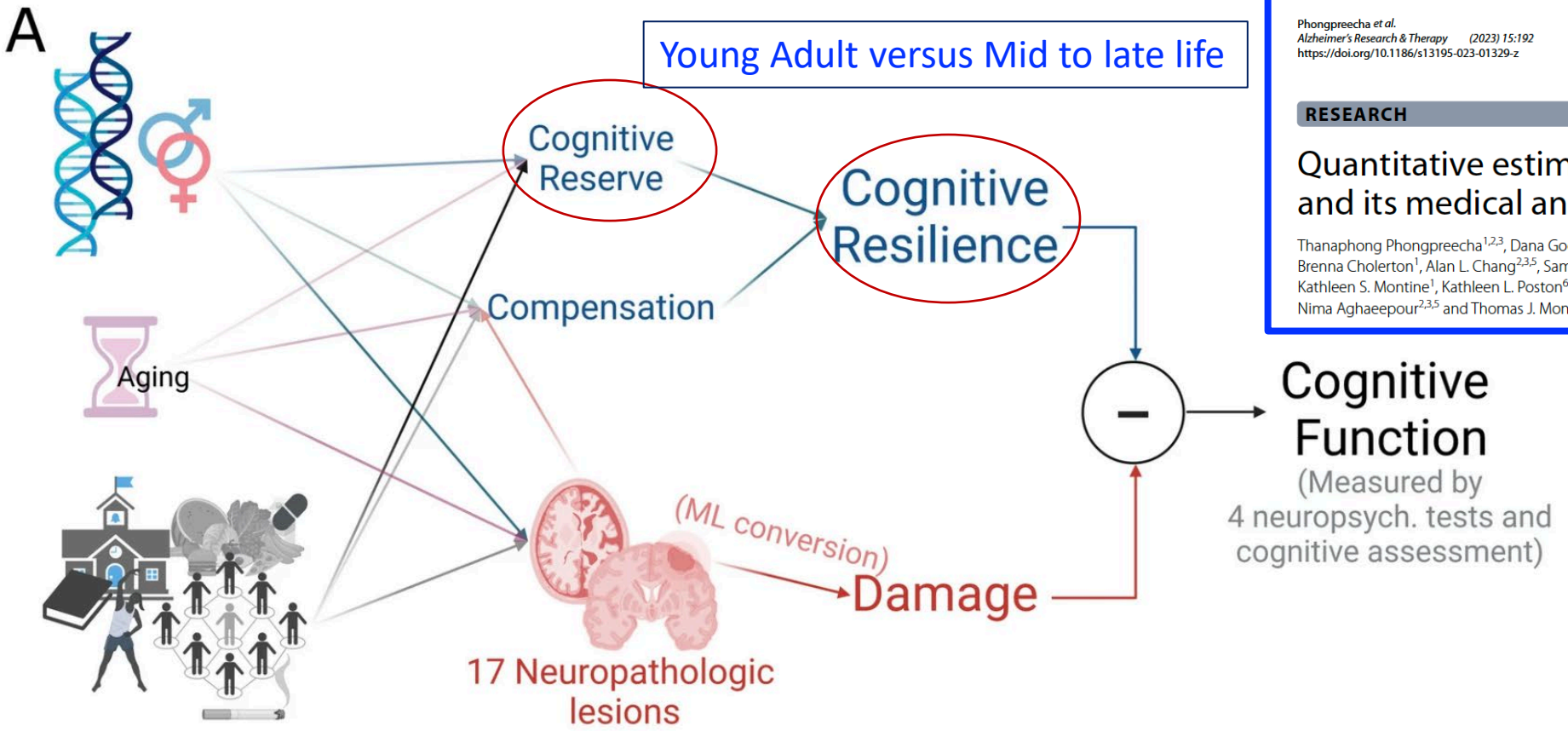
Alzheimer's Research & Therapy

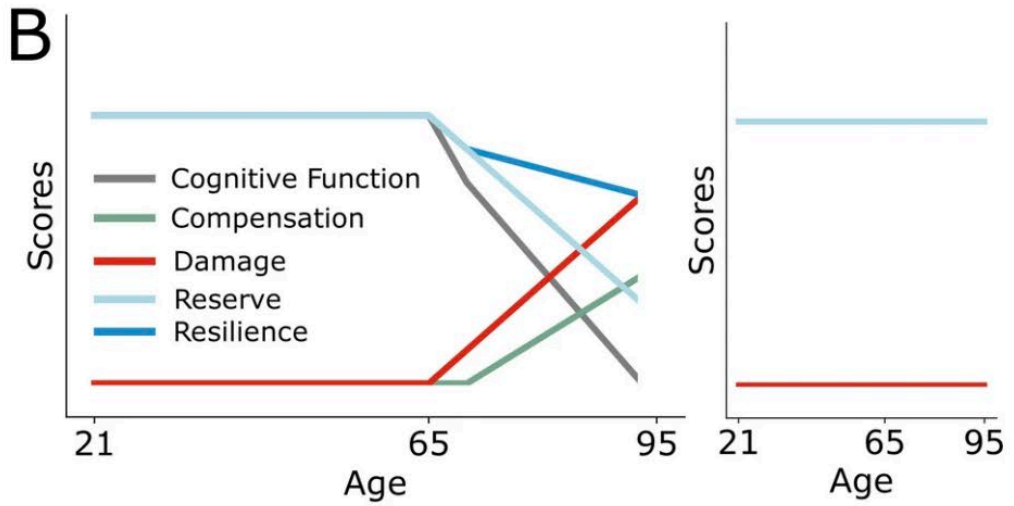
RESEARCH Open Access

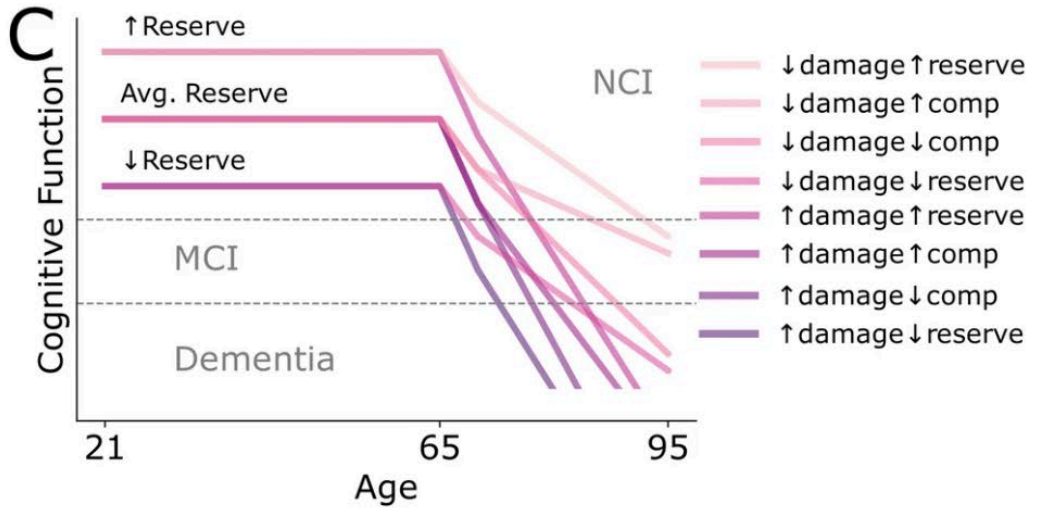
Quantitative estimate of cognitive resilience and its medical and genetic associations

