The Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing

AUSTRALIAN ADNI

April 2010 UPDATE
The Australian Imaging, Biomarkers and Lifestyle Study of ageing (AIBL): methodology and baseline characteristics of 1112 individuals recruited to follow up for a prospective longitudinal study of Alzheimer’s disease and related disorders.

Ellis KA, et al.

Amyloid Imaging Results from the Australian Imaging, Biomarkers and Lifestyle Study of Ageing (AIBL).

Rowe CC, et al.
Neurobiology of Aging - 2010 ADNI special edition.

Baseline MRI and PiB scans and corresponding clinical data on 237 participants are available from

www.loni.ucla.edu/ADNI/Data/

(go to Current Project drop down menu and select AIBL)
or from http://aibl.csiro.au/adni/
### Imaging Results

#### Demographics  
*(n=287)*

<table>
<thead>
<tr>
<th></th>
<th>HC</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>73.6 ± 7.6</td>
<td>77.4 ± 7.5*</td>
<td>74.0 ± 8.7</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.8 ± 1.2</td>
<td>27.1 ± 2.3*</td>
<td>20.5 ± 4.9*</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>87/90</td>
<td>28/29</td>
<td>23/30</td>
</tr>
<tr>
<td>%ApoE ε4</td>
<td>43%</td>
<td>54%</td>
<td>71%*</td>
</tr>
</tbody>
</table>

*Significantly different from HC, p <0.05*
Aβ burden by clinical classification

**Neocortical SUVR**

- **HC**: 1.49 ± 0.43
- **MCI**: 1.96 ± 0.64
- **AD**: 2.46 ± 0.49

*Significantly different from HC, p < 0.05
†Significantly different from AD, p < 0.05
PiB vs Age and ApoE-ε4

(A) Neocortical SUVR vs Age (years) for HC, slope = 0.022 SUVR/year

(B) Neocortical SUVR vs Age (years) for HC ε4, slope = 0.037 SUVR/year

(C) Neocortical SUVR vs Age (years) for HC non-ε4, slope = 0.019 SUVR/year
### Accuracy for AD vs HC at Baseline

<table>
<thead>
<tr>
<th></th>
<th>PiB</th>
<th>HV</th>
<th>GM Vol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Threshold</strong></td>
<td>1.5</td>
<td>0.004</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>98% (95% CI, 88-100%)</td>
<td>78% (95% CI, 63-89%)</td>
<td>67% (95% CI, 52-80%)</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>66% (95% CI, 59-73%)</td>
<td>80% (95% CI, 73-86%)</td>
<td>71% (95% CI, 63-78%)</td>
</tr>
<tr>
<td><strong>Test accuracy</strong></td>
<td>73%</td>
<td>73%</td>
<td>64%</td>
</tr>
</tbody>
</table>
Preclinical Alzheimer’s Disease?

Prevalence of AD (~15 yrs) (Tobias, 2008)

Prevalence of PiB+ve PET in HC

Prevalence of plaques in HC

(Davies, 1988, n=110)
(Braak, 1996, n=551)
(Sugihara, 1995, n=123)

~15 yrs

Prevalence of AD (Tobias, 2008)
<table>
<thead>
<tr>
<th>Demographics</th>
<th>Clinical follow-up (n=206)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HC</td>
</tr>
<tr>
<td>Age</td>
<td>73.2 ± 7.4</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.3 ± 1.0</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>53/48</td>
</tr>
<tr>
<td>Comp Memory</td>
<td>-0.20 ± 0.8</td>
</tr>
<tr>
<td>%ApoE ε4</td>
<td>31%</td>
</tr>
</tbody>
</table>

*Significantly different from HC, p <0.05
PiB Change Over Time

*PiB+/PiB- SUVR cut-off = 1.5*
% Converters PiB Positive vs Negative.
(note the little change in PiB binding despite progression)

14% vs 1% to MCI/AD @ 20 mths (5% overall)

66% vs 5% to AD at 20 mths (48% overall)

* PiB+/PiB- SUVR cut-off = 1.5

* * *
Longitudinal PiB PET
5-year follow-up
Comparison of Tests for Prediction of Conversion of MCI to AD

\[(n=65)\]

<table>
<thead>
<tr>
<th>Test</th>
<th>ACCURACY</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neocortical PiB+ve (SUVR &gt;1.5)</td>
<td>0.82</td>
<td>0.95 (CI 0.73-1.00)</td>
</tr>
<tr>
<td>ApoE ε4+</td>
<td>0.80</td>
<td>0.87 (CI 0.65-0.97)</td>
</tr>
<tr>
<td>Composite Memory (&lt;2.0)</td>
<td>0.78</td>
<td>0.81 (CI 0.61-0.93)</td>
</tr>
<tr>
<td>Hippocampal Volume (&lt;0.76)</td>
<td>0.76</td>
<td>0.76 (CI 0.52-0.91)</td>
</tr>
<tr>
<td>Post. Cing FDG (SUVR &lt;1.08)</td>
<td>0.66</td>
<td>0.59 (CI 0.39-0.77)</td>
</tr>
<tr>
<td>Plasma Aβ_{42}/Aβ_{40} (&lt;0.17)</td>
<td>0.62</td>
<td>0.77 (CI 0.46-0.94)</td>
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</tbody>
</table>
Subject Selection for Therapy Trials in MCI

