

Introducing The Human Brain Protectome - A Precision Health Framework for Operationalizing Biobehavioral Resilience and Dementia Prevention

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Advancing Geriatrics Research: AGS/NIA Conference Series – Optimizing Resilience

3rd of March, 2026

Atlantic Fellows

FOR EQUITY
IN BRAIN HEALTH

Overview

Prevention is better than Cure!

Desiderius Erasmus, 1500s

- Significant need for global efforts towards cognitive resilience science, dementia prevention and care – **The neuroprotectome framework**
- WWFINGERS in Africa: Community-grounded contextual interventions to boost biobehavioural resilience across underserved regions
- A look to the future: re-conceptualizing brain and cognitive resilience strategies for global applicability



Can we Boost Resilience against Dementia in the Real World? African studies may offer insights...

Chi Udeh-Momoh, Advancing Geriatrics Research: AGS/NIA Conference Series; 2026
Topic: Optimizing Resilience

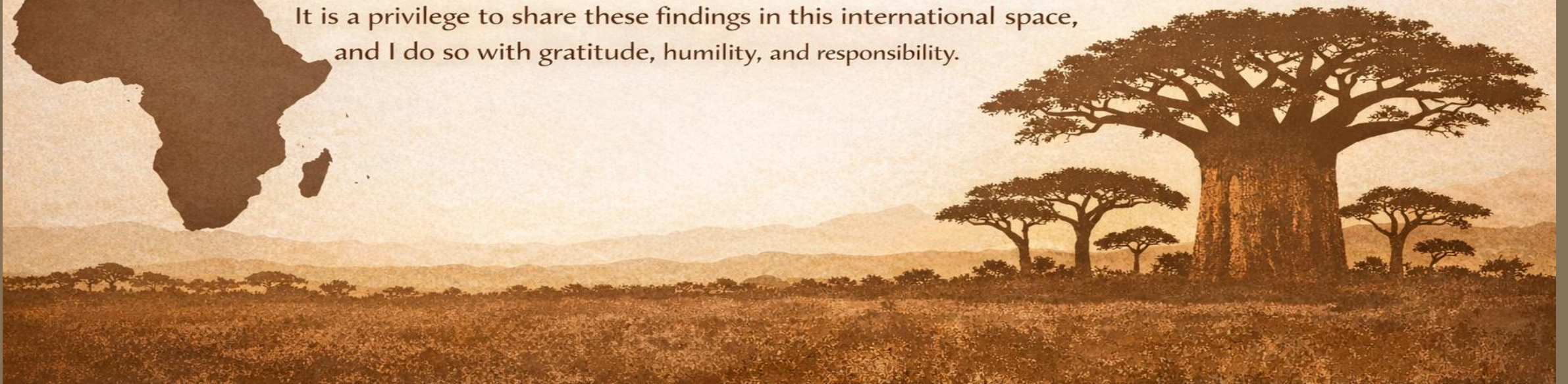


With Gratitude and Respect

I acknowledge and honour the African communities and institutions whose partnership, trust, and leadership underpin the work I will present today.

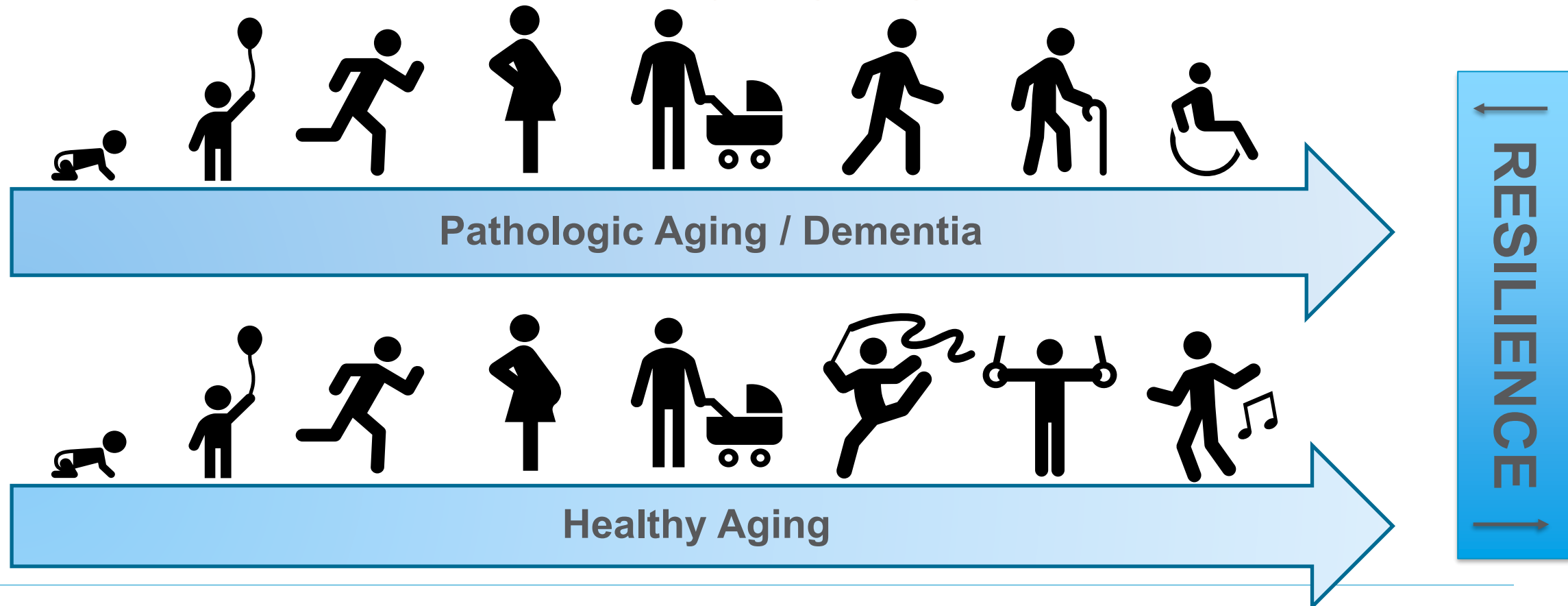
I pay deep respect to our study participants, whose lives, experiences, and generosity make this work possible, and honour the custodians of the lands from which these data emerge; elders past and present, and the ancestral knowledge systems that have sustained health and resilience across generations.

It is a privilege to share these findings in this international space,
and I do so with gratitude, humility, and responsibility.



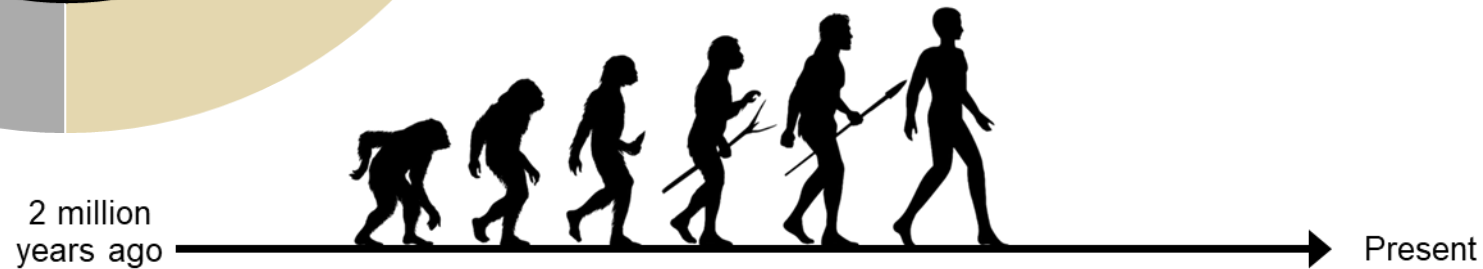
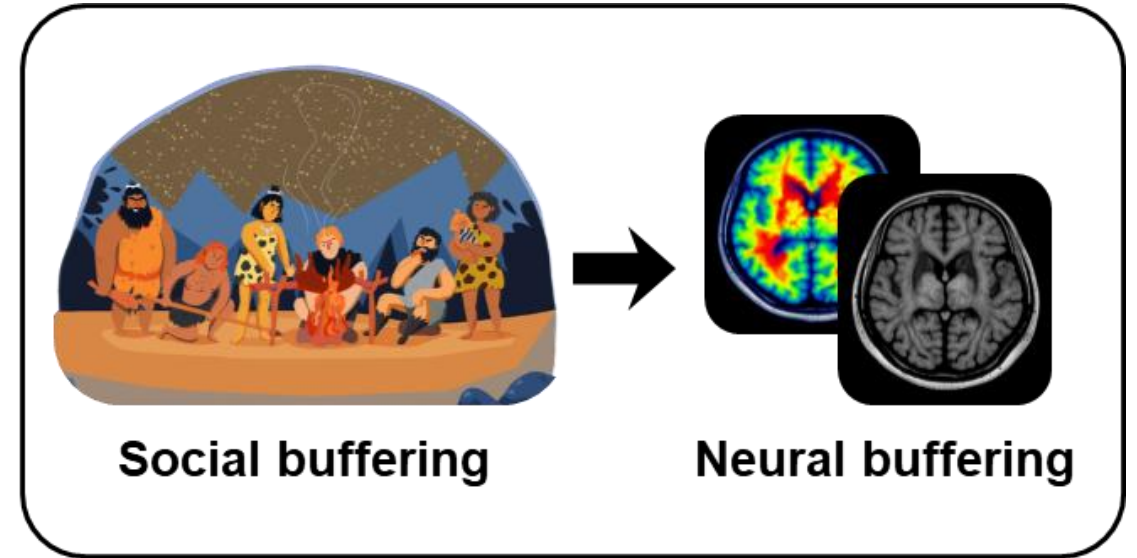
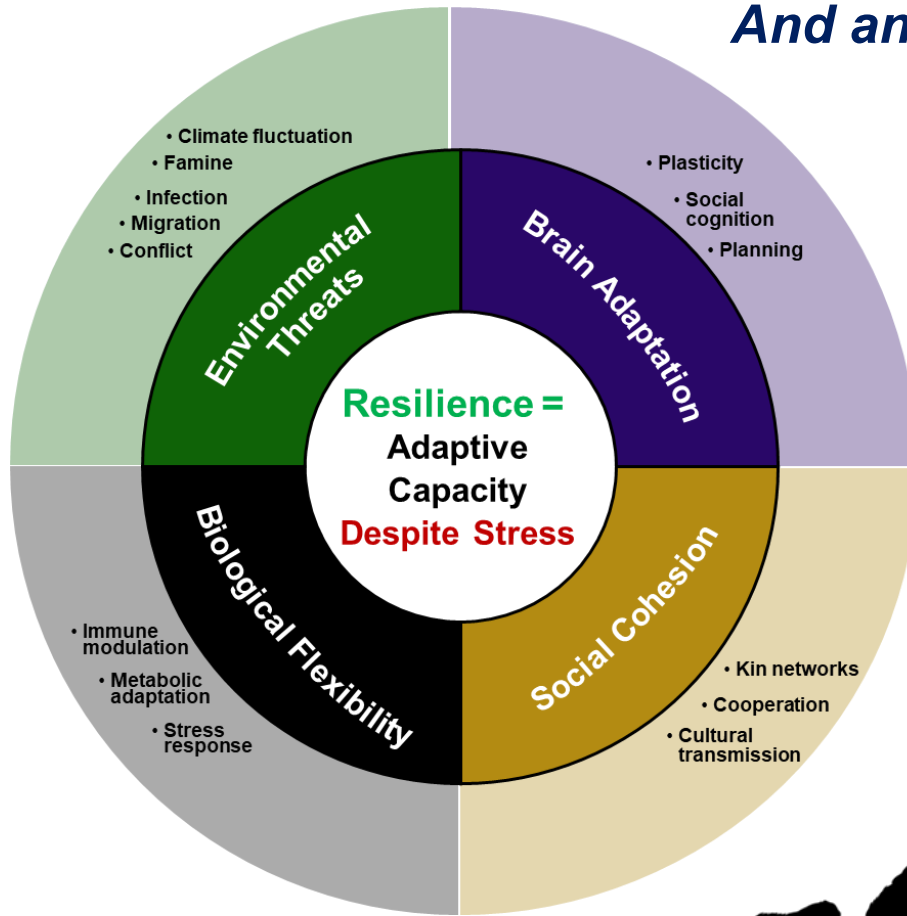
Introduction

There is a difference between pathologic and healthy aging



Resilience: The Original Human Survival Technology

And an Evolutionary Imperative



Refs: McEwen BS. (2007). Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev*; Sapolsky RM. (2004). Why Zebras Don't Get Ulcers; Ellis BJ & Del Giudice M. (2019). Developmental adaptation and evolutionary models; Stern Y. (2009). Cognitive reserve. *Neuropsychologia*.

From Evolutionary Resilience to The Protectome

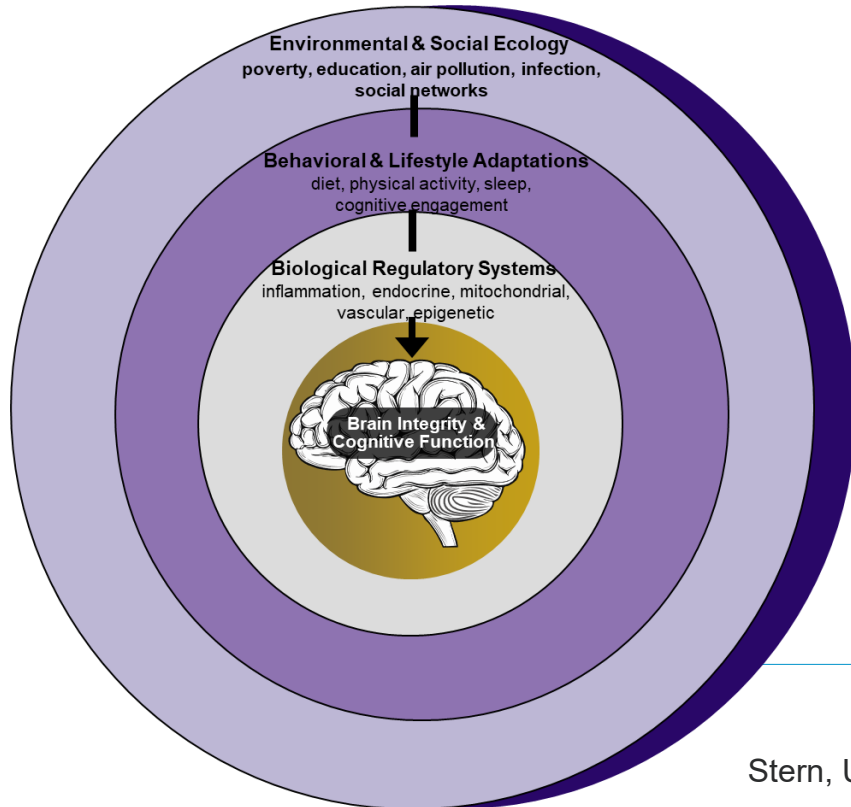
**nature
medicine**

Resilience as an Emergent Systems Property

Review > Nat Med. 2025 Aug;31(8):2518-2531. doi: 10.1038/s41591-025-03846-w.
Epub 2025 Jul 29.