Thanaphong Phongpreecha[1,2,3], Dana Godrich[4], Eloise Berson[1,3,5], Camilo Espinosa[2,3,5], Yeasul Kim[2,3,5], Brenna Cholerton[1], Alan L. Chang[2,3,5], Samson Mataraso[2,3,5], Syed A. Bukhari[1], Amalia Perna[1], Koya Yakabi[1], Kathleen S. Montine[1], Kathleen L. Poston[6], Elizabeth Mormino[6], Lon White[7], Gary Beecham[4], Nima Aghaeepour[2,3,5] and Thomas J. Montine[1*]

Young Adult versus Mid to late life





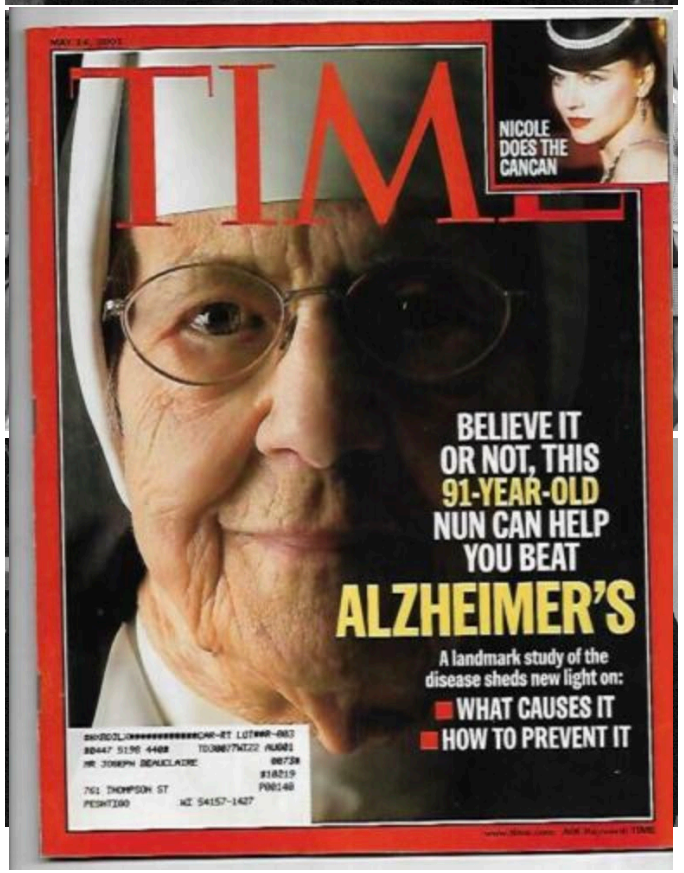


Cognitive Reserve

And

Cognitive Resilience

May be assessed together



What Determines Resilience: Lessons from The Nun Study

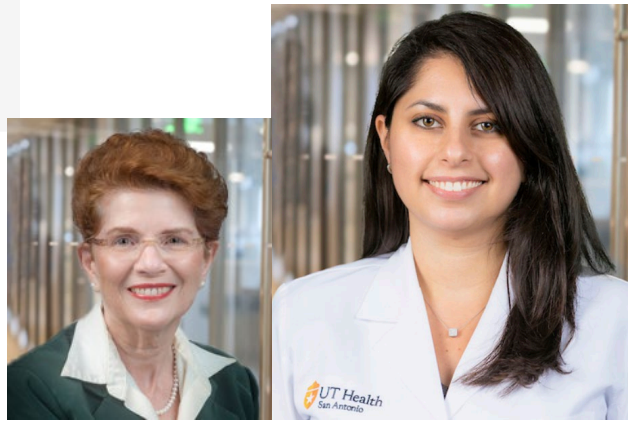
- School Sisters of Notre Dame congregation
- 678 women aged 75+, enrolled in 1991
- 20+ years of cognitive and other assessments
- Similar living condition, healthcare & lifestyle
- Observation from healthy to dementia

90% Brain Donors, Dementia results when disease > reserve

Now these data and brain specimens are being studied at the Biggs

Petrie Dish

San Antonio researchers revive 1979 Heart and Mind Study



Societal Prevention:

Behavioral and Social Determinants

Loneliness decreases brain resilience

At same brain volume, cognition was better with ‘someone to talk to’

2300 persons in Framingham study

Original Investigation | Neurology

Association of Social Support With Brain Volume and Cognition

Joel Salinas, MD, MBA, MSc; Adrienne O'Donnell, BA; Daniel J. Kojis, BA; Matthew P. Pase, PhD; Charles DeCarli, MD; Dorene M. Rentz, Lisa F. Berkman, PhD; Alexa Beiser, PhD; Sudha Seshadri, MD

