TOWARDS AN EARLY PRECLINICAL DIAGNOSIS AND PREVENTION OF ALZHEIMER'S DISEASE

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LIONS ALZHEIMER'S FOUNDATION

MACQUARIE University

Alzheimer's Research Australia

AUSTRALIA ECU EDITH COWAN UNIVERSITY

5 Million New Cases Every Year

Estimated number of new dementia cases diagnosed worldwide annually.

150 Million Patients by 2050

The number of people with dementia is expected to double every 20 years, reaching 150 million by 2050.

Economic Burden

Dementia leads to substantial healthcare costs and economic impact, straining healthcare systems globally.

Lorinda Klaric

Mother, Wife, WA resident.

Rita Hayworth

American actress, dancer, and pin-up girl.

Hazel Hawke

Hazel Susan Hawke was the first wife of Bob Hawke.

Bruce Willis

American actor.

Sugar Ray Robinson

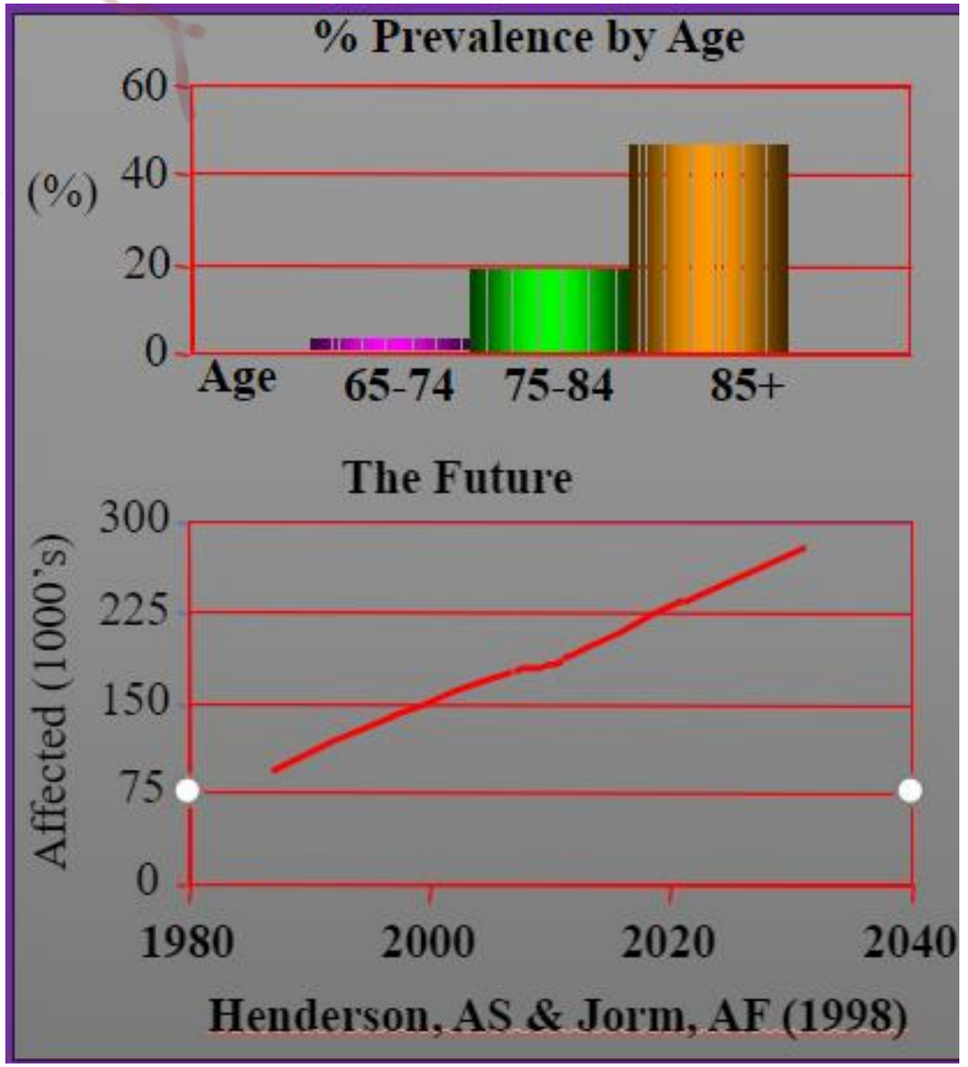
American professional boxer who competed from 1940 to 1965.

Ronald Reagan

40th president of the United States from 1981 to 1989.

Aaron Spelling

American film and television.

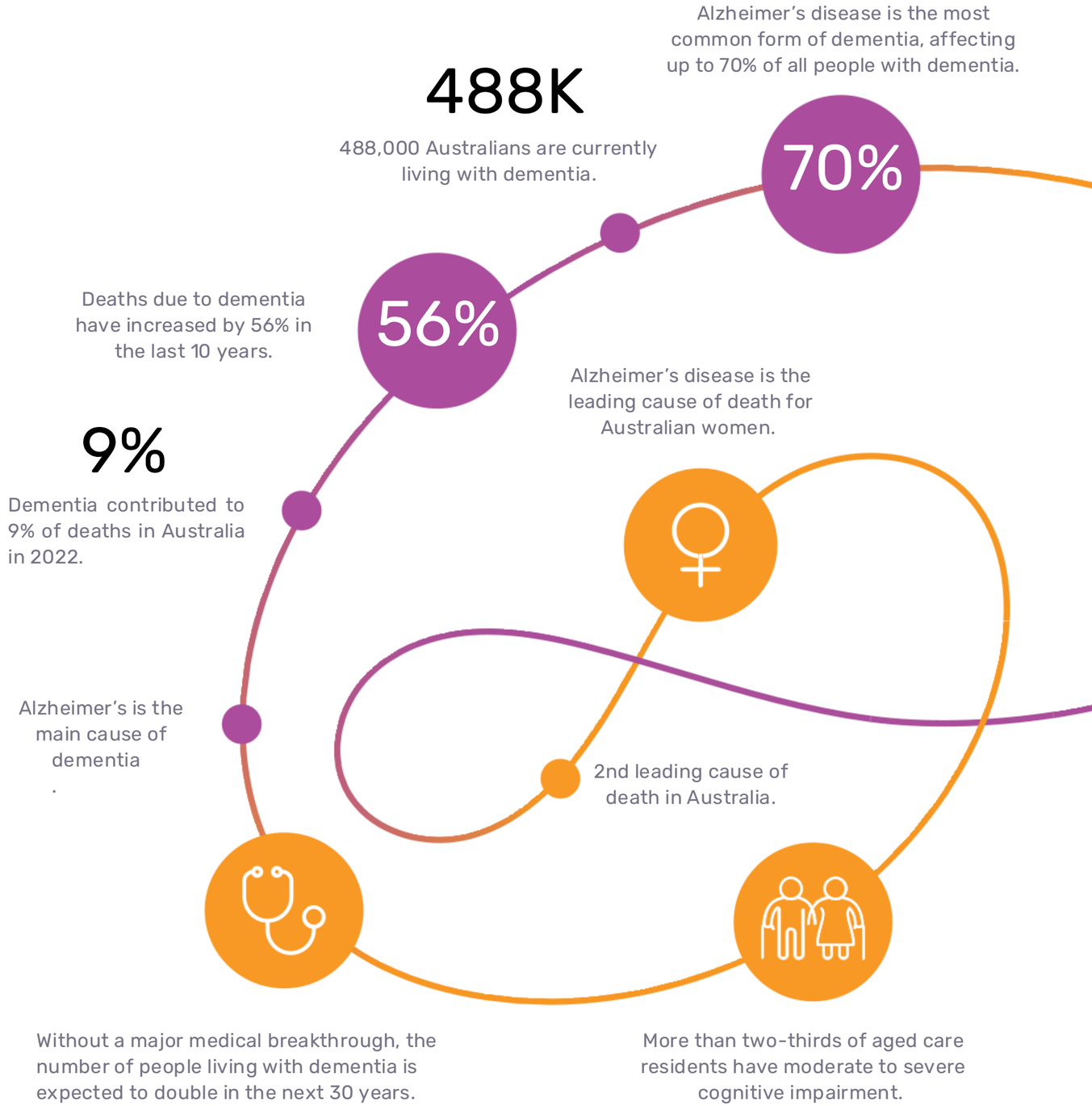


ALZHEIMER'S & DEMENTIA

KEY FACTS

- Dementia is NOT a normal part of ageing.
- **250** Australians are diagnosed with dementia every day.
- Dementia including Alzheimer's disease is the **2nd leading** cause of death in Australia.
- Over the next 40 years, **6.4 million Australians** will be diagnosed with dementia at a cost of over 1 trillion dollars.

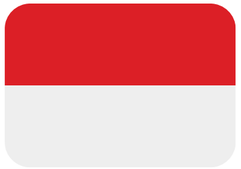
THERE IS CURRENTLY NO CURE.



$1,340

$924

$615



$540

$471

$406

If dementia were a country, it would rank as the world's 18th largeest economy.

GDP (Billion USD)

$96.4 Billion

In direct costs related to medical care (e.g. Hospital care, drugs, and visits to clinics).

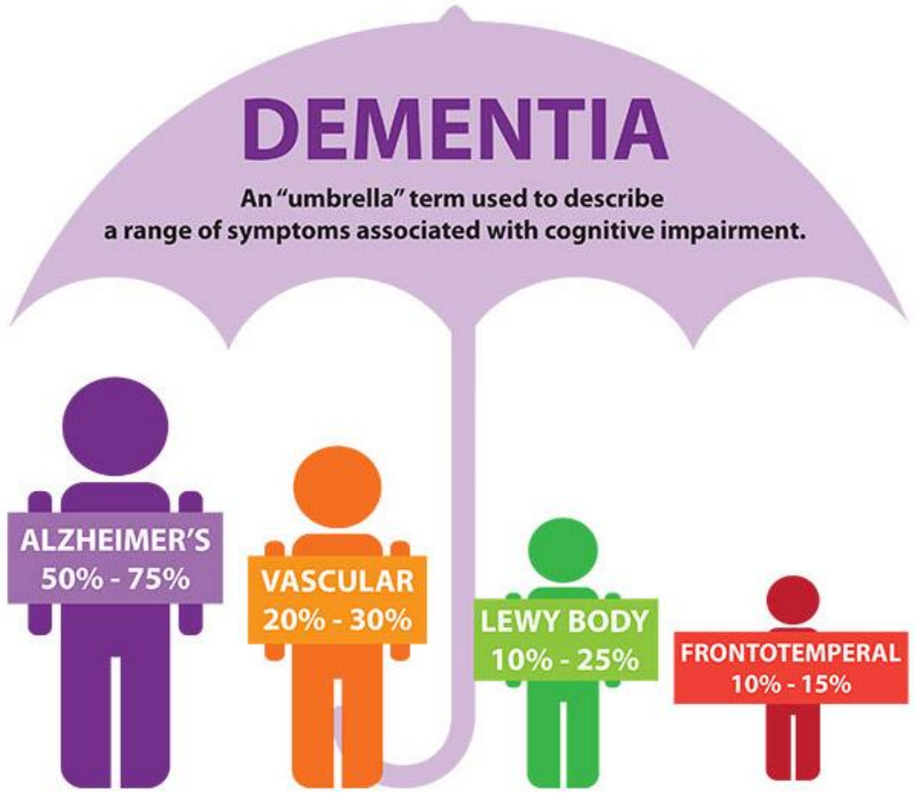
$255.7 Billion

in direct social care costs from formal services outside of the medical care system (e.g. Home care and transport)

$251.9 Billion

In indirect costs (e.g. Unpaid care by loved ones).

Dementia vs Alzheimer’s



- Dementia is a category of age-associated neurodegenerative disorders that causes a gradual decline in memory, cognition, linguistic skills, behaviour and the ability to perform one’s daily tasks.

- Dementia is a major public health concern of the 21st century and one of the leading causes of morbidity and mortality in aging population

- Alzheimer’s disease (AD) is the most common form of dementia that attributes to 60-80% (2/3) of all dementia cases occur over the age of 65 years

UNDERSTANDING ALZHEIMER'S DISEASE

Neurodegenerative Disease: Progressive loss of brain function.

Most Common Form of Dementia: Affects memory, thinking, and behaviour.

Typical Onset: 65 years and older.

Early Onset: Can occur between 30s and mid-60s.

Sixth Leading Cause of Death: Significant impact on mortality.

Gender Difference: Affects two women for every one man.

THE HISTORY OF ALZHEIMER'S DISEASE

ALOIS ALZHEIMER- PIONEER IN ALZHEIMER'S RESEARCH

- Discovered the first published case of "presenile dementia" in 1906.
- Identified abnormal clumps (amyloid plaques) and tangled bundles of fibers (neurofibrillary tangles) in the brain of a deceased patient.
- His work laid the foundation for understanding Alzheimer's disease, which was later named in his honor.
- Legacy: His groundbreaking research continues to influence the study and treatment of Alzheimer's disease today.

Alois Alzheimer

AUGUSTA D - THE FIRST ALZHEIMER'S PATIENT

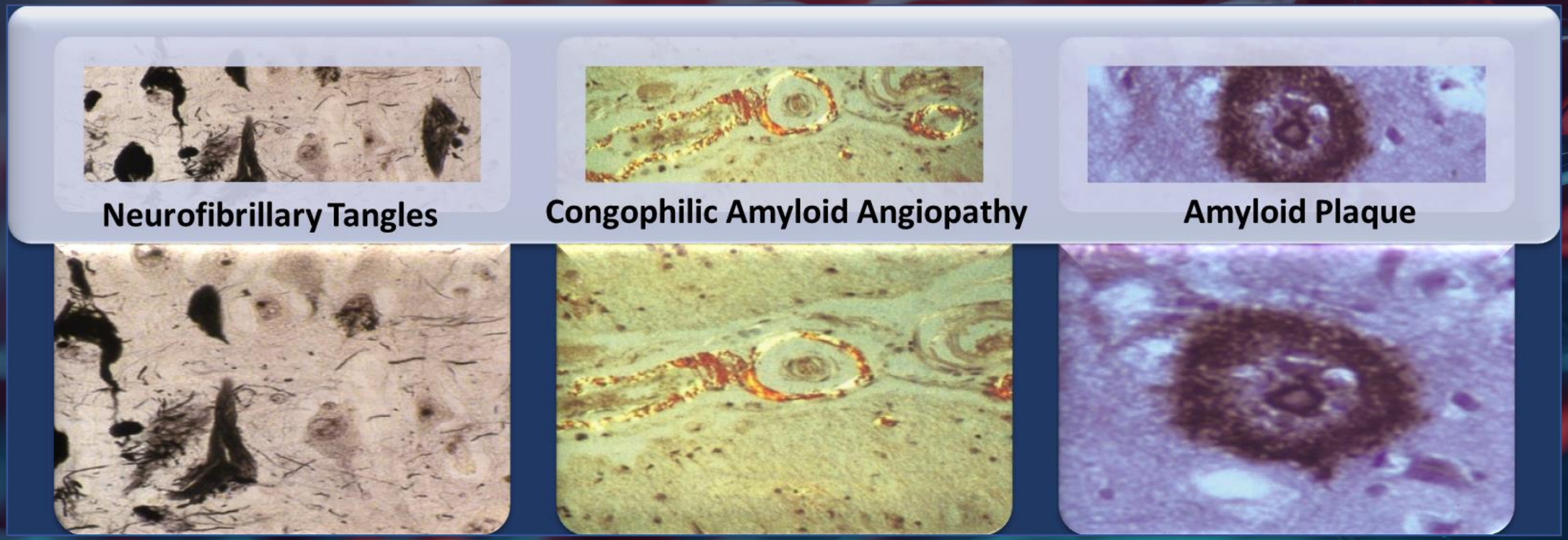
- Augusta Deter was the first person diagnosed with Alzheimer's disease.
- Admitted to a mental institution in 1901 due to severe memory loss, confusion, and unpredictable behavior.

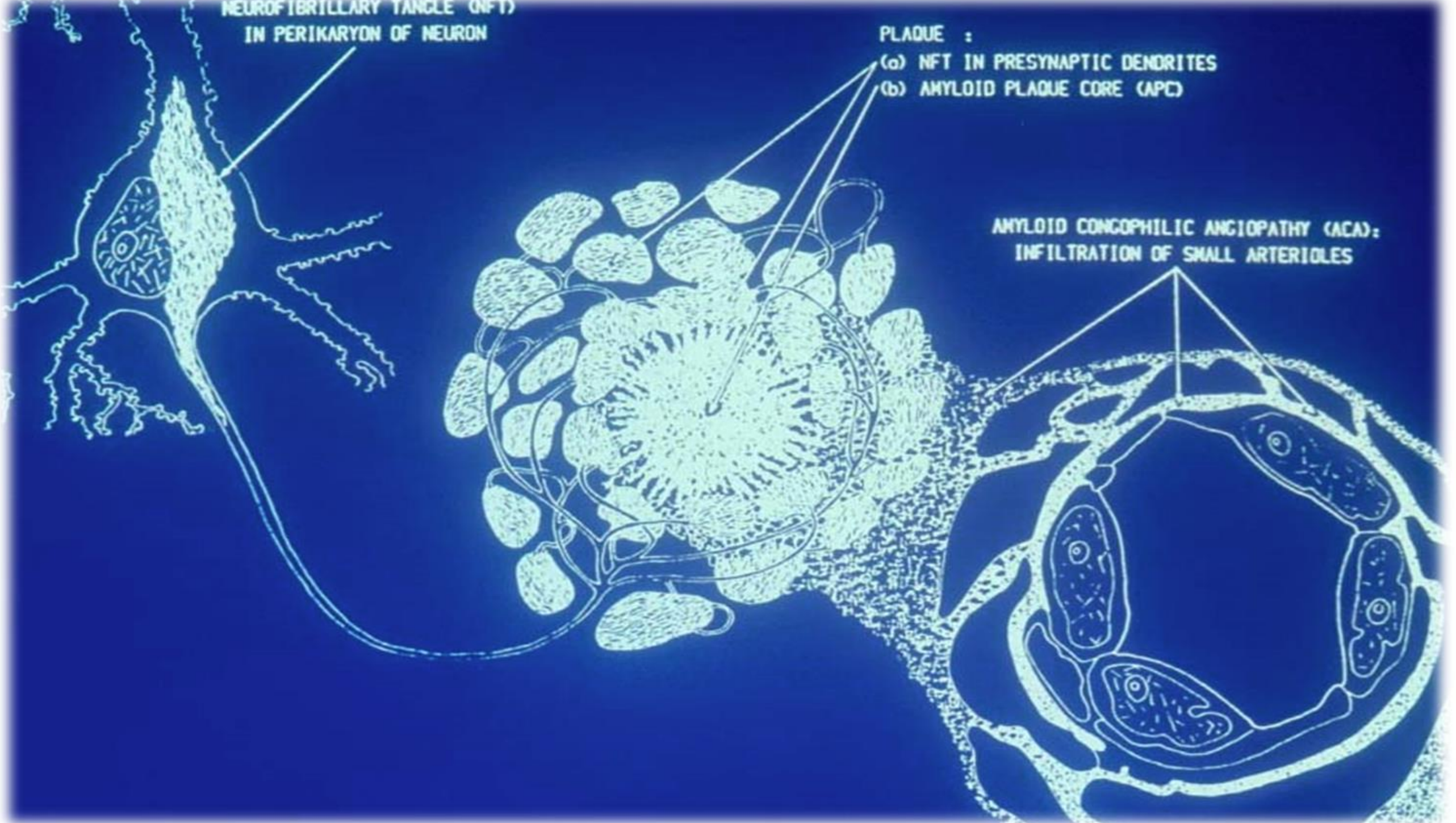
- Her case was studied by Dr. Alois Alzheimer, who identified the characteristic amyloid plaques and neurofibrillary tangles in her brain after her death.

- Legacy: Augusta Deter's case provided crucial insights that led to the identification and understanding of Alzheimer's disease.

Augusta D

ALZHEIMER'S DISEASE PATHOLOGY




NEUROFIBRILLARY TANGLE (NFT)
IN PERIKARYON OF NEURON
PLAQUE :
(a) NFT IN PRESYNAPTIC DENDRITES
(b) AMYLOID PLAQUE CORE (APC)
AMYLOID CONGOPHILIC ANGIOPATHY (ACA):
INFILTRATION OF SMALL ARTERIOLES

BETA AMYLOID PROTEIN

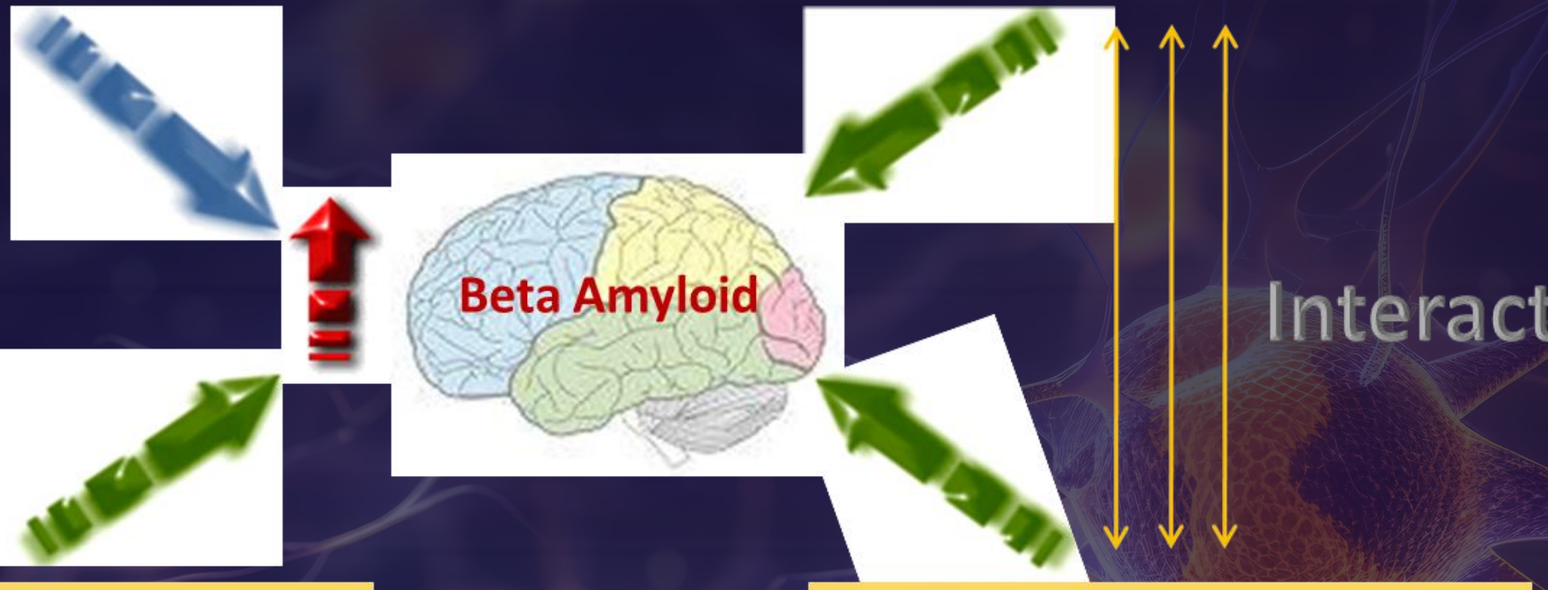
DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIAT

Aβ 1-40

Aβ 1-42

Defective Genes: Mutations in APP, PS1, PS2 < 3% of Cases

Genetic Risk Factors: APOE E4 > 50% of Cases



Lifestyle Factors: High Fat Diet, Lack of Exercise

Changes in Hormone Levels: Oestrogen, Testosterone, Luteinizing Hormone, Insulin

Responsible for >90% of all AD cases

Responsible for <3% of all AD cases

MUM WITH RARE DISEASE FEARS FOR DAUGHTERS

THE WEST AUSTRALIAN SATURDAY, MAY 1, 2010

News 5

thewest.com.au

Mum with rare disease fears for daughters

JOSEPH CATANZARO

Lorinda sits on the veranda of her parent's Swan Valley home, tears streaming down her face as she holds 15-month-old daughter Andjelina close.

Some day soon Lorinda will not remember Andjelina is her baby — and she will not recognise her two other daughters either.

At 32, Lorinda has accepted the fact that she is dying. But it is not her greatest fear.

More than anything, Lorinda is terrified about what the future holds for her girls.

About a month ago, Lorinda was diagnosed with a rare and aggressive form of Alzheimer's disease called presenilin one.

her. I slept with her and looked after her. I was hoping that it wouldn't happen to me."

About six months after the birth of Andjelina, Lorinda found she had a slight limp.

Almost immediately, her family noticed she was increasingly forgetful.

"I knew what it was straight away," Lorinda said. Since her diagnosis, Lorinda's condition has deteriorated rapidly. She has trouble with her short-term memory, often forgetting to do simple things such as eating.

Her speech has become slurred, she repeats questions and is losing her sense of balance and her ability to distinguish temperature.

Lorinda's life, which she

Dying: Lorinda with husband Zeljko and their daughters Nikolina, left, Andjelina and Maria.

Lorinda's Story: Diagnosed with a rare, aggressive form of Alzheimer's called presenilin one at 32.
Condition caused by a defective gene producing beta amyloid, destroying brain neurons.

Family Impact: Lorinda's daughters, Maria (9), Nikolina (8), and baby Andjelina, have a 50% chance of inheriting the disease. Lorinda witnessed her mother's suffering from the same disease.

Current Challenges: Rapid deterioration: memory loss, slurred speech, balance issues.
Family depends on Lorinda’s father’s single wage; her husband awaits permanent residency.

Future Concerns: Fearful for her daughters' futures and their potential diagnosis.

METHODS

Table 1: The Family history of the patient and her affected bloodline relatives

	Age at onset	*Age at death*	*Disease duration**	*Patient's Status in the first 3 years*
DIAN 1 (DIAN Participant)	30	36	3 years	Stable; similar to diagnosis time
1: Grandmother	Uncertain	Uncertain	Uncertain	Uncertain
2: Mother	36	41	5	Rapid decline was reported by family; was in wheelchair
3: Aunt	30	38	8	Rapid decline was reported by family
4: Cousin 1	28	31	3	Very quick decline and passed away quickly
5. DIAN 2 (Cousin 2)		Still alive		Not diagnosed yet

EARLY DIAGNOSIS & BIOMARKERS - DIAN

Duration: 6 years
Scope: Multicentre study involving 10 sites worldwide

Major Aim:
To collect and analyze clinical and neuropsychological sequences of changes occurring in dominantly inherited Alzheimer's Disease (AD) using neuroimaging (MRI, FTD-PET, and PIB-PET) and neuropathological testing.

