The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing – an example of Australian research on Alzheimer’s disease
AIBL: Two site collaborative study

Study is conducted at two sites: Perth (40%) and Melbourne (60%).

CSIRO Preventative Health Flagship
University of Melbourne
Neurosciences Australia Ltd (NSA)
Edith Cowan University (ECU)
Mental Health Research Institute (MHRI)
National Ageing Research Institute (NARI)
Austin Health
University of WA (UWA)
CogState Ltd.
Charles Gairdner Hospital
Alzheimer’s Australia
Macquarie University
The Cohort

- A$3+ million study launched Nov 14th 2006
  - largest study of its kind in Australia
- Prospective longitudinal study

- Large scale cohort study: 1112 participants
- Patients with AD, MCI and healthy volunteers
- Multi-disciplinary approach, 4 research streams cognitive, imaging, biomarkers and lifestyle

Baseline
Clinical/cognitive data
80ml blood
Lifestyle information
PET & MRI scans (250 volunteers)

Follow-up (every 18 months)
Clinical/cognitive data
80ml blood
PET & MRI scans
Why AIBL?

Why would we want pre-symptomatic detection?
- To enable research into causes
- To identify at risk individuals for lifestyle research
- To identify at risk individuals for putative drug therapies
- Ultimately, to identify people who can have the onset of AD delayed by intervention
- Essential arm of a twin track strategy (early detection and effective intervention)
1. To improve the understanding of the pathogenesis and diagnosis of Alzheimer’s disease using neuropsychological, neuroimaging and biomarker techniques, with a focus on early diagnosis of AD

2. To examine lifestyle and diet factors that may be involved in the pathogenesis of AD, towards future lifestyle intervention
OVERVIEW: AIBL is the most comprehensive, longitudinal study of its kind in Australia, and aims to discover a way to develop biomarkers, diagnose patients earlier and prevent disease onset.

**COHORT**
N = 1,112 (aged 60+ yrs)

- Healthy Controls
- Subjective Memory Complainers
- Mild cognitive Impairment
- Alzheimer’s Disease

**METHODOLOGY**
- Cognitive and clinical assessment
- Biomarkers
- Diet & Lifestyle
- Neuroimaging
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 (initially in 287 volunteers)**
- PET Pittsburgh Compound B (PiB)
- Magnetic Resonance Imaging
  - 3D T1 MPRAGE
  - T2 turbospin echo
  - FLAIR sequence
Assessments

- BP, HR, weight, height, abdominal girth
- 80 ml blood
- 2 hours neuropsychological testing
- HADS and GDS
- Medication list
- Diet and lifestyle questionnaires
- PiB PET scan and MRI for ¼
- Diagnostic panel evaluation
- DA file review
- Repeat every 18 months
AIBL: Longitudinal cohort: Baseline to 54 months

Baseline (1,112)

Non-return: 112
Deceased:
NMC 2
SMC 4
MCI 5
AD 17
Non-AD dementia:
PDD 1

18 month (972)*

Non-return: 120
Deceased:
NMC 3
SMC 3
MCI 4
AD 34
Non-AD dementia:
PDD 1
MCI-X 1
VDM 3

36 month (824)*

returned at 36 months:
NMC 11
SMC 1
MC 1
AD 3
Non-AD dementia:
PDD 2
MCI 2
VDM 1

54 month (718)*

Returned at 54 months:
NMC 1
SMC 5
MCI 1
AD 4

Total active participants at each time point including non-AD dementia.

(NMC) Non-Memory Complainer, (SMC) Subjective-Memory Complainer, (MCI) Mild Cognitive Impairment, (AD) Alzheimer's disease, PDD (Parkinson's Disease Dementia), FTD (Frontotemporal Dementia), VDM (Vascular Dementia), MCI-X (Mild Cognitive Impairment non-AD related).
Imaging results

- Imaging collaboration led by Chris Rowe and Victor Villemagne at Austin Health and by Nat Lenzo, Roger Price and Peter Robins in WA with strong input from CSIRO via Olivier Salvado et al.
SUVR, standardized uptake value ratio.
Villemagne VL, Rowe CC. Int Psychogeriatr. 2011;23(suppl 2):S41-S49.
The binding of PIB matches the histopathology of Abeta

Braak Stages (1997) A B C
Tau, Aβ, and Glucose Metabolism in Alzheimer’s Disease

FDG, fluorodeoxyglucose.
Villemagne and Rowe; used with permission (unpublished).
## Imaging Cohort Baseline demographics (n=288)

<table>
<thead>
<tr>
<th></th>
<th>HC*</th>
<th>MCI</th>
<th>AD</th>
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<tbody>
<tr>
<td></td>
<td>178</td>
<td>57</td>
<td>53</td>
</tr>
<tr>
<td>Age</td>
<td>73.6 ± 7.6</td>
<td>77.4 ± 7.5*</td>
<td>74.0 ± 8.7</td>
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<tr>
<td>MMSE</td>
<td>28.8 ± 1.2</td>
<td>27.1 ± 2.3*</td>
<td>20.5 ± 4.9*</td>
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<tr>
<td>%ApoE ε4</td>
<td>43%</td>
<td>54%</td>
<td>71%*</td>
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*Significantly different from HC, p <0.05

*enriched with ApoE ε4
Percentage of PiB + volunteers

Significant differences between the three groups (p<0.001)
Aβ burden quantification

**NEOCORTICAL SUVR**

<table>
<thead>
<tr>
<th>Group</th>
<th>SUVR Range</th>
<th>Positivity</th>
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</thead>
<tbody>
<tr>
<td>HC</td>
<td>40-70</td>
<td>30%</td>
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<tr>
<td>MCI</td>
<td>64%</td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>70-100</td>
<td></td>
</tr>
<tr>
<td>DLB</td>
<td>20-40</td>
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<tr>
<td>FTD</td>
<td>10-30</td>
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* Villemagne and Rowe
Influence of ApoE ε4 status on PiB+ in Healthy Controls

ApoE ε4-ve

21% PiB+ve

79% PiB-ve

ApoE ε4+ve

49% PiB+ve

51% PiB-ve
PiB+ vs Age in Healthy Controls
(AIBL ApoE ε4 prevalence corrected data)

Prevalence of AD
(Tobias, 2008)

Prevalence of plaques
in HC
(Davies, 1988, n=110)
(Braak, 1996, n=551)
(Sugihara, 1995, n=123)

Prevalence of AD
(Tobias, 2008)

ε4 corrected AIBL data
Longitudinal PiB PET follow-up

*PiB+/PiB− SUVR cut-off = 1.5*
ApoE-ε4 and Risk of Amyloid in Healthy Older Persons

Years of age

- 50-59: 10%
- 60-69: 25%
- 70-79: 65%
- 80+: 80%

< 60 yrs data from Washington University

[Graph showing the risk of amyloidosis in healthy older persons by age group, with increasing risk as age increases.]
Average rate of atrophy over one year in HC PiB- vs PiB+.
BASELINE $\text{A\beta}$ burden correlates with memory decline over 3 years in HC

$r = 0.38 \ (p = 0.0005)$
AIBL+
Prediction of Progression: HC to MCI/AD

36 months
n=195

PiB-ve Subjects: 129
Converters to MCI/AD 7%

PiB+ve Subjects: 66
Converters to MCI/AD 19%
AIBL+
Prediction of Progression: MCI to Dementia
36 Months
n=92

PiB -ve :

- Converters to AD: 10%
- Other dementia: 17%
- No dementia: 73%

PiB +ve :

- Converters to AD: 56%
- No dementia: 44%