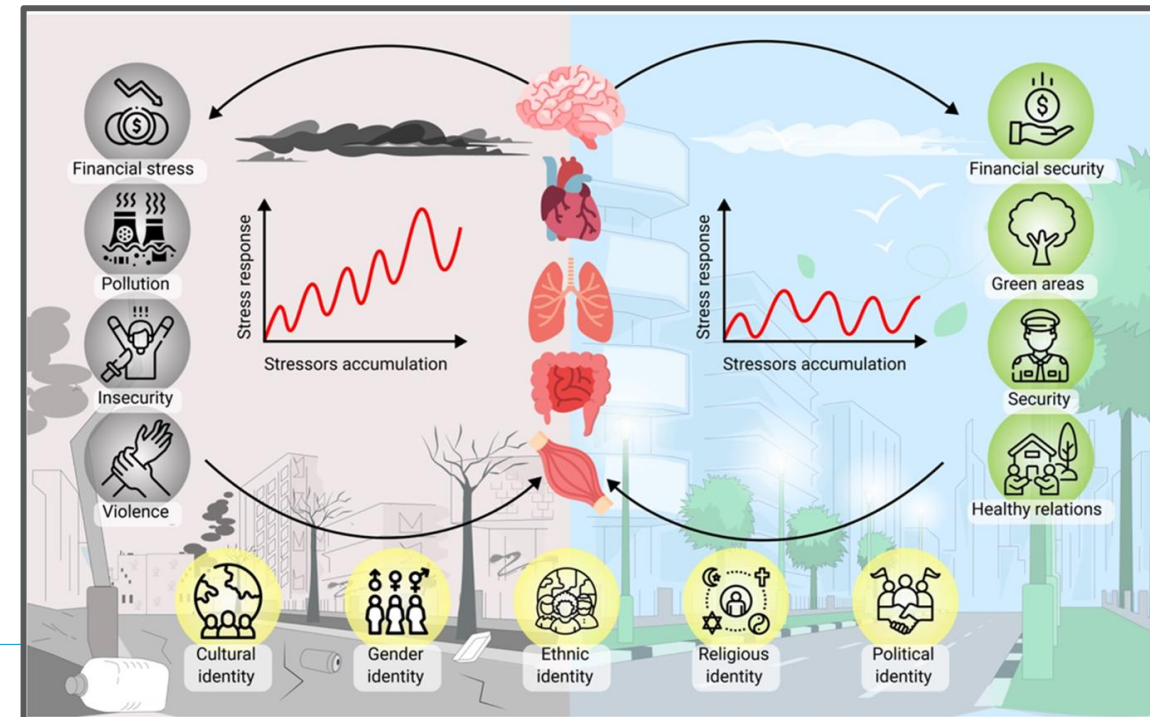
Resilience and brain health in global populations

Chinedu T Udeh-Momoh^{1 2 3 4}, Joaquin Migeot^{5 6 7}, Karen Blackmon^{2 8}, Michelle M Mielke¹,
Margherita Melloni⁵, Lynne Cox⁹, Kristine Yaffe¹⁰, Hernando Santamaria-Garcia^{6 7 11},
Yaakov Stern¹², Agustin Ibanez^{13 14 15 16}



The human neuro-protectome:

Multidimensional synergetic framework for brain resilience dynamically interacting across biological, behavioral, cognitive, social, cultural, ecological and environmental domains



Stern, Udeh-Momoh... et al., *Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance.* *Alzheimers and Dement.* 2019

The whole-body exposomic concept for brain health

Integrative multi-dimensional modelling of multi-dimensional [genetic, socio-ecological, cultural, environmental] exposures for precise and tailored target identification

Ibanez..Udeh-Momoh.. et.al; 2025
Nature comms

Computational whole-body-exposome models for global precision brain health

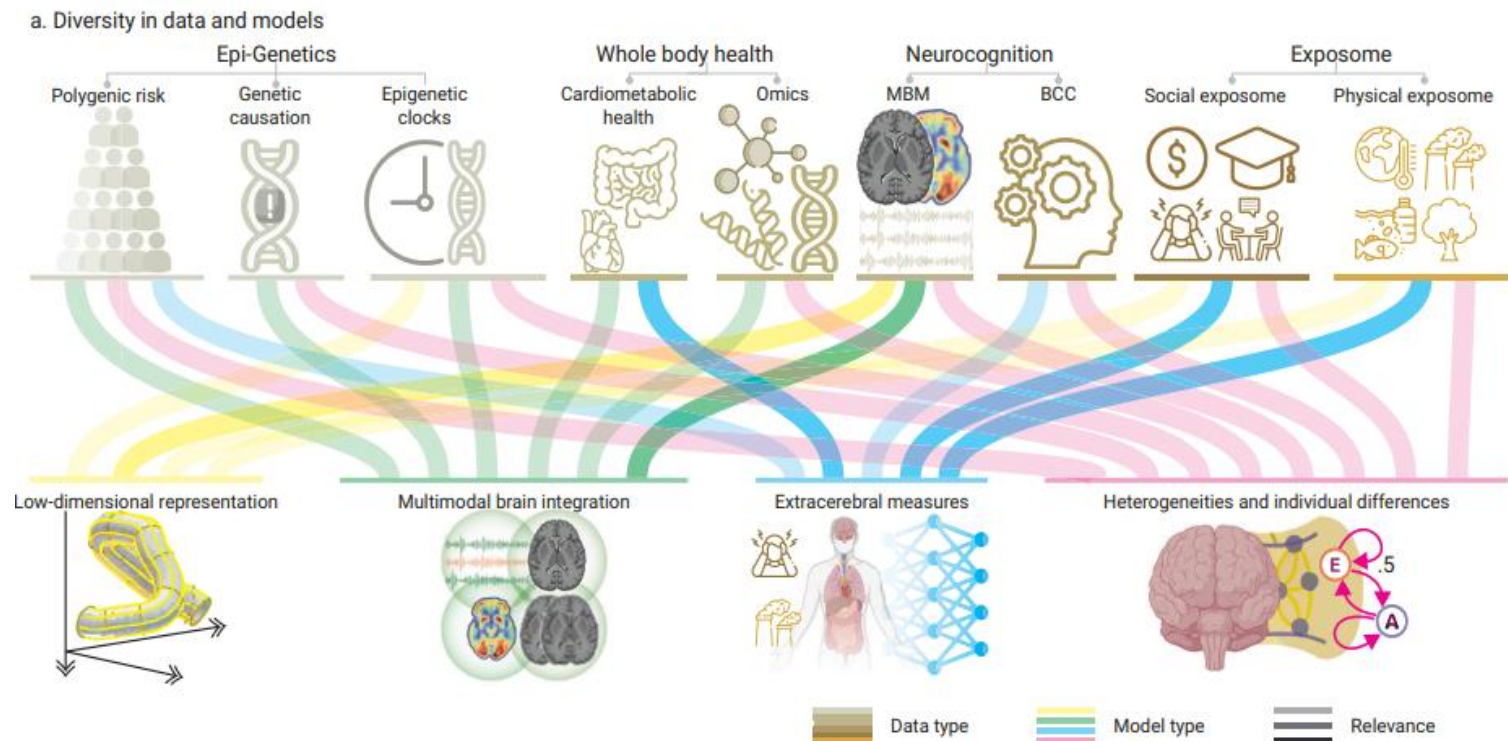
Received: 9 May 2025

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 Check for updates

Agustín Ibáñez^{1,2,3,4,5}✉, Claudia Duran-Aniotz¹, Joaquín Migeot^{1,2}, Sandra Báez^{1,6}, Sol Fittipaldi^{1,2,7}, Carlos Coronel-Oliveros^{1,2}, Harris A. Eyre^{8,9,10,11}, Chinedu Udeh-Momoh^{9,12,13}, Henrik Zetterberg^{14,15,16,17}, Suvarna Alladi¹⁸, Carmen Sandi¹⁹, Ian H. Robertson^{2,20}, Sanne Franzen²¹, Temitope Farombi^{2,22}, Janitza L. Montalvo Ortiz²³, Sudha Seshadri²⁴, Felipe Court^{25,26,27,28}, Pedro Valdes-Sosa^{29,30}, Jiayuan Xu^{31,32}, Chunshui Yu^{31,32}, Lea Grinberg^{9,33,34,35,36}, Brian Lawlor², Perminder S. Sachdev³⁷, Kristine Yaffe^{34,35}, Vladimir Hachinski³⁸, Karl Friston³⁹, Enzo Tagliazucchi^{1,40} & Hernando Santamaría-García^{9,41,42}✉

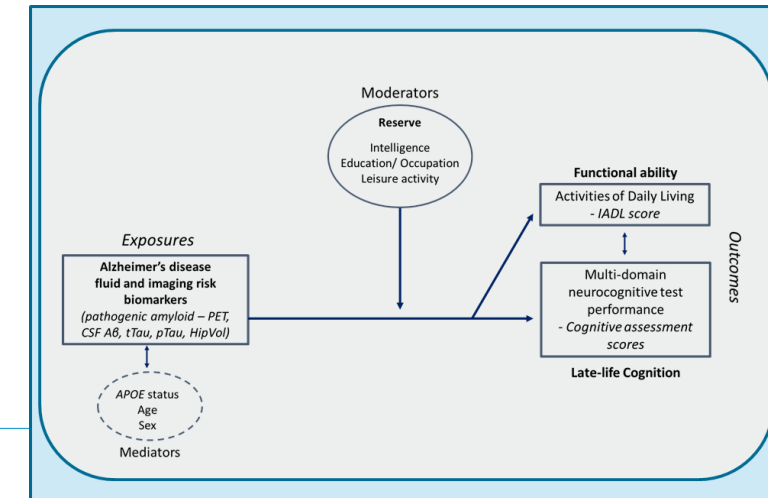
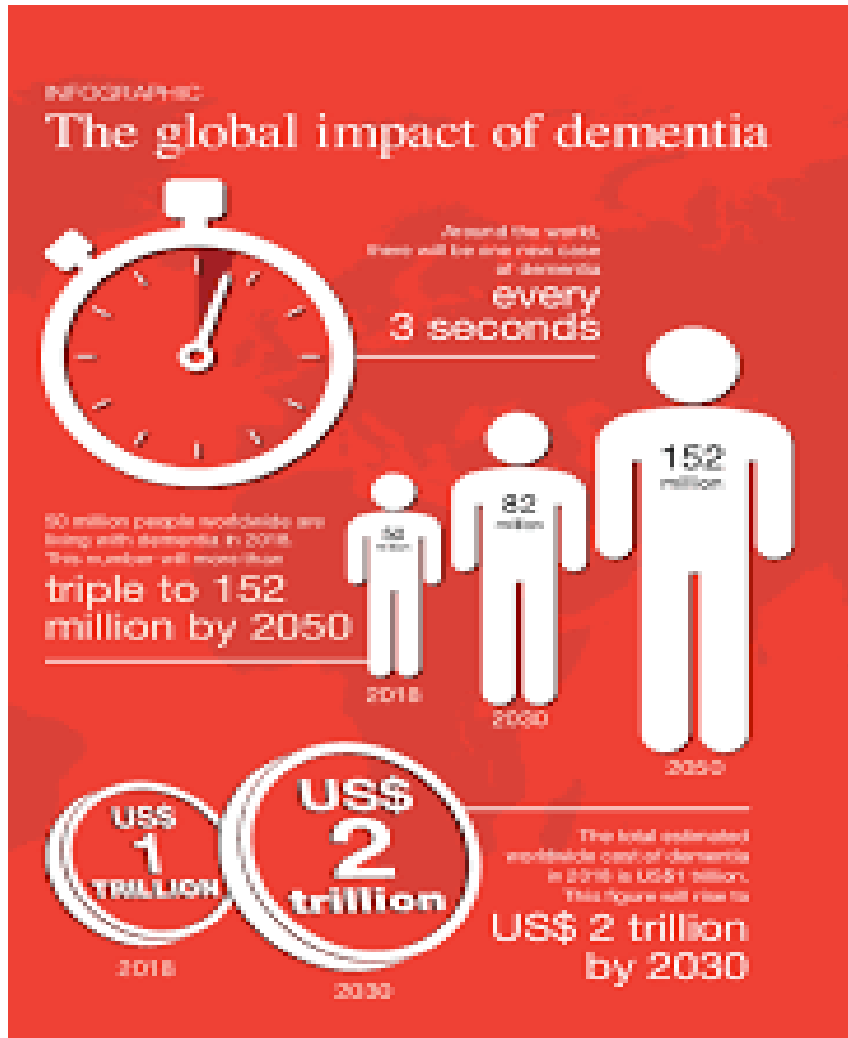


Why Dementia as a cognitive ageing model?

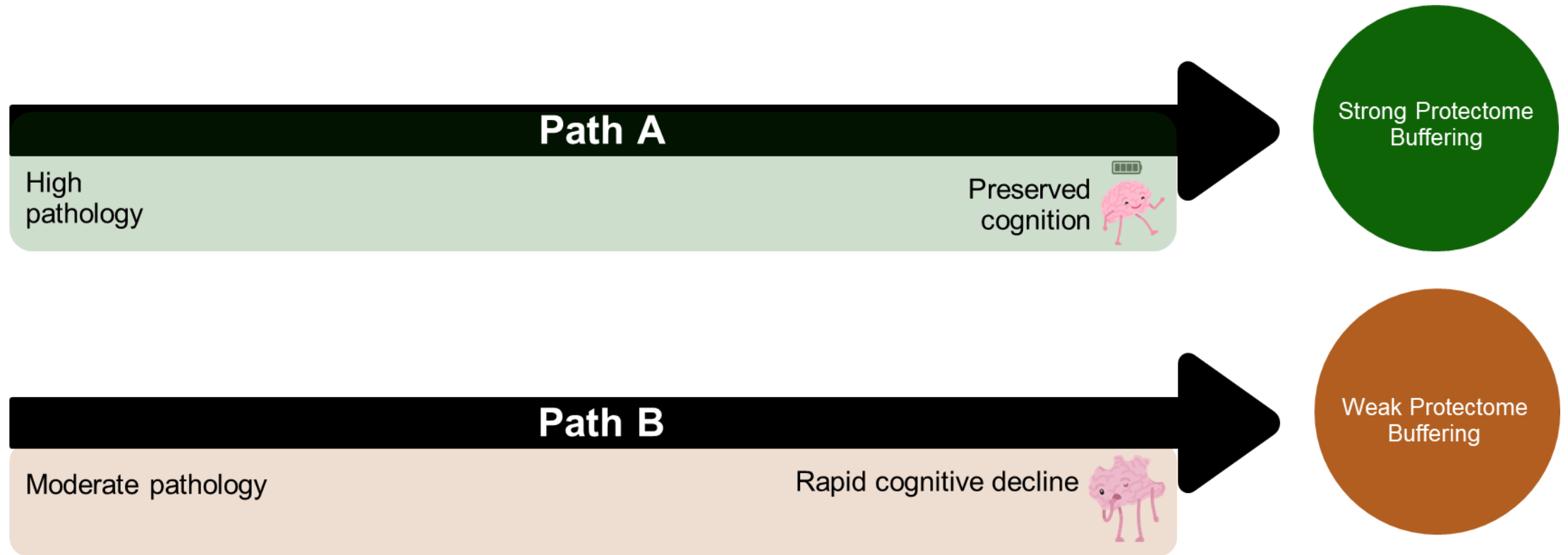
Why Not...

Significant threat to global health

- Global incidence: >50 million -> 152M by 2050 (3/sec). Estimated cost: >\$2 trillion by 2030; AD: >60% of cases worldwide will arise from LMICs
- Neuropathological correlates: amyloid, tau proteins**, brain atrophy; followed by progressive cognitive and functional decline
- Yet: Not everyone with overt pathology or quantifiable risk will develop dementia...
- They are Resilient!!!**



Aberrant Cognitive Aging/ Dementia as a Failure of Adaptive Reserve?



