AMYLOID BURDEN AND DEPRESSIVE SYMPTOMS

Amyloid Burden and Incident Depressive Symptoms in Cognitively Normal Older Adults

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Abstract

Objective: Several studies have reported that non-demented older adults with clinical depression show changes in amyloid- β ($A\beta$) levels in blood, cerebrospinal fluid, and on neuroimaging that are consistent with those observed in Alzheimer's disease (AD) patients. These findings suggest that $A\beta$ may be one of the mechanisms underlying the relation between the two conditions. We sought to determine the relation between elevated cerebral $A\beta$, and the presence of depression across a 54 month prospective observation period.

Method: Cognitively normal older adults from the Australian Imaging Biomarkers and Lifestyle (AIBL) study of aging who were not depressed and had undergone a positron emission tomography (PET) scan to classify them as either high $A\beta$ ($n = 81$) or low $A\beta$ ($n = 278$) participated. Depressive symptoms were assessed using the Geriatric Depression Scale-Short Form (GDS-S) at 18-month intervals over 54 months.

Results: Whilst there was no difference in probable depression between groups at baseline, incidence was 4.5 (95% CI 1.3-16.4) times greater within the high $A\beta$ group (9%) than the low $A\beta$ group (2%) by the 54 month assessment.

Conclusions: Results of this study suggest that elevated $A\beta$ levels are associated with a 4.5-fold increased likelihood of developing clinically significant depressive symptoms on follow

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up in preclinical AD. This underscores the importance of assessing, monitoring, and treating depressive symptoms in older adults with elevated A β .

Introduction

Converging evidence indicates that life-time depression increases the risk of clinically classified Alzheimer's disease (AD; da Silva et al., 2013, Richard et al., 2013), and that increasing number, longer duration or higher frequency of depressive episodes across the lifespan may further increase this risk (Byers and Yaffe 2011; Piccinni, et al. 2013). In older adults depression and AD often co-occur and can be difficult to differentiate clinically (especially in mild AD) due to overlap between the cognitive and functional impairments associated with the two diagnoses (Tsuno and Homma 2009; Wells 1979). There has been speculation that in older adults, depressive symptoms and AD may share a common biological mechanism and even that increased depressive symptoms are an early clinical indicator of the presence of AD-related pathophysiology (Byers and Yaffe 2011; Nascimento, et al. 2015).

Post mortem and *in vivo* studies suggest that amyloid-beta (A β) accumulation may provide a mechanistic link between depression and AD. For example, AD patients with clinical depression show greater numbers of neuritic A β plaques upon post mortem examination compared to those without depression (Meynen, et al. 2010; Rapp, et al. 2006). Further, non-demented older adults who met clinical criteria for major depressive disorder

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(MDD), or showed elevated depressive symptoms, were more likely to also have AD-like A β levels determined from *in vivo* assessments of A β using positron emission tomography (PET) amyloid neuroimaging (Chung, et al. 2015b; Kumar, et al. 2011; Lavretsky, et al. 2009; Wu, et al. 2014), cerebrospinal fluid (CSF) sampling (Gudmundsson, et al. 2001; Pomara, et al. 2012; Tsuruga, et al. 2014) or blood markers (Baba, et al. 2012; Kita, et al. 2009; Namekawa, et al. 2013). However relationships between increased amyloid and depressive symptoms have not been observed consistently (Butters, et al. 2008; Chung, et al. 2015a; Madsen, et al. 2012; Reis, et al. 2012; Wilson, et al. 2014). Furthermore, the majority of studies linking A β and depression conducted to date have been limited by their use of cross-sectional designs, non-representative clinical samples and have failed to account for potential confounds from key risk factors for dementia presence and severity, such as the apolipoprotein E (*APOE*) ϵ 4 allele within their samples (Harrington, et al. 2015).