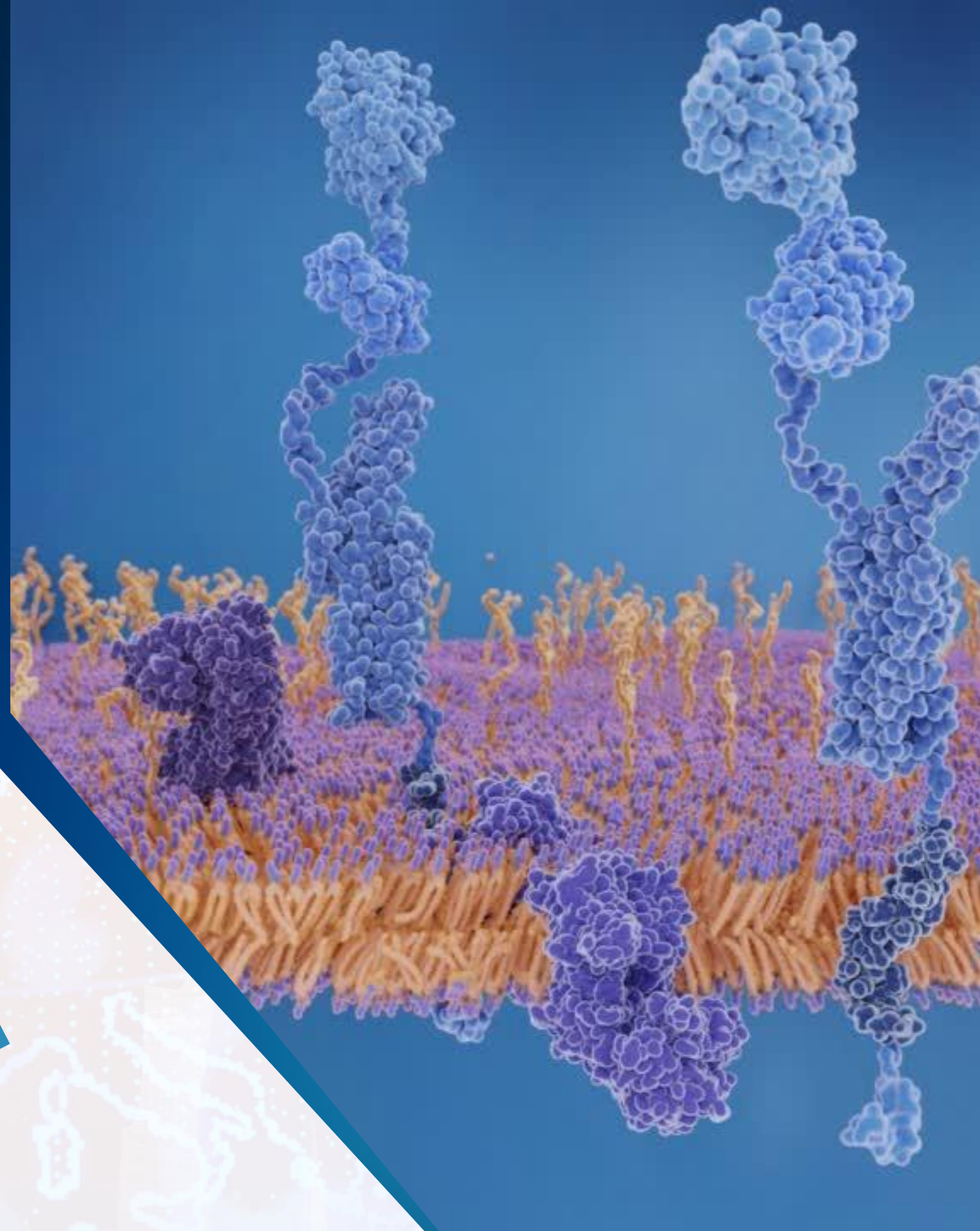
Requirements:
Establish a cohort of 400 individuals at high risk of developing autosomal dominant AD.
Research cost: US$10,000 per person every 3 years.

Study Layout:
Each site, including the Sir James McCusker Alzheimer's Disease Research Unit (ADRU), aims to recruit 40 participants.

Assessments: Participants will undergo periodic assessments over 6 years, including:
Clinical and neuropsychological evaluations Collection of blood and cerebrospinal fluid (CSF) Neuroimaging.

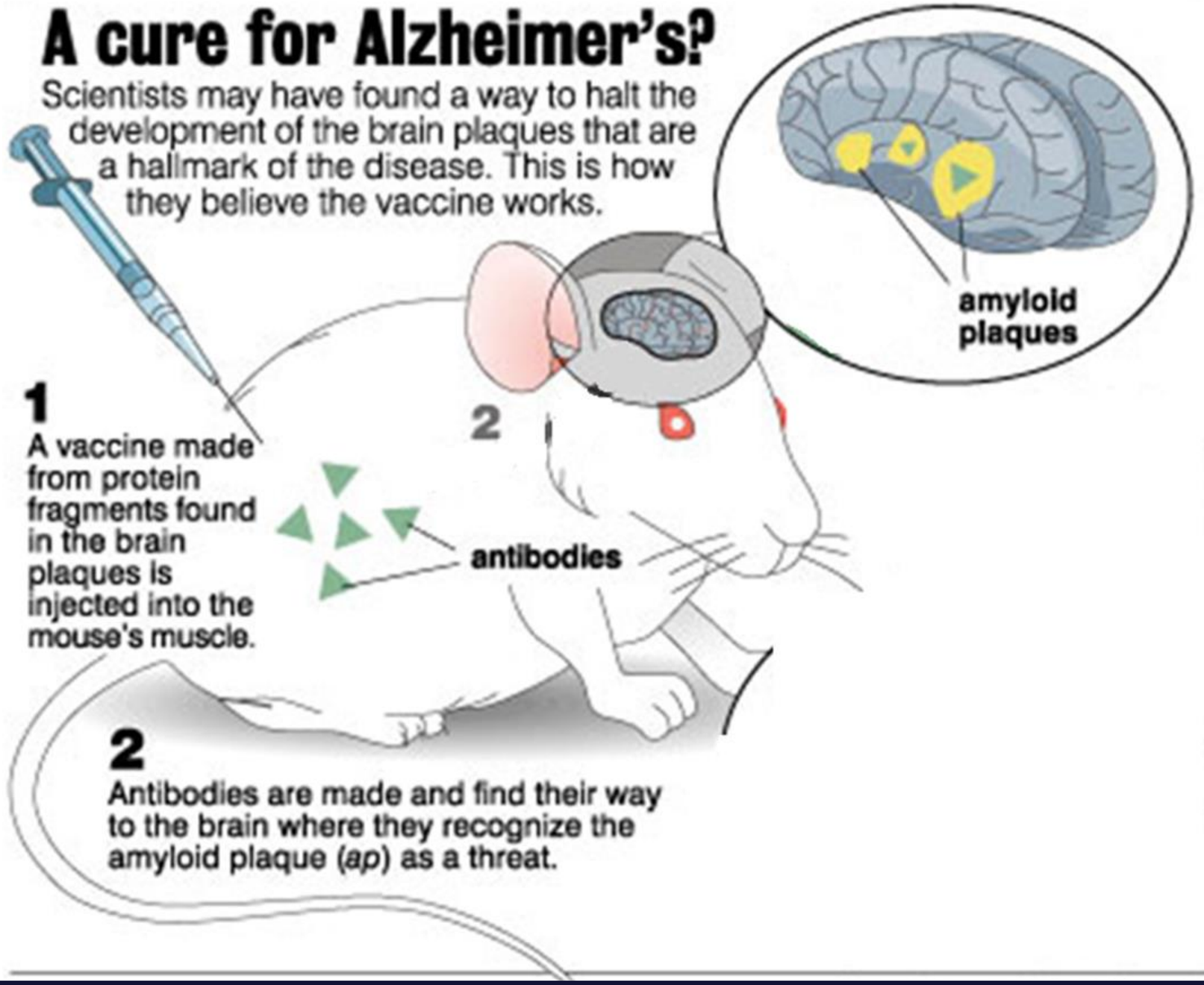
A CURE
AMYLOID PROTEIN

Therapies that reduce its production, prevent aggregation, and promote clearance from the brain.



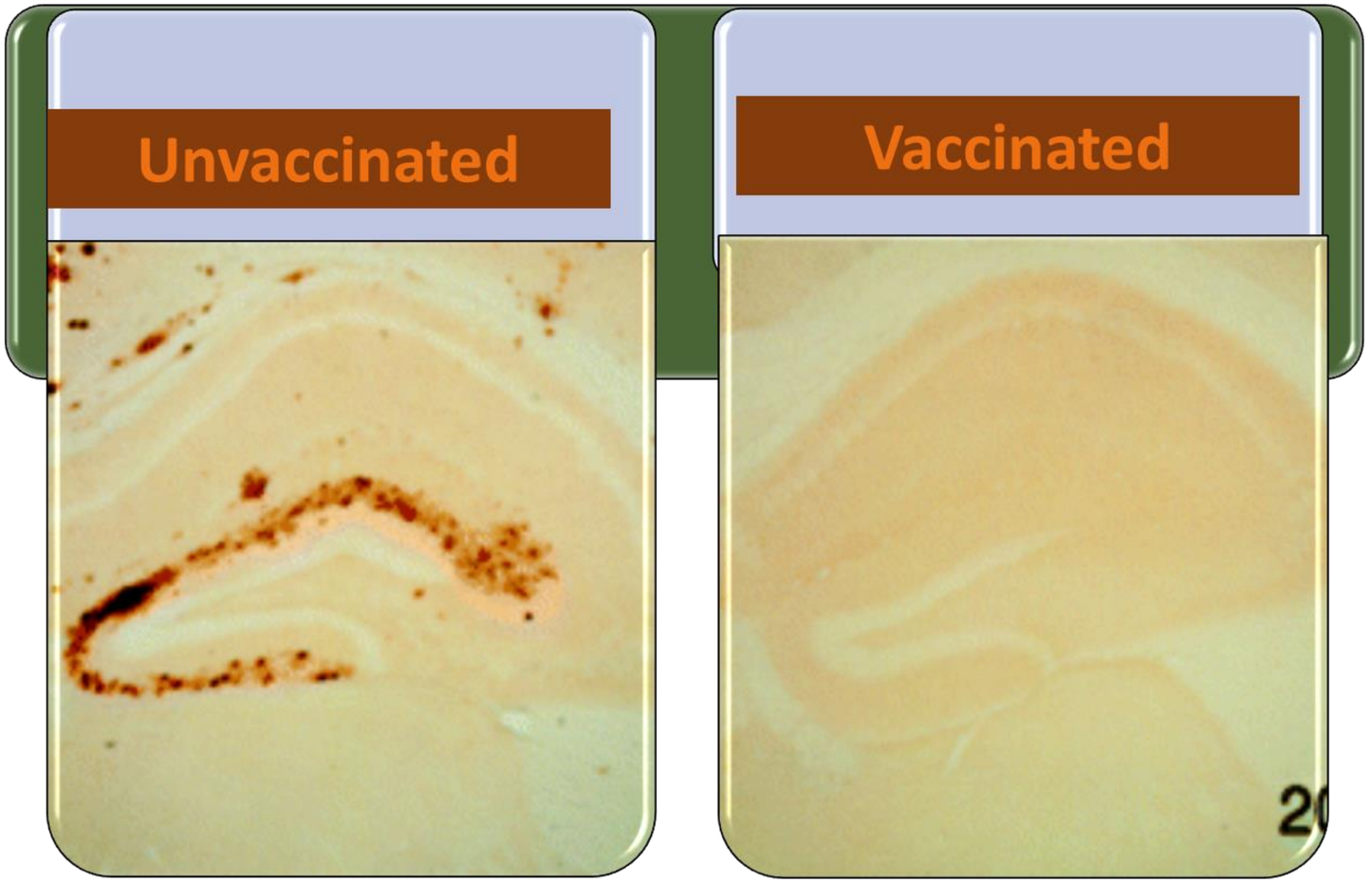
A cure for Alzheimer's?

Scientists may have found a way to halt the development of the brain plaques that are a hallmark of the disease. This is how they believe the vaccine works.



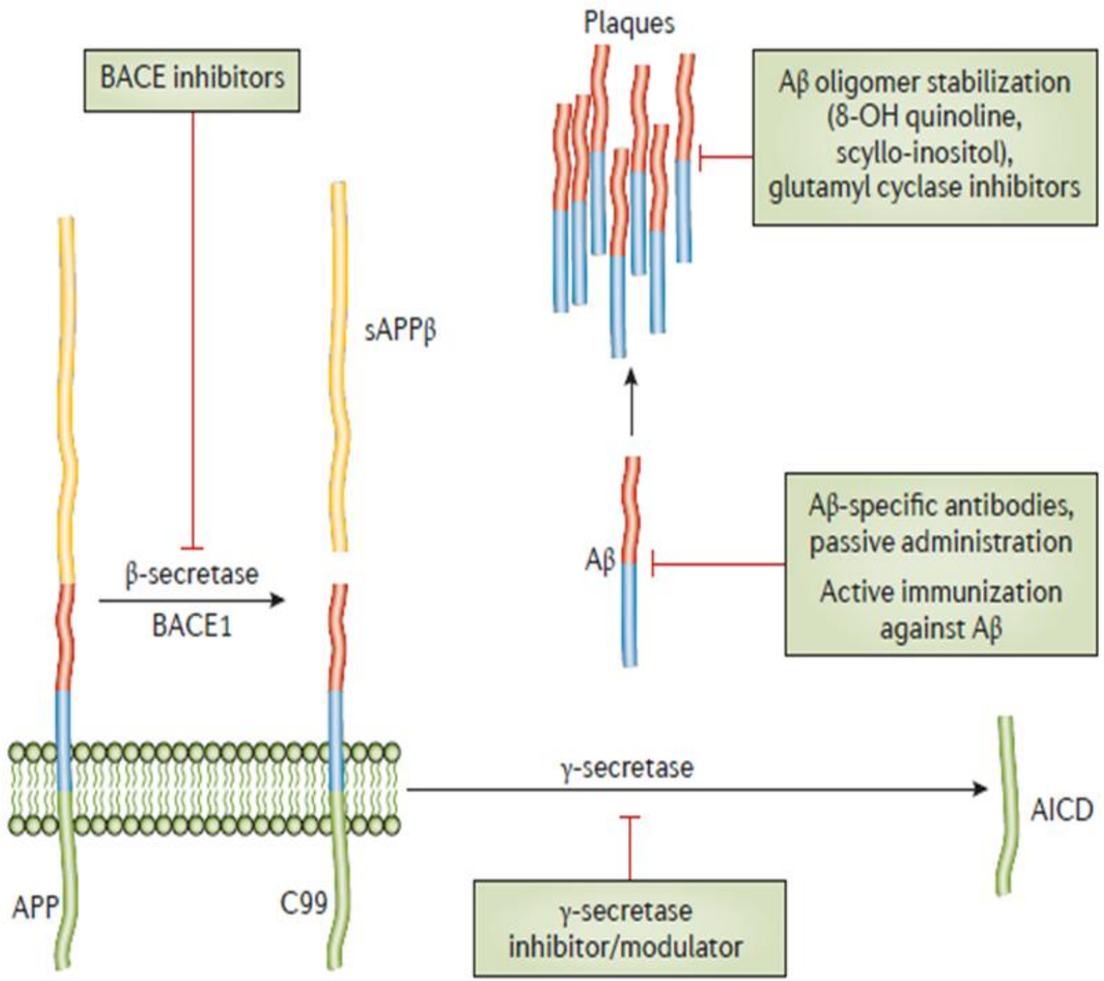
IMMUNISATION with $A\beta_{42}$

Sections of Mouse Brain



Schenk D, Barbour R, Dunn W, et al. (1999) Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature, 400*: 173-177.

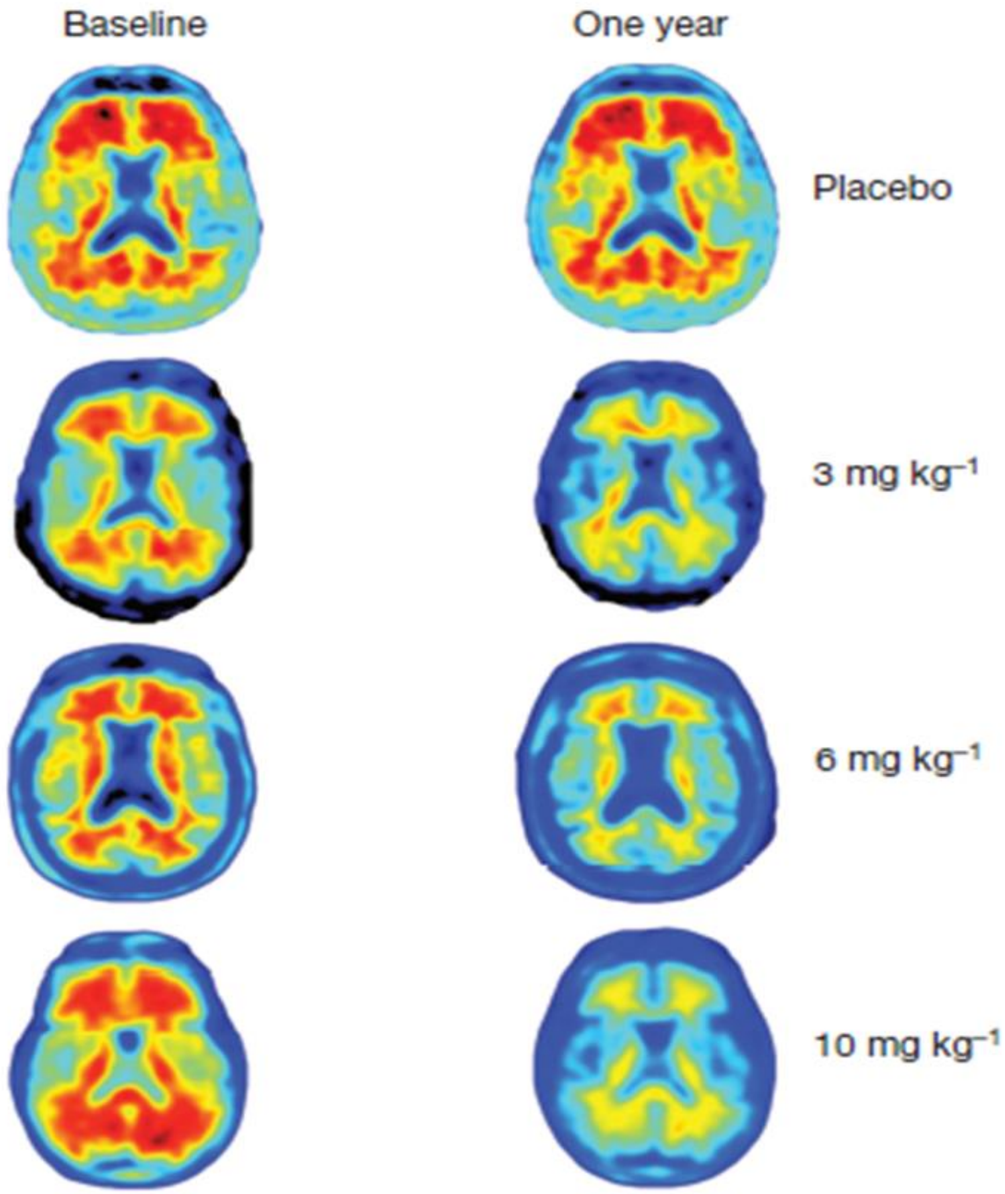
POTENTIAL STRATEGIES TO MANIPULATE beta-amyloid in Alzheimer's disease



First AD Modifying Drug

Aduhelm

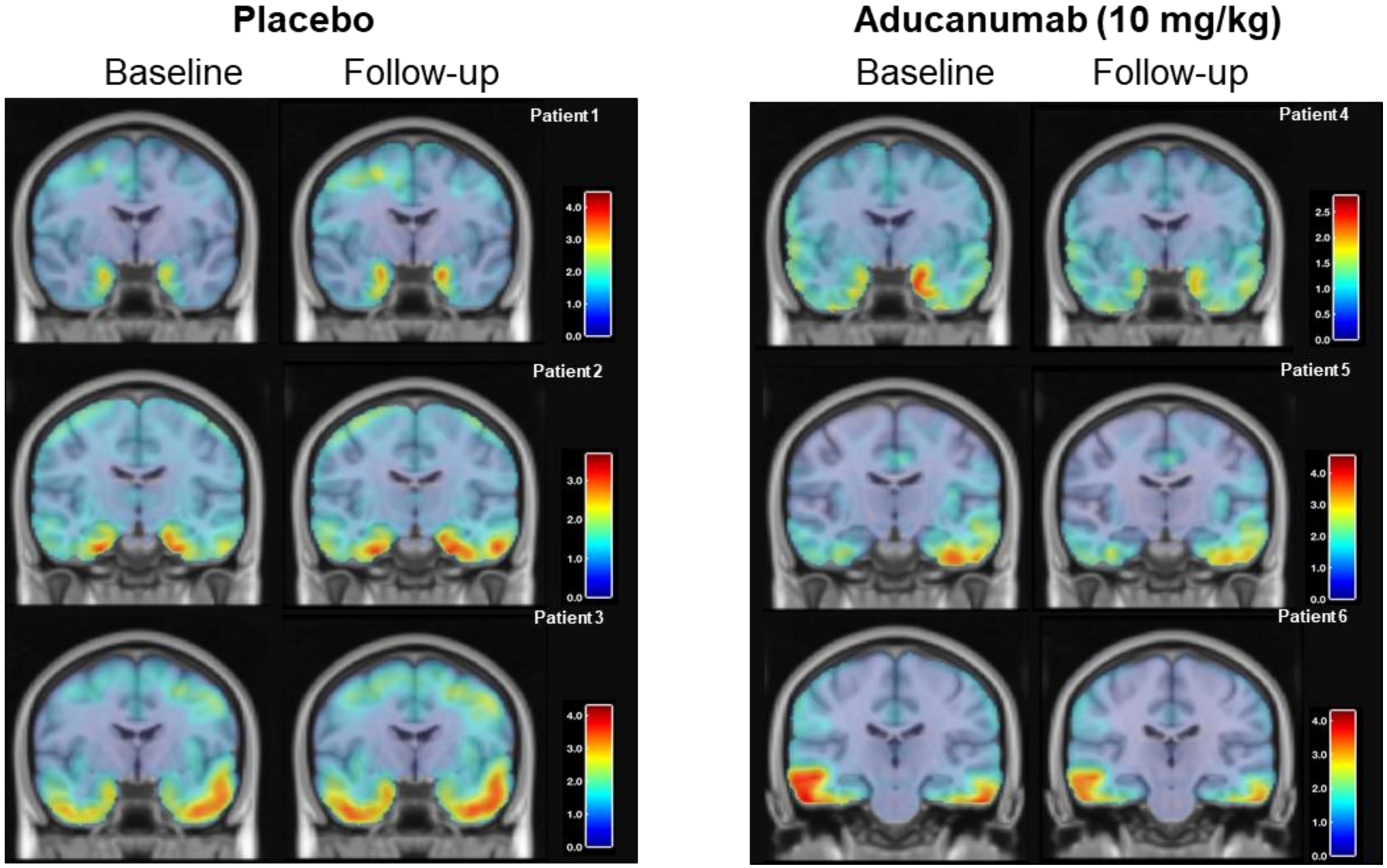
Aduhelm, also known as aducanumab, was the first disease-modifying drug approved for Alzheimer's disease on June 7, 2021.