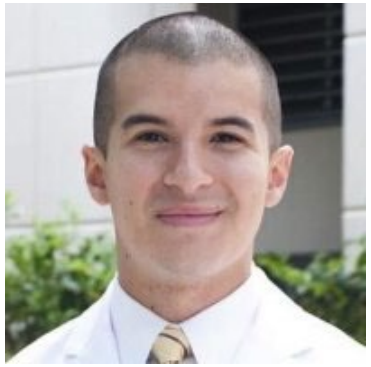
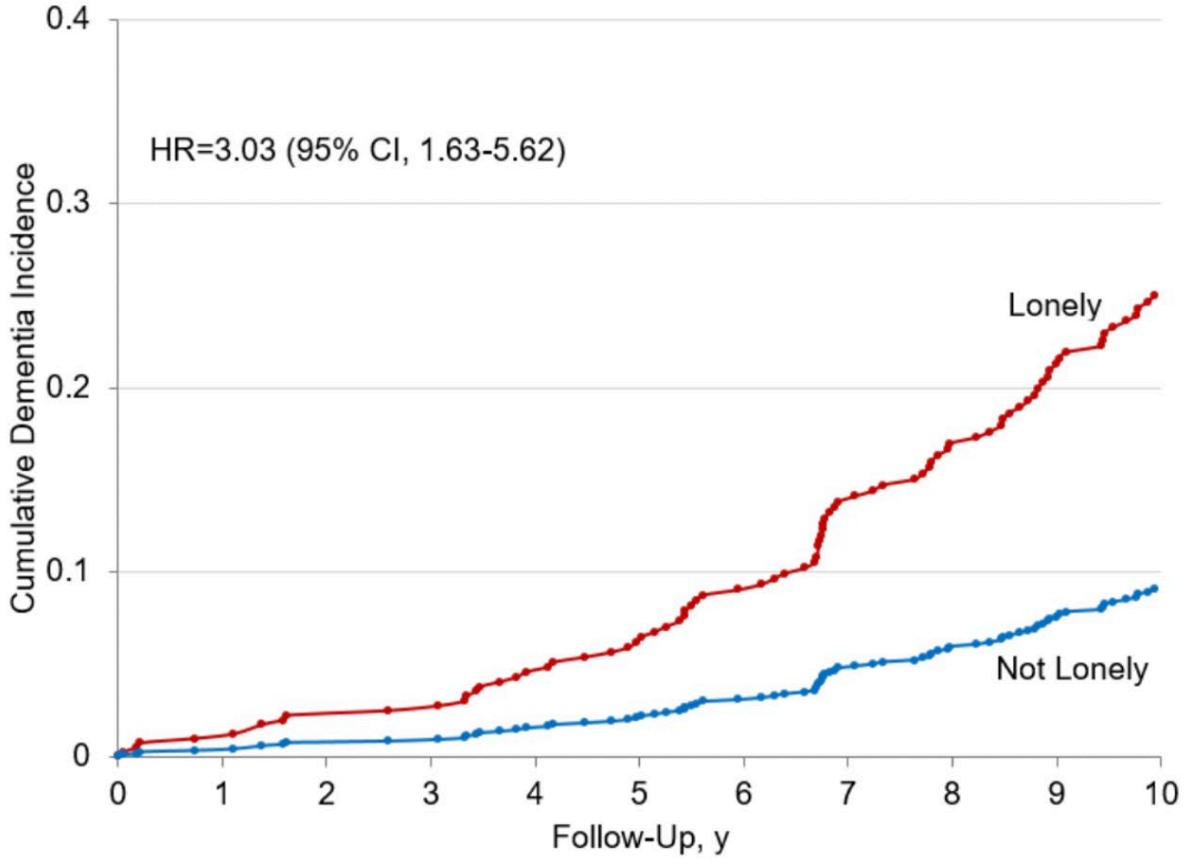
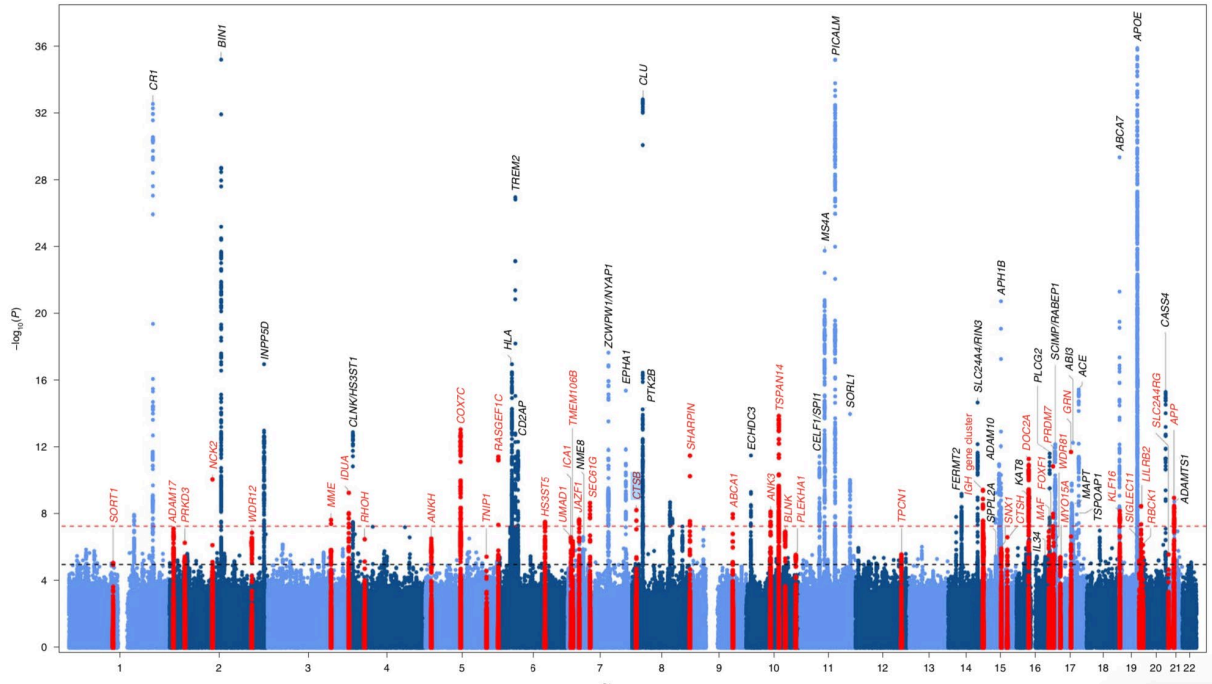


Figure 2. Cumulative Incidence of Dementia by Loneliness Status: Participants Below Age 80 Without an Apolipoprotein E ε4 Allele



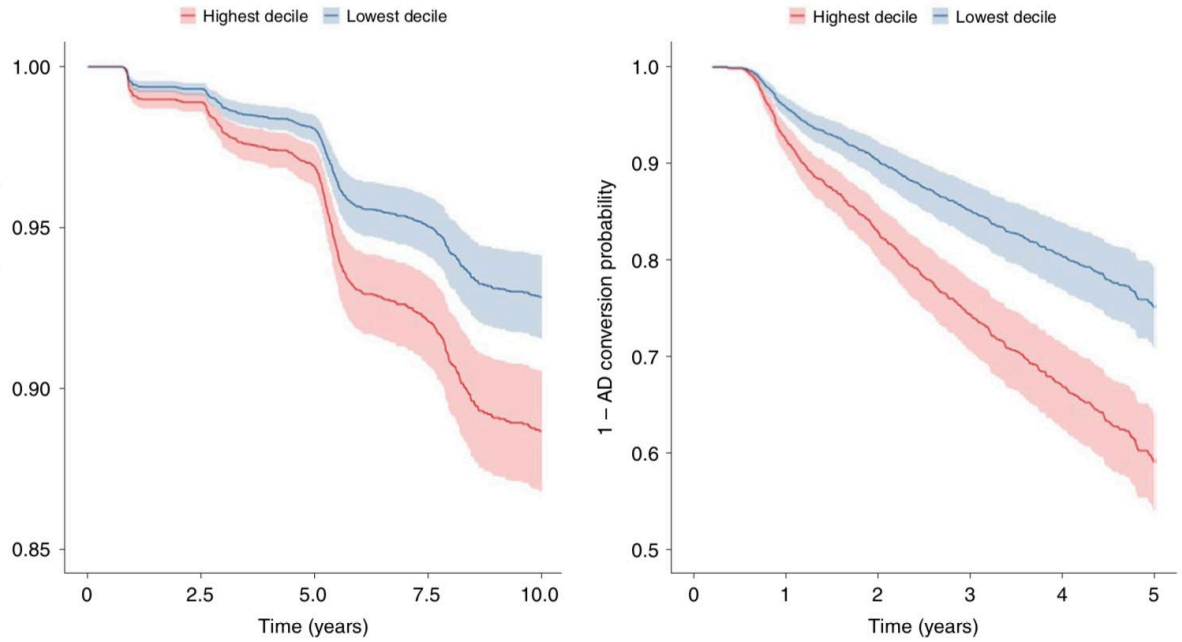


New insights into the genetic etiology of Alzheimer's disease and related dementias