Protective architecture modifies Pathology – Clinical expression relationship

Need for **effective strategies to boost resilience to accelerated cognitive ageing** and prevent dementia



The “rights” of precision drug development for Alzheimer’s disease

Jeffrey Cummings^{1*}, Howard H. Feldman² and Philip Scheltens³

Framework
for
Enhancing
Resilience to
Dementia

- The right **biomarker**
- The right **target**
- The right **participant**
- The right **therapy**
- The right **trial**

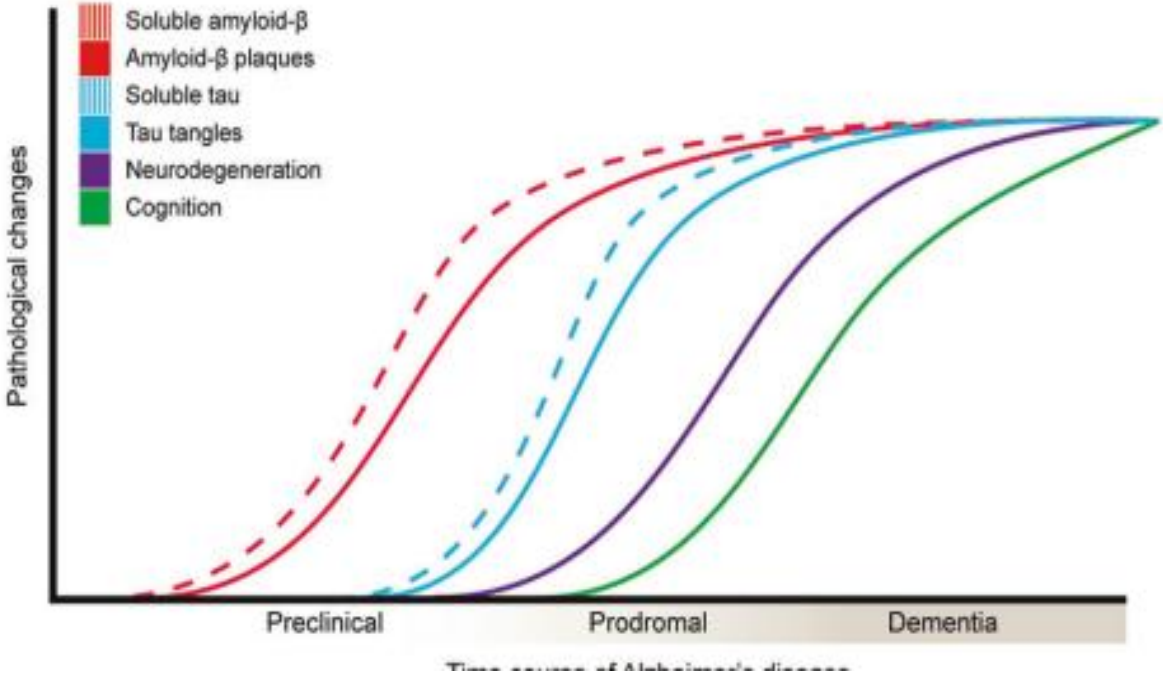
The right biomarkers for ADRD Prevention

Biomarker selection for neurodegenerative diseases must prioritize diagnostic and predictive **accuracy**, **population relevance** *including health complexities and risk profiles*, and a defined **regulatory context of use**



Pathophysiological processes of AD – Timing is everything

Core Biomarkers		
Core 1		
A (Aβ proteinopathy)	Aβ 42	Amyloid PET
T ₁ : (phosphorylated and secreted AD tau)	p-tau217, p-tau181, p-tau231	
Core 2		
T ₂ (AD tau proteinopathy)	MTBR-tau243, other phosphorylated tau forms (e.g., p-tau205), non-phosphorylated mid-region tau fragments ^a	Tau PET
Biomarkers of non-specific processes involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MRI, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD copathology		
V vascular brain injury		Infarction on MRI or CT, WMH
S α-synuclein	αSyn-SAA ^a	



Jack CR Jr, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013 PMID: 23332364; Jack CR Jr, et al., Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimers Dement. PMID: 38934362.

The ADRD brain may vary in terms of race and ethnicity...evidence synthesis: Biomarkers

Received: 25 November 2020 | Revised: 10 September 2021 | Accepted: 15 September 2021
DOI: 10.1002/alz.12511

REVIEW ARTICLE

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

Alzheimer's disease biomarkers in Black and non-Hispanic White cohorts: A contextualized review of the evidence

Carey E. Gleason^{1,2,3} | Megan Zuelsdorff^{2,4} | Diane C. Gooding^{5,6} | Amy J. H. Kind^{1,2,3,7} | Adrienne L. Johnson⁸ | Taryn T. James^{1,2} | Nickola Mary F. Wyman^{3,5} | Fred B. Ketchum⁹ | Alexander Gee¹⁰ | Sterling C. Johnson¹¹ | Barbara B. Bendlin^{1,2} | Henrik Zetterberg^{11,12,13,14,15}

Recommendations: Disparities may be non-biological, rather influence of recruitment bias, life course experiences including social and structural determinants

Brain AD Biomarkers	Results of racial comparison (n=28)
Amyloid PET	Disparate findings
CSF Aβ42	Disparate findings
Tau PET	No differences
CSF pTau181/ tTau	Less pathology in AA
Other biomarkers - NFL - HV - Vascular burden	No differences Greater pathology in AA No differences, but greater burden in AA

**Majority of data from
Western, Educated,
Industrialized, Rich and
Democratic (W.E.I.R.D)
populations**



The tragic consequences of brain health inequity

Need for accessible markers for addressing diagnostic inequities²

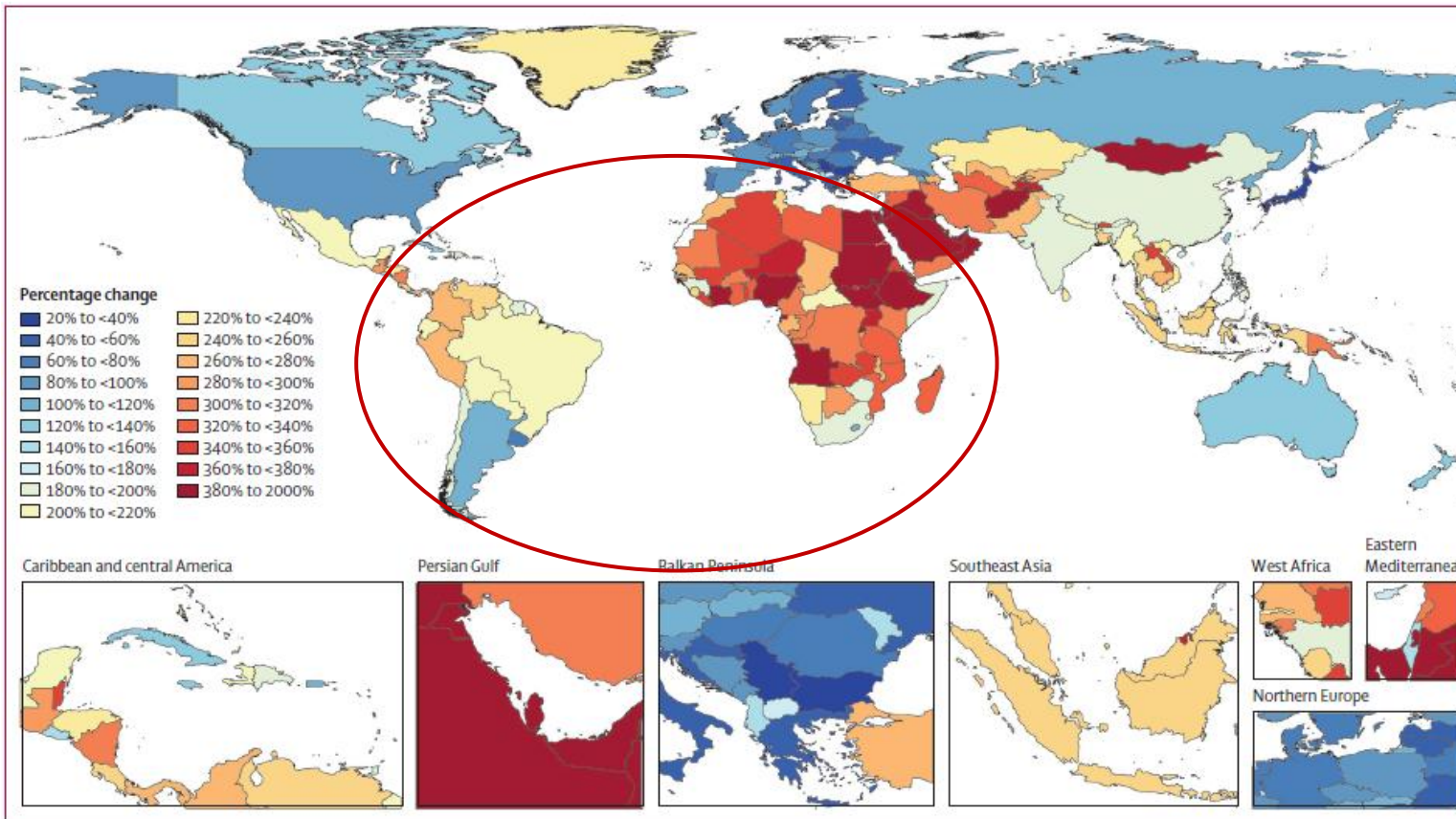


Figure 3: Percentage change between 2019 and 2050 in all-age number of individuals with dementia by country

Dementia research in Africa/S. Asia/ LAC = <10%¹
NDD biomarker studies in LMICs = limited



1) Global Burden of Disease Dementia Forecasting, Lancet 2019; 2) Udeh-Momoh CT, et al; Dementia risk reduction in the African context: Multi-national implementation of multimodal strategies to promote healthy brain aging in Africa (the Africa-FINGERS project). Alzheimers Dement. 2024 PMID: 39511921.

The IMBA Team

IMBA Co-Directors:
Chi Udeh-Momoh, PhD
Karen Blackmon, PhD



Vision and Leadership



Co-Investigator Team



Research and Clinical Project Managers

Communications

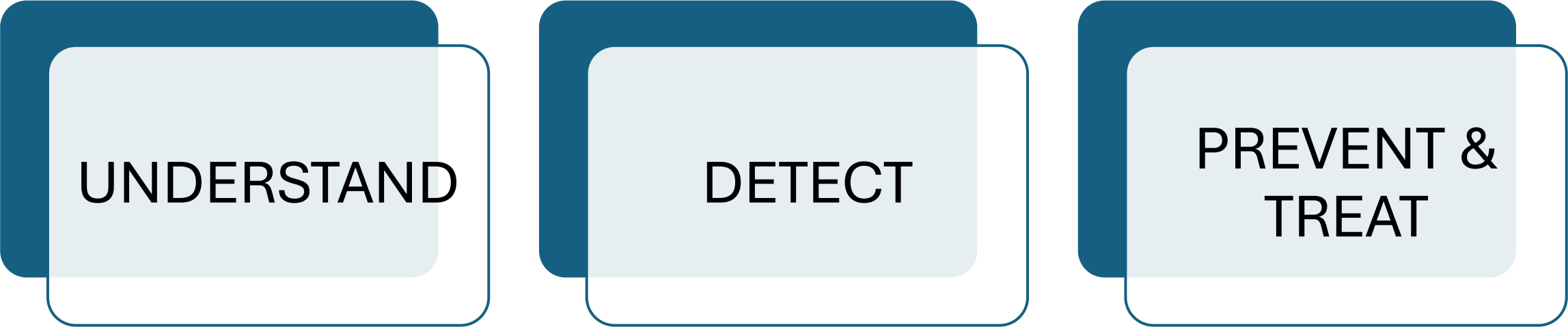
Operations



Up to 40 Staff: Postdoctoral Fellows, Research Associates, Research Assistants, Lab Technologists



IMBA Research Strategy



The diagram illustrates the IMBA Research Strategy as a three-step process. It consists of three identical rectangular boxes arranged horizontally. Each box has a dark blue header and a light blue body. The first box contains the word 'UNDERSTAND', the second 'DETECT', and the third 'PREVENT & TREAT'. The boxes are slightly offset to the right, creating a sense of progression.

UNDERSTAND

DETECT

PREVENT &
TREAT



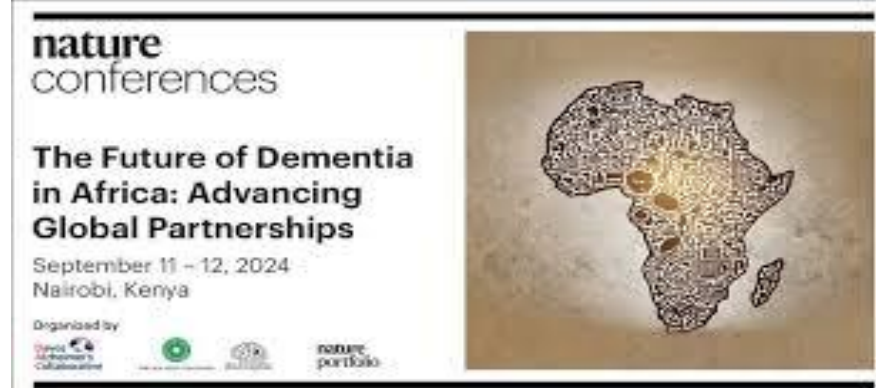
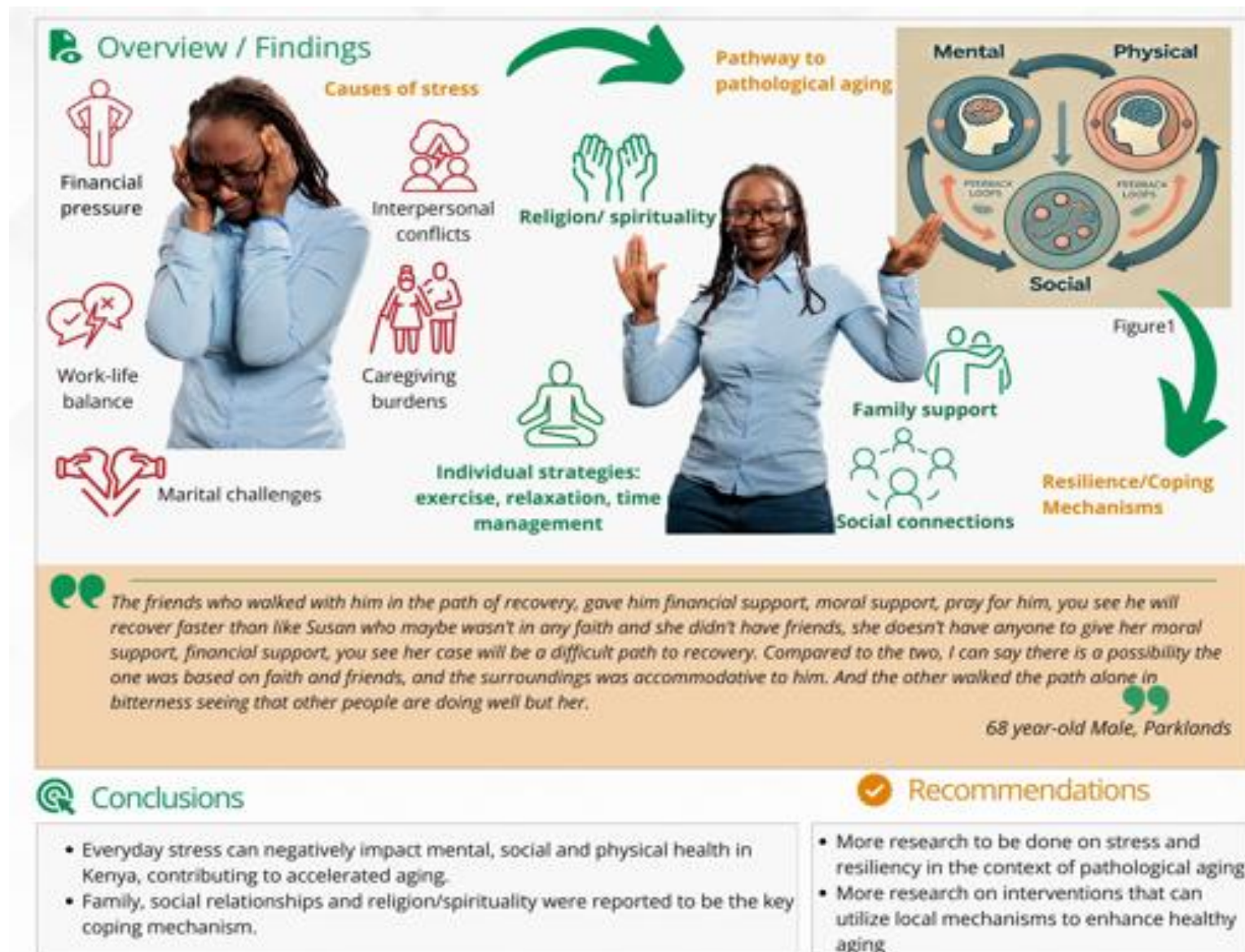
Bosire, Udeh-Momoh et al. Journal of Alzheimer's Disease. 2025; 108(4):1537-1548.