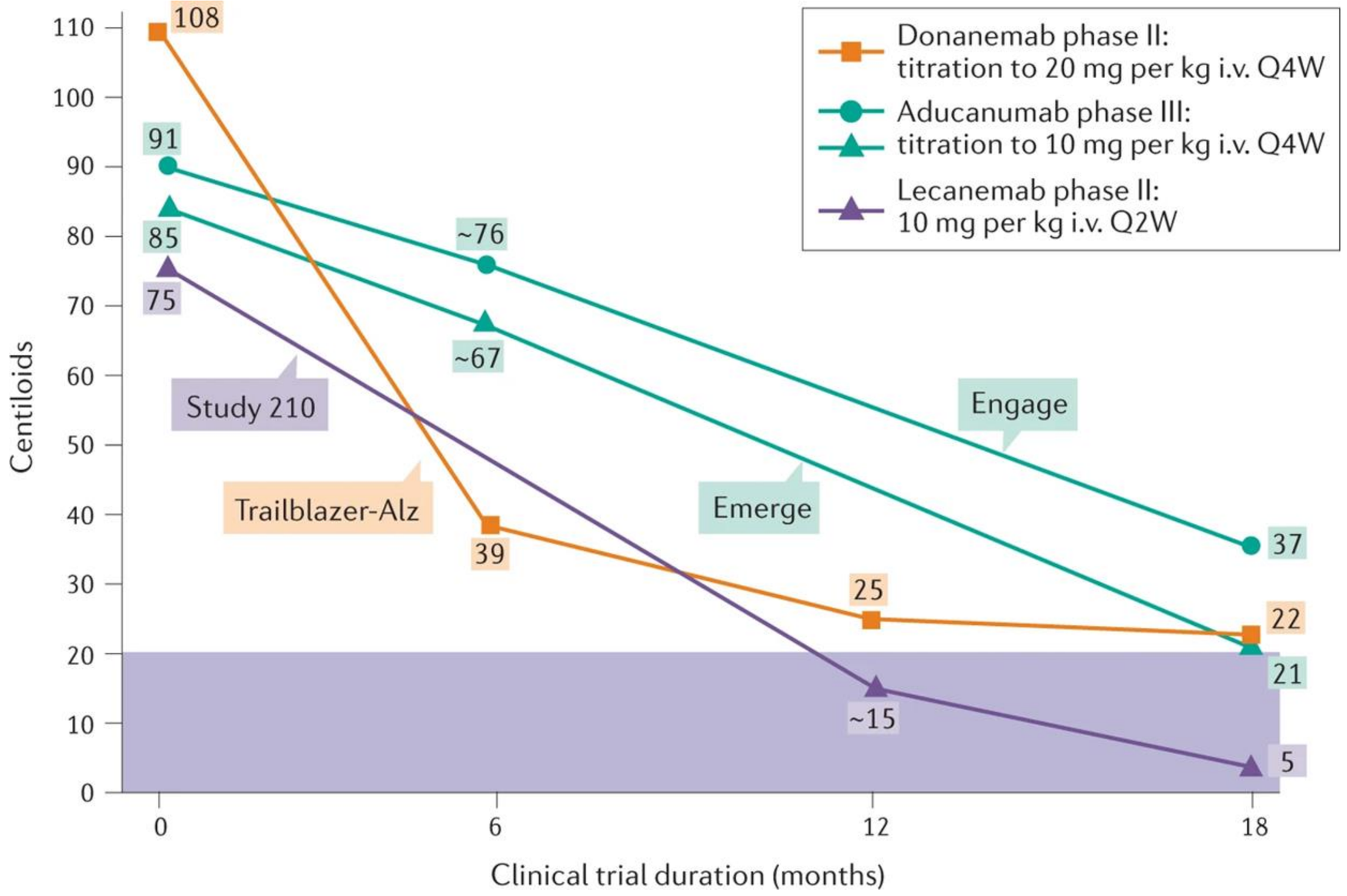
SEVIGNY ET AL, NATURE, SEPTEMBER 2016

Aβ amyloid reduction with aducanumab:? example florbetapir PET images at baseline and week 54

TAU DEPOSITION IN REPRESENTATIVE PATIENTS



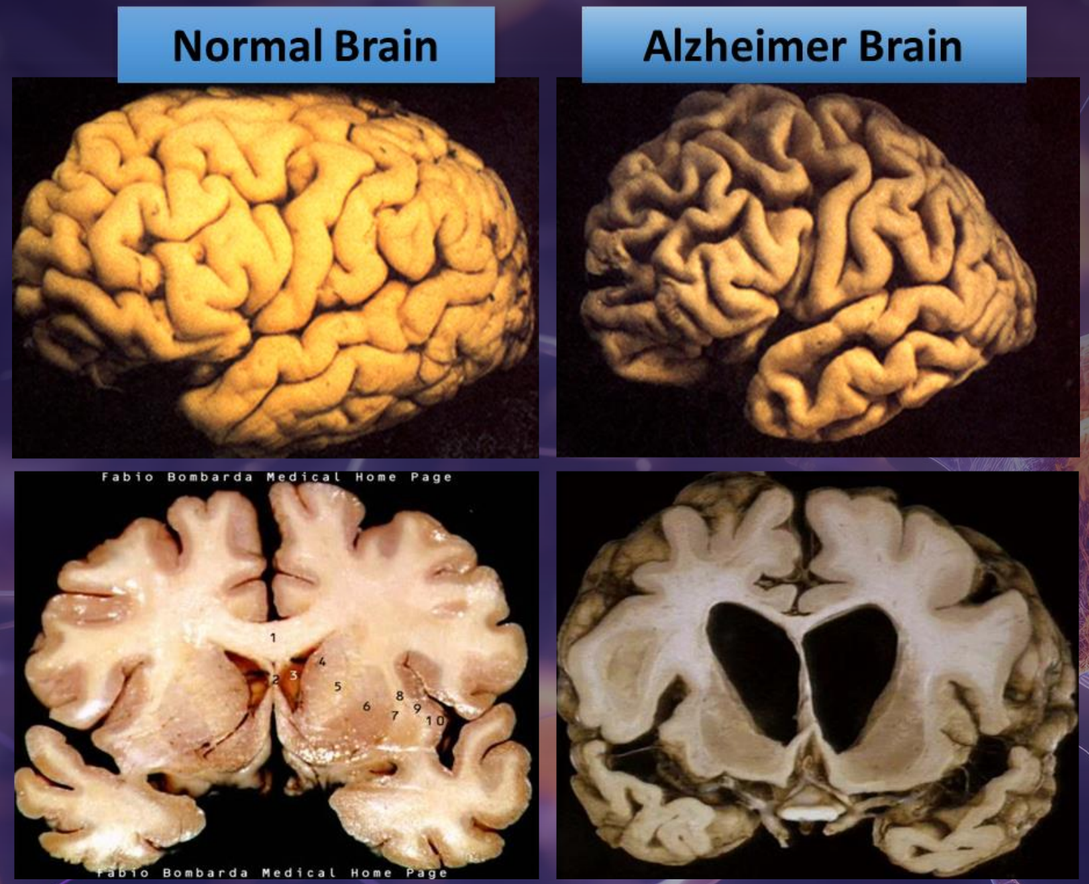
Amyloid-β removal profiles for Aducanumab, Donanemab and Lecanemab



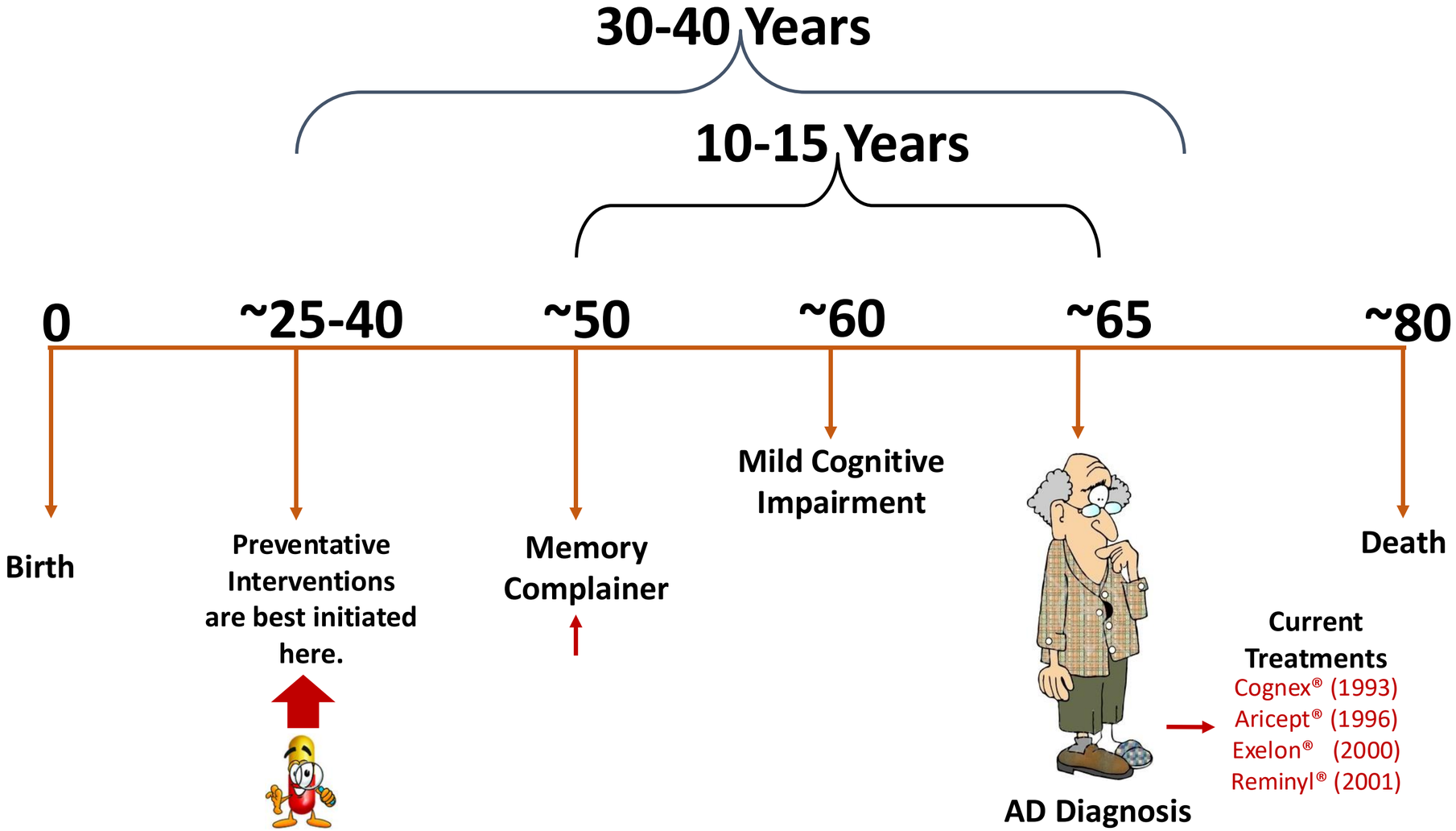
FINALLY: BIG WIN ON ALL OUTCOMES FOR LECANEMAB IN PHASE 3 TOPLINE RESULTS

- Biogen, Eisai refresh amyloid hypothesis with Phase III showing Alzheimer's medicine slows cognitive decline in 1,795 participants with early AD
- The drug slowed decline on the primary endpoint, CDR-SB, by 27% over 18 months ($p=0.00005$)
- Decline on all secondary clinical endpoints, comprising the ADAS-Cog14, ADCOMS, and ADCS MCI Activities of Daily Living ($p<0.01$)
- The incidence of the brain edema known as ARIA-E was one-third of that seen with Aduhelm
- FDA Set Accelerated Approval Decision for January 2023

BRAIN – Gross Anatomy



Alzheimer's Disease: Progression



The Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing

aibl

Commenced 2006

PiB and MRI with follow-up in 288 of the 1100 participants

Imaging increased to 650 participants in 2011-12

CSIRO

THE UNIVERSITY OF MELBOURNE

NNF NATIONAL NEUROSCIENCE FACILITY

NARI

MENTAL HEALTH Research Institute

ECU EDITH COWAN UNIVERSITY

Alzheimer's Australia Living with dementia

THE UNIVERSITY OF WESTERN AUSTRALIA

CogState

Austin Health

MACQUARIE UNIVERSITY SYDNEY ~ AUSTRALIA

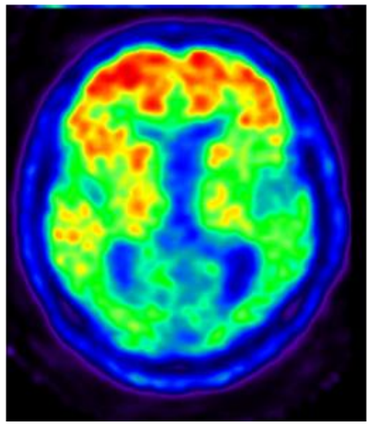
A MULTIMODALITY CLINICAL STUDY

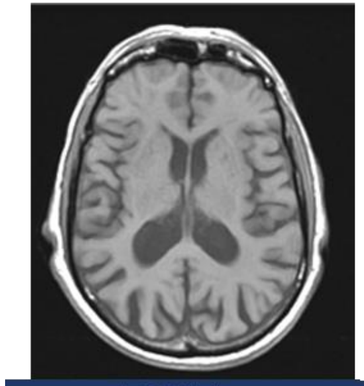
Databases

- Cognitive functions
- Blood biomarkers
- Genomic
- Demographic And Lifestyle

PET-PiB

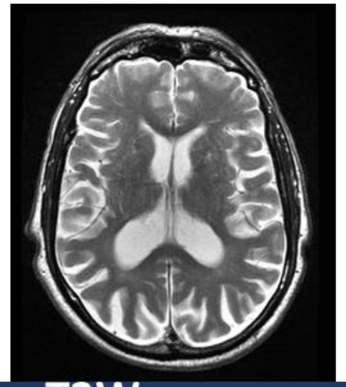
Amyloid beta load





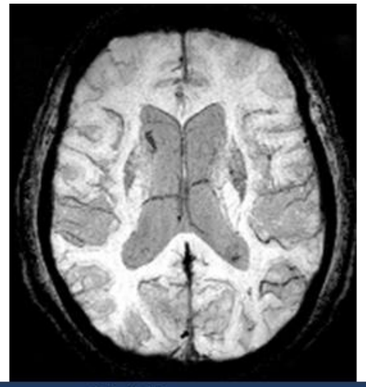
T1W

Anatomy



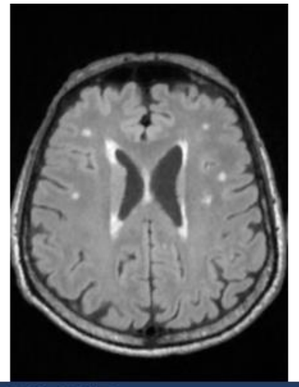
T2W

CSF and structures



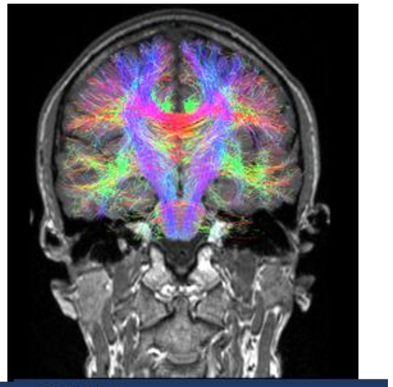
SWI

Venous tree



FLAIR

White matter lesions



DWI

White matter connection

METHODOLOGY: KEY OUTCOMES

CLINICAL/COGNITIVE

Clinical and cognitive measures
• MMSE, CDR, Mood measures, Neuropsychological battery

Clinical classification information
• NINCDS-ADRDA (possible/probable) AD classifications
• ICD-10 AD classifications
• MCI classifications
• Memory complaint status (in HC)

Medical History, Medications and demography

LIFESTYLE

Lifestyle information

Detailed dietary information
Detailed exercise information
Objective activity measures (actigraph – 100 volunteers)
Body composition scans (DEXA)

BIOMARKERS

Comprehensive clinical blood pathology

Genotype
• Apolipoprotein E, WGA in subgroup

Stored fractions (stored in LN within 2.5 hrs of collection)
• Serum
• Plasma
• Platelets
• red blood cell,
• white blood cell (in dH20)
• white blood cell (in RNAlater, Ambion).

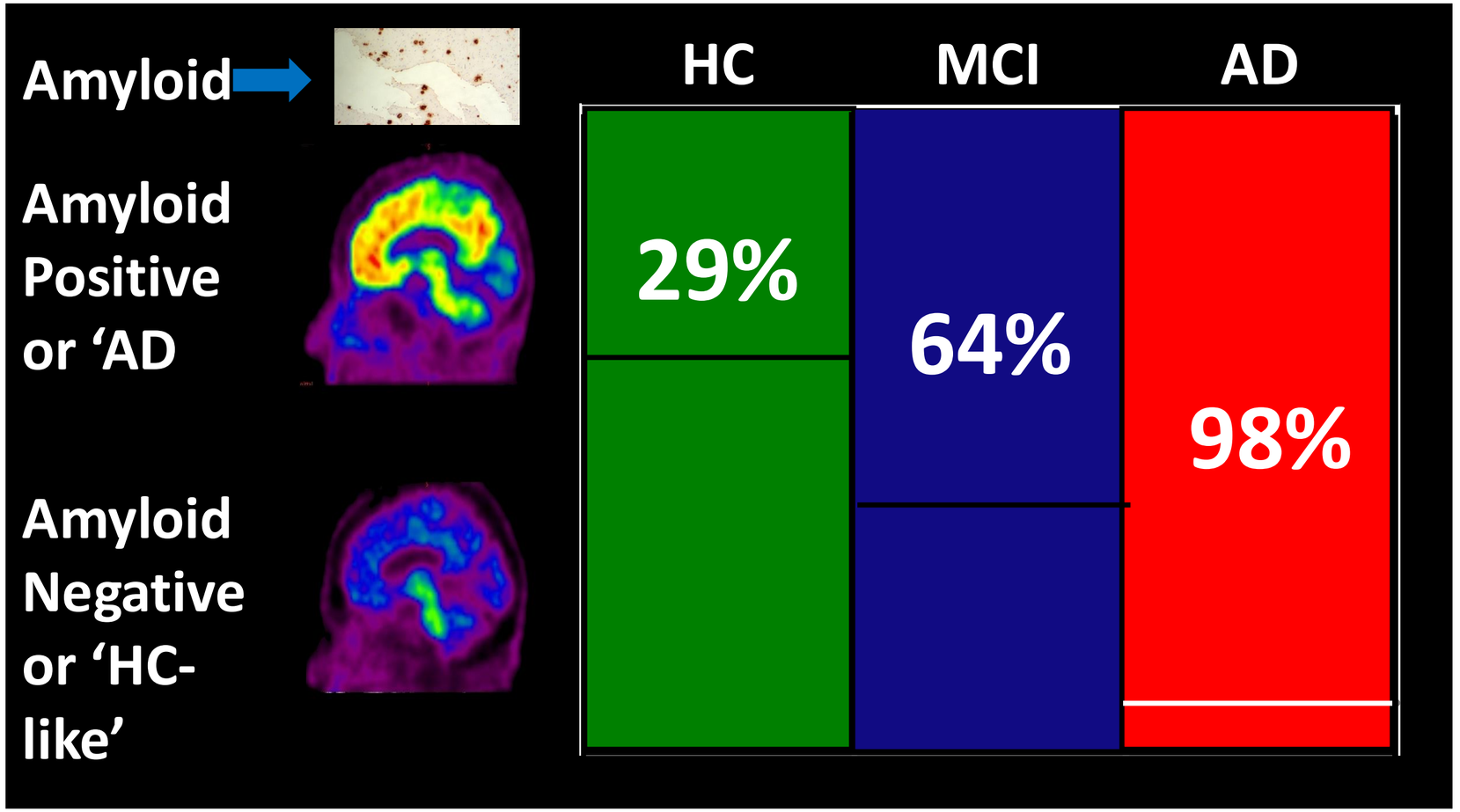
NEUROIMAGING

Neuroimaging scans (in 287 volunteers)

PET Pittsburgh Compound B (PiB)

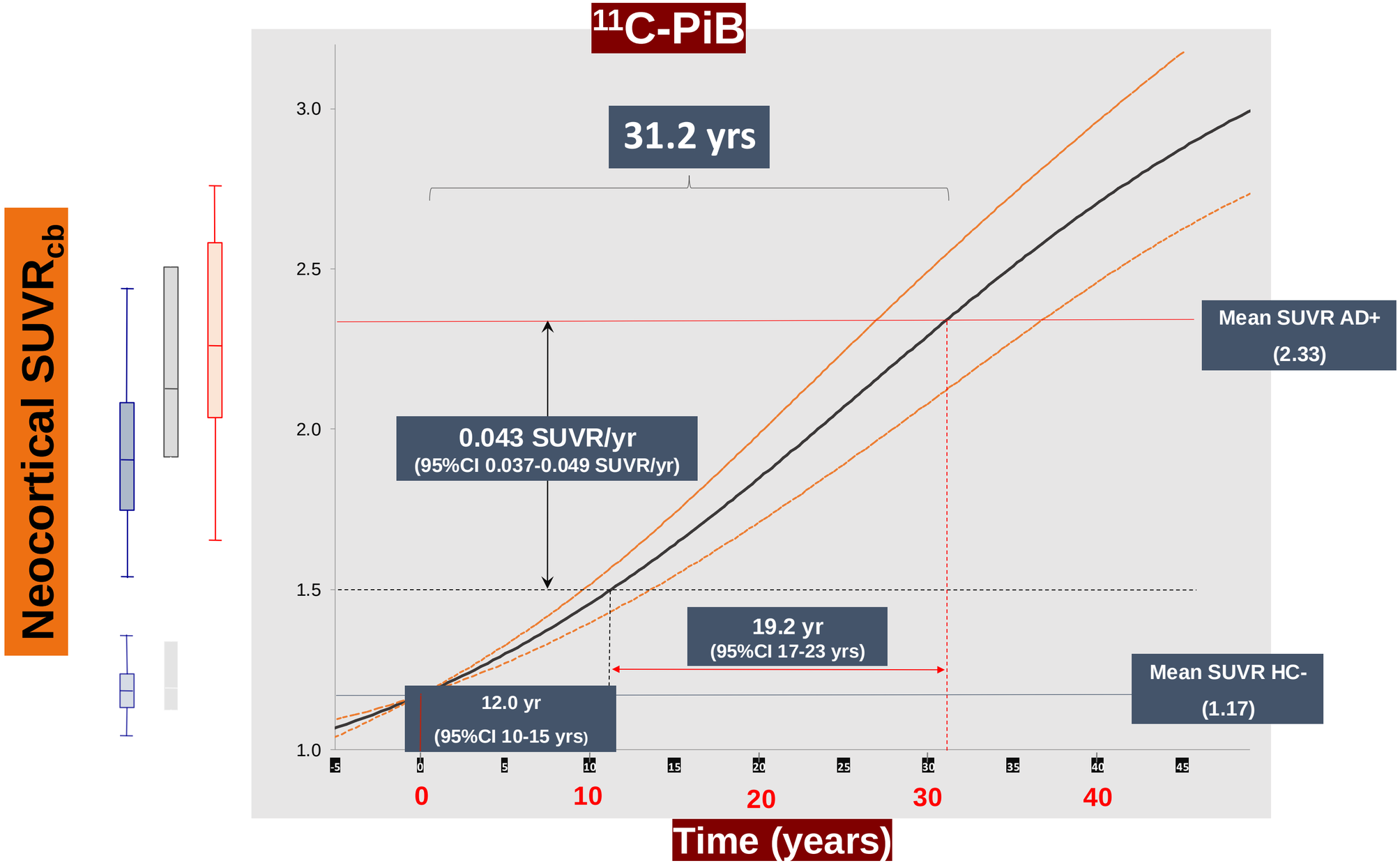
Magnetic Resonance Imaging
• 3D T1 MPRAGE
•T2 turbospin echo
•FLAIR sequence

Amyloid Load in the Brain of AIBL Participants: PiB +ve volunteers (%)



Significant differences between the three groups ($p<0.001$)

Sporadic AD: Aβ deposition over time



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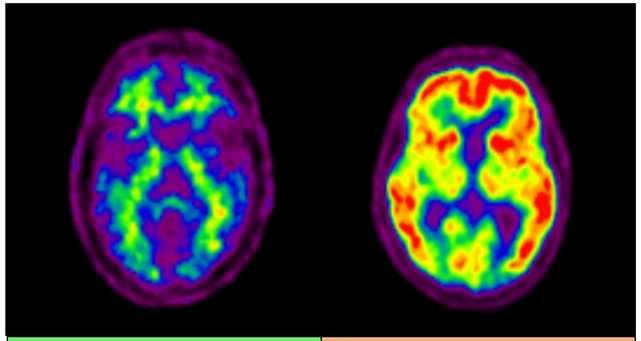
The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing

Villemagne et al., Lancet Neurol, 2013

Current Gold Standard Markers for AD

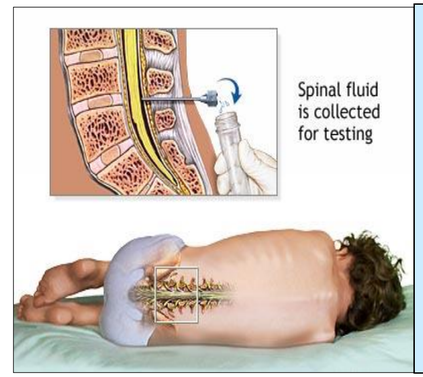
Changes in AD biomarkers appear ~2 decades before symptoms manifest

Amyloid-β PET



Expensive!!!

Cerebrospinal fluid biomarkers



Amyloid-β, Total-tau, P-tau.

Invasive!!!

Challenges and Solutions

Identify preclinical biomarkers suitable for community wide screening:	Solution
-It can be performed in any clinical laboratory -Economical -Non-invasive -Easily accessible -Enable therapeutic administration while the neural substrate is responsive to treatment	1. Developing a diagnostic blood test for preclinical AD

SIMOA HD-X ANALYZER

The Simoa HD-X machine is an exceptional tool designed for detecting protein biomarkers in minute quantities within diverse matrices, including blood (plasma and serum), cerebrospinal fluid, urine, and cell extracts. It plays a crucial role in the early detection of various neurological conditions, such as Alzheimer’s disease.

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Key Features:

Groundbreaking Sensitivity: Simoa can detect protein signals up to 1000 times fainter than traditional tests, making it possible to identify proteins that were previously challenging to detect.

Enhanced Precision: This heightened sensitivity revolutionizes biomarker analysis, allowing researchers to measure biomarkers with unparalleled accuracy.

The Simoa HD-X machine represents a significant advancement in research technology, empowering our researchers to explore biomarkers with unprecedented precision and reliability.

In 2023 our researchers worked with collaborators in 20 countries around the world.


