Plasma Aβ biomarker associated with cognitive decline in preclinical Alzheimer's disease

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Introduction

We recently showed in two independent cohorts, that a plasma Aβ composite biomarker, which was generated by combining plasma ratios of $APP_{669-711}/Aβ_{1-42}$ and $Aβ_{1-40}/Aβ_{1-42}$ as measured by immunoprecipitation-mass spectrometry (IP-MS) assay, had very high areas under the receiver operating characteristic curves (AUCs) (94-96%), with an accuracy of ~90% for the classification of high Aβ levels based on Pittsburgh Compound B (PiB) PET. This plasma Aβ composite biomarker may therefore have great clinical utility for predicting Aβ levels. We aimed to examine the relationship between this plasma Aβ composite biomarker and cognitive function in cognitively normal older adults in two independent cohorts.

Methods

Participants enrolled in the Australian Imaging, Biomarkers and Lifestyle (AIBL) study and the National Centre for Geriatrics and Gerontology (NCGG) study had undergone Aβ neuroimaging using positron emission tomography (PET), cognitive assessments and provided blood samples. We derived a high-performance plasma Aβ composite biomarker by immunoprecipitation with mass-spectrometry. The composite biomarker was computed by averaging normalized scores of $APP_{669-711}/Aβ_{1-42}$ and $Aβ_{1-40}/Aβ_{1-42}$ as set out in the following formula.

$$\text{Composite biomarker} = [\text{normalized}(APP_{669-711} / Aβ_{1-42}) + \text{normalized}(Aβ_{1-40} / Aβ_{1-42})] \times 1/2 \quad \ldots[1]$$

$$\text{normalized}(APP_{669-711} / Aβ_{1-42}) = [(APP_{669-711}/Aβ_{1-42}) - \text{mean}(APP_{669-711}/Aβ_{1-42})] / SD(APP_{669-711}/Aβ_{1-42})$$

$$\text{normalized}(Aβ_{1-40}/Aβ_{1-42}) = [(Aβ_{1-40}/Aβ_{1-42}) - \text{mean}(Aβ_{1-40}/Aβ_{1-42})] / SD(Aβ_{1-40}/Aβ_{1-42})$$

Retrospective and prospective cognitive data were modelled longitudinally with linear mixed-effects models (unstructured covariance matrix), and time and participant specified as random factors.

Results

Clinical and demographic characteristics were equivalent across groups defined according to their plasma Aβ composite score in both the AIBL and NCGG cohorts (Table 1). Both continuous and categorical measures of the plasma Aβ composite biomarker were significantly related to decline in episodic memory in both the AIBL and NCGG cohorts (Fig 1). The magnitude of effects of the plasma Aβ composite on episodic memory and executive function were comparable to that observed for the effects of PET Aβ levels on these same outcome measures.

Fig 1. Plasma Aβ associated with faster decline in (A) episodic memory and (B) executive function