Community Perceptions and Willingness to Donate Biospecimen for Alzheimer's Disease Research in Nairobi, Kenya

Edna Bosire, Lucy Kamau, Caroline Kiio, Karen Blackmon, Olivera Nesic Taylor, Jasmit Shah, Dilraj Sokhi, Sylvia Mbugua, Irene Meier, Juzar Hooker, Vaibhav Narayan, Zul Merali and Chinedu Udeh-Momoh



Exploring Stress and Resiliency in the Context of Pathological Aging in Kenyans

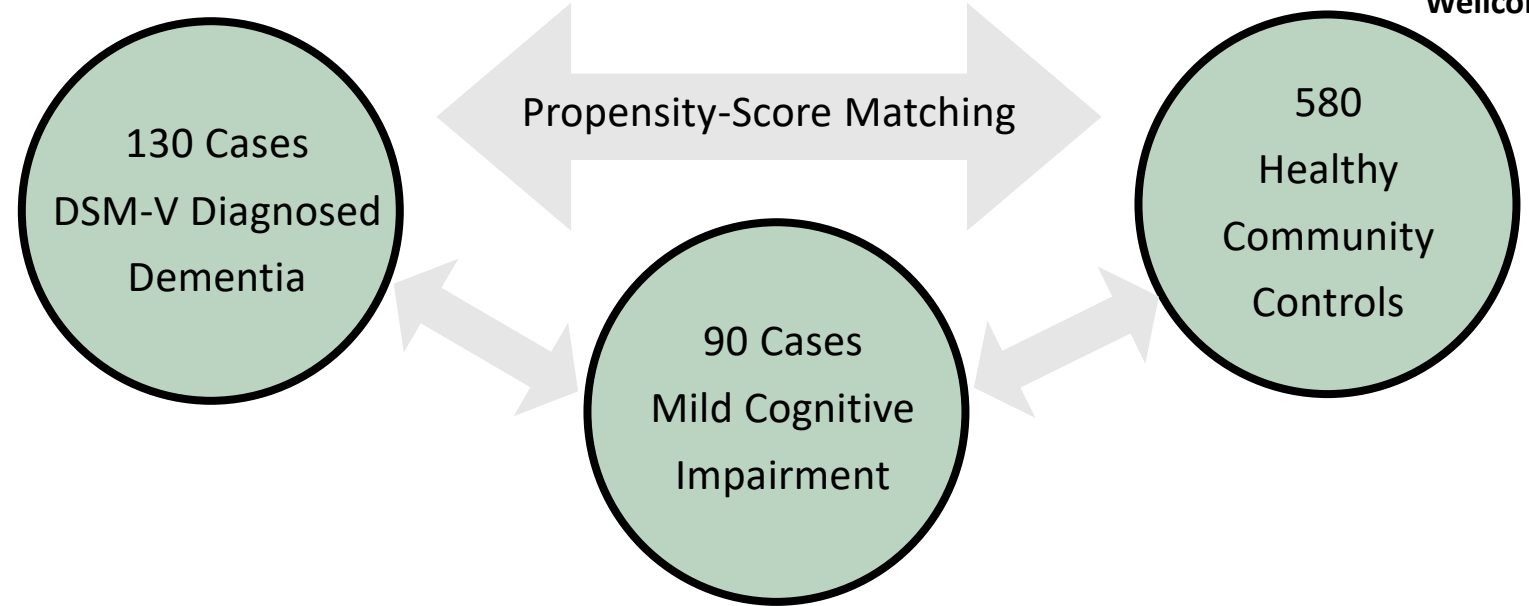


Study Designs (n=4): Case-Control/ Prospective

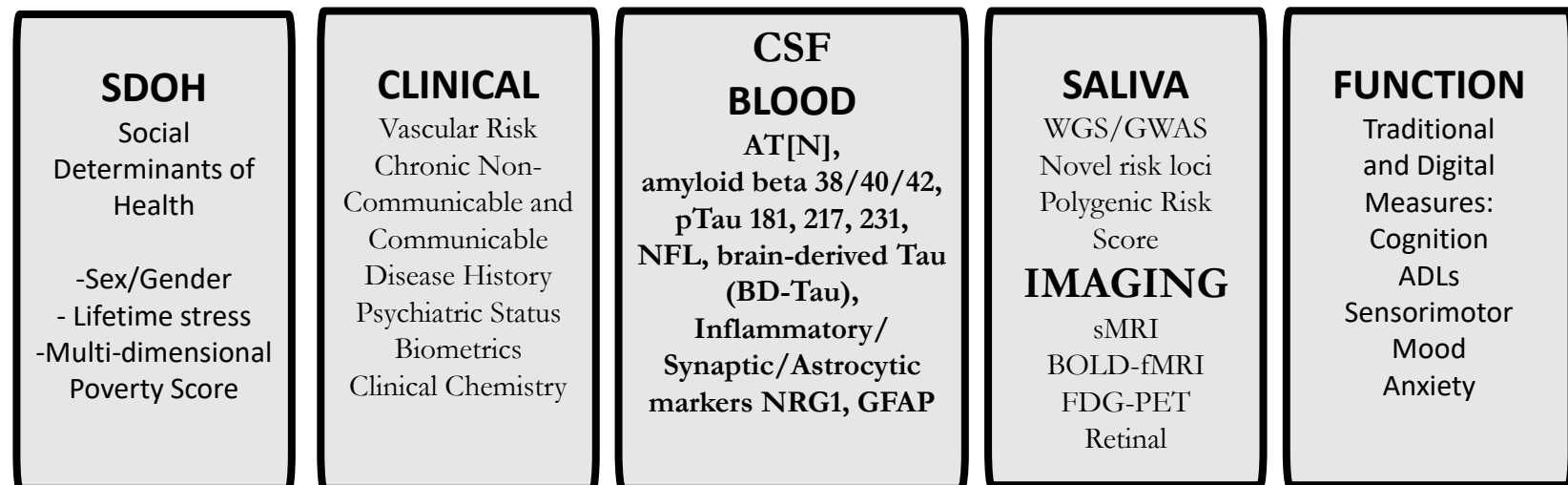
STUDIES

BHAP-KENYA (BRIDGE)
 AD-DETECT-KENYA
 FEMBER-AFRICA
 BRAIN-RESILIENCE-KENYA
 Identify **novel biomarkers** of
Pathological and
Resilient Aging in
 Kenyan Adults

PI and Biomarker Lead:
 Chi Udeh-Momoh, PhD
 Co-PI and Neuropsych Core
 Lead: Karen Blackmon, PhD



DEEP PHENOTYPING FOR BIOMARKER DISCOVERY



*NRG=Neuregulin; GFAP=Glial Fibrillary Acidic protein; GWAS=Genome-Wide Association Study; ADL=Activities of Daily Living

Blood-based CNS Biomarker Profile across cognitive groups

Dr Tolulope Akinyemi

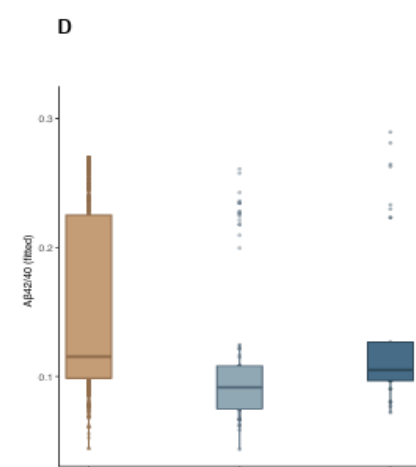
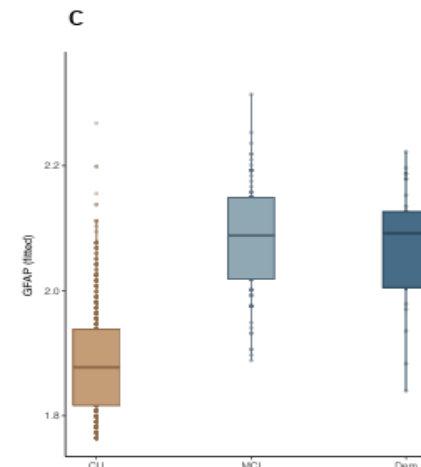
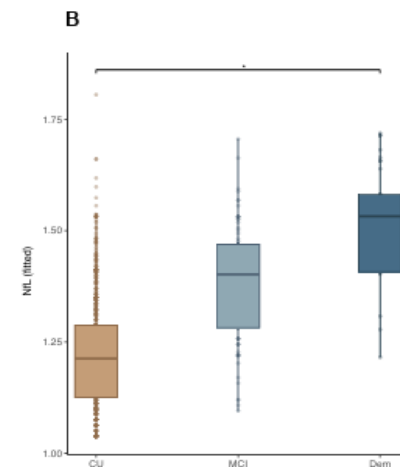
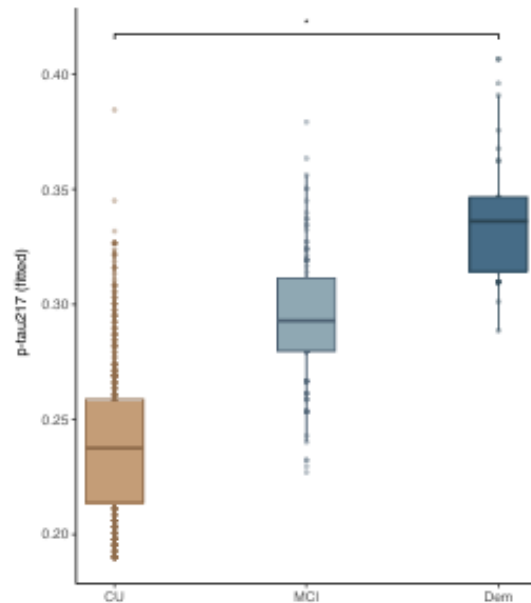


Project Type - Pilot Projects

Vascular heALTH, frailty and cognition in Ageing Nigerians sTudy [VALIANT]

Investigate the association of cardiovascular health with cognition and frailty

Western Africa



Biomarker	CU	MCI	Dementia
Ab42/40	0.14±1.05	0.11 ±0.19	0.13±0.26
pTau 217	0.35±0.19	0.44±0.30	0.48±0.33***
NFL	23.20±51.77	31.14±28.90	47.55±57.41**
GFAP	121.59±95.71	181.89±181.73	173.23±111.94***

Akinyemi T, Kalaria R, Pericak-Vance M, Zetterberg H, Udeh-Momoh C, Akinyemi R et al., Neurodegenerative Disease plasma biomarkers in in community dwelling Nigerian middle aged and older adults across the dementia clinical continuum; *manuscript under review – Nature Communications*

Framework for Prevention: The right biomarker (+ target)

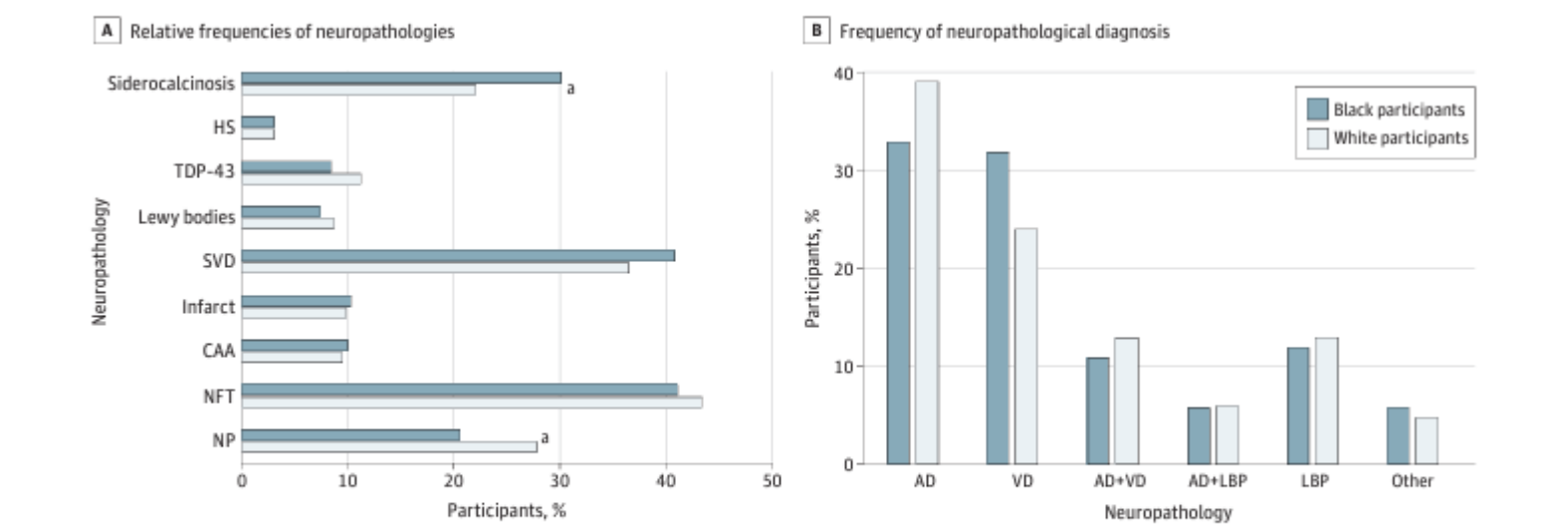


Original Investigation | Neurology

Neuropathological Lesions and Cognitive Abilities in Black and White Older Adults in Brazil

Claudia K. Suemoto, MD, PhD; Renata E. P. Leite, PhD; Vitor R. Paes, MD; Roberta Rodriguez, MD, PhD; Alberto F. O. Justo, PhD; Michel S. Naslavsky, PhD; Mayana Zatz, PhD; Carlos A. Pasqualucci, MD, PhD; Ricardo Nitrini, MD, PhD; Eduardo Ferrioli, MD, PhD; Wilson Jacob-Filho, MD, PhD; Lea T. Grinberg, MD, PhD

Figure 1. Frequencies of Neuropathologies and Neuropathological Diagnoses in Black and White Participants



A total of 747 participants had a neuropathological diagnosis. AD indicates Alzheimer disease; CAA, cerebral amyloid angiopathy; HS, hippocampal sclerosis; LBP, Lewy body pathology; NFT, neurofibrillary tangles (Braak and Braak staging $\geq$ III); NP, neuritic plaques (Consortium to Establish a Registry for Alzheimer Disease grade $\geq$ B); SVD, small vessel disease; TDP-43, TAR DNA-binding protein 43; and VD, vascular dementia.

^a $P < .05$.

Key Points

Question Do neuropathology and cognitive abilities differ by race?

Findings In a cross-sectional autopsy study with 1815 Black and White older adults in Brazil, neuritic plaques were less frequent in Black participants than White participants, while small vessel disease and siderocalcinosis were more frequent. Alzheimer disease was more common among White than Black participants, while vascular dementia was more common among Black than White participants; however, cognitive abilities were similar between Black and White participants.