Quanterix
LIONS ALZHEIMER'S FOUNDATION
and
LIONS CLUBS INTERNATIONAL

Blood Biomarkers reflecting AD-related neuropathology

Aβ pathology:Aβ 40 & Aβ 42

Tau pathology: total tau, ptau 181 & ptau 231

KARVIAH

Kerr Anglican Retirement Village Initiative in Ageing Health

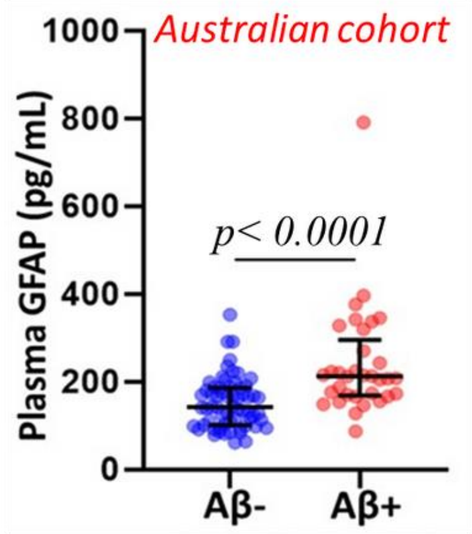
- 100 cognitively normal participants who have undergone brain Aβ imaging via Positron Emission Tomography (PET)
- 67 Aβ- cognitively normal, 33 Aβ+ cognitively normal.
- Aged between 60 and 90 years
- Good general health, not diagnosed positive for dementia based

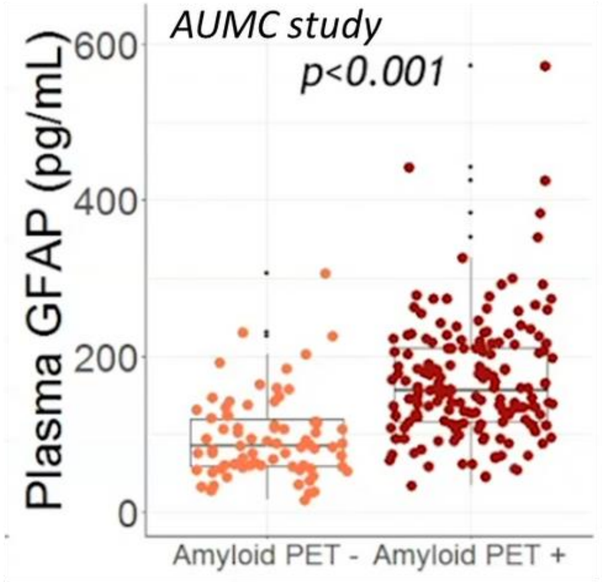
KARVIAH

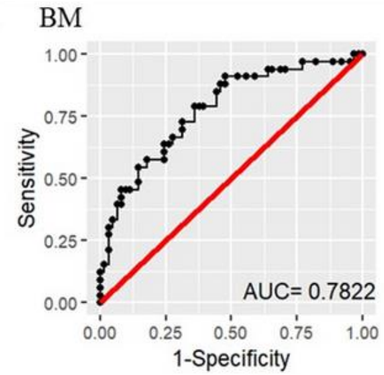
Cohort characteristics

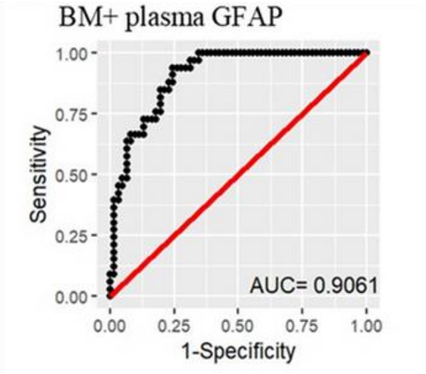
	Aβ–	Aβ+	p
Age (years, mean ±SD; Aβ– =67, Aβ+ =33)	77.78±5.56	79.00±5.44	.300
Sex (Male/Female; Aβ– =67, Aβ+ =33)	19/48	13/20	.266
BMI (mean ±SD; Aβ– =67, Aβ+ =33)	27.46±4.43	27.94±4.85	.626
APOE ε4 carriers (N (%); Aβ– =67, Aβ+ =33)	5 (7.46)	16 (48.48)	<.0001
Subjective memory complainers (N (%); Aβ– =67, Aβ+ =33)	52 (77.61)	24 (72.72)	.591
MMSE (mean ±SD; Aβ– =67, Aβ+ =33), baseline	28.54±1.16	28.76±1.12	.368
MMSE (mean ±SD; Aβ– =64, Aβ+ =32), 12m	28.87±1.12	28.81±1.50	.818
Hippocampal volume % (mean ±SD; Aβ– =63, Aβ+ =31), baseline	0.40±0.039	0.39±0.038	.901
Hippocampal volume % (mean ±SD; Aβ– =52, Aβ+ =29), 12m	0.38±0.04	0.38±0.04	.562
FBB-PET SUVR (mean ±SD; Aβ– =67, Aβ+ =33), baseline	1.16±0.09	1.70±0.24	-
FBB-PET SUVR (mean ±SD; Aβ– =64, Aβ+ =32), 12m	1.16±0.09	1.72±0.24	-

In cognitively unimpaired cohort, plasma GFAP levels are higher in the Aβ+ vs Aβ-

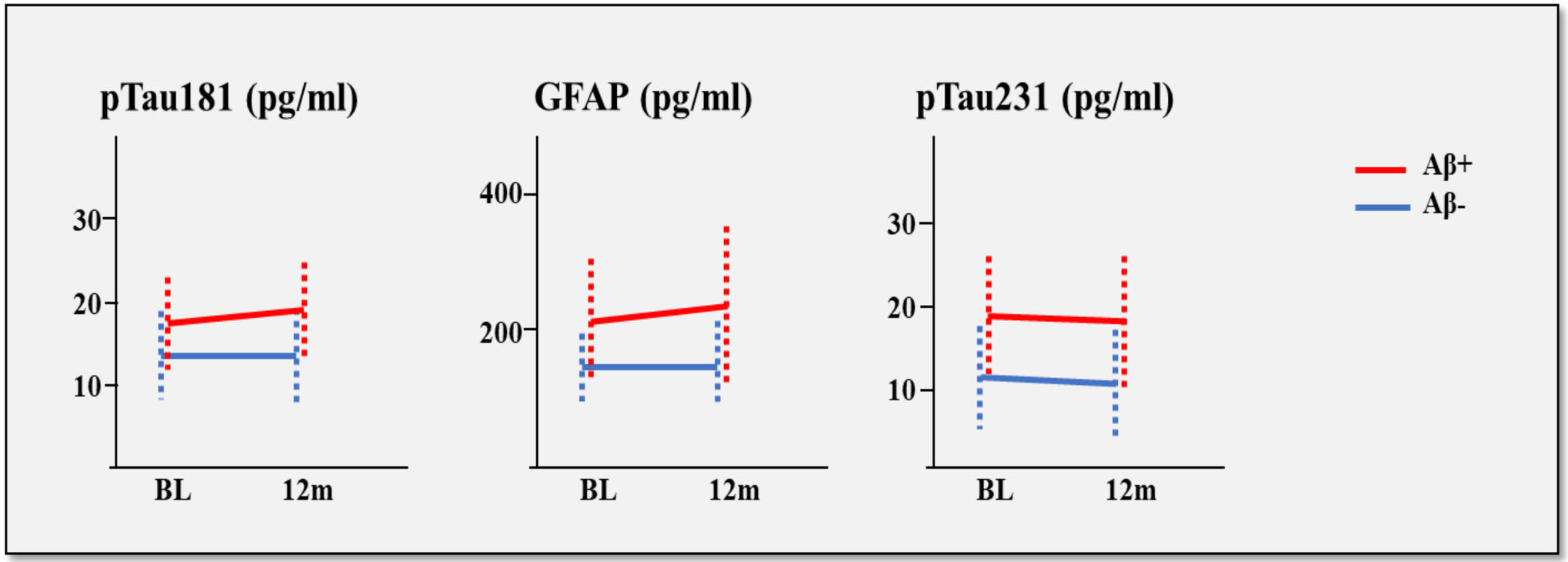




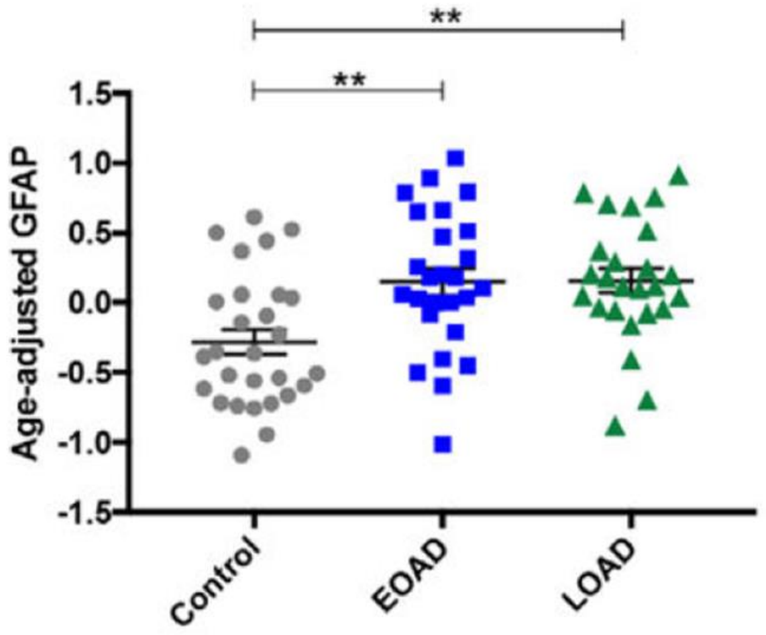


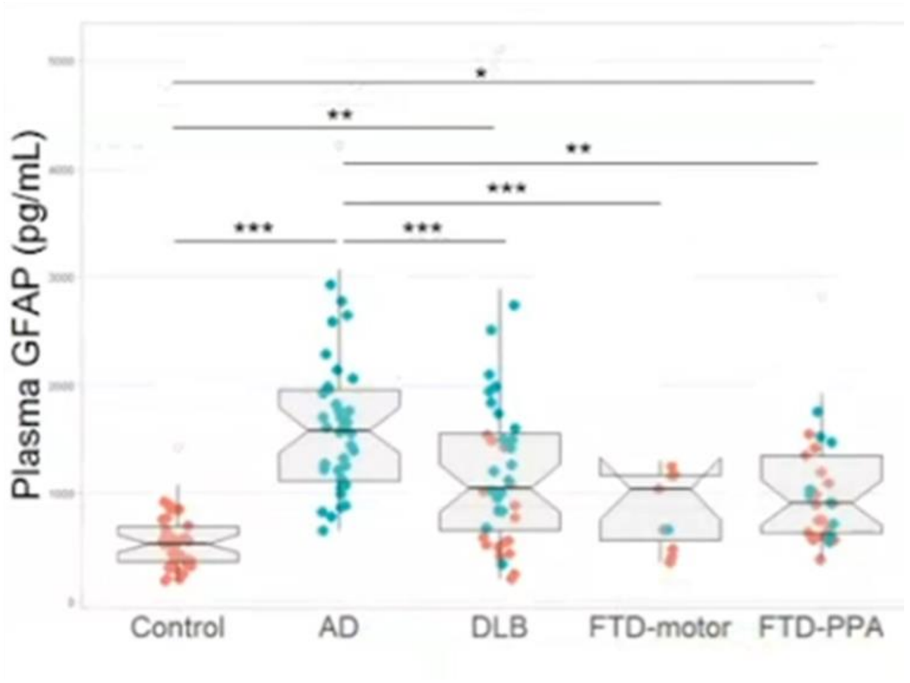


Comparison of plasma GFAP, p-tau181 and p-tau231 between Aβ- and Aβ+ cognitively normal older adults at baseline and the 12-month follow-up timepoint



Plasma GFAP as a biomarker for AD





- Plasma GFAP levels are higher in AD vs HC
- Plasma GFAP levels are higher in AD vs other dementias

AIBL STUDY

The Australian Imaging, Biomarker & Lifestyle (AIBL) Study of Ageing assesses the biomarkers, genetic factors, cognitive characteristics, and health and lifestyle factors that determine the development of Alzheimer's disease.

Using this data, AIBL researchers make world-class contributions to understanding the natural history of Alzheimer's disease progression.

The AIBL cohort is a prospective longitudinal study comprising more than 2300 participants, with data and blood samples collected every 18 months.

Among these participants, 800 have associated imaging data available, including brain Aβ load via PET and/or brain regional volumetric MRI.

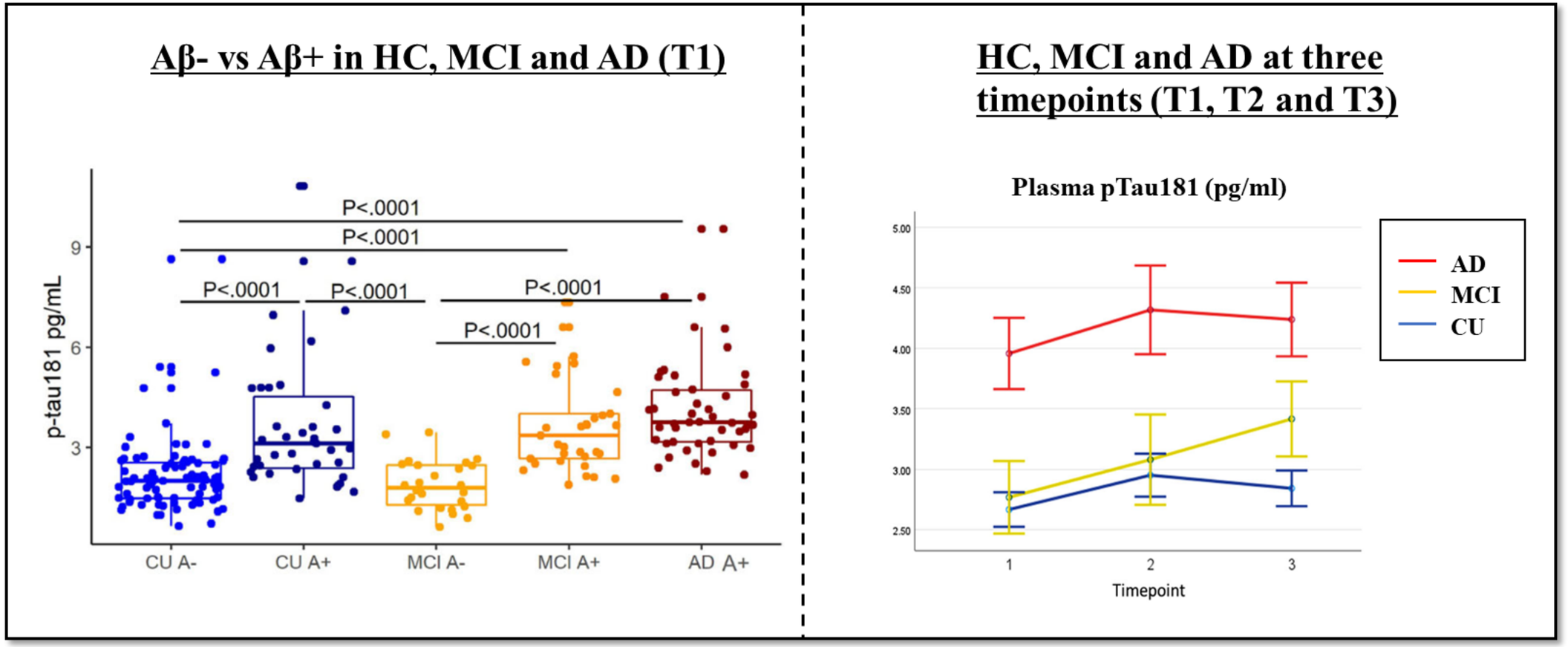
The cohort includes Aβ- cognitively normal individuals, Aβ+ cognitively normal individuals, mild cognitively impaired (MCI) individuals, and Alzheimer's disease (AD) participants.

AIBL provides unique cross-sectional and longitudinal data, including comprehensive clinical (e.g., neuropsychological) and neuroimaging data. These datasets can be utilized as quantitative traits in various analyses.

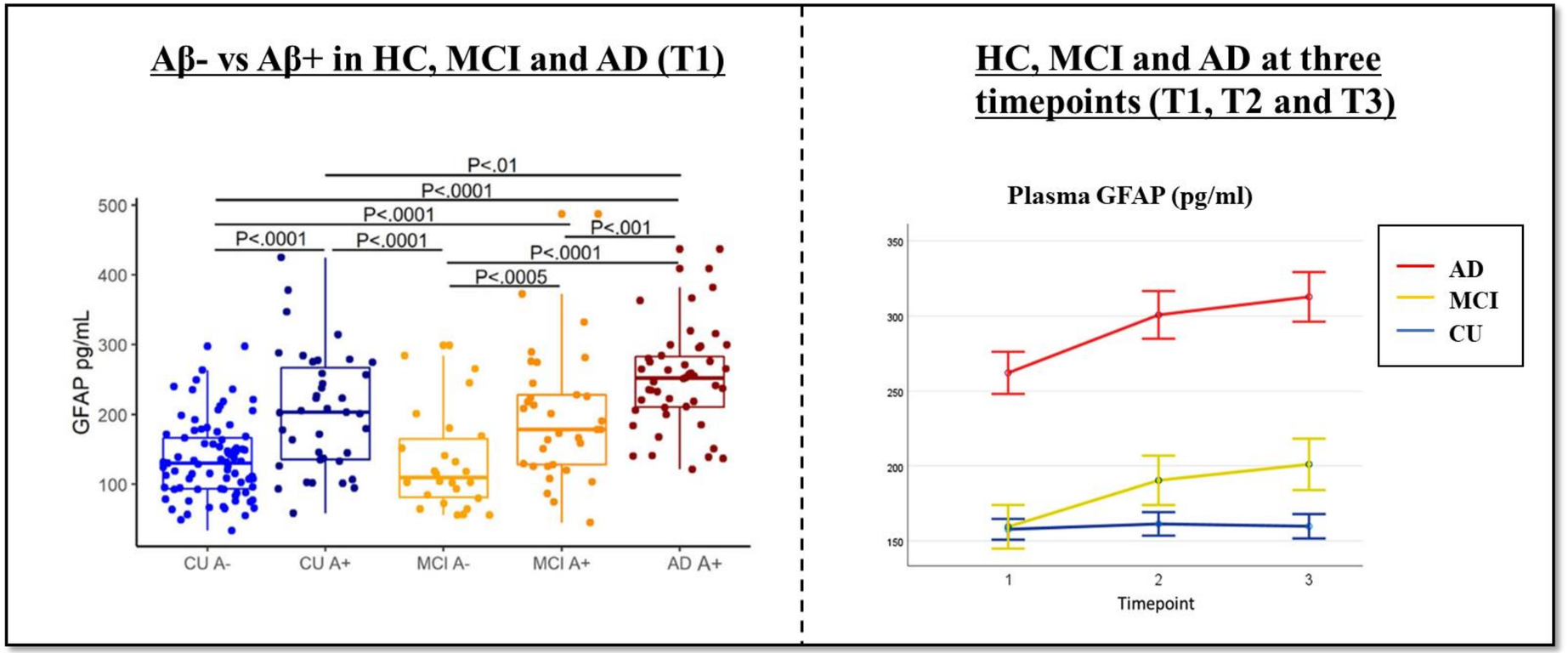
Exclusion criteria for participation in the study encompass a history of non-AD dementia, schizophrenia, bipolar disorder, current depression (GDS score above 5/15), Parkinson’s disease, uncontrolled hypertension (systolic BP > 170 or diastolic BP > 100), cancer (other than basal cell skin carcinoma) within the last two years, symptomatic stroke, uncontrolled diabetes, or regular alcohol use exceeding two standard drinks per day for women or four per day for men.

aibl
The Australian
Imaging, Biomarkers & Lifestyle
Flagship Study of
Ageing

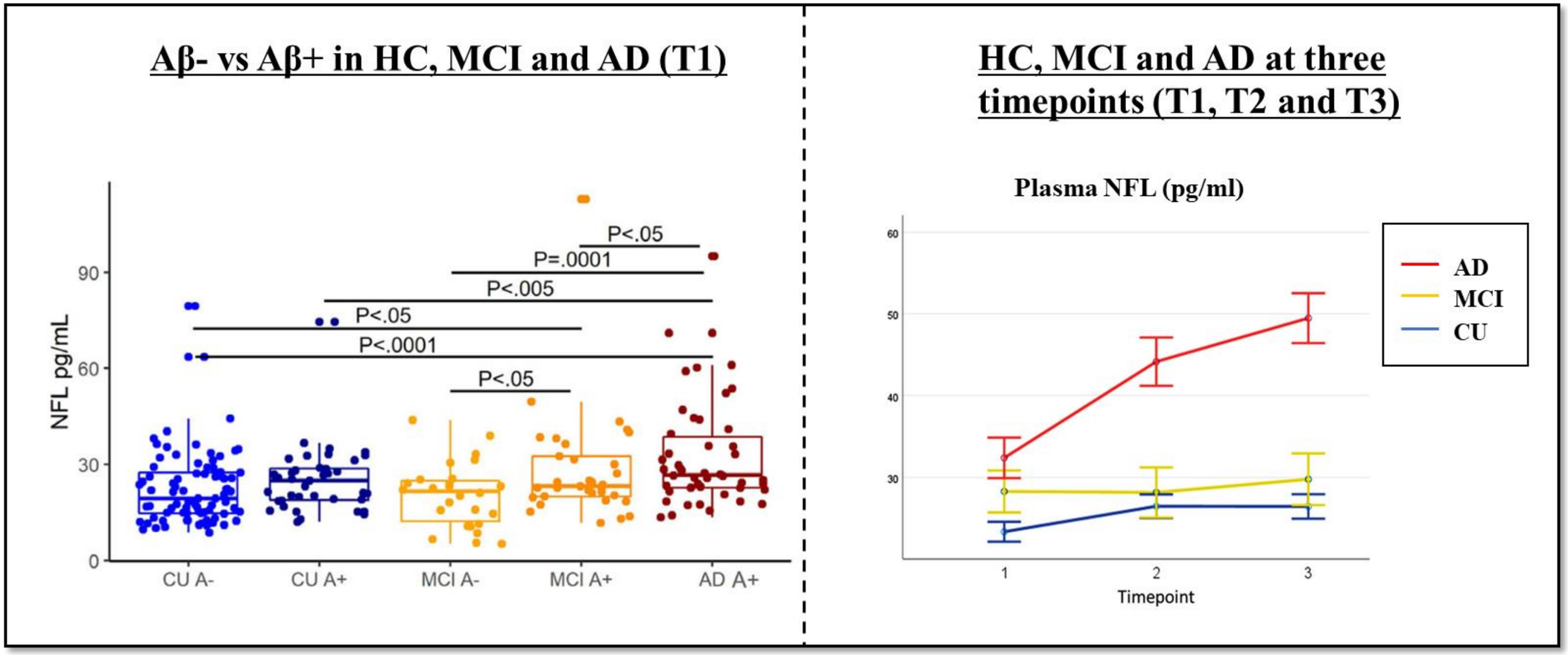
Comparison of plasma pTau181 between Aβ- and Aβ+ (in HC, MCI and AD at timepoint T1) and between HC, MCI and AD at three follow-up timepoints (T1, T2 and T3)



Comparison of plasma GFAP between Aβ- and Aβ+ (in HC, MCI and AD at timepoint T1) and between HC, MCI and AD at three follow-up timepoints (T1, T2 and T3)



Comparison of plasma NFL between Aβ- and Aβ+ (in HC, MCI and AD at timepoint T1) and between HC, MCI and AD at three follow-up timepoints (T1, T2 and T3)



DIAN

DOMINANTLY INHERITED ALZHEIMER NETWORK

The Dominantly Inherited Alzheimer Network (DIAN) is an international research effort focused on dominantly inherited Alzheimer's disease

The DIAN Observational Study enables researchers around the world to monitor and identify changes in individuals who carry one of the gene mutations known to cause dominantly inherited Alzheimer's disease.

DIAN

Participant Composition:
Biological offspring of individuals with an ADAD mutation (genes: APP, PSEN1, PSEN2)
50% chance of inheriting the mutation

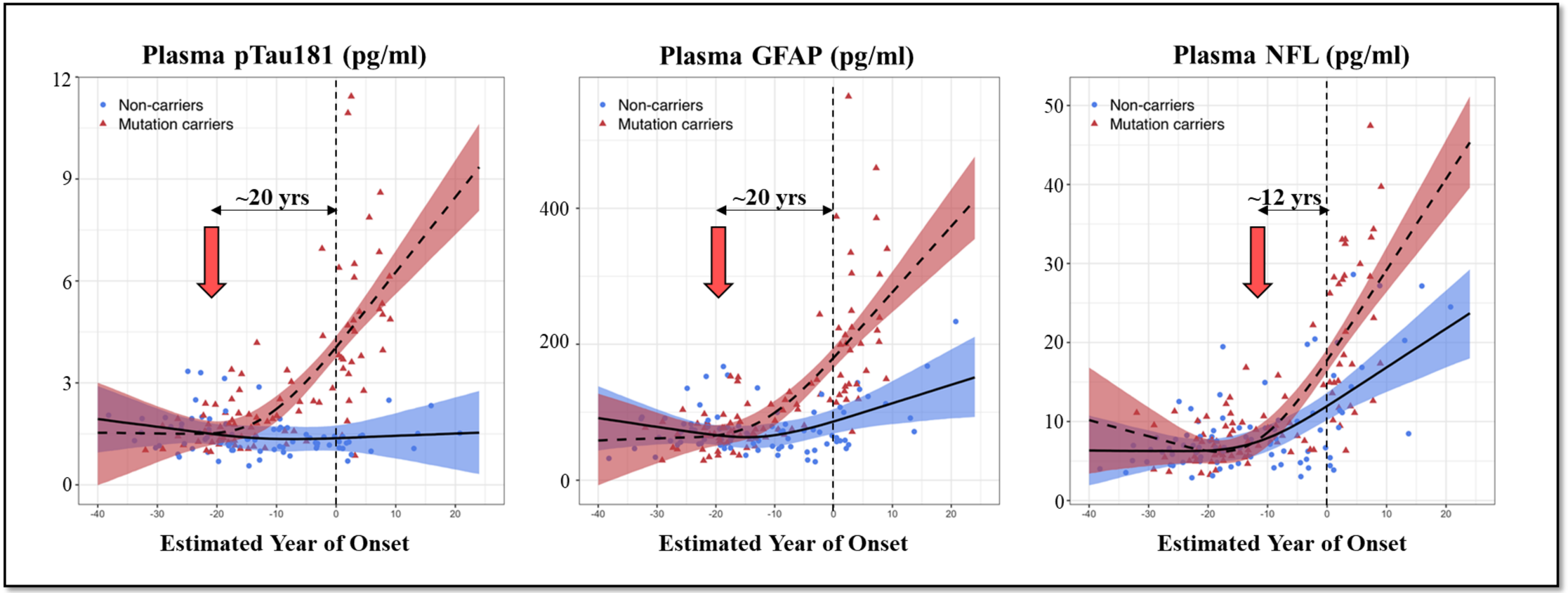
Sample Availability:
Plasma samples: 86 mutation non-carriers, 98 mutation carriers
Paired serum and CSF samples: 30 mutation non-carriers, 30 mutation carriers

Estimated Time to Symptom Onset (EYO):
Calculated based on the difference between participant's age and average age of onset for the specific mutation
Includes both mutation carriers and their non-carrier siblings

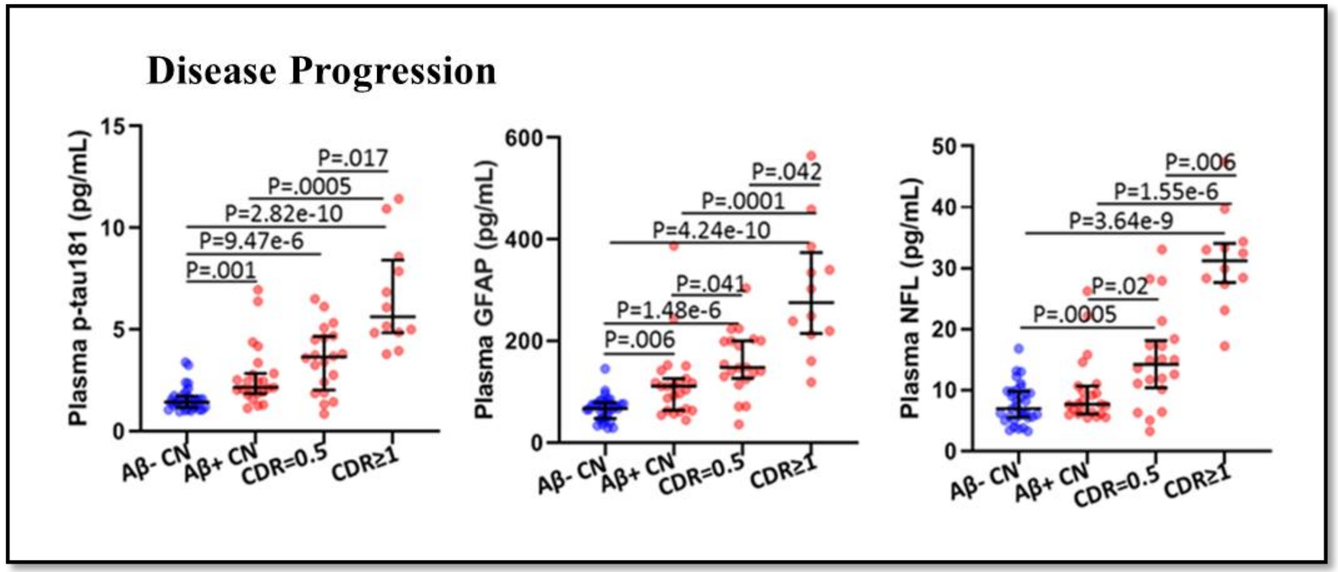
Assessments Conducted:
Comprehensive clinical evaluations
Neuroimaging
Blood and CSF collection