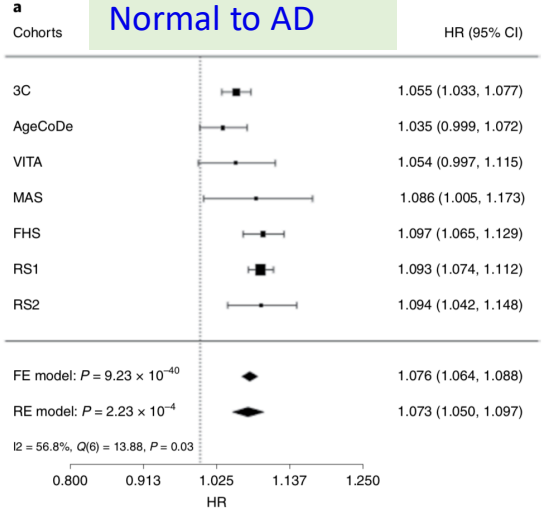
Bellenguez et al.,

Over 90 AD risk genes **Polygenic risk scores**

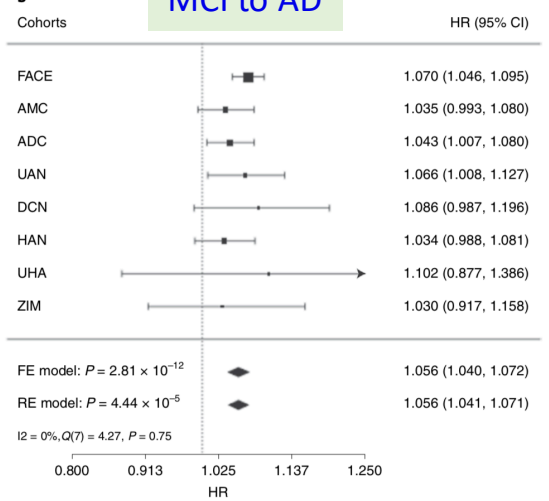
Top versus Bottom Deciles of Risk



Normal to AD

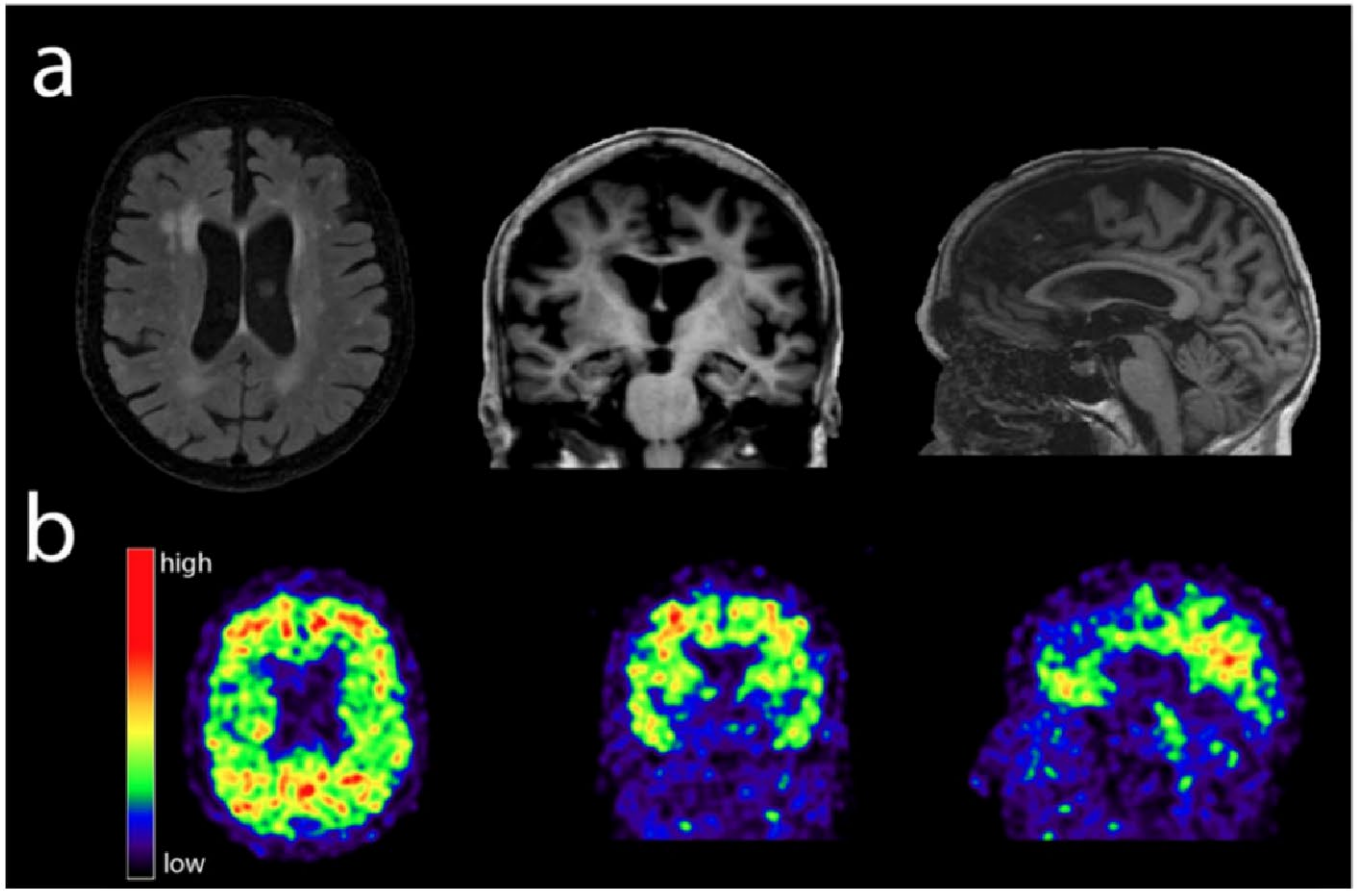


MCI to AD

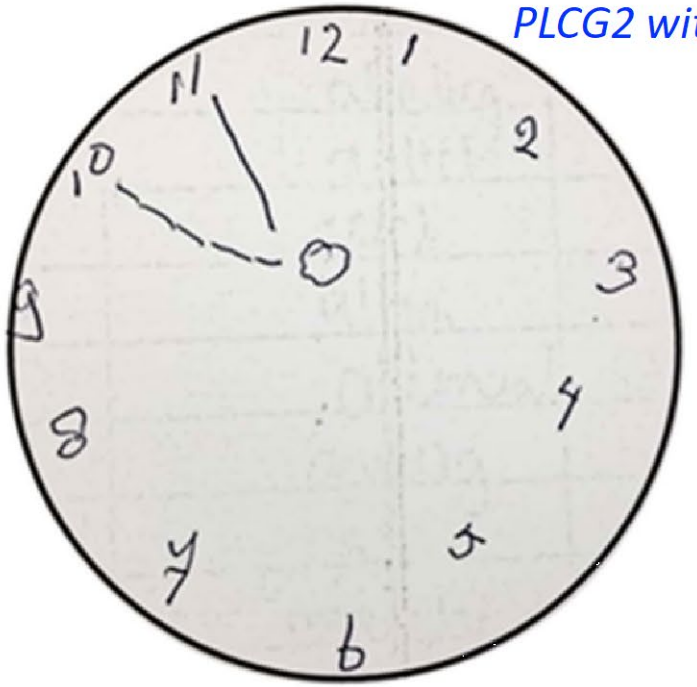


nature genetics

https://doi.org/10.1038/s41588-022-01024-z



102 year old E4/4 carrier with protective variant in *PLCG2 with Normal Cog*



10 minutes before 11

Acta Neuropathologica (2019) 138:237–250
https://doi.org/10.1007/s00401-019-02026-8