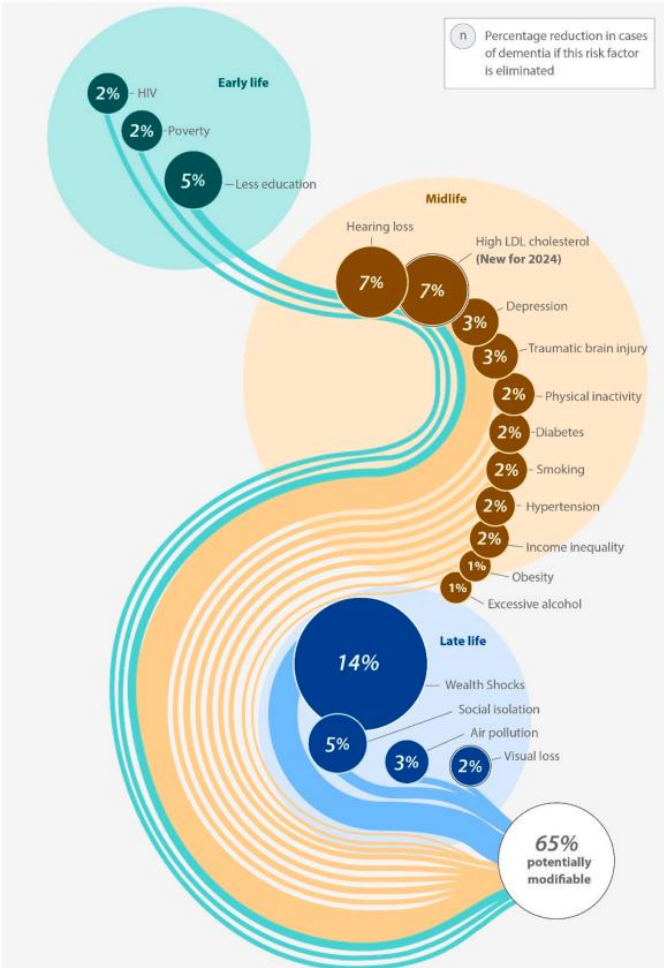
Meaning This study found differences in frequency of specific neuropathologies by race, but no difference in cognitive impairment.



The Right Target:
identifying key risk/
resilience factors for
appropriate biologic
process

Broadening dementia risk models: building on the 2024 Lancet Commission report for a more inclusive global framework

Cyprian M. Mostert,^{a,b,c,*} Chinedu Udeh-Momoh,^{a,b,e} Andrea Sylvia Winkler,^{f,g,h} Connor McLaughlin,ⁱ Harris Eyre,^j Mohamed Salama,^{a,k} Kirti Ranchod,^l Dominic Trepel,^a George Vradenburg,ⁱ William Hynes,^{m,n} Graham Fieggen,^o Shehzad Ali,^{p,q} Najat E. L. Mekkaoui,^r Alan Landay,^s Kirsten Bobrow,^t Levi Muyela,^b Kelly Atkins,^u Antonella Santucci Chadha,^v Roberta Marongiu,^{v,w} Mariapaola Barbato,^v Sam Nightingale,^x John Joska,^y Alfred K. Njamnshi,^{z,aa,af} Mie Rizig,^{ab} James G. Kahn,^{ac} Karen Blackmon,^{b,ad} Zul Merali,^b and Agustin Ibanez^{a,d,ae}



Prevention potential $\approx$ 65%
18 modifiable risk factors

Risk factors

- Diabetes
- High blood pressure
- Obesity at midlife
- Physical inactivity
- Depression
- Smoking
- Low education
- Hearing loss
- Traumatic Brain Injury
- High alcohol consumption
- Social isolation
- Air pollution
- Uncorrected vision loss
- LDL cholesterol
- Poverty
- Wealth shocks
- Income Equality
- HIV

Protective factors

- Healthy nutrition
- Sense of safety
- Spirituality/ Mindfulness
- Cognitive enrichment

Other important factors

- Loneliness
- Hopelessness
- Chronic Stress
- Sleep disturbances
- Impaired oral health
- Other Infections?

Publication Alert!

[nature](#) > [nature reviews neurology](#) > [perspectives](#) > article

Perspective | Published: 11 July 2025

Translating lifestyle interventions for optimal brain health in Africa

[Chinedu T. Udeh-Momoh](#) , [Celeste A. de Jager Loots](#), [Tamlyn J. Watermeyer](#), [Udunna C. Anazodo](#), [Catherine Ajalo](#), [Edna N. Bosire](#), [Ameenah Sorefan](#), [Christine Musyimi](#), [Chido Rwafa](#), [Njideka Okubadejo](#) & [Miia Kivipelto](#)

nature medicine

Review article

<https://doi.org/10.1038/s41591-025-03846-w>

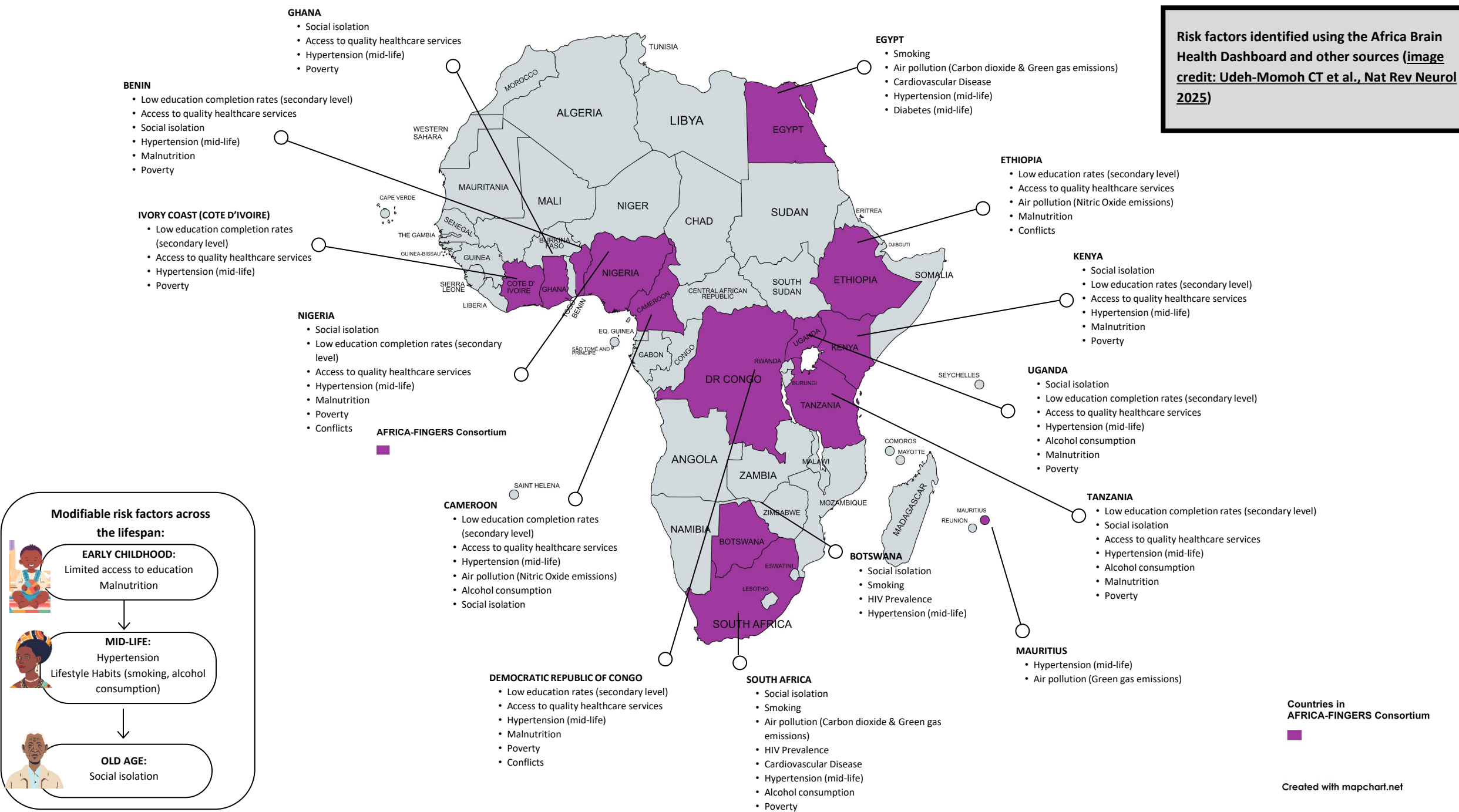
Resilience and brain health in global populations

Received: 12 February 2025

Accepted: 18 June 2025

Chinedu T. Udeh-Momoh^{1,2,3,4}, Joaquin Migeot^{5,6,7}, Karen Blackmon^{2,8}, Michelle M. Mielke⁹, Margherita Melloni⁹, Lynne Cox⁹, Kristine Yaffe¹⁰, Hernando Santamaria-Garcia^{6,7,11}, Yaakov Stern¹² & Agustin Ibanez^{5,6,7,13} 

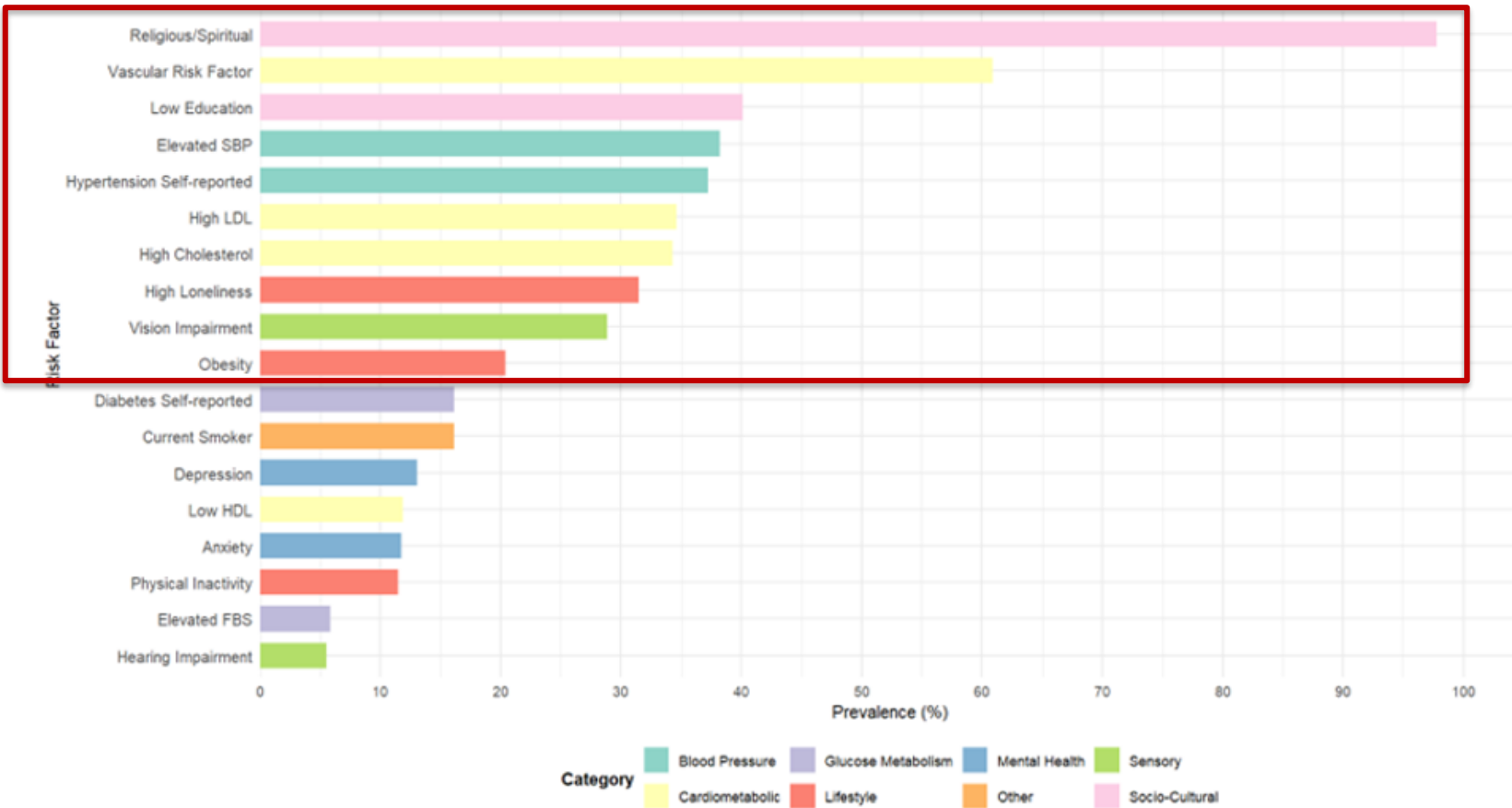
Risk factors identified using the Africa Brain Health Dashboard and other sources ([image credit: Udeh-Momoh CT et al., Nat Rev Neurol 2025](#))



Countries in AFRICA-FINGERS Consortium

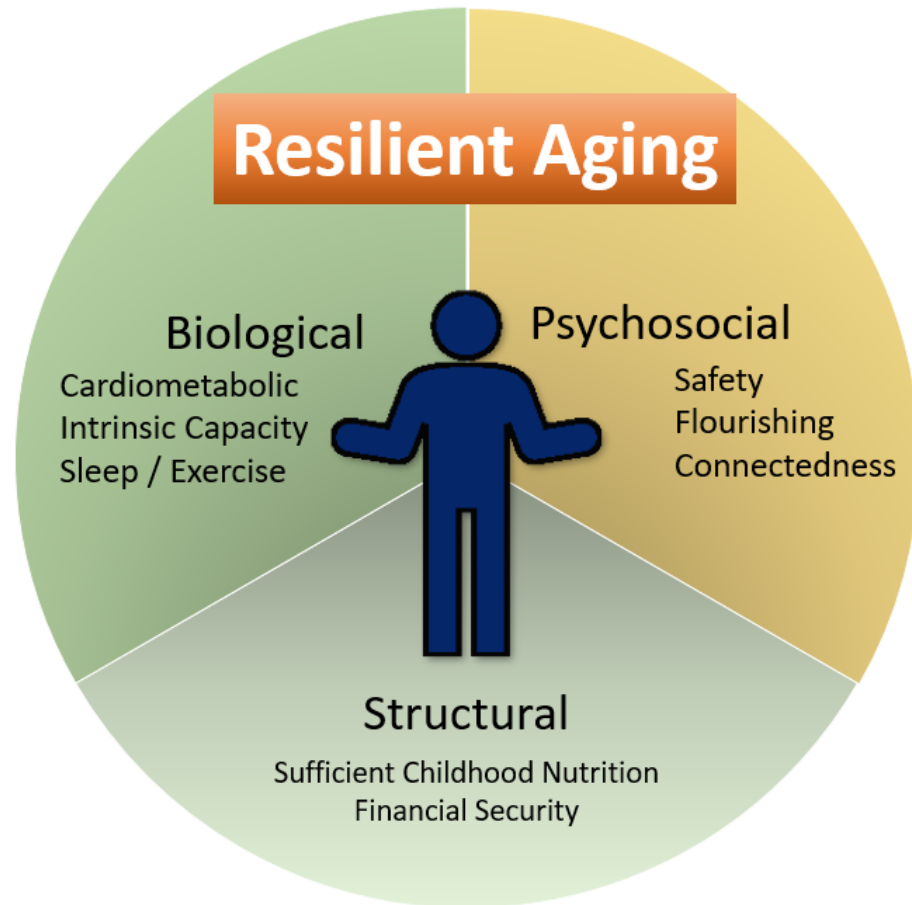
Dementia risk factors in Africans

Prevalence of modifiable risk factors in multi-ethnic aging and dementia cohorts in Nairobi Kenya (n=451; 56.6±13.6 years [33-97yo]; 58.4% Female; 35% Clinically Diagnosed Dementia)



Non-Dementia: 383 cases (Age: 53.7 years) | Dementia: 68 cases (Age: 72.9 years) | Sex Distribution: F:263 (58.4%), M:187 (41.6%)

The Cognitive Protectome: Life-course Determinants of Resilient Cognitive Aging



Predictors of Resilient Cognitive Aging

Above Poverty Threshold $F=15.79$; $p<0.001$

Better Sleep $F=5.1$; $p=0.007$

Higher Intrinsic Capacity $F=6.9$; $p<0.001$

Lower Loneliness $F=7.9$; $p<0.001$

Higher Sense of Safety $F=10.2$; $p<0.001$

Less Perceived Stress $F=8.4$; $p<0.001$

Higher Flourishing $F=6.3$; $p=0.002$

Lower “self” stress life events $F=3.9$; $p=0.02$

Lower MET score $F=4.8$; $p=0.009$

Nutrition (MNA) $F=3.0$; $p=0.05$

Childhood Nutrition $\text{Chi-square}=24.2$; $p<0.001$

The Right Participant:
identifying optimal risk
and resilient profiles in
appropriate disease phase