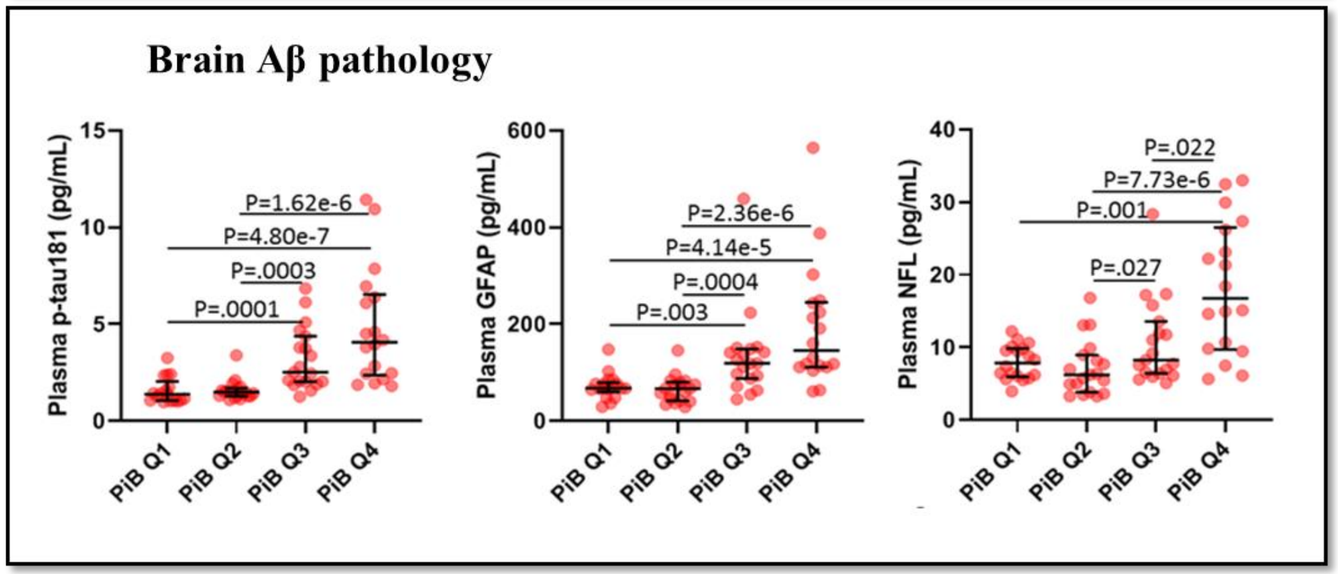
Exclusion Criteria:
Participants with the Dutch mutation (APP Glu693Gln) were excluded due to their atypical clinical syndrome

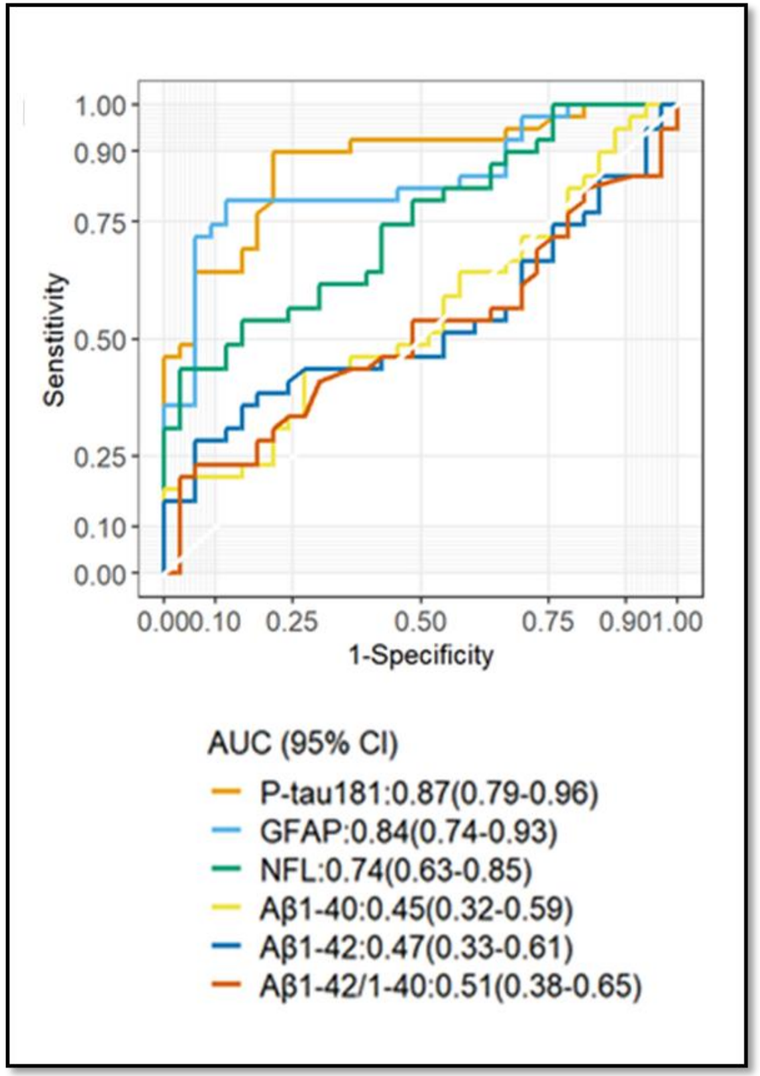
CROSS-SECTIONAL PLASMA MARKERS FOR MUTATION CARRIERS (RED) AND NON-CARRIERS (BLUE)



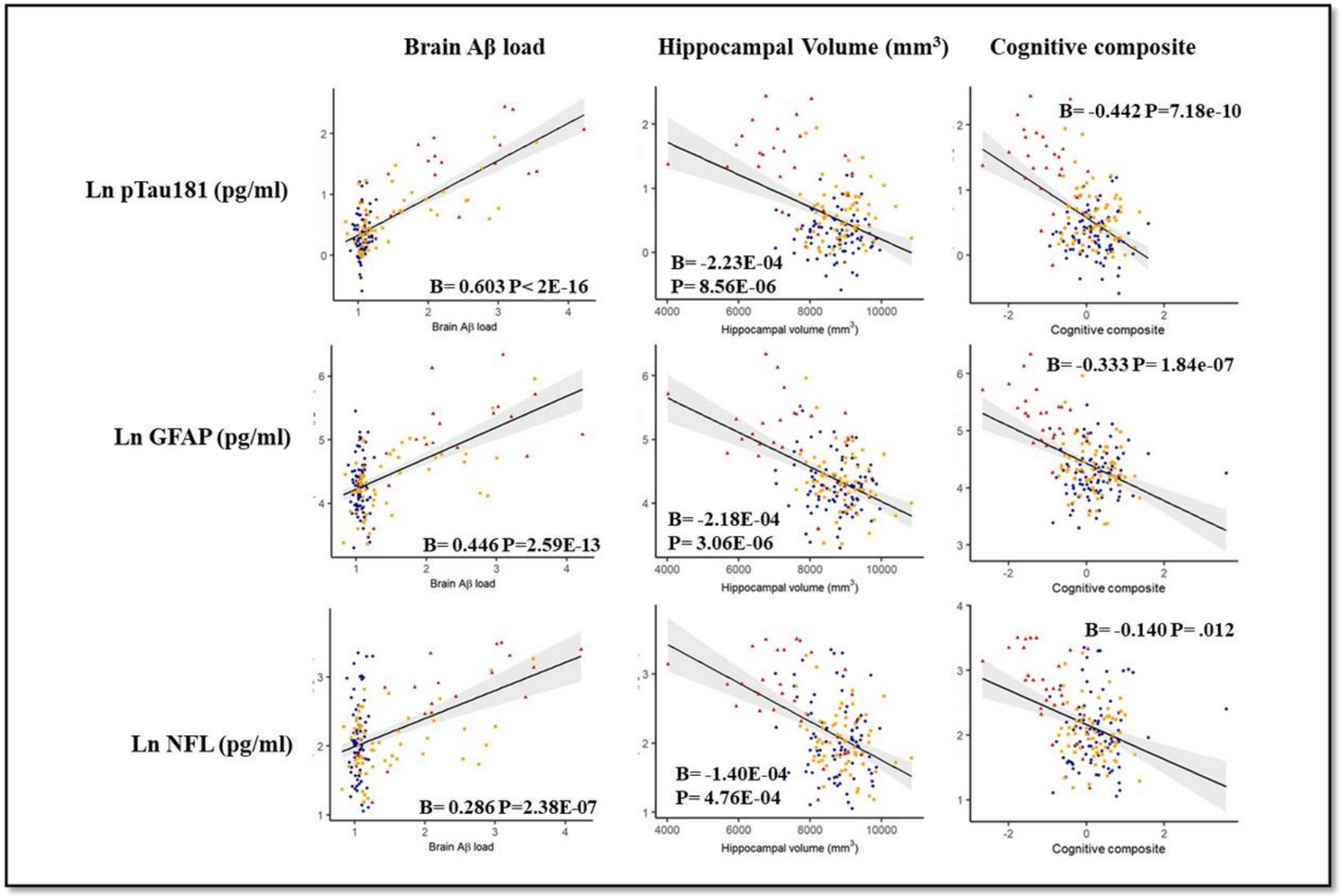
ASSOCIATION OF PLASMA P-TAU181, GFAP AND NFL LEVELS WITH Aβ PATHOLOGY IN ADAD AND DISEASE PROGRESSION







ASSOCIATION OF PLASMA P-TAU181, GFAP AND NFL WITH BRAIN AB LOAD, HIPPOCAMPAL VOLUME AND COGNITIVE COMPOSITE



SUMMARY

- Aduhelm is the first disease modify drug to be released in 20 years. Its markedly lowers brain amyloid levels but its clinical benefits are uncertain.
- Its more likely to be clinically beneficial in primary or secondary prevention emphasizing the importance of early intervention.
- Lecanemab is the second disease modifying drug which also improves memory with few side-effects compared to Aduhelm.
- PET amyloid imaging demonstrates cerebral amyloid build up decades before the onset of symptoms and serves as a gold standard for developing surrogate markers.
- Promising blood biomarkers that reflect brain amyloid load are Aβ 1-42, ptau181, ptau 231 and GFAP.
- ptau 181, ptau 231 and GFAP are equivalent as biomarkers.
- However combination with age, APOE genotype and gender indicates that GFAP is a front runner which was demonstrated in the KARVIAH cohort and validated in the AIBL and DIAN cohort.

AU-ARROW

The *AU*stralian-Multidomain *A*pproach to *R*educe Dementia *R*isk by prOtecting brain health *W*ith lifestyle intervention Study.

Australia's Growing Dementia Problem

2nd leading cause of death of Australians

Leading cause of death in Australian women

- Currently (2022), there are 487,500 people living with dementia in Australia, and it's estimated that almost 1.6 million people are involved in the care of these people
- The number of people with dementia is expected to increase to 1,076,000 by 2058 (Dementia.org.au/statistics)
- Dementia has: Known risk factors , Known protective factors
- Protective factors include LIFESTYLE MODIFICATIONS, providing the opportunity to develop easily adoptable programs to DELAY or PREVENT dementia onset, thus reducing the number of people who will develop dementia, or possibly the severity of dementia
- In Australia, a 5% REDUCTION in the annual age-sex specific incidence rates for dementia in people aged 65 years and above would lead to savings of $120.35 billion by 2056

5% Reduction	2036	2056
$$ saved	$26.8 billion	$120.4 billion
Reduction in dementia cases	13%	24%

Background To The AU-ARROW Study

Research has shown that regular exercise (both aerobic exercise and resistance training) improves cognitive function

Population studies have shown that the Mediterranean and MIND diets can both reduce the risk of cardiovascular disease, type 2 diabetes and dementia symptoms

Accredited brain training and regular social activity also improve aspects of cognitive function

Regular monitoring (and treatment) of vascular and type 2 diabetes risk factors promotes prevention

COMBINATION TRIALS AND GLOBAL INITIATIVES

- Brain training + regular exercise = cognitive improvements
- Global Studies:

- Combination lifestyle changes show additive effects
- The FINGER Study (Finland):

- Combines exercise, brain training, MIND diet, and vascular risk monitoring
- Significant cognitive benefits
- World-Wide FINGERS:

- Global initiative inspired by FINGER study
- Includes 16 studies in countries like Germany, Japan, South Korea, China, and Ireland
- Australia participates via AU-ARROW
- US-POINTER Study:

- U.S. study focused on lifestyle interventions to protect brain health
- AU-ARROW aligns closely with US-POINTER methods and outcomes

AU-ARROW Clinical Study Design

AU-ARROW

Site 2 **Site 1**

2-year intervention

Men & women 60-79 years

Health status indicates at risk of developing dementia

600 participants total

300 participants

300 participants

Multidomain Lifestyle Group

Health Education and Coaching Group

MIND diet (dietitian support)

Regular aerobic & resistance exercise (gym membership, Fitbit)

Online cognitive training program

Health monitoring & social activity

Supportive monthly meetings

Group meetings to educate on value of exercise, healthy diet, cognitive and social activity (Fitbits, but no facilitation)

AU-ARROW is Aligned with US-POINTER

US-POINTER (Structured Lifestyle Intervention)	AU-ARROW (Multidomain Lifestyle Intervention)
EXERCISE • YMCA • Fitbit • Log of exercises one week/month • Short Physical Performance Battery (SPPB, 6-monthly)	**EXERCISE** • Local gyms (attendance recorded) • Fitbit • Log of exercises one week/month • Phone calls and gym (group) visits • SPPB (6-monthly), Grip test, SOZO body comp.
DIET • MIND diet • Personal daily food intake log • Monthly phone calls • Rush Food Frequency Questionnaire (6-monthly)	**DIET** • MIND diet + minor changes to Australian foods & following Aust. Dietary Guidelines • Easy Diet Diary App (Australian) to log diet • Monthly phone calls • Cancer Council of Victoria Food Frequency Questionnaire (6-monthly)
COGNITIVE EXERCISES • BrainHQ • Personal activity log 1 week/month • BrainHQ assessment (6-monthly)	**COGNITIVE EXERCISES** • BrainHQ • Log of cognitive/social activities, 1 week/ month • BrainHQ assessment (6-monthly)
HEALTH MONITORING • 6-monthly blood tests (Glc, HbA1c, lipids) blood pressure, weight. • Encouraged to measure BP regularly at YMCA, pharmacy or fire station	**HEALTH MONITORING** • 6-monthly blood tests (Glc, HbA1c, lipids), blood pressure, weight. • BP measurement by staff at monthly meetings, encouraged to check regularly at chemist

Multidomain Lifestyle Group	
Physical activity education (weeks 1-4)	4
Nutrition education (weeks 5-8)	4
Brain training information (weeks 9-12)	4
General Health education (weeks 13-16)	4
Monthly group meetings (months 5-24)	20
Exercise reviews at gym or by phone	8
Telehealth calls to review diet	25
Clinic visits for blood tests, health review, questionnaires, clinician review (4 visits, 2 in-person, 2 telehealth) and memory/cognitive assessments	6
Extra memory/cognitive tests (with study partner)	2
Total interactions (group meetings, telehealth calls, clinic visits, not including baseline visits)	**77**

Health Education and Coaching Group	
Group meetings for lifestyle & health education, goal-setting	5
Clinic visits for blood tests, health review, questionnaires, in-person clinician review (at 2 visits) and memory/cognitive assessments	4
Extra memory/cognitive tests (with study partner)	2
Total interactions (group meetings, telehealth calls, clinic visits, not including baseline visits)	**11**

AU-ARROW Study Group Meeting and Assessments are Aligned to that of US-POINTER Study

AU-ARROW Study Outcomes

SLEEP

Sleep quality monitoring and assessments, using WatchPAT™, Fitbit data, and 3 surveys

DIET

Cancer Council of Victoria Food Frequency Questionnaire, MIND diet survey

FITNESS

short physical performance battery, grip test, 400 m walk

BRAIN HEALTH

6-monthly neurocognitive assessments *(memory, brain function)*

BRAIN TRAINING

BrainHQ program 6-monthly assessment

PSYCHOLOGICAL HEALTH

Surveys to assess quality of life, mood, mindfulness, physical & cognitive activities

EYE BIOMARKER RESEARCH

Hyperspectral retinal imaging, Optical coherence tomography

URINE BIOMARKER RESEARCH

Investigating potential preclinical AD biomarkers

BLOOD BIOMARKER RESEARCH

Investigating potential preclinical AD biomarkers

APOE genotyping (possession of APOE4 alleles strongest genetic risk factor)

BRAIN BIOMARKER RESEARCH

Brain regional volume (MRI) and brain Aβ-specific imaging (PET)

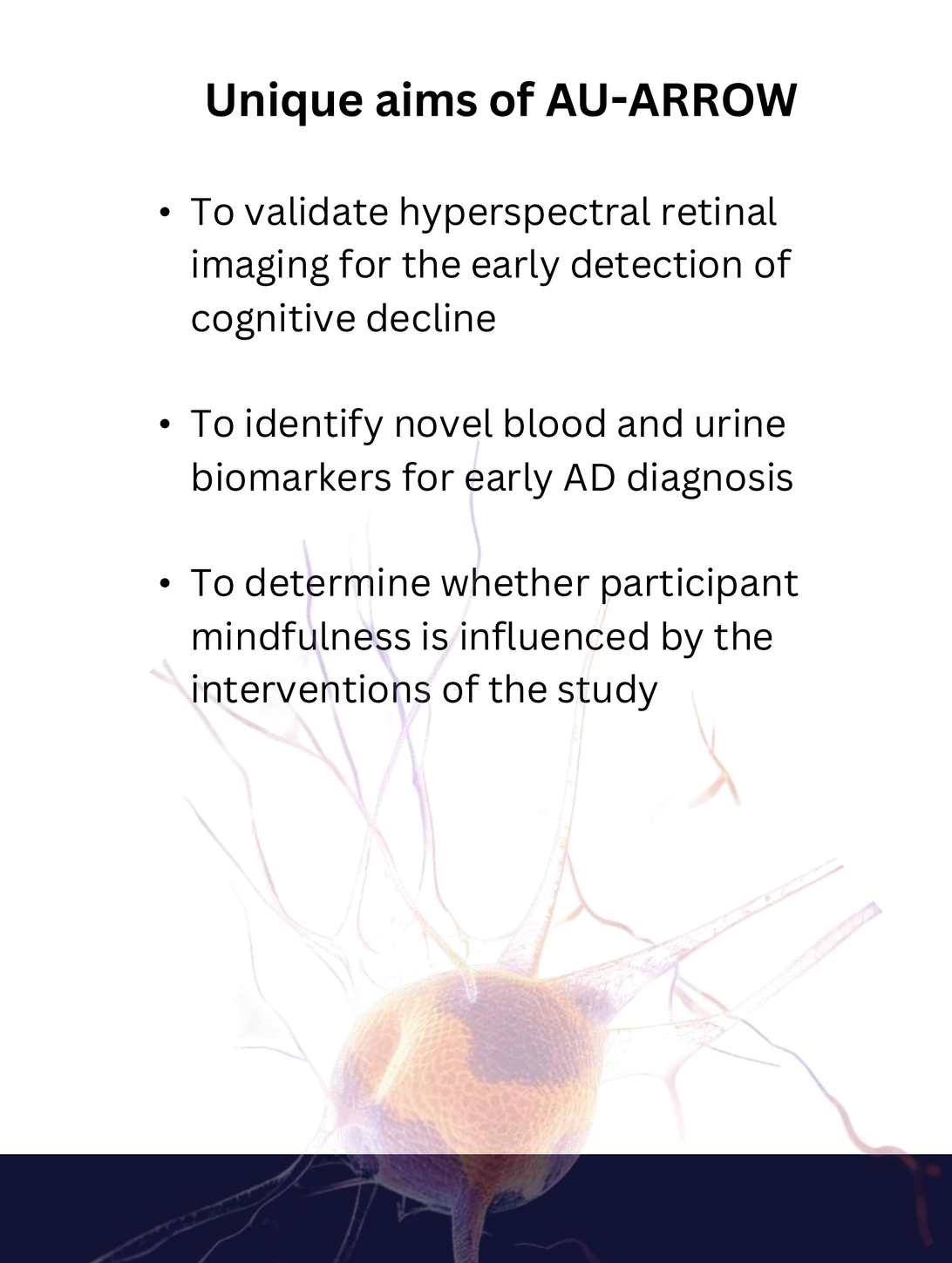
GENERAL HEALTH

6-monthly blood tests: glucose (fasting), glycated haemoglobin (Hb1Ac), lipids

BP, weight, body composition (SOZO)

Unique aims of AU-ARROW

- To validate hyperspectral retinal imaging for the early detection of cognitive decline
- To identify novel blood and urine biomarkers for early AD diagnosis
- To determine whether participant mindfulness is influenced by the interventions of the study



Secondary aims

- Investigate the effects of the interventions on risk of cardiovascular disease, type 2 diabetes/metabolic syndrome and/or hypertension
- Determine the safety and feasibility of the interventions
- To investigate the effects of the interventions on physical function, dietary changes, mood, pain levels, social isolation, loneliness, levels of physical and cognitive activities, hearing, mindfulness, overall quality of life and measures of healthcare utilisation
- To examine whether results are influenced by a known Alzheimer's disease genetic risk factor (APOE)
- To assess the perceptions and engagement of study participants with study interventions
- To investigate the effects of the study interventions on brain Aβ load and hippocampal volume (known biomarkers of developing Alzheimer's disease)
- To collaborate with international investigators to promote harmonisation of protocols, outcomes, data management and data analytics to facilitate data sharing and inter-study comparisons

Potential benefits of such a program, if as effective as the original Finland FINGER study

Quality of Life for the elderly

- The maintenance of good cognitive health, good physical health, and quality of life, for as long as possible, are usually the most important aspects of life for ageing members of any society, also benefiting their families and friends
- The specific aims of AU-ARROW's combined lifestyle intervention are to preserve or improve cognitive and physical health, and to encourage the long-term maintenance of such a lifestyle

Potential financial benefits

- Such a program would not be cheap to implement as part of a country's public health program
- However, economic modelling following the FINGER study has revealed that such a program is economically worthwhile, even if only considering improvements in cognitive health
- When the financial benefits of improved cardiac health and reductions in other chronic conditions are factored into the equation – these are likely to increase the value of the program

Other synergistic projects to AU-ARROW

- The development of dietary guidelines for cognitive health among older adults
- Undertaken by the dietitians involved in AU-ARROW, led by Dr Juliana Chen (nutrition and dietetics lead of AU-ARROW) along with Dr Malika Fernando (Sydney arm), Carolina Castro and Tristan Schwartzkopff (Perth arm)

Systematic literature reviews of:

- Multidomain lifestyle interventions for the prevention of dementia, with a focus on the role and impact of dietitians in these interventions
- Impact of dietary patterns on cognition and dementia in older adults
- Could inform future reviews of the Australia Dietary Guidelines for older adults
- Dietary interventions to improve nutrition, food and subsequently the cognitive health of older Australians in aged care through collaborations with the Maggie Beer Foundation

AU-ARROW study Key Investigators

- Professor Ralph Martins (Edith Cowan University (ECU) Perth, WA and Macquarie University, NSW) Australia. Project director
- Dr Andrew Gleason, old-age psychiatrist, and Dr Catriona Ireland, geriatrician (Macquarie University) and Dr Roger Clarnette, geriatrician (Australian Alzheimer's Research Foundation, WA), are the site clinicians of the study
- A/Professor Laura Baker (Wake Forest School of Medicine, USA) and Professor Miia Kivipelto (Karolinska Institute, Finland) principal international investigators of the US-POINTER and FINGER studies respectively, have advised on harmonisation of protocols
- Professor Kaarin Anstey (University of NSW) Protocol development, particularly dietary intervention
- Professor Sharon Naismith (The University of Sydney, NSW) The role and impact of depression and sleep-wake characteristics in relation to study findings
- Dr Edward Barin (MQ Health, NSW) Cardiologist advising on vascular health and ECG assessments, and Dr Rowena Mobbs (Macquarie University, NSW) neurologist advising on inclusion/exclusion criteria, and participant suitability; and Dr Paul Yates (Austin Health, VIC) geriatrician in the clinical team
- A/Professor Hamid Sohrabi (Murdoch University, WA) and Professor Greg Savage (Macquarie University, NSW) Neuropsychology experts, has designed the cognitive-clinical assessment battery
- Dr Samantha Gardener (ECU, WA) is clinical trial coordinator for the Perth site and contributing to the dietary intervention component of AU-ARROW, and Dr Stephanie Fuller (Macquarie University, NSW) is clinical trial coordinator for Sydney
- Dr Belinda Thompson (Macquarie University, NSW) and Dr Belinda Brown (Murdoch University, WA) Planning and executing the physical exercise component of the study
- Assoc Prof Nicola Armstrong (Curtin University, WA) Will be joining as study statistician
- Dr Juliana Chen (University of Sydney, NSW) and Dr Malika Fernando (Macquarie University) Planning, execution, and analysis of dietary aspect of the study
- Dr Stephanie Rainey-Smith (Murdoch University) Conducting the sleep study associated with AU-ARROW
- Dr Ruth Peters (University of NSW) Vascular risk reduction advice and study's clinical governance
- Dr Genevieve Steiner (Western Sydney University, NSW) Identification of novel AD brain biomarkers
- Dr Stuart Grieve (University of Sydney, NSW) and Dr Jurgen Fripp (CSIRO, VIC), MRI and PET analysis respectively
- Dr Pratishtha Chatterjee (Macquarie University, NSW) analysis of blood proteins, lipids and metabolites concentrations
- Dr Ruey Leng Loo (Murdoch University WA) conducting Urine analysis for AU-ARROW
- The research support teams at both sites also include research assistants, exercise physiologists, and dieticians who will be directly involved in conducting the AU-ARROW clinical trial

COMBINATION TRIALS

Our own combination trials of brain training together with regular exercise have reported cognitive improvements in participants. Similarly, other studies around the world have shown combinations of these lifestyle changes can provide additive effects.

The FINGER STUDY
The Finland FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) study showed that the combination of regular exercise, brain training exercises, adherence to the MIND diet, and regular monitoring of vascular risk factors significantly benefits cognition.

World-Wide FINGERS
The results of FINGER have led to a world-wide initiative: World-Wide FINGERS (WW-FINGERS), including countries such as Germany, Japan, South Korea, China and Ireland. Currently 16 studies are underway or have been completed.