ORIGINAL PAPER

A nonsynonymous mutation in *PLCG2* reduces the risk of Alzheimer's disease, dementia with Lewy bodies and frontotemporal dementia, and increases the likelihood of longevity

Genes Altering Resistance to all Dementias

'Age at Onset' is an Endophenotye

Association with:	N-cases	N-controls	Odds-ratio	P-value
Alzheimer's disease (AD)	4,985	8,492	0.57 [0.41-0.78]	0.00063*
Dementia with Lewy-bodies (DLB)	1,446	5,286	0.54 [0.30-0.99]	0.045*
Frontotemporal dementia (FTD)	2,437	10,647	0.61 [0.41-0.89]	0.011*
Progressive supranuclear palsy (PSP)	882	3,187	1.46 [0.83-2.58]	0.19
Amyotrophic lateral sclerosis (ALS)	10,953	20,673	1.07 [0.87-1.33]	0.52
Parkinson's disease (PD)	28,448	108,438	1.18 [0.97-1.44]	0.10
Multiple sclerosis (MS)	4,476	5,714	0.99 [0.74-1.32]	0.95
Reaching the age of >90 years	3,516	9,677	1.50 [1.13-2.00]	0.0051*

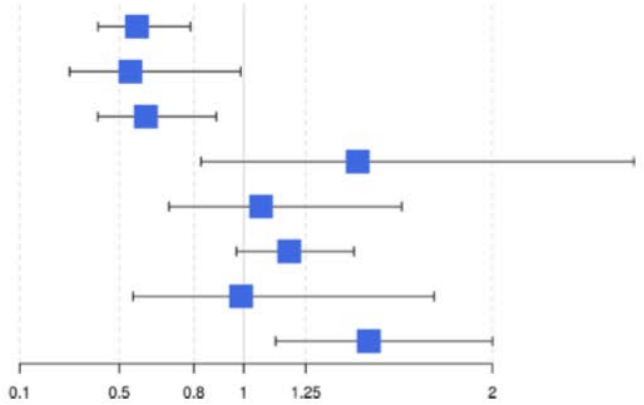
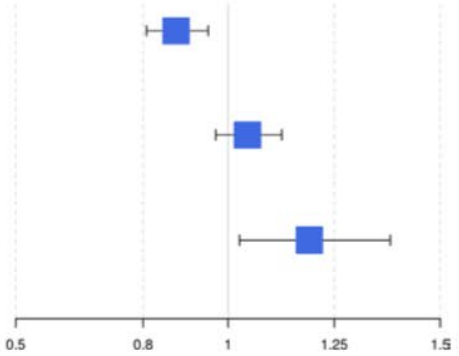


Fig. 1 Association results of rs72824905-G with seven brain diseases and longevity. *P values < 0.05. Numbers (N) of cases (patients or long-lived individuals) and controls studied. The figure shows the odds-ratio (box) of the rs72824905-G with the 95% confidence intervals (whiskers)

PLCG2 protective against all types of dementia and increasing longevity?

Association with:	Comparing:	Odds-ratio	P-value
Parental dementia	16,968 father cases vs. 358,468 father controls + 32,262 mother cases vs. 346,999 mothers controls	0.88 [0.81-0.95]	0.0018*
Parental age >90 years	17,558 father's age =90 years vs. 353,100 father age <90 years + 35,256 mother's aged =90 years vs. 342,810 mother's aged <90 years	1.05[0.97-1.13]	0.24
Parental age >95 years	3043 father's age =95 years vs. 353,100 father's age <90 years + 7790 mother's aged =95 years vs. 342,810 mother's aged <90 years	1.19 [1.03-1.38]	0.021*



Association results of rs72824905-G with dementia by-proxy and longevity by-proxy analysis in the UK Biobank. *P values < 0.05. The figure shows the odds-ratio (box) of the rs72824905-G with the 95% confidence intervals (whiskers)

WHO's work on the UN Decade of Healthy Ageing (2021–2030)

Translational Psychiatry

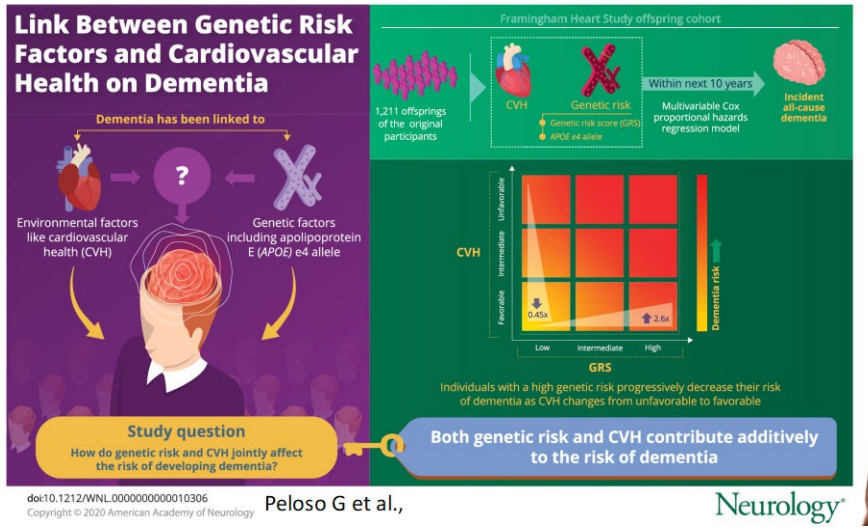
www.nature.com/tp

ARTICLE OPEN

Check for updates

Polygenic resilience scores capture protective genetic effects for Alzheimer's disease