Dementia risk factors

Predictors of AD-dementia in African ancestry

Outcome: AD-dementia at FU	
Ibadan (AFR)	Indianapolis (AA)
Increasing Age (HR: 1.72)	Increasing Age (HR: 1.92)
Female Sex (HR: 1.49)	Female Sex (HR: 0.76)
Stroke Hx (HR: 3.31)	Stroke Hx (HR: 1.61)
Higher Systolic BP (HR: 1.42)	Higher Systolic BP (HR: 1.19)
High HDL (HR: 1.37)	High HDL (HR: 1.09)
Smoking (HR: 1.68)	Smoking (HR: 0.76)
Low social engagement (HR: 1.56)	Low social engagement (HR: 0.81)
Low physical activity (HR: 1.66)	Low physical activity (HR: 1.17)
APOEε4 carriage (HR: 0.96)	APOEε4 carriage (HR: 1.92)

- Data from Ibadan-Indianapolis Dementia Project (1992-2006, n=4353)
- Lower AD incidence in Africans* [5% of the cohort developed dementia vs 7% AA (mean±SD follow-up: 7±4 years)]
- Higher mortality in Africans (10% vs 5%)



APOE ε4 dependent risk of dementia is attenuated in Africans (Rajabli et al., 2022 Plos Genetics)

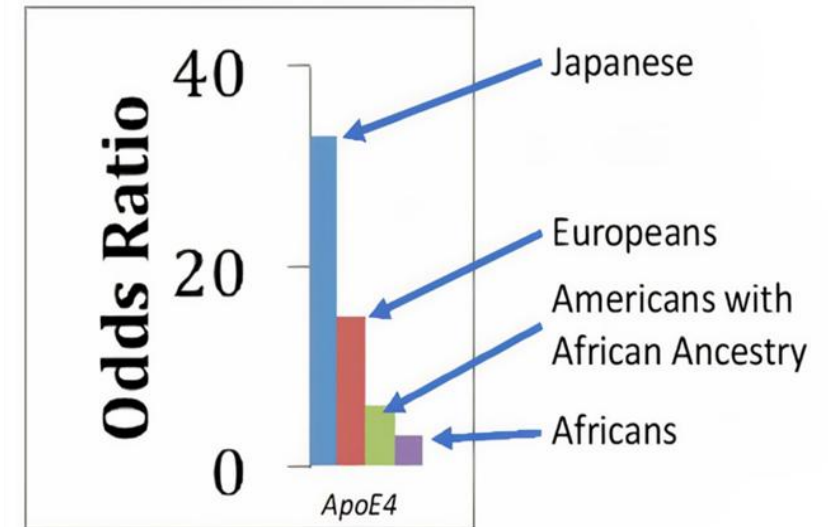


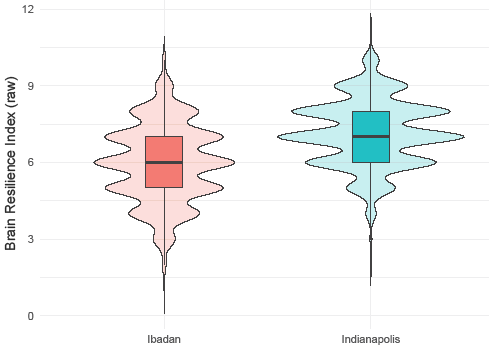
Fig 1. Odds ratios for developing Alzheimer disease according to ApoE ε4/ε4 genotypes carriers relative to the ε3/ε3 carriers across the multiple ancestries.

Dementia Resilience factors

*Predictors of AD-dementia in African ancestry

Outcome: MCI/Dementia at FU

IBADAN (AFR)	INDIANAPOLIS (AA)
BRI (HR: 0.83)/ APOEε2/ε2 (HR: 0.35)	BRI (HR: 0.80)/ APOEε2/ε2 (HR: 1.38)
Education Attainment (HR: 1.00)	Education Attainment (HR: 0.46)
High Cognitive Activities (HR: 0.81)	High Cognitive Activities (HR: 0.48)
High Social engagement (HR: 0.95)	High Social engagement (HR: 0.39)
High ADLs (HR: 0.53)	High ADLs (HR: 0.52)
High physical activity (HR: 0.86)	High physical activity (HR: 0.79)
Non-smoker (HR: 0.67)	Non-smoker (HR: 0.75)
Non-drinker (HR: 0.86)	Non-drinker (HR: 0.74)
Low FBG (HR: 2.02)/ Low LDL (HR: 1.37)	Low FBG (HR: 0.99)/ Low LDL (HR: 1.00)
Normal BMI (HR: 1.23)	Normal BMI (HR: 1.04)



Cognitive & Educational

- ≥ 6 years education
- Any cognitively stimulating activity

Social & Functional

- Social engagement
- Functional independence

Behavioral Health

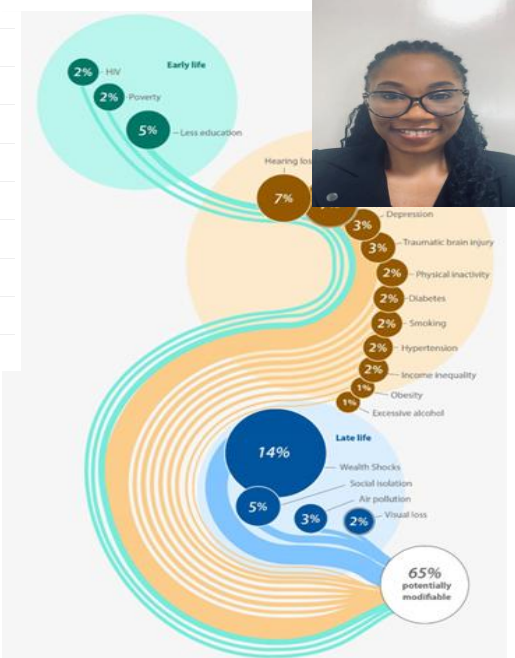
- Any physical activity
- Non-smoker
- Non-drinker

Cardiometabolic Health

- SBP < 130 mmHg
- FBG < 126 mg/dL
- LDL < 100 mg/dL
- BMI < 25 kg/m²

Brain Resilience Index (BRI)

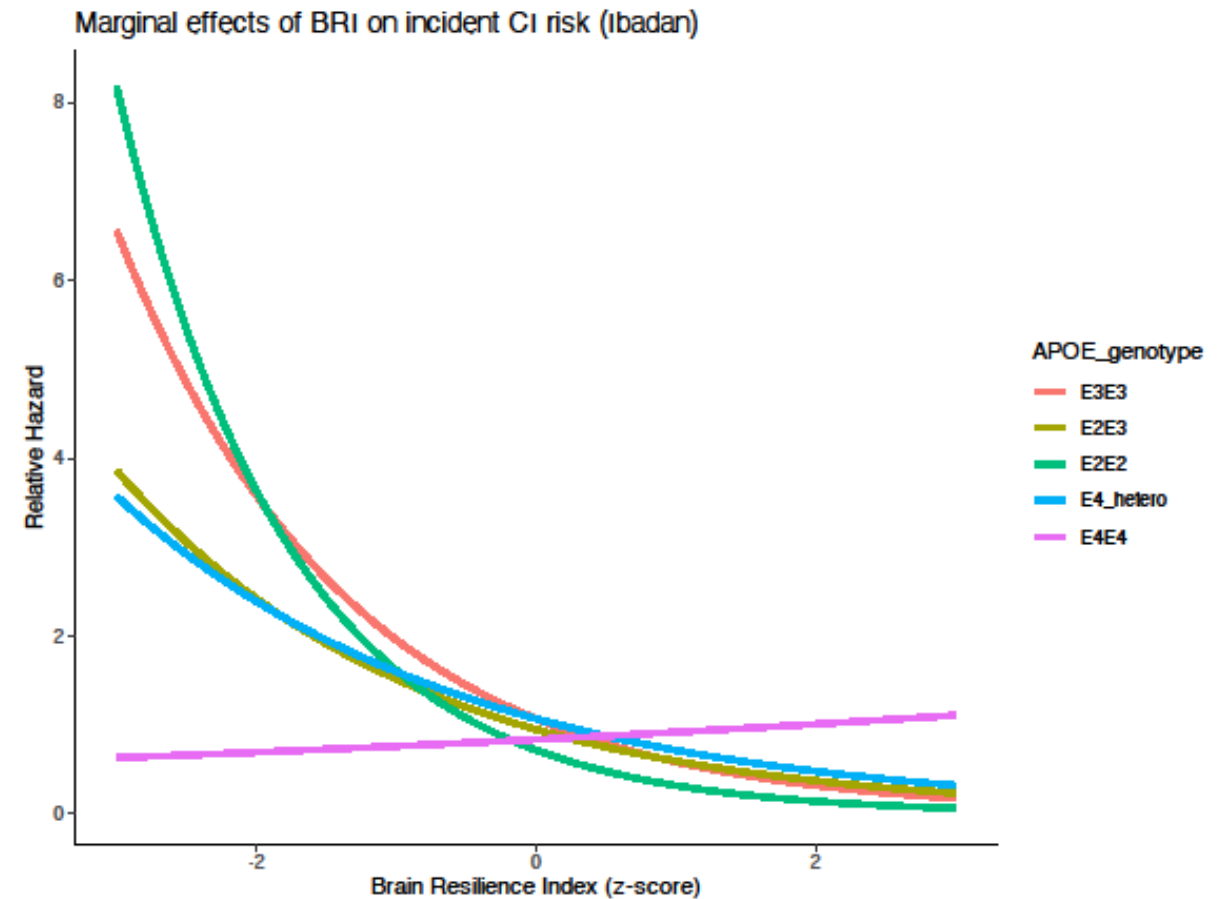
Sum of 11 binary indicators
Range: 0–11



*Udeh-Momoh CT, Jiakponnah NN, Curran J. et al; manuscript under preparation. Informed by modifiable dementia risk factors identified by the Lancet Commission (Livingstone et al., 2024) and Mostert, Udeh-Momoh et al., 2025).

APOE allele-dependent modification of resilience to accelerated cognitive ageing in indigenous Africans

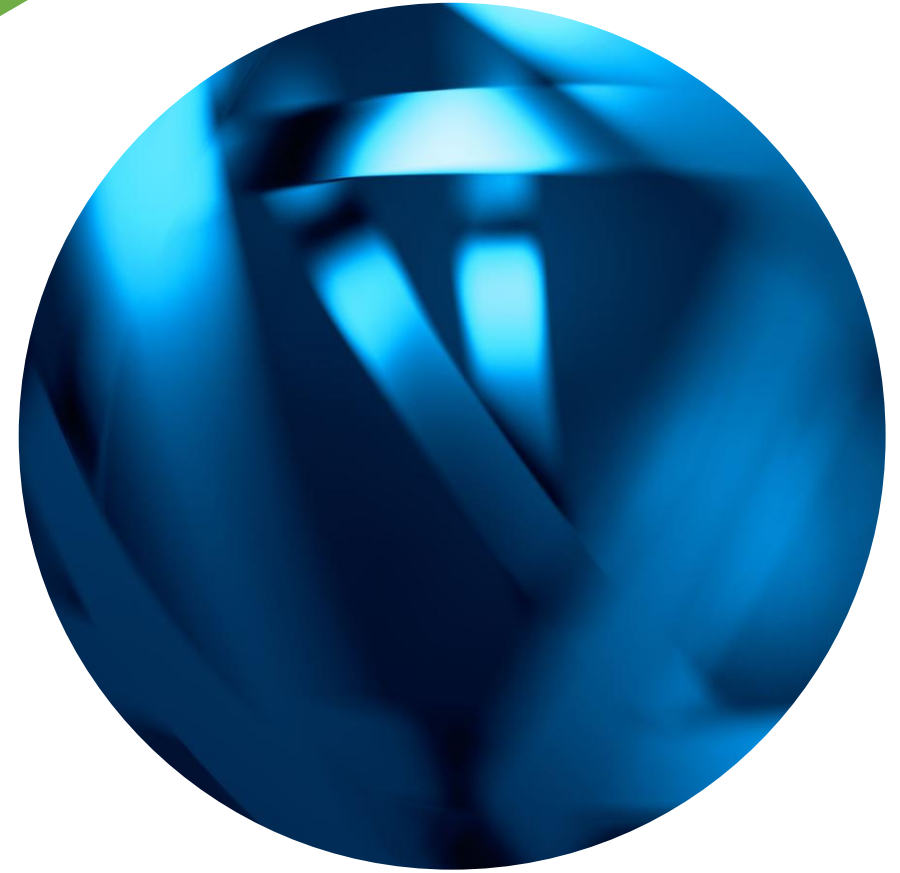
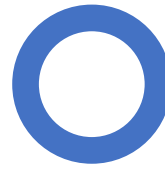
- APOE $\epsilon 2$ homozygosity significantly modified associations of BRI and incident cognitive impairment in Ibadan cohort ($p=0.04$) but not Indianapolis ($p>0.01$)
- APOE $\epsilon 4$ penetrance remained non-significant





The Right Trial/ Therapy:

safe, tolerable, effective
with appropriate outcomes
to detect clinically-
meaningful differences



FROM KNOWLEDGE ABOUT RISK FACTORS TO CLINICAL TRIALS AND SUSTAINABLE IMPLEMENTATION

Lessons Learned

Multidomain approaches targeting multiple risk factors and tailored at individual and population level can be effective and feasible for dementia risk reduction

-> LMICs potential

Stephen et al., Frontiers Neurol, 2021

RISK REDUCTION OF COGNITIVE DECLINE AND DEMENTIA

WHO GUIDELINES

EVIDENCE PROFILES

- Physical activity interventions
- Tobacco cessation interventions
- Nutritional interventions
- Interventions for alcohol use disorder
- Cognitive interventions
- Social activity
- Weight management
- Management of hypertension
- Management of diabetes
- Management of dyslipidaemia
- Management of depression
- Management of hearing loss

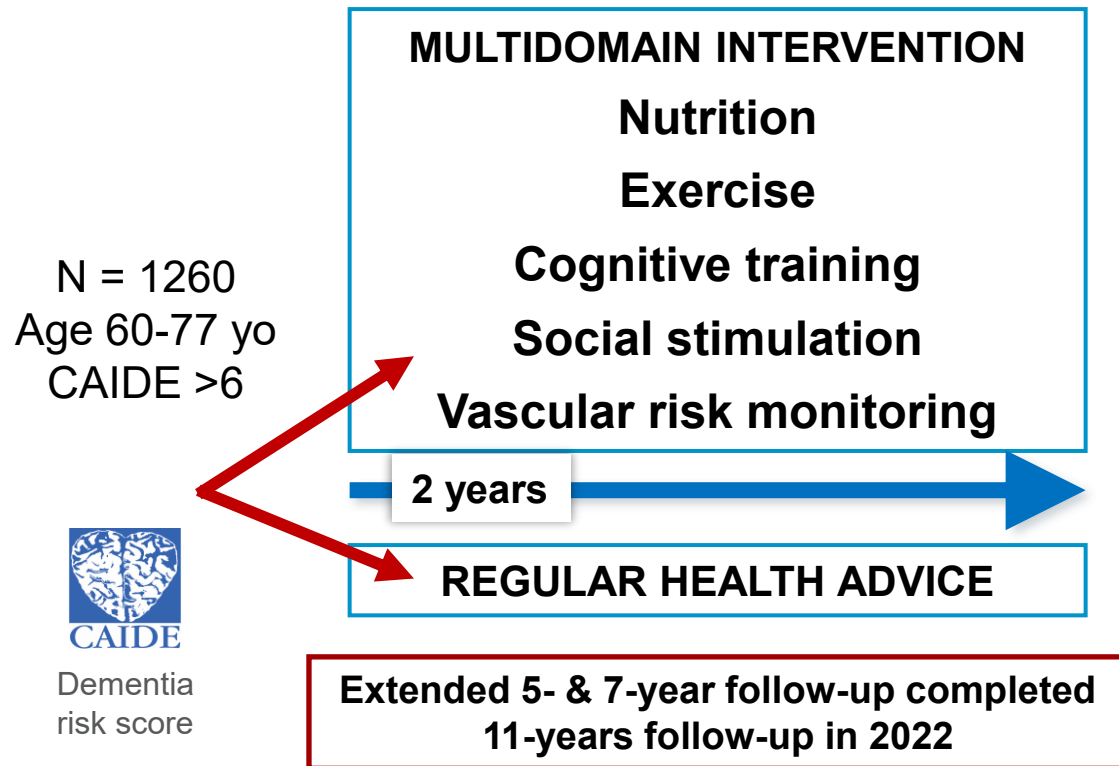


2019; 2026 – multidomain
intervention (under dev.)