Australia has joined this initiative via AU-ARROW

AU-ARROW COLLABORATORS

THANK YOU to our major sponsors and collaborators

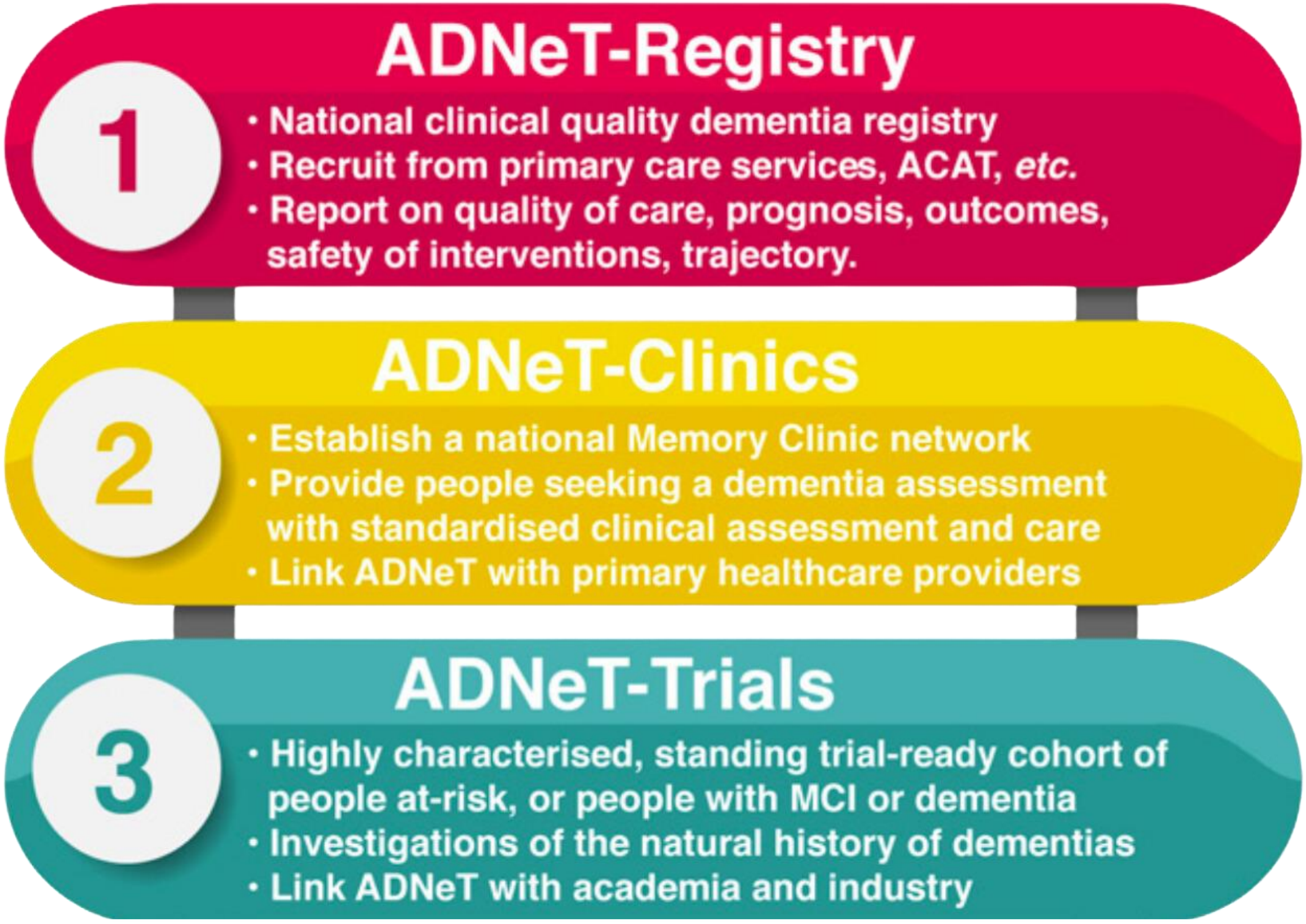
Australian Dementia Network

REGISTRY. CLINICS. TRIALS.

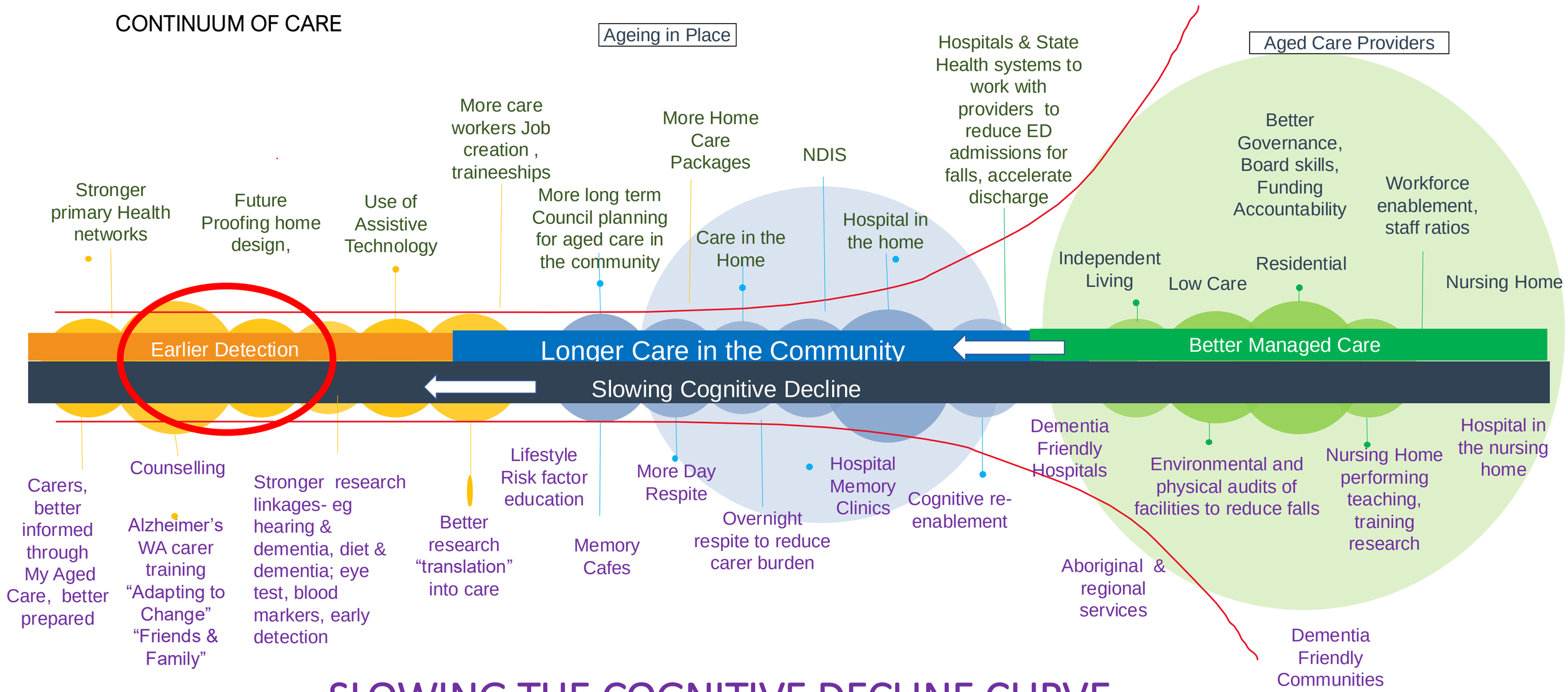
MAIN AIM

To establish an integrated network of dementia researchers, clinicians, service providers, industry, and consumers. We would like ADNeT to be the one-stop-shop for all people who need help and those who want to help either offering a service (clinicians, carers, aged care facilities, industry), doing research or volunteering.

- National Collaboration Across Major Cities of Australia
- Prof. Christopher Rowe (Austin Health)
- Prof. Colin Masters (Florey Institute, University of Melbourne)
- Prof. Ralph Martins (Macquarie University and Edith Cowen University)
- Prof. Nick Martin (The Council of the Queensland Institute of Medical Research)
- Prof. Ashley Bush (Florey Institute, University of Melbourne)
- Prof. Maria Crotty (Flinders University)
- Dr. Jurgen Fripp (CSIRO)
- Prof. Perminder Sachdev (University of New South Wales)
- Prof. Sharon Naismith (University of Sydney)
- Prof. James Vickers (University of Tasmania)
- Prof. Michael Breakspear (University of Newcastle)


ADNeT-Registry
1
• National clinical quality dementia registry
• Recruit from primary care services, ACAT, etc.
• Report on quality of care, prognosis, outcomes, safety of interventions, trajectory.
ADNeT-Clinics
2
• Establish a national Memory Clinic network
• Provide people seeking a dementia assessment with standardised clinical assessment and care
• Link ADNeT with primary healthcare providers
ADNeT-Trials
3
• Highly characterised, standing trial-ready cohort of people at-risk, or people with MCI or dementia
• Investigations of the natural history of dementias
• Link ADNeT with academia and industry

EARLY DIAGNOSIS AND EARLY INTERVENTION IN AGED CARE



SLOWING THE COGNITIVE DECLINE CURVE

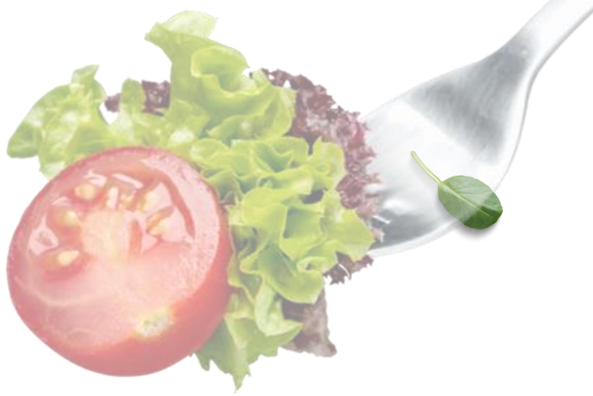
Warren Harding, Adjunct Professor Curtin Faculty of Health Sciences , Chair Alzheimer's WA

DIET

Diet can play a significant role in the prevention and progression of Alzheimer's disease (AD).

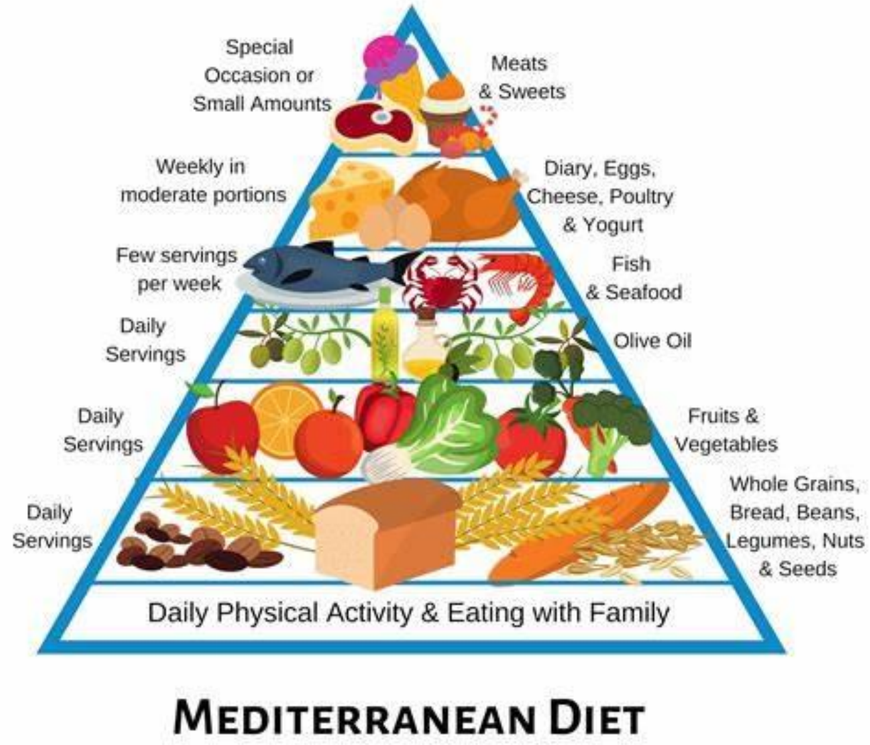
Research indicates that certain dietary patterns may contribute to brain health and potentially reduce the risk of AD.

The Mediterranean Diet (MeDi)



The MeDi diet is a plant-based dietary pattern rich in fruits, vegetables, whole grains, beans, nuts, seeds, and extra virgin olive oil. It is characterised by:

- Daily consumption of vegetables, fruits, whole grains, and healthy fats, which are rich in unsaturated fatty acids.
- Weekly intake of fish, poultry, beans, and eggs.
- Moderate intake of dairy products.
- Low intake of red meat.
- Moderate consumption of wine with meals.



MEDITERRANEAN DIET

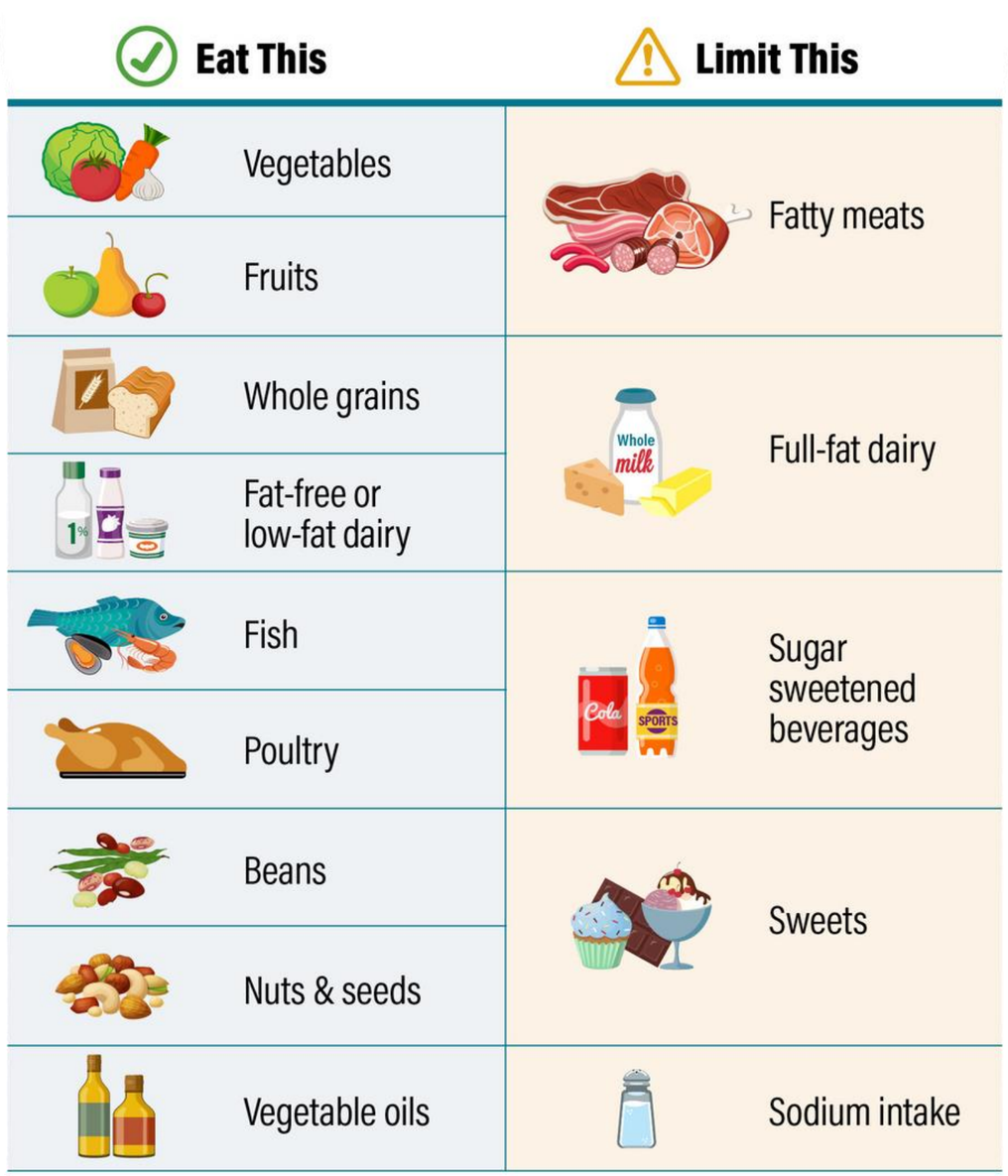
The MeDi diet is believed to have a neuroprotective role due to its high content of unsaturated fatty acids and antioxidants. This aids in free-radical scavenging, anti-inflammatory effects, and inhibition of beta-amyloid and Acetylcholine-esterase in the brain.

Dietary Approaches to Stop Hypertension (DASH) Diet

The DASH diet is primarily designed to reduce blood pressure by encouraging a reduction in sodium intake and an increased intake of nutrient-rich foods that help lower blood pressure. This dietary pattern offers several benefits for adults aiming to control blood pressure, manage cholesterol levels, prevent diabetes, reduce cognitive decline, and enhance overall health and longevity.

Key Characteristics of the DASH Diet:

- Low Consumption of:
  - Saturated fat
  - Total fat
  - Red and processed meat
  - Sugar
  - Salt
- Promoted Intake of:
  - Fruits and vegetables
  - Low-fat dairy products
  - Whole grains
  - Fish and poultry
  - Legumes, nuts, and seeds
  - Vegetable oils



How does the MIND diet protect your brain?

The potential mechanisms behind the beneficial role of the MIND diet on brain health include:

•Decreasing vascular risk factors:
•Better blood lipid profiles
•Lower blood pressure
•Less insulin resistance
•Weight loss
•Less inflammation and less oxidative stress
•Reducing the accumulation of toxic proteins in the brain known to be signs of Alzheimer's disease

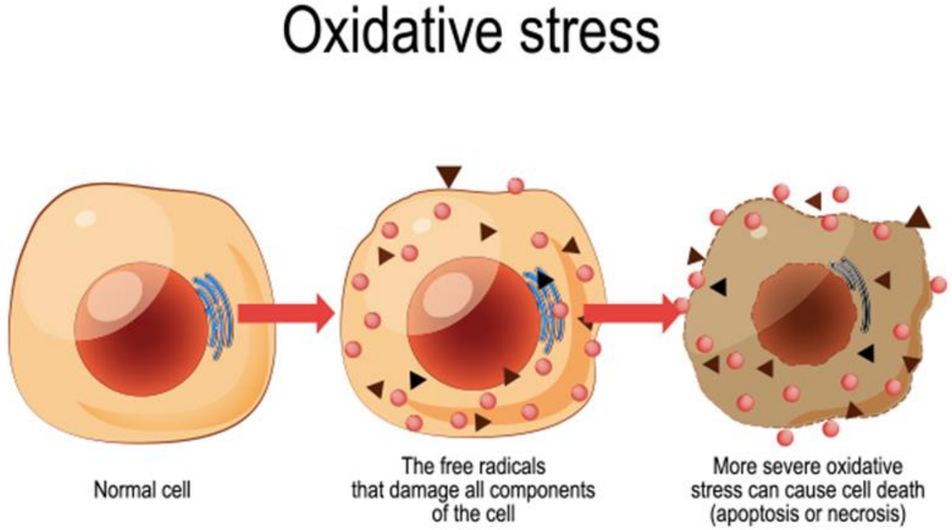
Oxidative stress and inflammation is decreased via high abundance of antioxidants and anti-inflammatory agents in the MIND diet (antioxidant phytochemicals are found especially in fresh brightly coloured fruits and vegetables and omega-3 polyunsaturated fatty acids are found in oily fish)

HOW DOES THE MIND DIET PROTECT YOUR BRAIN? CONTINUED..

BOTH OXIDATIVE STRESS AND CHRONIC INFLAMMATION ARE PRESENT IN AD AND ARE IN FACT THOUGHT TO BE INVOLVED IN DISEASE DEVELOPMENT

WHAT IS OXIDATIVE STRESS?

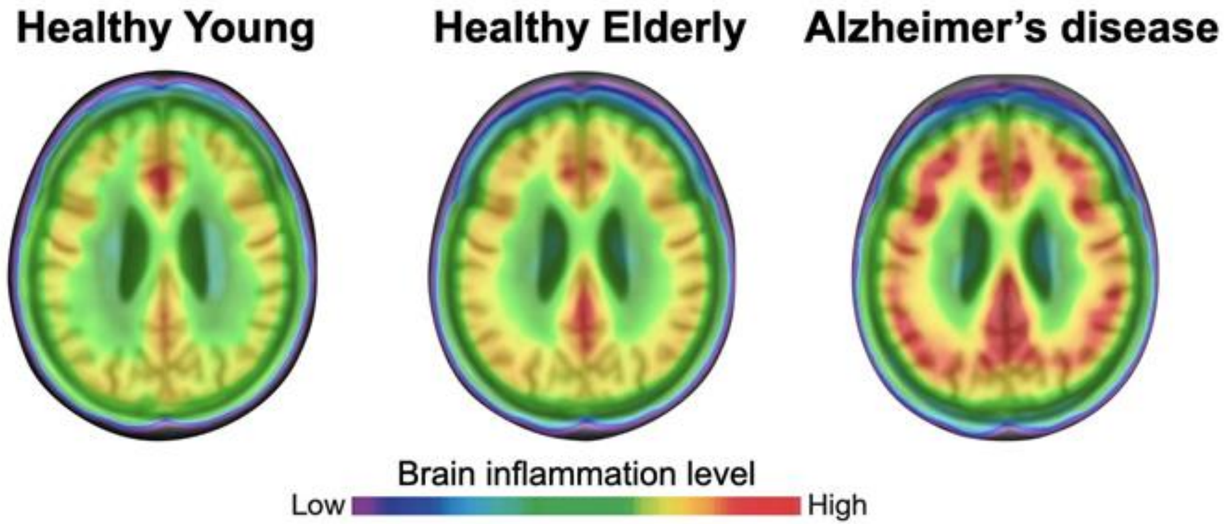
- Oxidative stress is an imbalance between free radicals and antioxidants in your body.
- When functioning properly, free radicals help our bodies fight off pathogens that lead to infections.
- Antioxidants stabilise free radicals to make them become less reactive.
- If free radicals > antioxidants the free radicals can start doing damage to fatty tissue, DNA, and proteins in your body.
- This can lead to a vast number of diseases over time, and they also speed up the ageing process.



HOW DOES THE MIND DIET PROTECT YOUR BRAIN? CONTINUED..

What is inflammation?

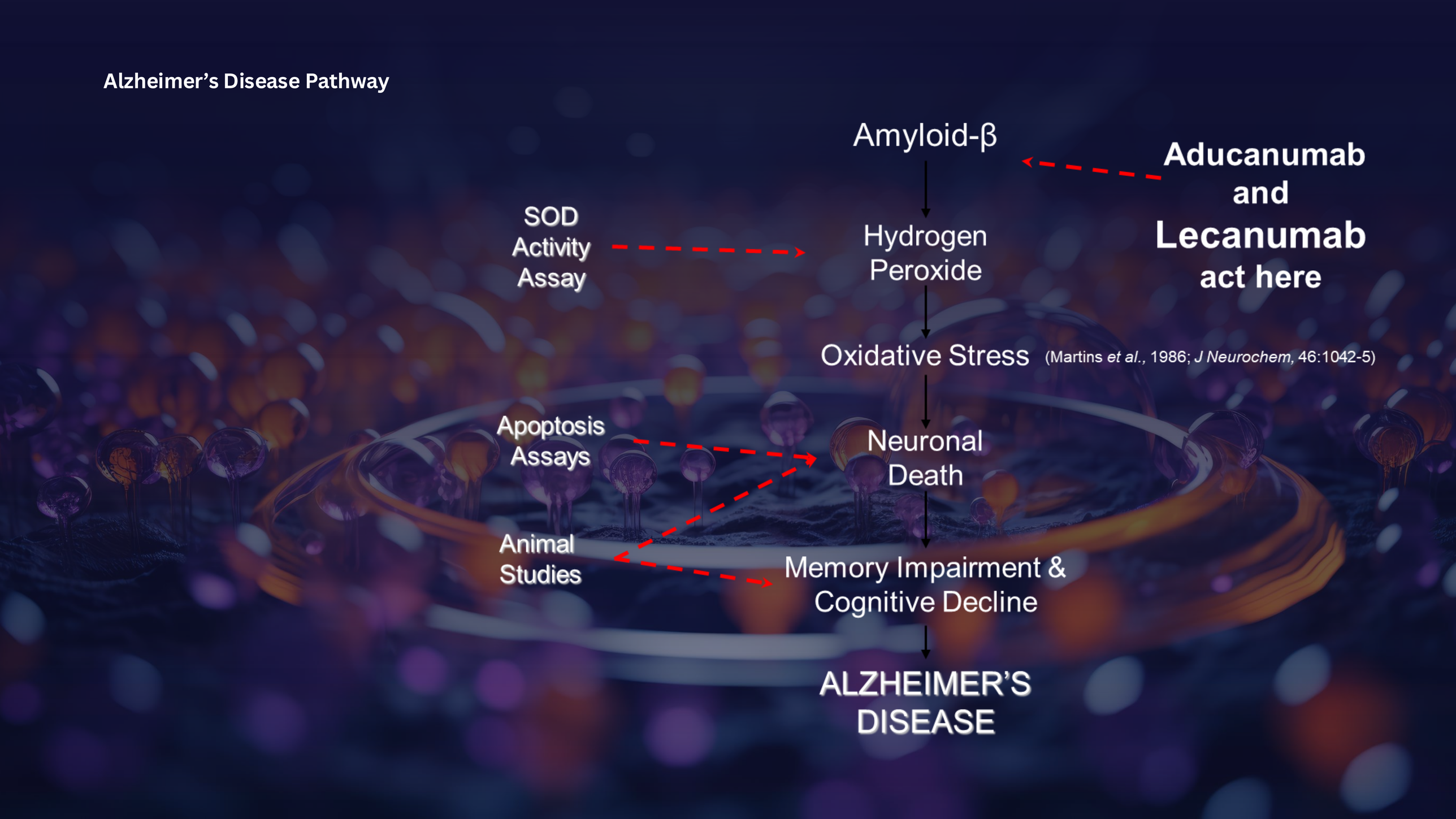
- Inflammation is your body's natural reaction to invasion by an infectious agent, toxin or physical, chemical or traumatic damage
- Inflammation helps fight disease and protect parts of the body, but it also suspends the body’s normal immune response and certain metabolic processes
- Short term inflammation helps fight infection, repair damages in body
- Long term inflammation causes progressive damage
- Chronic systemic inflammation is not confined to a particular tissue (e.g. site of damage/infection) but can involve the lining of blood vessels and many internal organs and systems
- Neuroinflammation: Specifically, inflammation of the central nervous system including the brain, and in the case of AD is a response to the build up Aβ, a small protein that is toxic if not removed



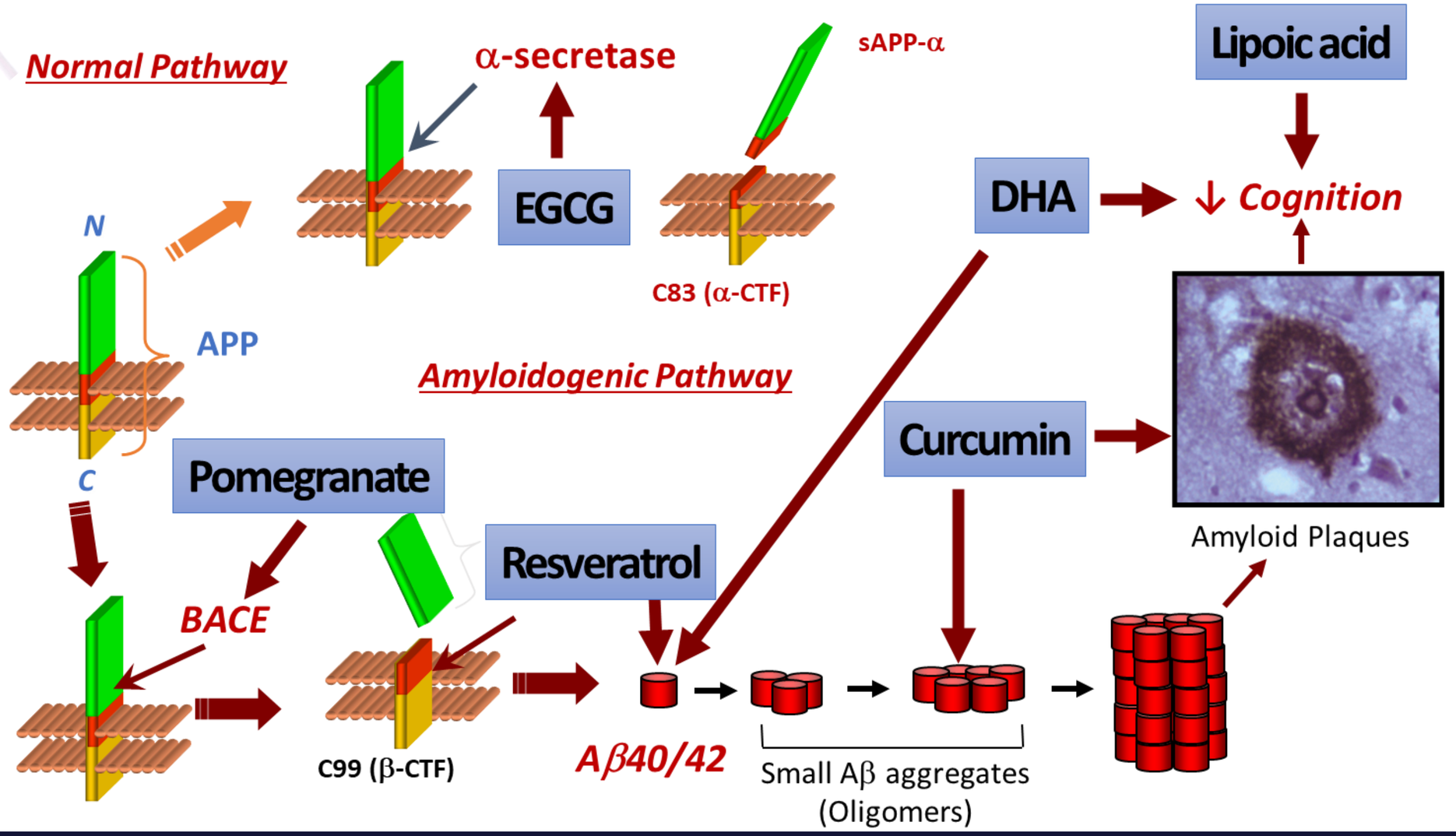
It is conceivable that the protective role of MeDi against cognitive decline is mediated by the inflammation pathway.