Jiahui Hou[1,2,3], Jonathan L. Hess[1,2,3], Nicola Armstrong[4], Joshua C. Bis[5], Benjamin Grenier-Boley[6], Ida K. Karlsson[7,8], Ganna Leonenko[9], Katya Numbers[10], Eleanor K. O'Brien[11,12], Alexey Shadrin[13], Anbupalam Thalamuthu[10], Qiong Yang[14], Ole A. Andreassen[13], Henry Brodaty[10], Margaret Gatz[7,15], Nicole A. Kochan[10], Jean-Charles Lambert[6], Simon M. Laws[11,12], Colin L. Masters[16], Karen A. Mather[10,17], Nancy L. Pedersen[7], Danielle Posthuma[18], Perminder S. Sachdev[10], Julie Williams[19], the Alzheimer's Disease Neuroimaging Initiative, Chun Chieh Fan[20], Stephen V. Faraone[2,3], Christine Fennema-Notestine[21], Shu-Ju Lin[22], Valentina Escott-Price[9,19], Peter Holmans[19], Sudha Seshadri[23], Ming T. Tsuang[22], William S. Kremen[22] and Stephen J. Glatt[1,2,3,24]✉



988 genetically high-risk "resilient" normal controls
and 6541 genetic risk-matched LOAD cases

Polytranscriptomic Risk Score

CHARGE Consortium and Cross Cohorts Collaboration

Table 1: Cohort	Acronym
Framingham Heart Study	FHS
Cardiovascular Health Study	CHS
Age, Gene/Environment Susceptiblity-Reykjavik Study	AGES
Three Cities study	3C
Rotterdam Study	RS
Atherosclerosis Risk in Communities Study	ARIC
Austrian Study of Stroke Prevention	ASPS
Study of Health in Pomerania	SHIP

Adding:
MEMENTO
San Antonio Heart Mind Study (SAHMS)
San Antonio Family Heart Study (SAFHS)
Multiethnic Study of Aging (MESA)
Strong Heart Study

DOI: 10.1002/alz.040324
PUBLIC HEALTH
POSTER PRESENTATIONS
Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

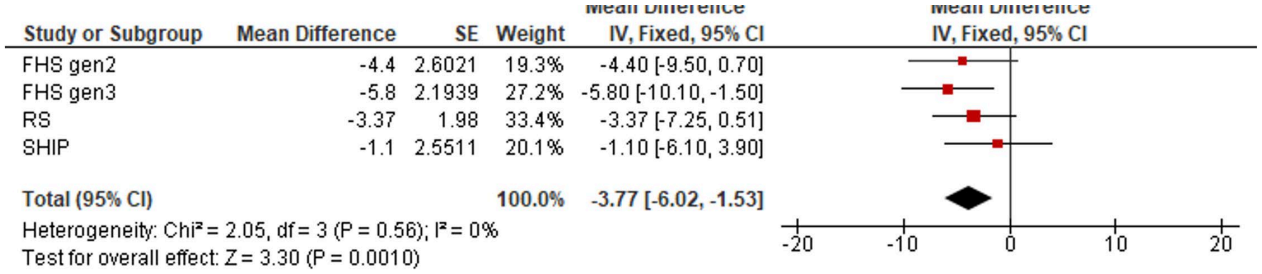
Epidemiology / Risk and protective factors in MCI and dementia

Impaired lung function as a risk factor for accelerated brain ageing

Stefan Frenzel[1] | Robin Bülow[1] | Ralf Ewert[1] | Mohamad Habes[2] | Beate Stubbe[1] | Henry Voelzke[1] | Wittfeld Katharina[1,3] | Sudha Seshadri[4,5] | Hans J. Grabe[1,3]

Multiomics and Biomarkers to Explore Biological Pathways

Non-Alcoholic Fatty Liver Disease, Liver fibrosis and measures of brain aging: the Cross-Cohort Collaboration



Various Brain MRI measures
LV Ejection Fraction and Heart Failure
Renal Function
Social Networks, Physical Activity, Marital Status, Bone density, Sleep
Diets: MIND, Inflammatory Index, Ultra-processed foods
CRP and Other Inflammatory Markers

Biology of Behavioral and Social Determinants

ELSEVIER
Alzheimer's & Dementia ■ (2017) 1-16
Alzheimer's & Dementia

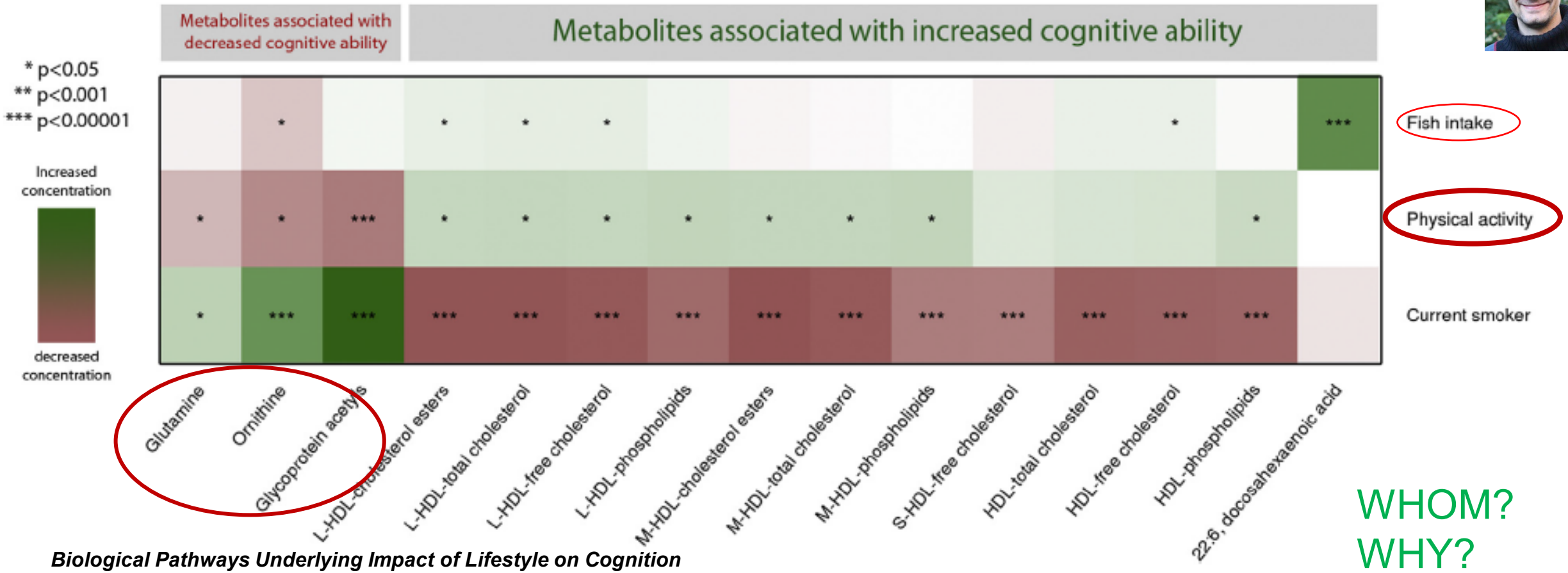
Featured Article

Circulating metabolites and general cognitive ability and dementia: Evidence from 11 cohort studies

ELSEVIER
Check for updates
Alzheimer's & Dementia 14 (2018) 723-733
Alzheimer's & Dementia

Featured Article

Association of branched-chain amino acids and other circulating metabolites with risk of incident dementia and Alzheimer's disease: A prospective study in eight cohorts