<table>
<thead>
<tr>
<th></th>
<th>Accuracy</th>
<th>% included</th>
<th>Conversion at 20 mths (48% for MCI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PiB</td>
<td>82%</td>
<td>69%</td>
<td>66%</td>
</tr>
<tr>
<td>HipVol</td>
<td>76%</td>
<td>45%</td>
<td>76%</td>
</tr>
<tr>
<td>PiB + HipVol</td>
<td>90%</td>
<td>34%</td>
<td>100%</td>
</tr>
<tr>
<td>PiB + EM</td>
<td>83%</td>
<td>46%</td>
<td>81%</td>
</tr>
<tr>
<td>HipVol + EM</td>
<td>78%</td>
<td>45%</td>
<td>85%</td>
</tr>
</tbody>
</table>
PiB Conclusions

- PiB SUVR increases by 1%, 1.5% and 4% per year in PiB +ve HC, MCI, & early AD respectively but appears to then plateau in AD.
- A positive PiB scan is associated with a 13 fold greater risk of progression to MCI or AD in both HC and MCI.
- Progression correlates somewhat with change in PiB binding.
- PiB+ve MCI with hippocampal atrophy all progress to AD within 20 months.
Biomarker Discovery

AIBL DATA ANALYSIS COLLABORATIONS

Prof. Ralph Martins, Dr. Simon Laws, Alinda Mondal and Assoc., Prof. Peng Lam ECU team
Dr. Noel Faux, Uni. Melb. team
Dr Simon McBride, Dr. James Doecke, CSIRO team
Prof. Colin Masters, Prof. Ashley Bush, MHRI
Biomarker Discovery

AIBL Cohort
n=1091
Gender, Age, APOE

MAP Marker Panel
152 markers

Classifier Models
6-13 Classifiers/model

Model | Accuracy | Kappa | Sensitivity | Specificity
---- | -------- | ------ | ----------- |--------
PLS   | 0.8333   | 0.4759 | 0.5366     | 0.9139 |
Sparse PLS | 0.8333 | 0.4855 | 0.561      | 0.9073 |
SVM   | 0.8177   | 0.4101 | 0.4634     | 0.9139 |
Boosted Trees | 0.8438 | 0.4793 | 0.4878     | 0.9404 |
Shr. Centroids | 0.8281 | 0.4645 | 0.5366     | 0.9073 |

Raw Dataset
152 Variables

Data Cleaning

Data Mining

Pfizer Dataset
116 Variables

Sample Assays
AIBL/RB

Data Analysis
AIBL
Mean of ApoE levels within Clinical Categories

Full AIBL cohort (n=1079)

ANOVA, $F = 14.105, P < 0.001$

*Tukey HSD, $P < 0.001$ vs. MC and NMC, $P = 0.016$ vs. MCI

Ralph Martins and Veer Gupta
Biomarker Discovery

- Plasma Aβ measures are not robust.
- Analysis done with RBM and Pfizer has identified candidate biomarkers with moderate diagnostic accuracy.
- Plasma ApoE and apoE4 were lower in AD and inversely correlated with Aβ load in the PiB-PET subset. ApoE levels were also significantly lower among ε4 homozygotes.
- GWAS of PiB cohort performed in collaboration with Harvard – results awaited.
Life Style: Physical Activity

Belinda Brown, Jeremiah Peiffer
The Effect of Physical Activity on the Development of Alzheimer’s Disease and Associated Bio-markers

Data Collection (collected at baseline & 18 month follow-up)

- Physical activity data
  - International Physical Activity Questionnaire (IPAQ)
    - Collected from entire cohort
  - Actigraph Activity Monitor
    - Subset of 350 participants
Exercise and Blood plasma Aβ

- 553 Healthy Volunteers (57% female, mean age 70 ± 8.5) completed the IPAQ (International Physical Activity Scale)
- IPAQ scores were correlated with plasma Aβ levels (ratio Aβ42/ Aβ40)

![Graph showing the correlation between IPAQ quartiles and Aβ42/Aβ40 ratio](image)

Quartiles
1 = lowest activity levels; 4 = highest activity levels
Brown et al. 2009
Life Style: Nutrition

Vanessa Ward and Christine Keogh (CSIRO)
Dietary Assessment

Baseline:
Cancer Council of Victoria Food Frequency Questionnaire (CCVFFQ)
- Self administration on paper
- 74 food and beverage items. Analyzed by software based on the NUTTAB95 Australian food composition database.
- Output includes intakes of over 30 food types as well as over 70 nutrients.

Proposed Follow-up:
CSIRO Food frequency Questionnaire
- Self administration online with minimisation of errors and instant data capture.
- Dietary intakes of focus foods relating to AD will be explored in detail.
- Output will include nutrient data not previously available.

Analysis:
- Comparisons between nutrient, cognitive and blood biomarker data
- Longitudinal analysis of nutrient intake and risk of AD.
The impact of nutrition on cognition in the elderly and its potential role in the prevention of Alzheimer’s Disease

Development of the new CSIRO FFQ

**Additional output to be obtained:**
- Metals
- Vitamin B12
- Flavonoids
- Choline metabolites
- Phytosterols
- Oxalic acid

**Focus foods to be added:**
- Specific types of fish to be consumed
- Method of preparations of fish
- Specific cuts of meat
- Addition of green tea, white tea, black tea.
- A variety of berries, fruits and nuts
- Use of spices
- Use of supplements

**Outcomes:**
- Nutrient intake profiles of a large Australian elderly cohort. (Flavonoid intakes have not previously been reported).
- Identification of foods and nutrients that can increase or decrease the risk of developing AD.
Financial Supporters

• Australian Government through CSIRO
• Pfizer
• Alzheimer’s Association
• Alzheimer’s Drug Discovery Foundation
The AIBL Team

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