Oxidative Stress is one of the earliest processes in the pathogenesis of AD. The MeDi could be capturing the composite effect of dietary anti-oxidants and this could explain the association with a lower risk of AD.

Alzheimer's Disease Pathway



Proposed Combination Nutritional Supplement Therapies (varying mechanisms of action)



The Role of Diet in Alzheimer's Disease

Dr Binosha Fernando

Polyphenols

Polyphenols are naturally occurring compounds found in plants, known for their antioxidant properties, and include flavonoids, phenolic acids, polyphenolic amides, and other types found in fruits, vegetables, tea, coffee, red wine, nuts, seeds, herbs, spices, dark chocolate, olives, and beans.

- Grapes
- Sea buckthorn
- Sorghum

Cell lines, worm

Fatty Acids

Fatty acids are essential building blocks of fats in our bodies and in the food we eat, and they include saturated, monounsaturated, and polyunsaturated types found in sources like meat, dairy products, fish, nuts, seeds, and vegetable oils.

- Short-chain
- (Butyric acid)
- Medium chain
- (Lauric acid)

Cell lines, worm

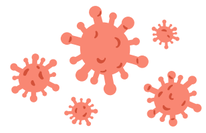
Protein & Fibre

Protein, fiber, and essential fatty acids are crucial macronutrients found in a variety of sources including meat, dairy products, fish, nuts, seeds, legumes, vegetables, whole grains, and vegetable oils, supporting muscle growth, digestion, and overall body function.

- Cognition and APOE
- Amyloid beta

Network analysis

Link with microorganisms

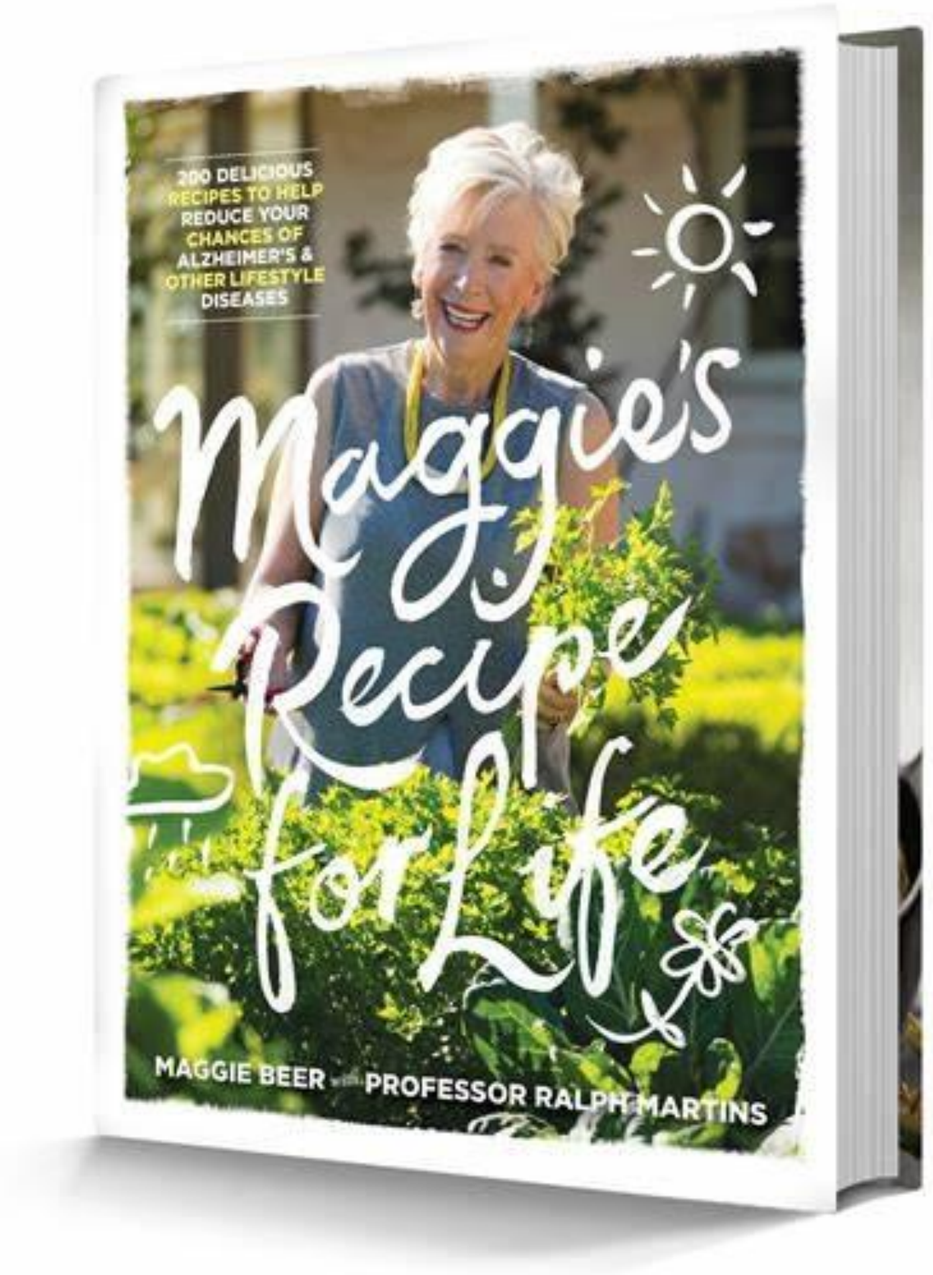


ILLUSTRATED BOOK WINNER OF THE YEAR

MAGGIE'S RECIPE FOR LIFE

This is such an important book for me and something I'm so very excited about, which is why I'm thrilled to reveal the cover for 'Maggie's Recipe for Life', my new book co-written with Prof Ralph Martins. Published in October by Simon & Schuster Australia, 'Maggie's Recipe for Life' includes 200 delicious recipes to reduce your chances of Alzheimer's and other lifestyle diseases. The book's proceeds will be shared between the Maggie Beer Foundation and the Lions Alzheimer's Foundation.

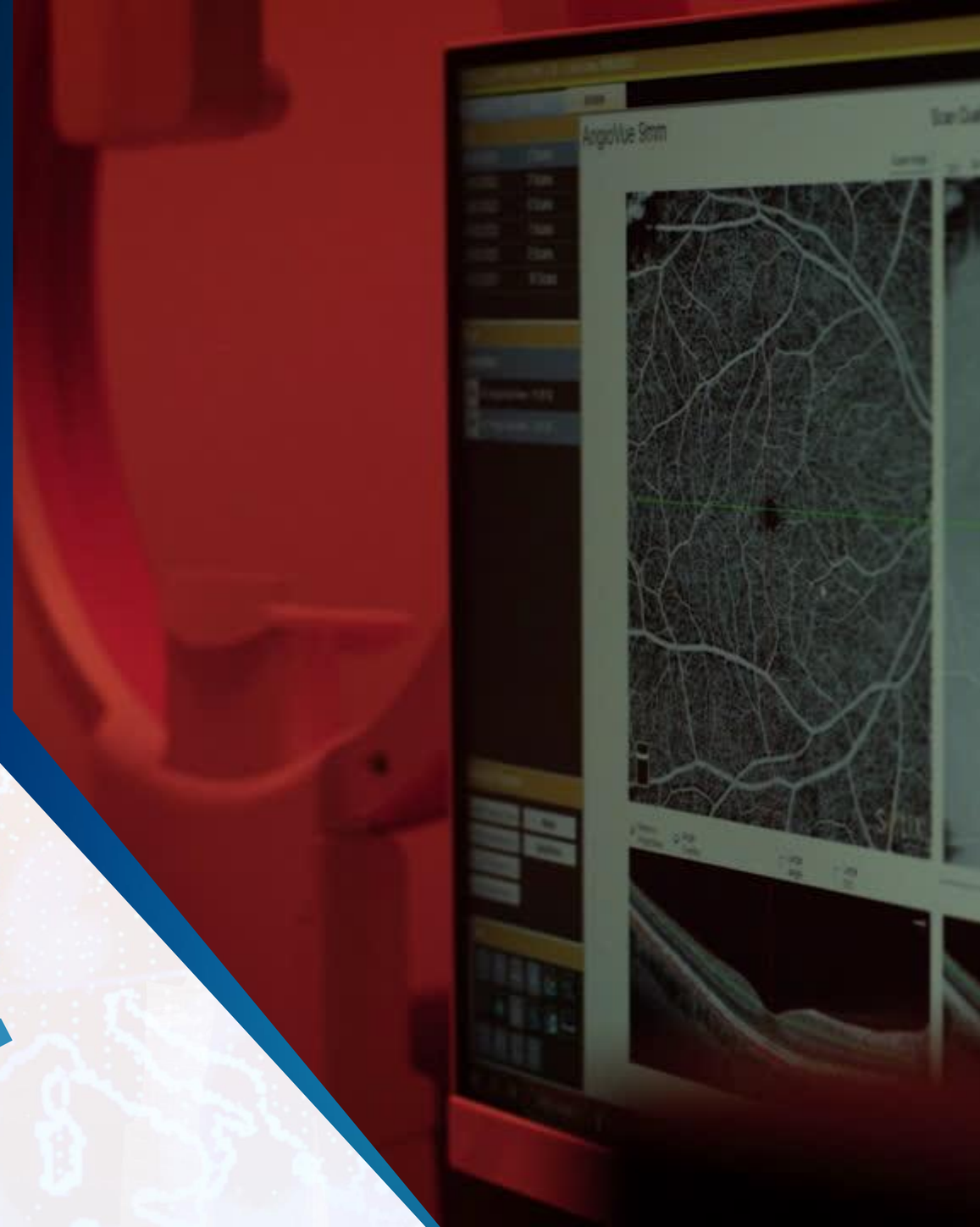
-Maggie Beer



Over 100,000 copies sold; for every book sold, $2 is donated to the Lion's Alzheimer's Foundation

RETINAL IMAGING

Retinal imaging is emerging as a promising tool for the early detection and monitoring of Alzheimer's disease.

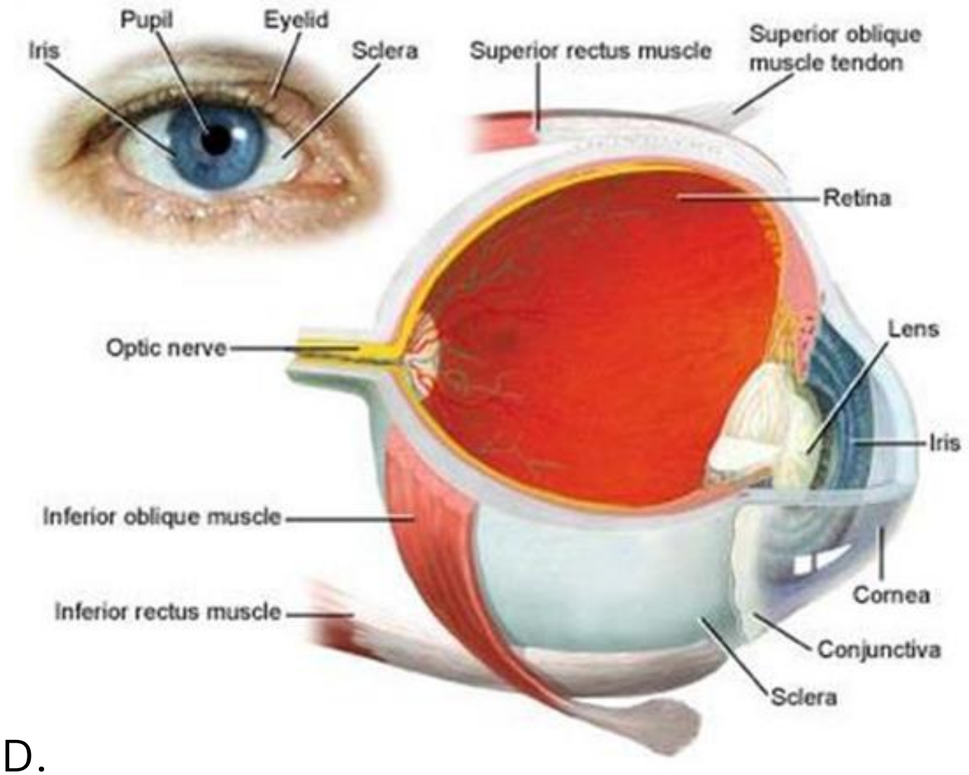


The Eye as a Window into the Brain

Non-invasive optical imaging of vasculature and neural tissue.
Homology between retinal and cerebral micro-vasculatures.
Changes in the AD-brain may be mirrored in the retina.
AD Peptides (Aβ, Tau) in the Eye

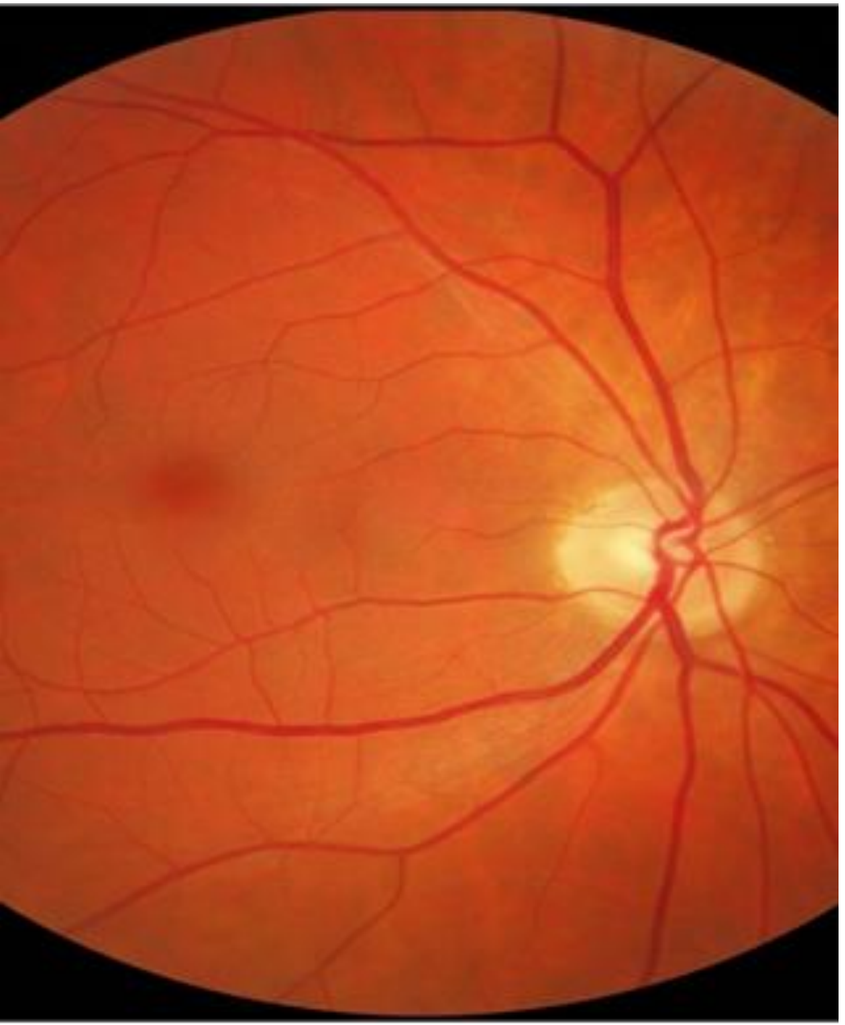
Present in the normal human eye and aged human retina.
Aβ deposits in the lens have been reported in AD.
Vision deficiencies are an early symptom of AD, affecting:
Visual field
Color
Static spatial contrast sensitivity
Visual attention
Shape-from-motion
Visuo-spatial construction
Ocular Morphology in AD

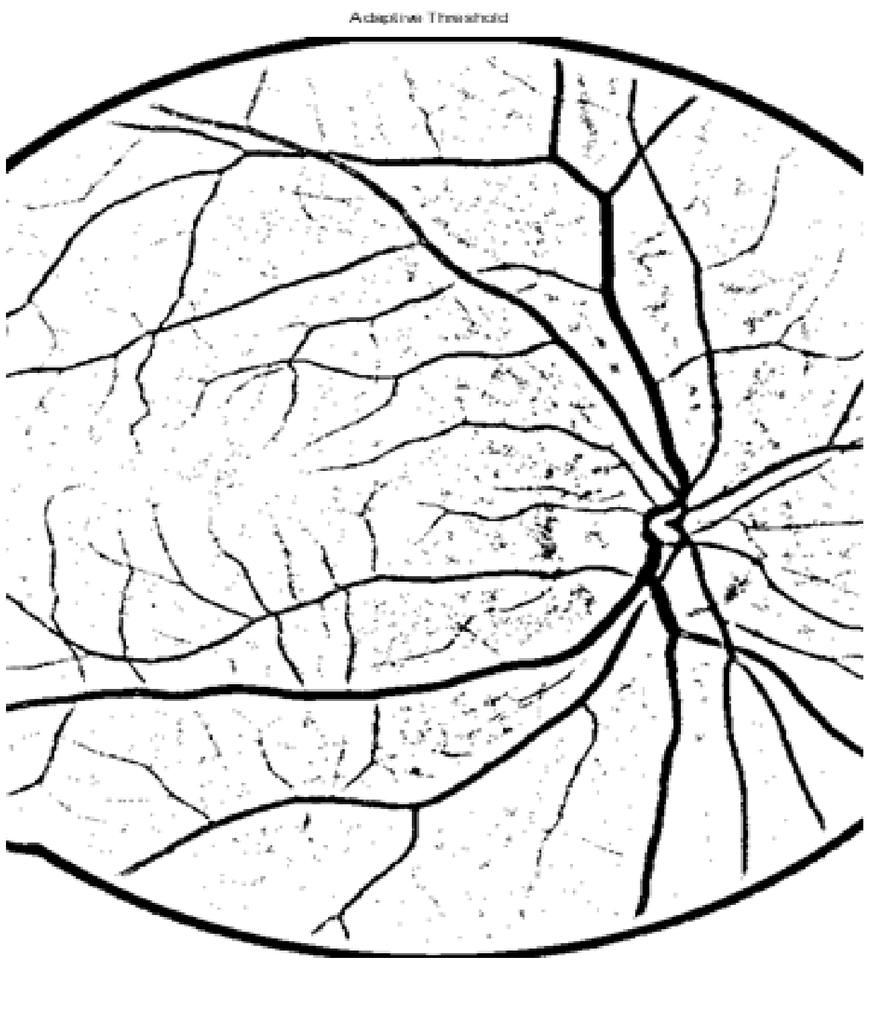
Changes in ocular morphology have already been reported in AD.

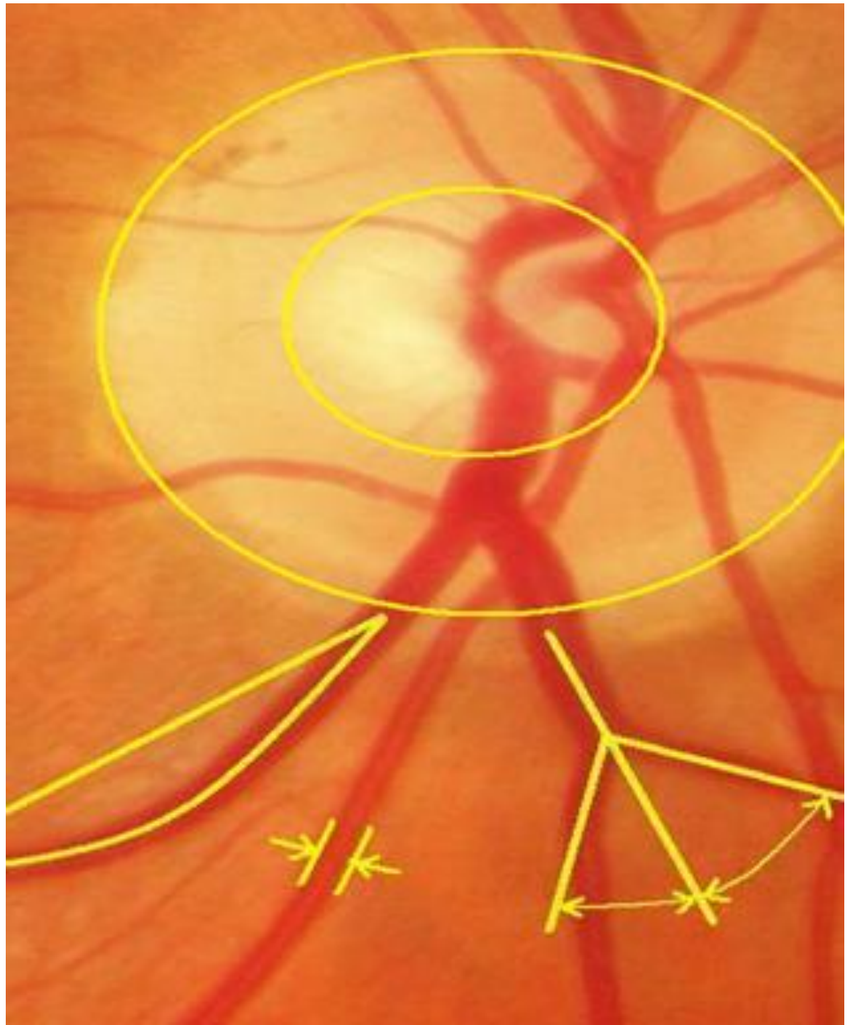


RETINAL PHOTOGRAPHY

Non-invasive methods can be used to study vascular geometry and vascular thickness, including arteriolar, venular, and the arteriolar-to-venular ratio (AVR).