Biological Pathways Underlying Impact of Lifestyle on Cognition

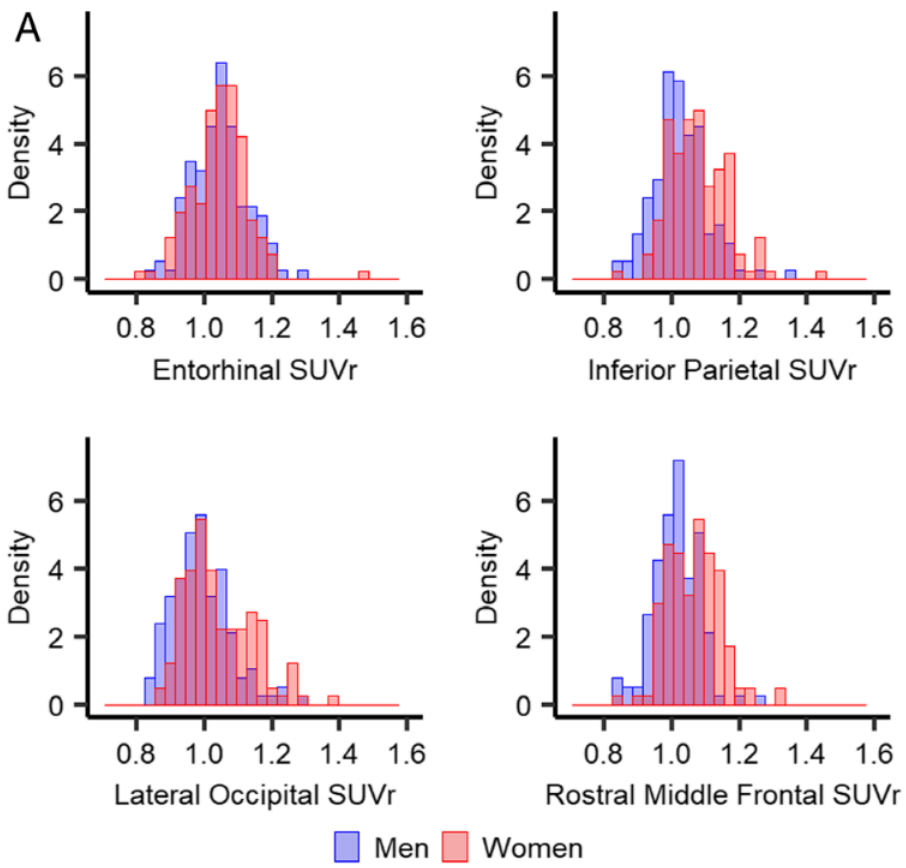
WHOM?
WHY?

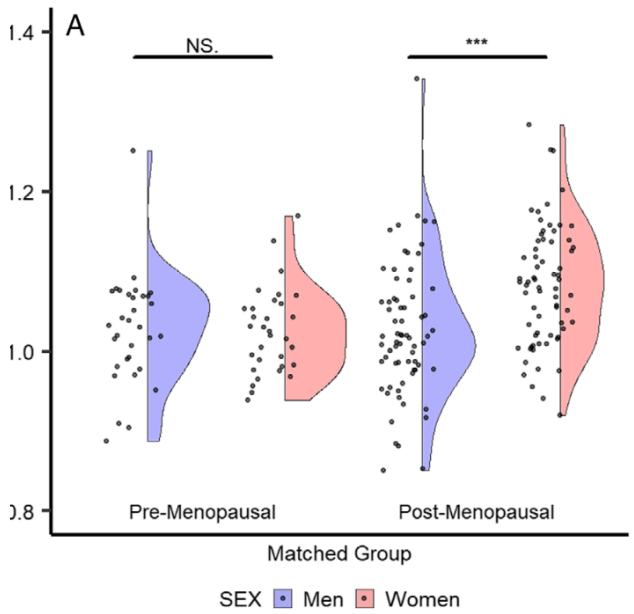
RESEARCH ARTICLE

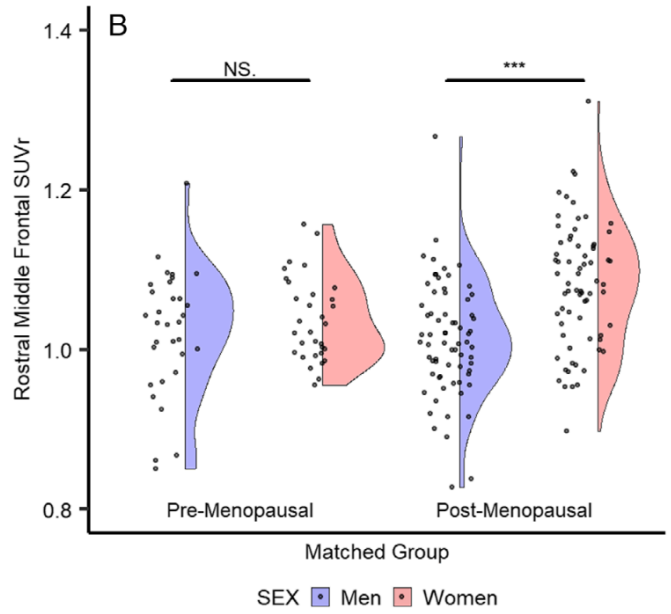
ANN NEUROL 2022;00:1–12

Menopause Status Moderates Sex Differences in Tau Burden: A Framingham PET Study

Rachel F. Buckley, PhD,[1,2,3†] Adrienne O'Donnell, BA,[4,5†] Emer R. McGrath, MB, PhD,[5,6] Heidi I.L. Jacobs, PhD,[7,8] Cristina Lois, PhD,[7] Claudia L. Satizabal, PhD,[5,9,10] Saptaparni Ghosh, PhD,[5] Zoe B. Rubinstein, BA,[7] Joanne M. Murabito, MD,[10] Reisa A. Sperling, MD,[1,2] Keith A. Johnson, MD,[2,7] Sudha Seshadri, MD,[5,9,10‡] and Alexandra S. Beiser, PhD[4,5,10‡]







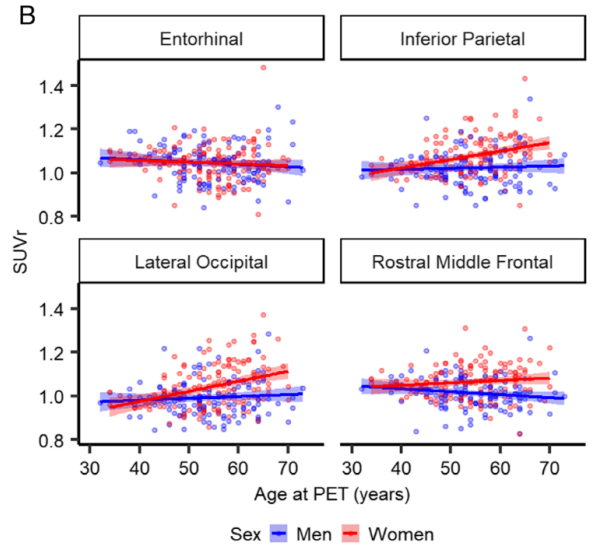


FIGURE 1: Multi-panel histogram/scatterplots of entorhinal, rostral middle frontal, inferior parietal and lateral occipital (unadjusted, raw scores) by (A) sex and (B) sex across the age span.