World Health
Organization

Multi-domain lifestyle intervention prevents cognitive decline in high AD risk individuals



Cognitive benefits



20% lower risk cardiovascular events



30% lower risk for functional decline



60% lower risk of chronic diseases



Better health related quality of life



Health-economical benefits

Lancet 2015; JAMA Neurology 2018, Eur Ger Med 2017, JAMDA 2017, JAGS 2019; Alzheimer's Dementia 2021; European J Cardiology 2022, Alzheimer's Dementia 2022, Age and Ageing 2024

☐ Reports showing improved health outcomes, including good adherence in older adults across diverse populations: WW-FINGERS

Impact of multidomain lifestyle intervention in relation to *APOE*ε4 carriage

- In FINGER, intervention benefit was more pronounced in global cognition (*p*=0.045) and complex memory test performance (*p*=0.03) amongst ***APOE*ε4 carriers** compared to non-carriers.

Hwang et al. *Alzheimer's Research & Therapy* (2025) 17:262
<https://doi.org/10.1186/s13195-025-01907-3>

Alzheimer's Research & Therapy

CORRESPONDENCE Open Access

Polygenicity and *APOE* ε4 shape response to intervention in mild cognitive impairment

Ji Yun Hwang^{1†}, So Young Moon^{2†}, Harim Lee¹, Jaejin Lee¹, Yoo Kyoung Park³, Jee Hyang Jeong⁴, Chang Hyung Hong⁵, Jiwoo Jung⁶, Hae Ri Na⁷, Soo Hyun Cho⁸, Joohon Sung^{1,9}, Soo Ji Lee^{1,9*} and Seong Hye Choi^{10*}

- Similar findings noted across SUPERBRAIN-MEET and JMINT, with incorporation of PRS revealing enhanced intervention benefits amongst ***APOE*4 carriers** with MCI.
- Complementary use of PRS and ***APOE*ε4** status is recommended for identifying high-risk subgroups most likely to benefit from multidomain interventions.

Effect of the Apolipoprotein E Genotype on Cognitive Change During a Multidomain Lifestyle Intervention
A Subgroup Analysis of a Randomized Clinical Trial

Alina Solomon, MD, PhD^{1,2,3}; Heidi Turunen, BM¹; Tiia Ngandu, MD, PhD^{3,4}; Markku Peltonen, PhD⁴; Esko Levälahti, MSc⁴; Seppo Helisalmi, PhD¹; Riitta Antikainen, MD, PhD^{5,6}; Lars Bäckman, PhD²; Tuomo Hänninen, PhD⁷; Antti Jula, MD, PhD⁴; Tiina Laatikainen, MD, PhD^{4,8,9}; Jenni Lehtisalo, MSc^{4,10}; Jaana Lindström, PhD⁴; Teemu Paajanen, MA, Psy¹¹; Satu Pajala, PhD¹²; Anna Stigsdotter-Neely, PhD^{13,14}; Timo Strandberg, MD, PhD^{5,15}; Jaakko Tuomilehto, MD, PhD^{4,16,17,18,19,20}; Hilikka Soininen, MD, PhD^{1,7}; Miia Kivipelto, MD, PhD^{1,2,3,4,21}

Received: 7 December 2023 | Revised: 1 March 2024 | Accepted: 16 March 2024

DOI: 10.1002/alz.13838

RESEARCH ARTICLE

Alzheimer's & Dementia
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Japan-Multimodal Intervention Trial for the Prevention of Dementia: A randomized controlled trial

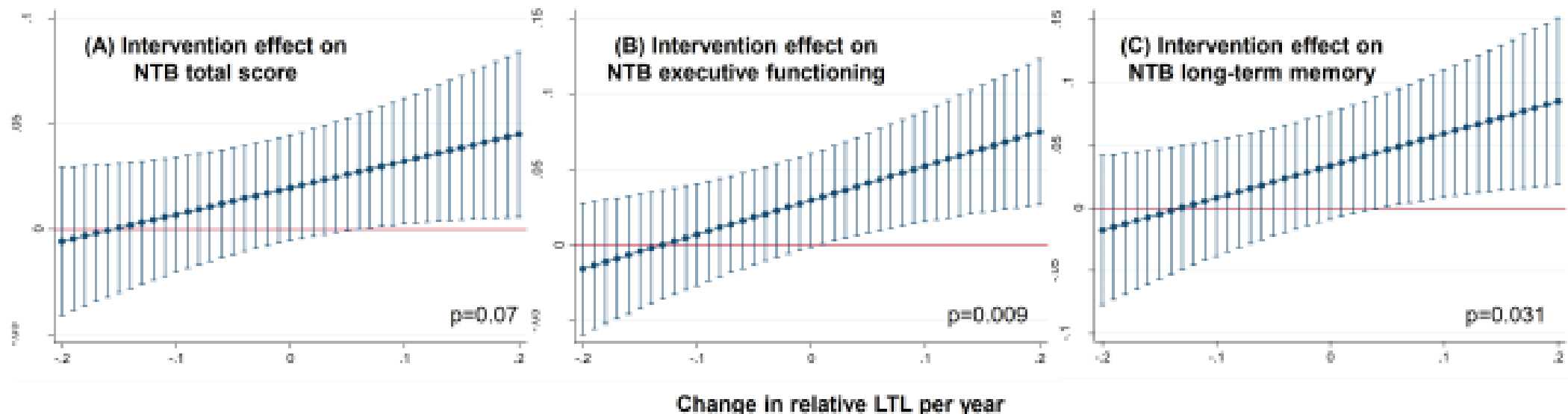
Takashi Sakurai^{1,2,3} | Taiki Sugimoto^{2,4} | Hiroyasu Akatsu⁵ | Takehiko Doi⁶ | Yoshinori Fujiwara⁷ | Akihiro Hirakawa⁸ | Fumie Kinoshita⁹ | Masafumi Kuzuya¹⁰ | Sangyoon Lee^{6,11} | Nanae Matsumoto² | Koichiro Matsuo¹² | Makoto Michikawa¹³ | Akinori Nakamura¹⁴ | Susumu Ogawa¹⁵ | Rei Otsuka¹⁶ | Kenji Sato¹⁷ | Hiroyuki Shimada¹⁸ | Hiroko Suzuki¹⁹ | Hiroyuki Suzuki¹⁵ | Hajime Takechi²⁰ | Shinya Takeda²¹ | Kazuaki Uchida² | Hiroyuki Umegaki²² | Satomu Wakayama^{17,23} | Hidenori Arai²⁴ | J-MINT study group

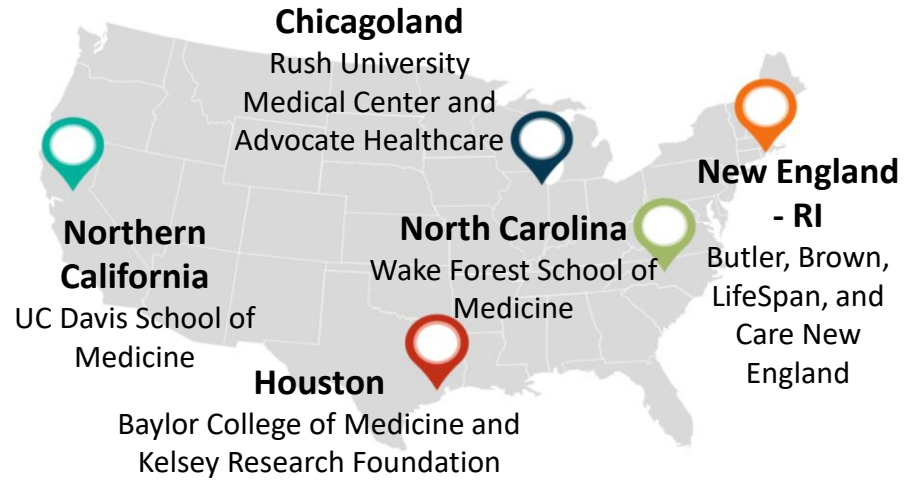
Research Article

Telomere Length Change in a Multidomain Lifestyle Intervention to Prevent Cognitive Decline: A Randomized Clinical Trial

Shireen Sindi, PhD,^{1,2,*†,○} Alina Solomon, MD, PhD,^{3,4,†} Ingemar Kåreholt, PhD,^{5,6} Iiris Hovatta, PhD,^{7,8} Riitta Antikainen, MD, PhD,^{9,10} Tuomo Hänninen, PhD,¹¹ Esko Levälahti, MSc,¹² Tiina Laatikainen, MD, PhD,^{12,13,○} Jenni Lehtisalo, PhD,^{3,12} Jaana Lindström, PhD,¹² Teemu Paaianen, PhD,¹⁴ Markku Peltonen, PhD,^{1,12} Dharma Singh Khalsa, MD,¹⁵ Benjamin Wolozin, PhD,¹⁶ Timo Strandberg, MD, PhD,^{9,17} Jaakko Tuomilehto, MD, PhD,^{18,19} Hilikka Soininen, MD, PhD,^{3,11} Tiia Ngandu, MD, PhD,^{1,12} and Miia Kivipelto, MD, PhD,^{1,2} for the FINGER Study Group

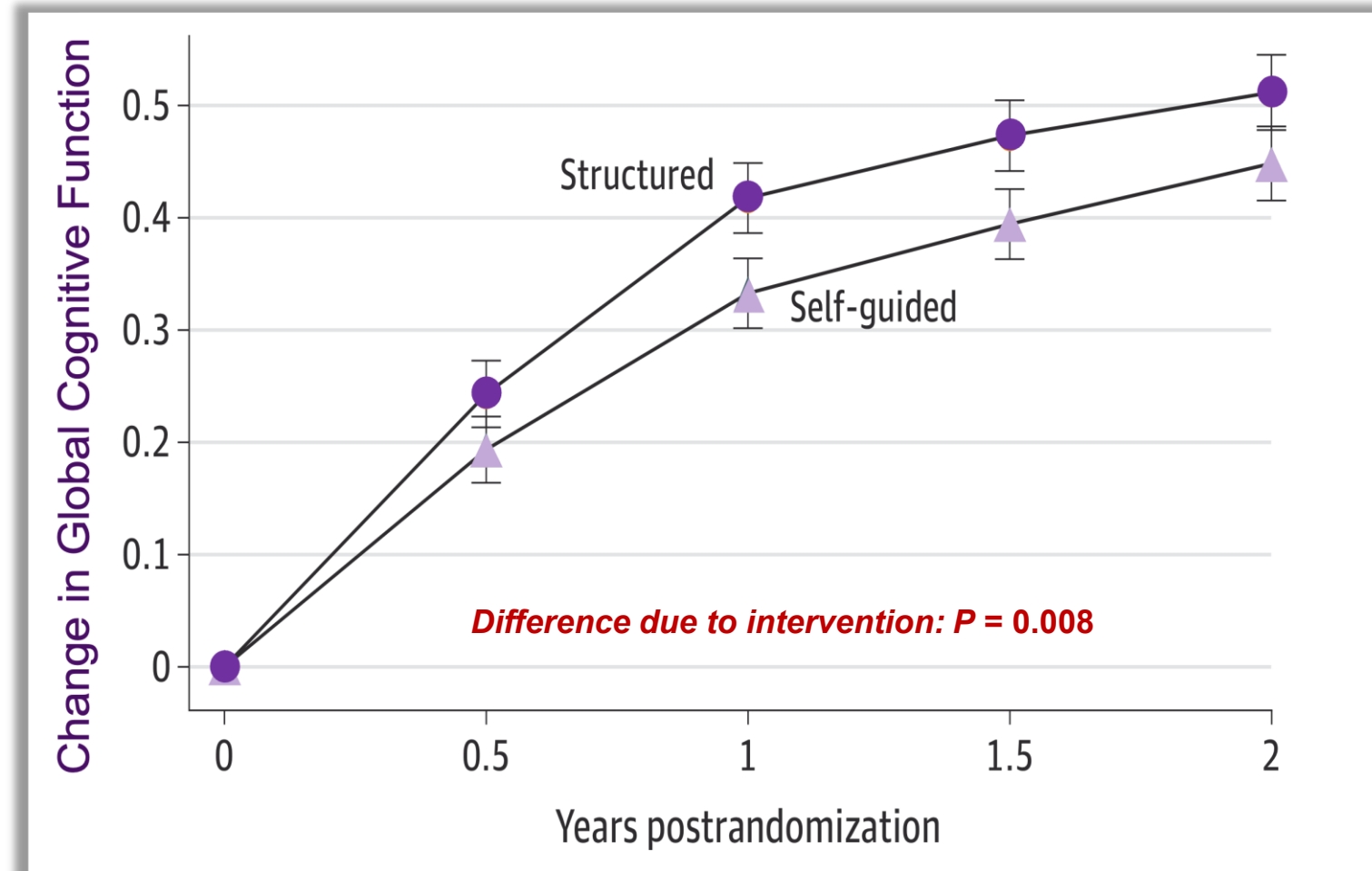
- Impact of FINGER intervention on LTL
- Intervention benefits on **executive functioning** ($\beta=0.227$ [CI:0.057-0.396]; **memory** ($\beta= 0.257$, [CI: 0.024-0.489], and to lesser extent global cognition ($\beta= 0.127$, [CI: –0.011- 0.264] **more pronounced** among participants with **better LTL maintenance**
- **Higher LTL maintenance** noted among apolipoprotein E (**APOE**)- $\epsilon 4$ carriers; **younger** participants; and those with **greater healthy lifestyle changes**





U.S. POINTER Interventions

- Increased physical activity to improve fitness
- Better nutrition – MIND diet
- Cognitive challenges / Social engagement
- Routine risk factor monitoring





~15 completed RCTs
20 ongoing RCTs

N= ~20,000
participants

Participating countries 2025: 72

The WWFINGERS-AFRICA Team (>70 Investigators, 14 African countries)

FINGERS BRAIN HEALTH INSTITUTE (FBHI)
 Co-Cl: Prof Miia Kivipelto (KI, ICL)
 Co-Cl: Dr Chi Udeh-Momoh (KI, ICL, AKU, GBHI)
 Dr Francesca Mangialasche (KI, ICL)
 Celeste Loots (ICL, UCT)
 Ina Solomon (UEF, KI, ICL)
 Anna Matton (KI, ICL)



Mauritius:

Dr. Geeta Dorkhy
 Dr Ameenah Sorefan

South Africa/ Botswana:

Dr Celeste Loots (UCT)
 Prof John Joska (UCT)
 Dr Marc Combrink (UCT)
 Dr Lingani Mbazile (U.Bot)