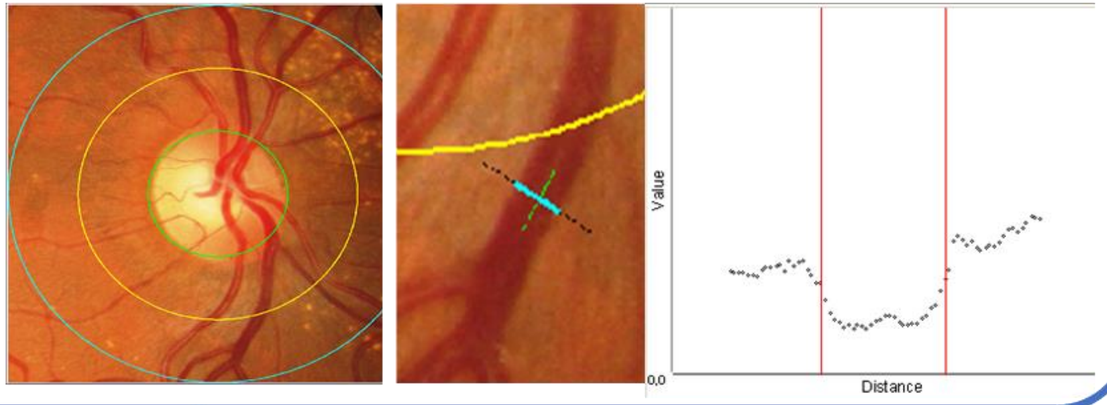




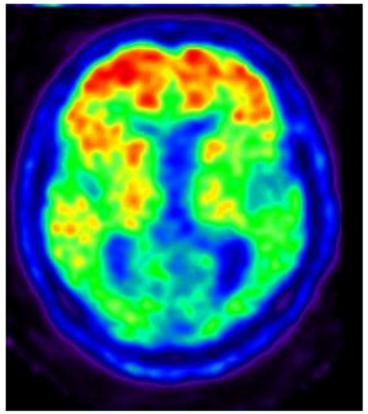


2) Retinal AVR Correlated With Plaque Burden

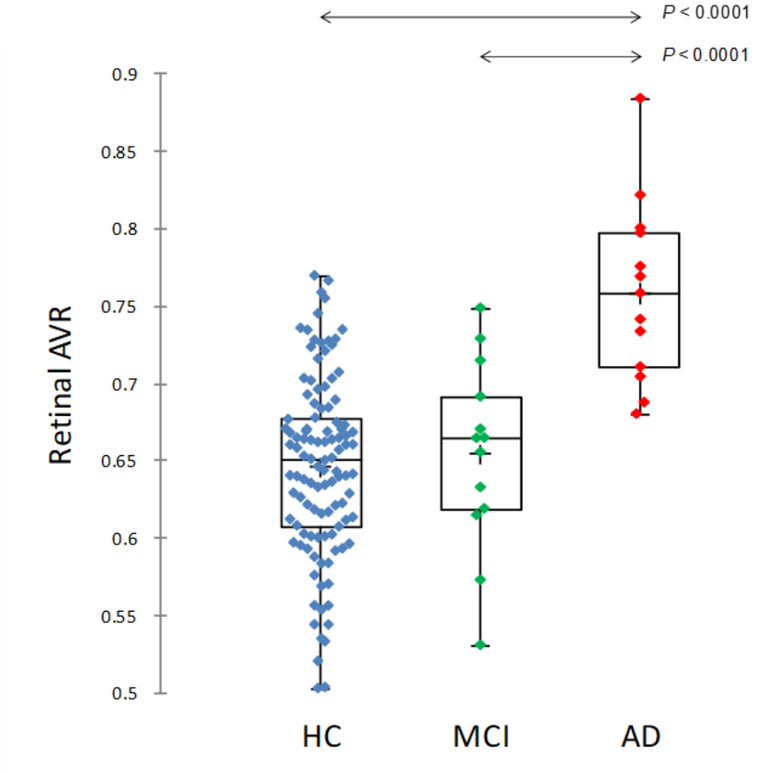
AVR = Arterio-Venular Ratio
(ratio of retinal vessel
thickness)

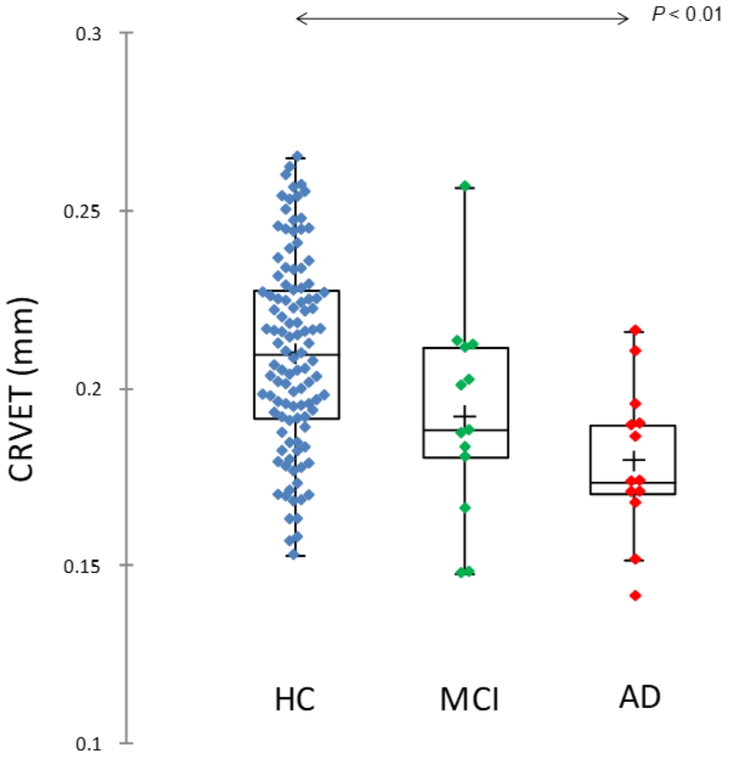


SUVR = Plaque-burden in the brain



1) Retinal AVR Different in AD





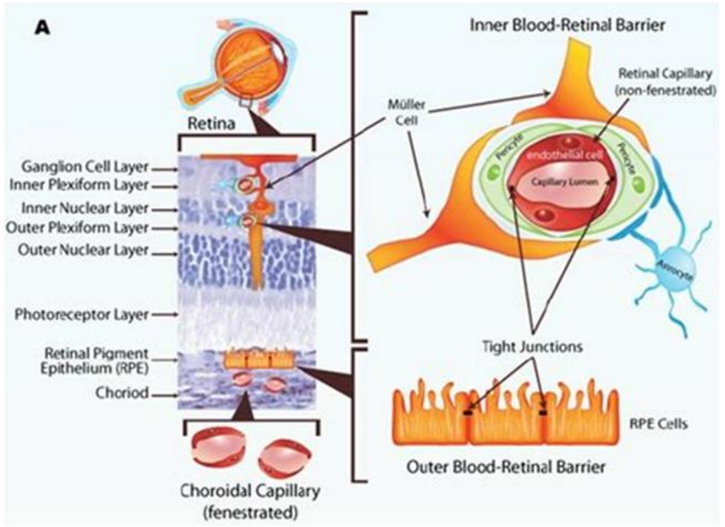
The retina shares many similarities with the brain.

E.g. The retina has a blood-retinal barrier, which protects it from harmful substances in the bloodstream and nourishes the retinal tissues. The analogue in the brain is the blood-brain barrier.

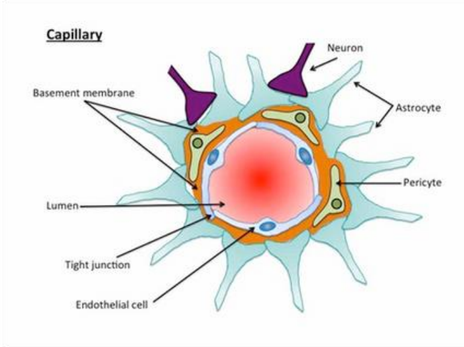
The retina shares many similarities with the brain.

E.g. The retina has a blood-retinal barrier, which protects it from harmful substances in the bloodstream and nourishes the retinal tissues. The analogue in the brain is the blood-brain barrier.

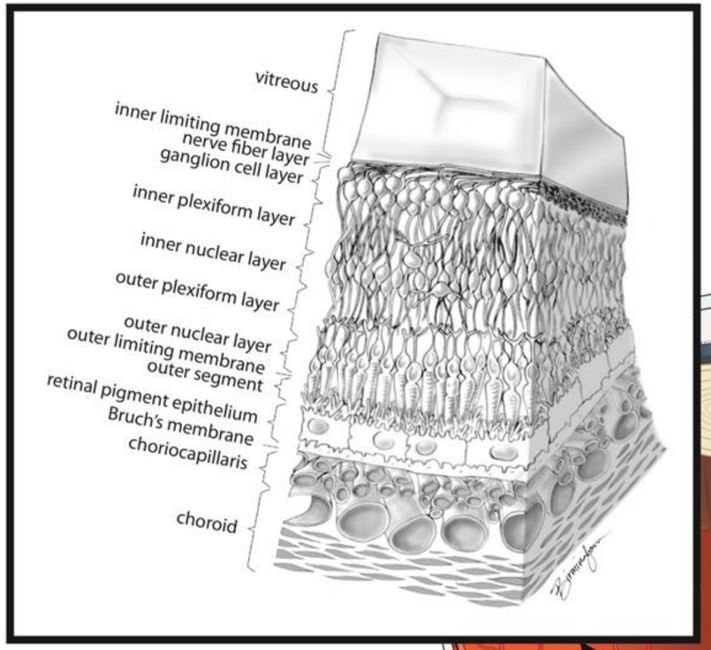
Blood-retina barrier

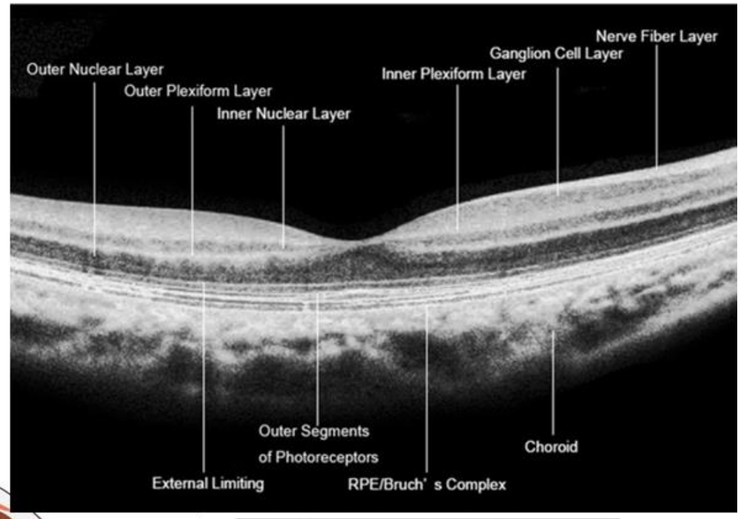


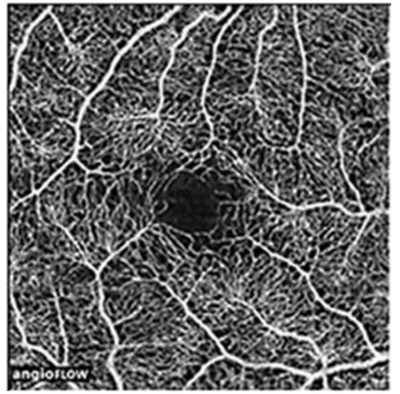
Blood-brain barrier

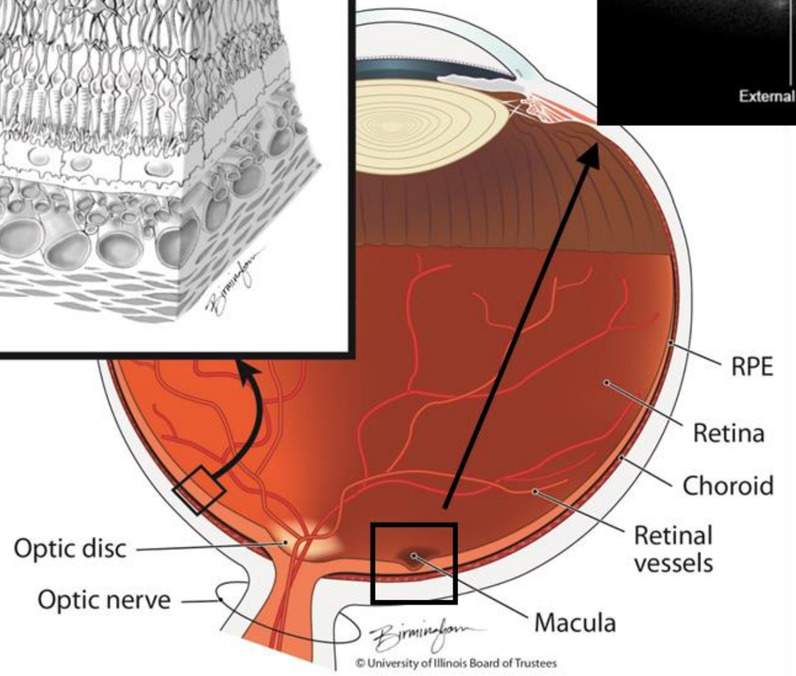


Like the brain, the retina is a multi-layered structure of neural tissue with an extensive blood supply









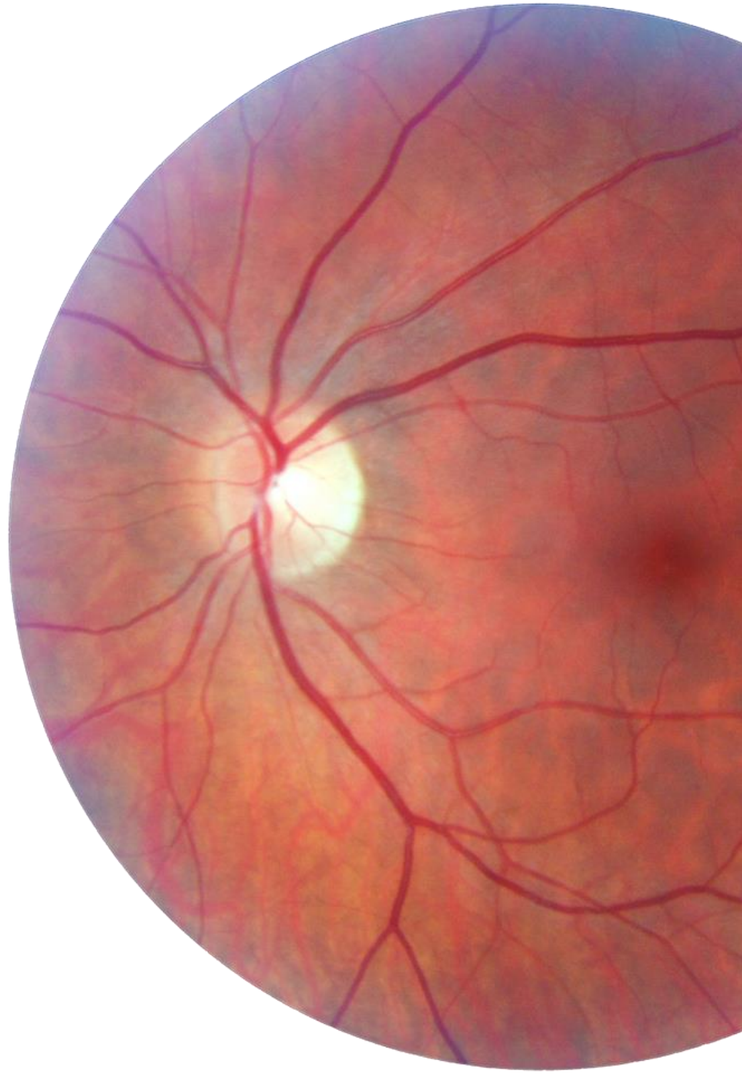
RETINAL HYPERSPECTRAL IMAGING PROJECT OVERVIEW

Dr Eugene Hone, (ECU Perth site, kindly sponsored by Alzheimer's Research Australia) supervises ECU PhD student, Mr. Purna Poudel with co-supervisors and collaborators, Dr. Shaun Frost (CSIRO), Dr. Rohith Thota (Macquarie University, NSW site), with Prof. Ralph Martins (ECU/Macquarie University) for project oversight.

Participants: High and low brain amyloid status identified via PET imaging
(Administered by Australian Alzheimer's Research Foundation, Perth site)

Exclusion criteria: History of major cognitive impairment not associated with AD, including trauma, stroke, hydrocephalus, lacunar infarcts and seizure
Presence of glaucoma or retinopathy (diabetic, macular degeneration, cataracts) or other conditions that obstruct retinal imaging
Pupil dilation inadequate or contraindication or allergy to dilating eye drops
Prior ocular surgery within two months of scan or in the course of post-surgery medications.

Research site: Ground floor, Ralph & Patricia Sarich Neuroscience Research Institute, RR Block, QEII Medical Centre, Nedlands WA



CHILDHOOD DEMENTIA

Dr Prashant R. Bharadwaj

NHMRC-ARC dementia research development fellow
Researcher - Alzheimer's Research Australia

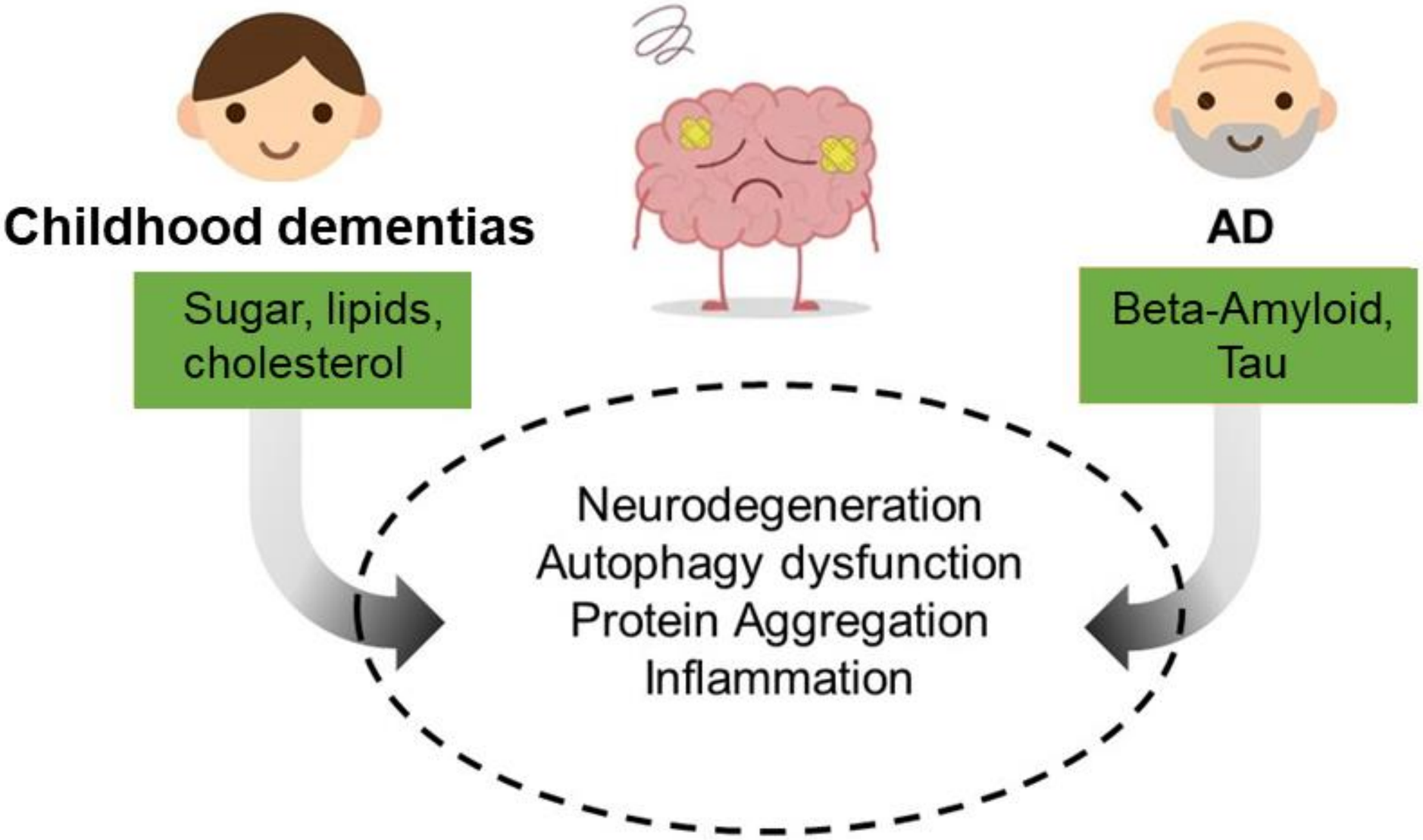
Government of Western Australia
Department of Health

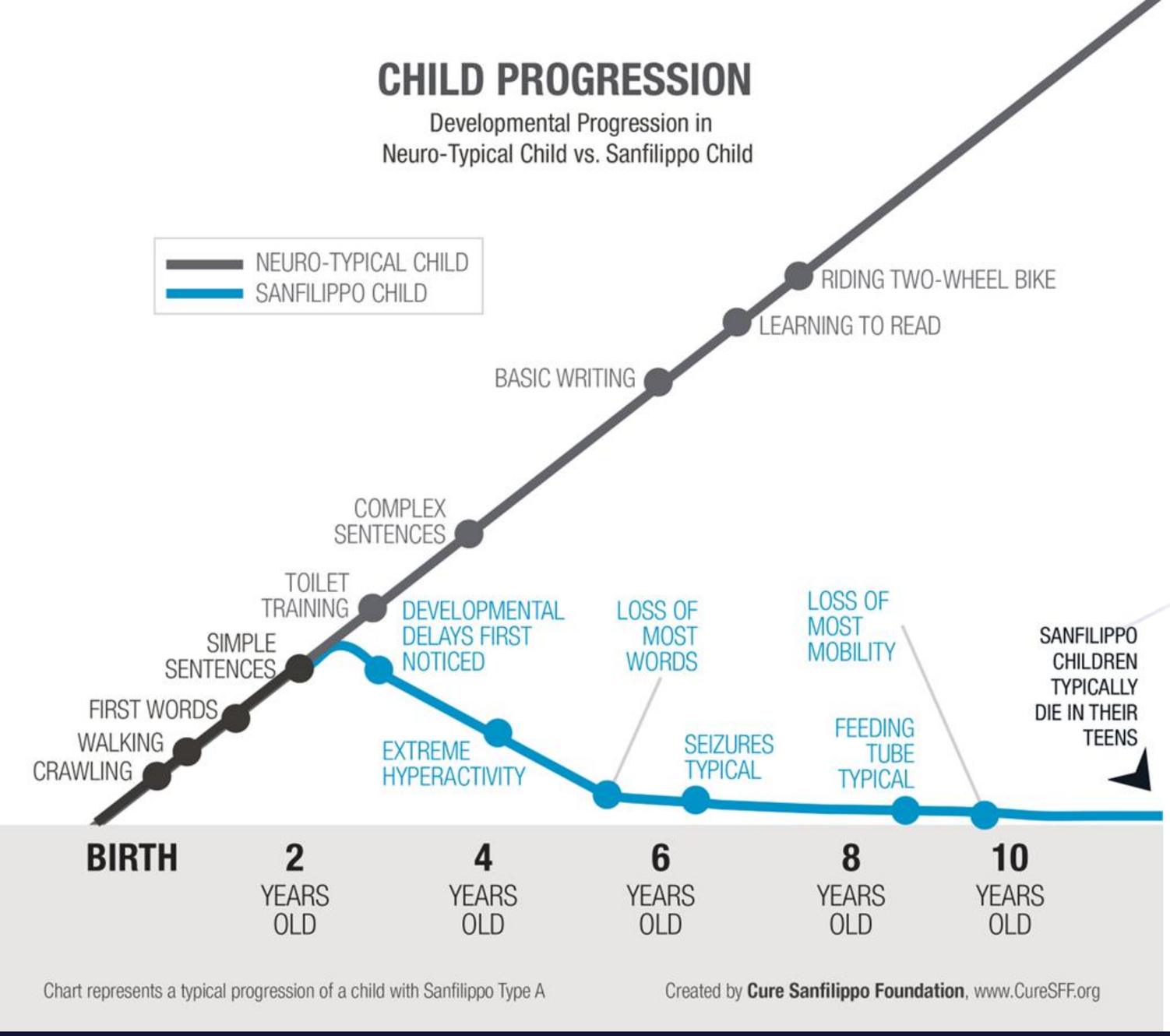
telethon 7

Alzheimer's Research Australia

AUSTRALIA ECU EDITH COWAN UNIVERSITY

CENTRE OF EXCELLENCE FOR ALZHEIMER'S DISEASE RESEARCH AND CARE
FOR A WORLD FREE OF ALZHEIMER'S DISEASE


Childhood dementias
Sugar, lipids, cholesterol
AD
Beta-Amyloid, Tau
Neurodegeneration
Autophagy dysfunction
Protein Aggregation
Inflammation



Progression of Childhood Dementia- Sanfilippo syndrome

Alzheimer's Research Australia

Acknowledgements

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Sam Gardener
Simon Gibson
Rodney Guzman
Kayla Perez
Kelly Pertile
Tenielle Porter
Stephanie Rainey-Smith
Jo Robertson
Mark Rodrigues
Christopher Rowe
Rebecca Rumble
Greg Savage
KaiKai Shen
Brendan Silbert
Harmid Sohrabi
Kevin Taddei
Tania Taddei
Christine Thai
David Ames
Alex Barac
Pierrick Bourgeat
Sveltana Bozinovski
Belinda Brown
Samantha Burnham
Lesley Cheng
Steven Collins
James Doecke
Vincent Dore
Denise El-Sheikh
Binosha Fernando
Christopher Fowler
Jurgen Fripp
Qiao-Xin Li
Yen Ying Lim
Florence Lim
Lucy Lim
Kathy Lucas
Lucy Mackintosh
Ralph Martins
Georgia Martins
Paul Maruff
Colin Masters
Simon McBride
Tash Mitchell
Steve Pedrini

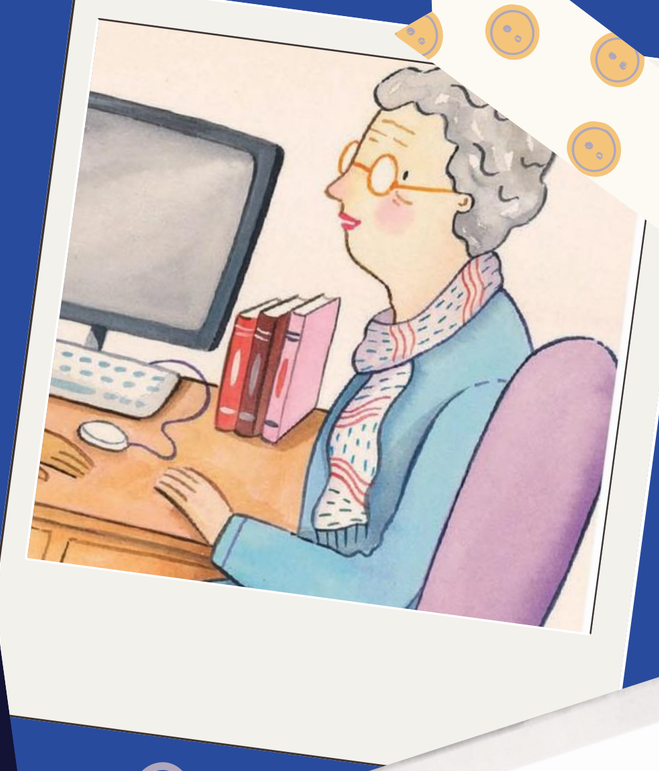
COMBAT-AD Perth arm

Cognition, Molecular Biomarkers And preventative Treatments for Alzheimer's Disease

Dancing with Memories

HAVE YOU MET LUCY?

Let’s take you on a journey!



ABOUT THE BOOK

- **Title:** "Dancing with Memories"
- **Authors:** Sally Yule, Ralph Martins, Cheryl Orsini
- **Theme:** Demystifying dementia for kids

STORY HIGHLIGHTS

- Beautifully illustrated
- Follows Lucy, a joyful lady living with dementia
- Emphasizes that Lucy is not defined by her condition
- Highlights creating a dementia-friendly environment

ADDITIONAL FEATURES

- **Bonus:** Maggie Beer’s healthy lunch box recipes included
- **Purchase QR Code:** Scan the QR copy to get yours today

Thank you

We extend our heartfelt gratitude to the following for their invaluable support and dedication:

- Bryan Shaw, Andrew DeLacey, and the Gold Coast Lions Clubs
- Alzheimer’s Research Australia
- Leo McManus, Chair of LAF
- Rob Davies, Treasurer of LAF
- Rod Fanner and Nutricia
- All participants and their families

Your contributions make a significant impact in the fight against Alzheimer's.

LIONS ALZHEIMER'S FOUNDATION

Alzheimer’s Research Australia

MACQUARIE University

AUSTRALIA ECU EDITH COWAN UNIVERSITY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