Cognitively normal persons in FHS; Age 35-75

Post-menopausal women have more tau than age-matched men

J Alzheimers Dis. 2022;86(3):1371-1383. doi: 10.3233/JAD-215409.

Non-Alcoholic Fatty Liver Disease, Liver Fibrosis, and Regional Amyloid-β and Tau Pathology in Middle-Aged Adults: The Framingham Study

Galit Weinstein [1], Adrienne O'Donnell [2 3], Kendra Davis-Plourde [2 3], Shira Zelber-Sagi [1 4], Saptaparni Ghosh [3 5], Charles S DeCarli [6], Emma G Thibault [7], Reisa A Sperling [7 8], Keith A Johnson [7 8], Alexa S Beiser [2 3 5], Sudha Seshadri [3 5 9]

Mean age=52±9y; 43% women

Table 2
Association between NAFLD and PET Amyloid-β and tau (N = 169)

	Model 1		Model 2	
	ß ± SE	*p*	ß ± SE	*p*
Amyloid FLR[a]	0.02 ± 0.16	0.92	0.06 ± 0.19	0.75
Inferior temporal amyloid[a]	–0.07 ± 0.13	0.60	0.03 ± 0.16	0.83
Parahippocampal amyloid	0.05 ± 0.17	0.78	0.13 ± 0.20	0.50
Entorhinal amyloid	0.16 ± 0.16	0.34	0.20 ± 0.19	0.30
Inferior temporal tau	0.15 ± 0.19	0.42	0.18 ± 0.22	0.42
Parahippocampal tau	–0.13 ± 0.20	0.53	–0.05 ± 0.24	0.84
Entorhinal tau	0.04 ± 0.21	0.85	–0.01 ± 0.25	0.96
Rhinal tau	0.07 ± 0.20	0.71	–0.10 ± 0.24	0.69

NAFLD, non-alcoholic fatty liver disease; PET, positron emission tomography; SE, standard error; FLR, frontal, lateral, and retrosplenial. Model 1: Adjusted for age, sex, time between exposure and PET, and camera. Model 2: Adjusted for age, sex, time between exposure and PET, camera, body mass index, alcohol consumption, smoking, cardiovascular disease, c-reactive protein, total to HDL-cholesterol ratio, diabetes, and hypertension. [a]log transformed.

Table 3
Association of liver fibrosis with PET Amyloid-β and tau (N = 177)

	Fib-4 score[a]				Fib-4 > 1.3			
	Model 1		Model 2		Model 1		Model 2	
	ß ± SE	*p*	ß ± SE	*p*	ß ± SE	*p*	ß ± SE	*p*
Amyloid FLR[a]	0.06 ± 0.24	0.82	0.10 ± 0.27	0.71	0.09 ± 0.20	0.66	0.17 ± 0.22	0.43
Inferior temporal amyloid[a]	–0.04 ± 0.19	0.82	–0.11 ± 0.21	0.59	0.05 ± 0.16	0.75	0.11 ± 0.17	0.52
Parahippocampal amyloid	–0.12 ± 0.24	0.62	–0.20 ± 0.26	0.44	–0.01 ± 0.20	0.96	0.06 ± 0.21	0.76
Entorhinal amyloid	–0.34 ± 0.24	0.16	–0.52 ± 0.26	0.05	–0.16 ± 0.20	0.42	–0.13 ± 0.21	0.55
Inferior temporal tau	0.52 ± 0.27	0.06	0.80 ± 0.31	**0.01**	0.16 ± 0.28	0.56	0.28 ± 0.28	0.33
Parahippocampal tau	0.65 ± 0.29	**0.03**	0.88 ± 0.32	**0.01**	0.32 ± 0.30	0.28	0.44 ± 0.30	0.13
Entorhinal tau	0.39 ± 0.30	0.20	0.82 ± 0.35	**0.02**	0.20 ± 0.31	0.51	0.39 ± 0.31	0.22
Rhinal tau	0.72 ± 0.30	**0.02**	1.03 ± 0.33	**0.002**[b]	0.12 ± 0.30	0.68	0.26 ± 0.30	0.39

PET, positron emission tomography; FIB-4, Fibrosis-4 score; SE, standard error; FLR, frontal, lateral, and retrosplenial. Model 1: Adjusted for age, sex, time between exposure and PET, and camera. Model 2: Adjusted for age, sex, time between exposure and PET, camera, body mass index, alcohol consumption, smoking, cardiovascular disease, c-reactive protein, total to HDL-cholesterol ratio, diabetes, and hypertension. [a]log transformed. [b]Significant at FDR-corrected α = 0.05 level. Bold values indicate *p*-value < 0.05.

Table 4
Association of liver fibrosis with PET Amyloid-β and tau in subjects with prevalent NAFLD (N = 41)

	Fib-4 score[a]		Fib-4 > 1.3	
	ß ± SE	*p*	ß ± SE	*p*
Amyloid FLR[a]	1.93 ± 0.47	**<0.001**[b]	1.33 ± 0.44	**0.005**[b]
Inferior temporal amyloid[a]	1.59 ± 0.38	**<0.001**[b]	1.10 ± 0.36	**0.005**[b]
Parahippocampal amyloid	1.52 ± 0.54	**0.008**[b]	1.00 ± 0.49	0.05
Entorhinal amyloid	0.89 ± 0.44	0.05	0.61 ± 0.39	0.13
Inferior temporal tau	2.01 ± 0.47	**<0.001**[b]	2.57 ± 0.56	**<0.001**[b]
Parahippocampal tau	1.60 ± 0.53	**0.007**[b]	1.72 ± 0.70	**0.02**[b]
Entorhinal tau	1.59 ± 0.47	**0.003**[b]	1.97 ± 0.58	**0.003**[b]
Rhinal tau	1.60 ± 0.42	**0.001**[b]	1.59 ± 0.59	**0.01**[b]

PET, positron emission tomography; NAFLD, non-alcoholic fatty liver disease; FIB-4, Fibrosis-4 score; SE, standard error; FLR, frontal, lateral, and retrosplenial. Adjusted for age, sex, time between exposure and PET, and camera. [a]log transformed. [b]Significant at FDR-corrected α = 0.05 level. Bold values indicate *p*-value < 0.05.

Large Consortia are needed to find small effects!

Summary

- Half of all dementia will soon be in the oldest-old
- Multiple Etiology Dementia is the norm
- Genetic and lifestyle, environmental risk and resilience factors modify clinical expression; usually present as multimorbidity
- Large collaborations are needed to identify nuances, understand biology leading to targeted prevention trials

Cohorts for Heart and Aging Research in Genomic Epidemiology & Neurepiomics; Oct 10-12 2023

https://www.chargeconsortium.com

https://sites.bu.edu/melodem/about/