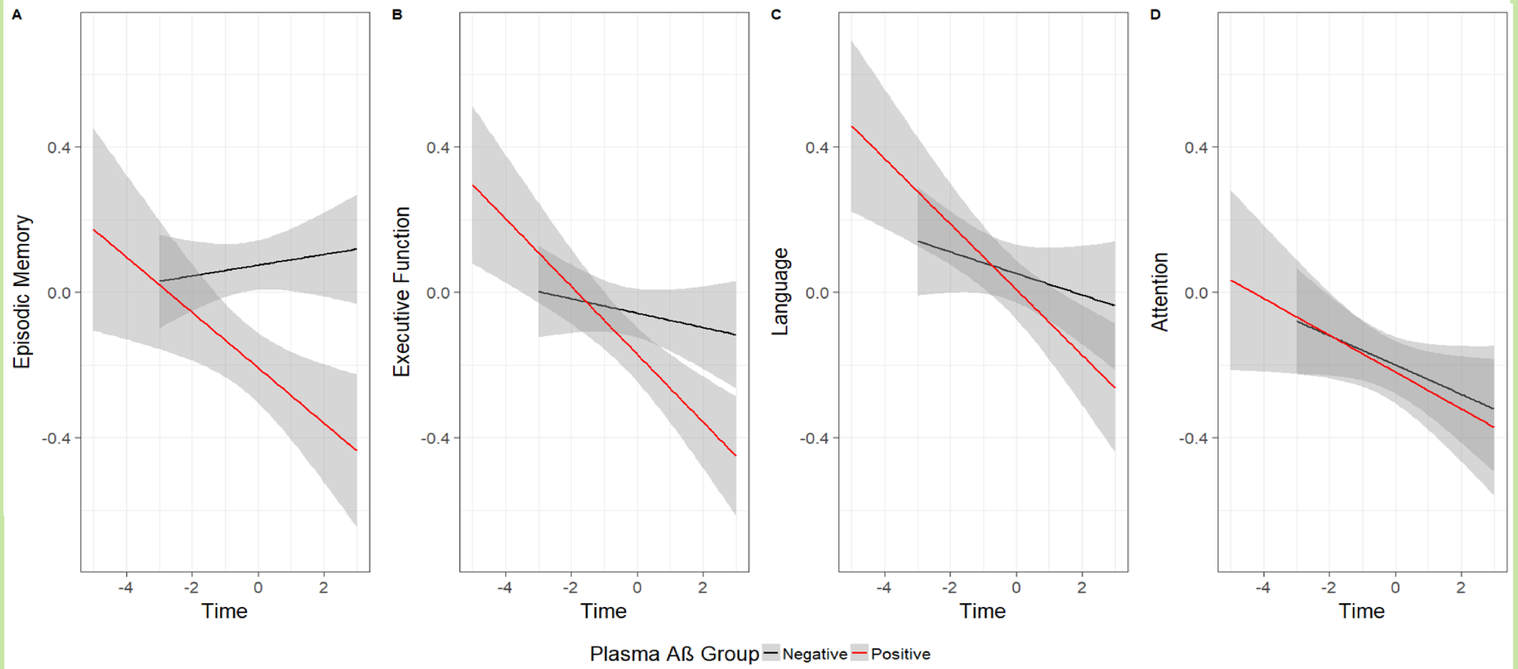

Table 1. Demographic characteristics.

AIBL Cohort				
	Overall (n=156)	Plasma Aβ- (n=82)	Plasma Aβ+ (n=74)	p
Age	74.07 (5.61)	74.17 (5.65)	73.96 (5.60)	.815
Years of Education	12.51 (2.97)	12.65 (2.94)	12.36 (3.03)	.557
MMSE	28.86 (1.21)	29.04 (1.07)	28.66 (1.33)	.053
CDR SB	0.03 (0.15)	0.03 (0.12)	0.03 (0.17)	.889
Plasma Aβ levels	0.40 (0.68)	-0.13 (0.35)	0.98 (0.44)	< .001
BeCKeT (SUVR)	1.51 (0.40)	1.30 (0.24)	1.74 (0.41)	< .001
N (%) Female	82 (52.6%)	43 (52.4%)	39 (52.7%)	.974
N (%) APOE ε4	57 (36.5%)	14 (17.1%)	43 (58.1%)	<.001
N (%) PET Aβ+	66 (42.3%)	11 (13.4%)	55 (74.3%)	<.001
NCGG Cohort				
	Overall (n=57)	Plasma Aβ- (n=48)	Plasma Aβ+ (n=9)	p
Age	72.18 (4.30)	72.33 (4.18)	71.33 (5.05)	.527
Years of Education	12.30 (2.66)	12.28 (2.53)	12.44 (3.43)	.864
MMSE	28.67 (1.37)	28.67 (1.40)	28.67 (1.22)	.999
ADAS-Cog	6.14 (2.39)	6.24 (2.48)	5.63 (1.90)	.494
Plasma Aβ levels	-0.55 (0.70)	-0.77 (0.53)	0.60 (0.21)	< .001
PiB-PET SUVR	1.23 (0.25)	1.19 (0.24)	1.46 (0.16)	.002
N (%) Female	28 (49.1%)	22 (45.8%)	6 (66.7%)	.433
N (%) APOE ε4	15 (26.3%)	10 (20.8%)	5 (55.6%)	.079
N (%) PET Aβ+	9 (15.8%)	5 (10.4%)	4 (44.4%)	.038

Summary

An elevated plasma Aβ composite score, measured in CN older adults using IP-MS, was associated with cognitive dysfunction. At the baseline assessment, individuals defined as Aβ+ based on the plasma Aβ composite score showed moderately worse episodic memory performance than matched Aβ- individuals, although the magnitude of this impairment was small-to-moderate (d=0.32, p = .05). Longitudinal models in both the AIBL and NCGG cohorts showed that higher plasma Aβ composite scores were moderately related to accelerated decline in both episodic memory and executive function, with the magnitude of effect, moderate for both measures (d=0.54 and d=0.51 respectively) (Fig 1). This was comparable to that observed between PET Aβ- and PET Aβ+ groups on episodic memory (d=0.47) and executive function (d=0.48). Plasma Aβ+ was not associated with changes in language or attention (Fig 1).

Acknowledgements AIBL is a large collaborative study and a complete list of contributors can be found at our website www.aibl.csiro.au. We thank all who took part in the study. This research is supported by the Science and Industry Endowment Fund.