**Alzheimer's
 Disease
 International**

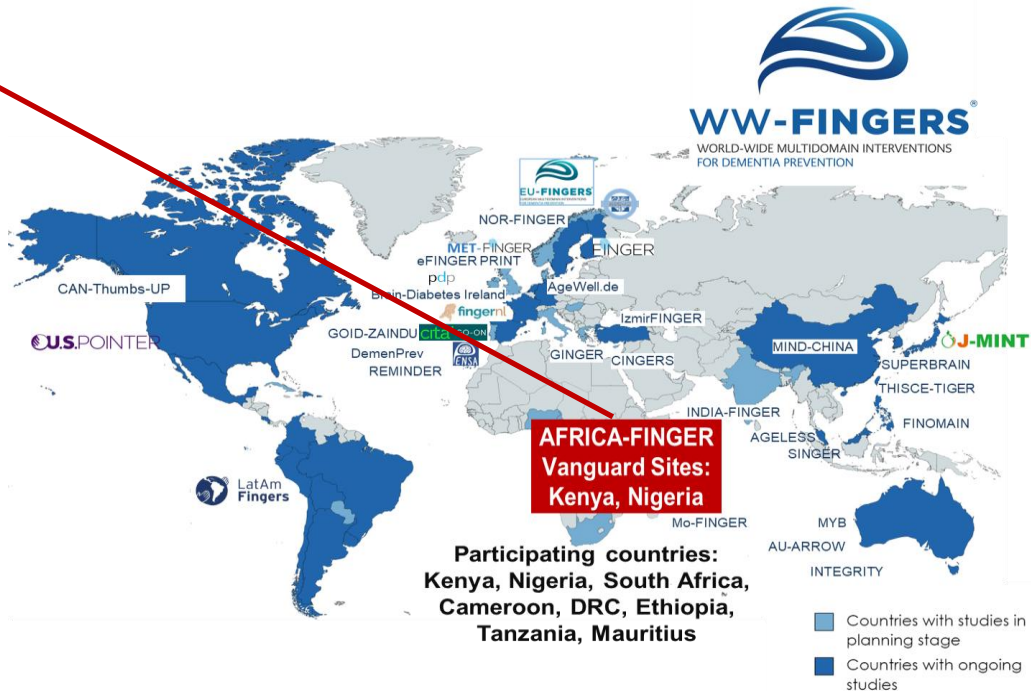
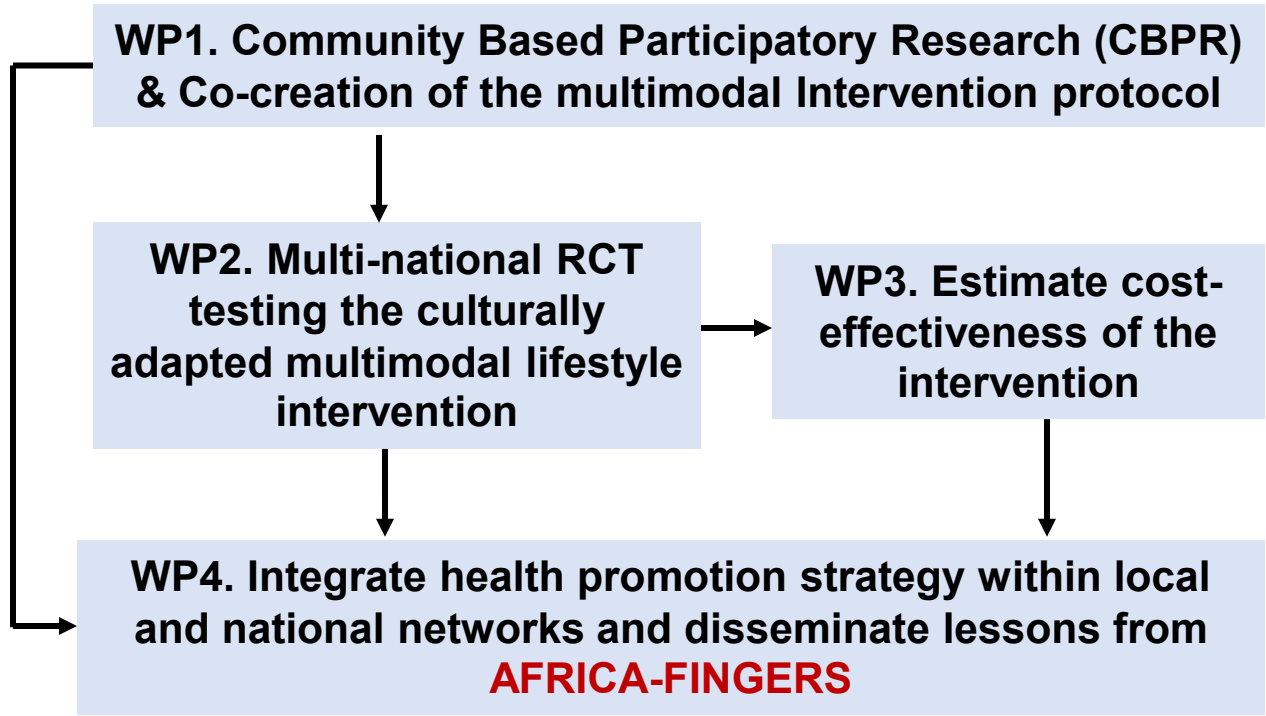




Dr Chi Udeh-Momoh

Prof Miia Kivipelto

Programme Overview: First WW-FINGERS trial in Africa adopting CBPR approach towards culturally-informed multimodal interventions with bespoke implementation and integration strategy



Settings (Each site has cohorts to be characterised for dementia risk using dementia risk score + enrichment criteria):

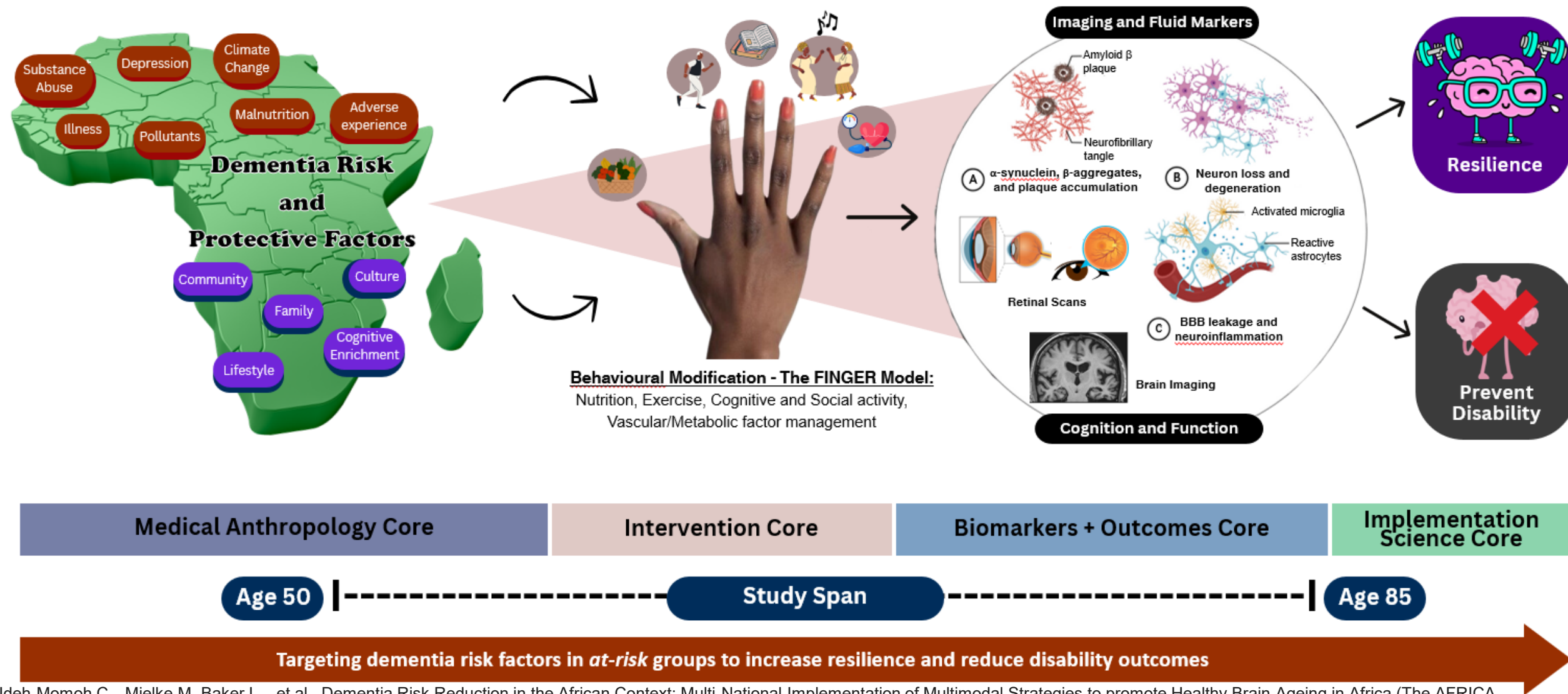
- Site 1: Brain and Mind Institute, Nairobi, Kenya - collaboration with AKU Clinical Trials Unit
- Site 2: Department of Epidemiology, Aga Khan University, Kenya – Kilifi county, Kenya
- Site 3: Nnamdi Azikiwe University, Awka, Nigeria
- Site 4: University of Lagos, Nigeria
- Site 5: University of Ibadan, Nigeria
- Site 6: University of Yobe, Nigeria

Time period: 2024 - 2029





Africa-FINGERS Program - Multideterminant framework for dementia risk reduction in Africa via pioneering precision prevention approach



AFRICA-FINGERS Precision Prevention RCT PLAN: Adaptive Design

Total Participants: N=600
Kenya N=300 & Nigeria N=300

Selection criteria:
1. Age 50-85 years
2. No dementia- IDEA Score ≥ 10 and not high fxn, i.e., if IDEA>80th centile
3. At risk status: ANU-ADRI, fam hx, AT[N]IVS cardiometabolic risk, loneliness; Poverty; +ve on up to 3 risk factors

Randomized



Active
n=300

Control
n=300

Analytical Plan: ITT
Primary Outcome: Multidomain Cognition;
Secondary Outcomes: Independent domains of cognition, functional/QOL data, risk profiles and scores; **Exploratory:** Multimodal Biomarkers

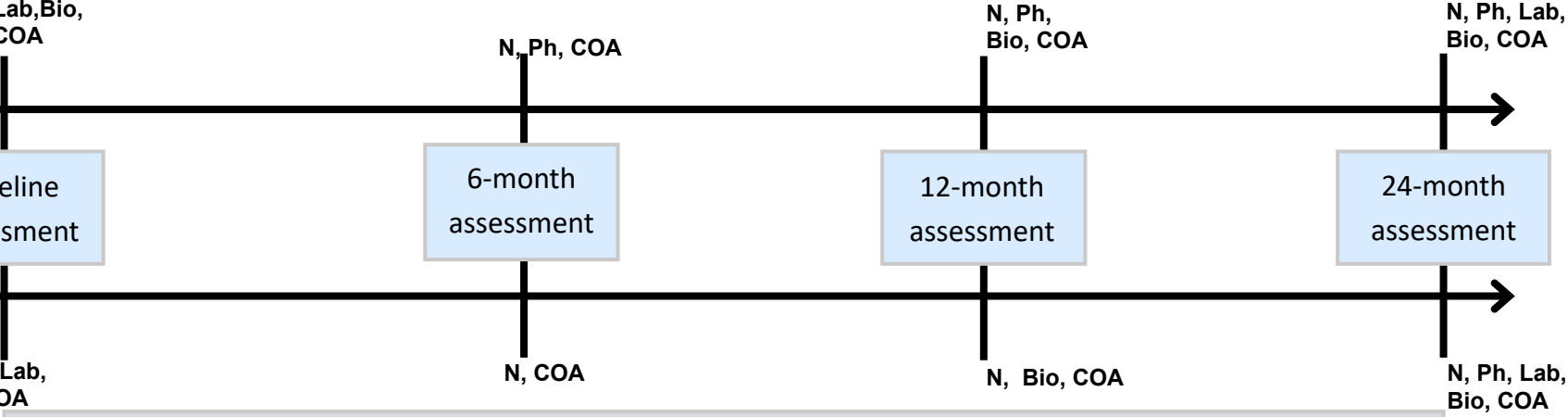
Monitoring and Management of vascular and metabolic risk factors
+ Other contextual factors (Financial literacy/ Reflective Practice – Stress Management)

Physical Activity (60 - 90mins): 4 group sessions, Individual sessions
1-2 X/week resistance/muscle strengthening AND 1-2 X/week aerobics (African traditional dance)

Nutritional counselling: 4 group sessions, Weekly self-monitoring using a food diary checklist

Cognitive Enrichment and Social Engagement:
2 group sessions featuring interactive, activities (e.g. games, storytelling), Individual practice 1X/week

Cognitive Enrichment and Social Engagement:
2 group sessions featuring interactive, activities (e.g. games, storytelling), Individual practice 1X/week



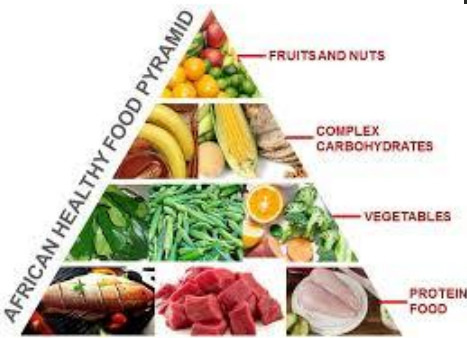
SELF-GUIDED MULTIMODAL INTERVENTION
Healthy lifestyle advice based on national guidelines (every 6 months)

N = Nurse; Ph = Physician
Lab = Total cholesterol, HDL, LDL, triglycerides, HbA1c, CRP, fasting glucose, creatinine, ASAT, ALAT, GGT;
Blood, saliva, urine, hair for biobanking
Bio = Imaging/CSF; COA = Clinical Outcome Assessments [Culturally-adapted harmonised test battery of study outcomes]

Udeh-Momoh CT, et al; Dementia risk reduction in the African context: Multi-national implementation of multimodal strategies to promote healthy brain aging in Africa (the Africa-FINGERS project). *Alzheimers Dement.* 2024

Gaps in neuro-Resilience Science to Consider

- **Conceptual gap:** Resilience is still treated as a *modifier*, not a *primary biological construct*
- **Measurement gap:** Lack of validated, cross-cultural resilience instruments that map onto biology
- **Biological gap:** Poor understanding of *mechanisms* of resilience (not just correlates)
- **Life-course gap:** Early-life resilience remains under-integrated in dementia science
- **Trial design gap:** Resilience outcomes are rarely trial-primary endpoints
- **Equity gap:** Resilience science is still exported, not co-created



Recommendations for precision resilience strategies

- **Start with a common global framework for modifiable risk/resilience factors** (e.g., WHO, Lancet Commission), then adapt measurement and thresholds to local realities and languages.
- **Pair clinical risk/pathological stratification** (vascular and lifestyle profiles) **with context-sensitive determinants** (poverty, education quality, food insecurity, infectious burden, and air pollution).
- **Use multi-level assessments**, e.g., brief community screening → clinic-based confirmation → targeted biomarker/imaging when available, *to maximise reach and equity*.
- **Prioritise tailored implementation**, i.e., **culturally acceptable tools, task-sharing, and community-based delivery**, as these help to increase uptake and reduce diagnostic delays.
- **Measure resilience alongside risk** (cognitive reserve, social support, mental health, and protective lifestyles) to inform personalised, strengths-based prevention.



GLOBAL
BRAIN HEALTH
INSTITUTE



Can we Prevent Dementia in the Real World?

Maybe we can reduce its risk and promote **resilient** aging using sustainable community-based approaches

Chi Udeh-Momoh PhD, FHEA

Wake Forest University, North Carolina, USA

Aga Khan University, Brain and Mind Institute Kenya and Pakistan

Contact: chinedu.momoh@wfusm.edu

Atlantic Fellows

FOR EQUITY
IN BRAIN HEALTH

I am what I am because of who we all are...



Building a tent of collaboration

If you want to go fast, go alone.

If you want to go far, go together.

... African Proverb



Thank you to our funders, partners and participants for supporting the work that will help our next generation thrive!



THE AGA KHAN UNIVERSITY

Thank you for listening!