The preclinical phase of AD may provide a unique context for studying the development of depressive symptoms and their relationship to A β , independent of issues related to overt cognitive and functional symptoms, or any reactive responses to such symptoms or diagnoses that occur in more advanced stages of the disease (McKhann, et al. 2011). The preclinical AD phase is proposed to commence up to 20 years prior to the clinical classification of dementia (Jack, et al. 2010; Sperling, et al. 2011; Villemagne, et al.) providing a long window within which relationships between depression and A β can be determined. Thus, prospective studies of the incidence of depressive symptoms throughout the preclinical phase of AD should provide understanding of their relationship to AD-related pathophysiology and any role they may have as a possible early clinical indicator of AD.

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The aim of this study was to examine prospectively relationships between A β and depressive symptoms in cognitively normal older adults enrolled in the Australian Imaging Biomarker and Lifestyle (AIBL) study of aging. As AIBL is an experimental study, designed to identify the link between amyloid accumulation and clinical manifestations across all stages of AD, Individuals with uncontrolled vascular risk factors, medical illnesses or psychiatric disorders which can confound these relationships are excluded. All individuals also undergo MRI to exclude the potential for non-amyloid CNS injury or disease (e.g. microvascular disease) to influence clinical outcomes. Therefore the AIBL sample provides a basis for examining the relationship between amyloid and the incidence of depressive symptoms in otherwise healthy and cognitively normal older adults. It was hypothesised that high levels of A β , as identified on positron emission tomography (PET) neuroimaging, would be associated with increased incidence of clinically significant depressive symptoms over 54 months.

Method

Participants

The present study included 359 participants (168 male and 191 female) from the AIBL study who were classified as cognitively normal at the AIBL baseline assessment and had undergone a positron emission tomography (PET) scan to determine their cerebral A β levels. Participants were not enrolled in the study if they had significant current depressive symptoms at the initial baseline assessment (i.e. Geriatric Depression Scale – Short Form score greater than 5/15 [Sheikh & Yesavage, 1986]).

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AIBL participants were recruited via a media campaign and referrals from specialised memory clinics during 2006-2008. Participants were excluded from enrolment in the AIBL study if they had a history of non-AD dementia, Parkinson's disease, schizophrenia, or bipolar disorder. Potential participants were also excluded at the commencement of the study if they had cancer (other than basal cell skin carcinoma) within the last two years, symptomatic stroke but not transient ischaemic attack, uncontrolled diabetes, or current regular alcohol use exceeding two standard drinks per day for women or four per day for men. These exclusion criteria ensured that individuals recruited to the study did not have frank pathology, other than AD, that might cause cognitive impairment.

At each AIBL assessment (baseline, 18, 36, and 54 month follow-ups), a clinical review panel, consisting of geriatric psychiatrists, neurologists, geriatricians, and neuropsychologists, examined all available data to confirm the clinical status of participants and ensure appropriate group allocation. The panel reviewed all available clinical and cognitive information, including informant reports, functional and neuropsychological assessments, in order to reach consensus on each participant's clinical status (cognitively normal, mild cognitive impairment [MCI], or AD). Classification of MCI was based on internationally agreed criteria (Winblad, et al. 2004) and AD according to NINCDS-ADRDA criteria (McKhann, et al. 1984). All individuals included in the present study did not meet criteria for MCI or AD at the baseline assessment. Clinical classification was blinded to neuroimaging results. This process has been described in greater detail elsewhere (Ellis, et al. 2009). Independent of this process participants were also classified as either high A β (n = 81) or low A β (n = 278) on the basis of A β PET neuroimaging according to standardised

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criteria (Jack, et al. 2008; Villemagne, et al. 2011). Retention of participants in the study was high across the 54 month study period, with 37 participants having withdrawn from the study by the 54 month assessment.

The AIBL study was approved by and complied with the regulations of three institutional research and ethics committees (St Vincent's Health, Austin Health, and Edith Cowan University). All participants provided written informed consent prior to participating in the study.

Assessments

Demographic and Clinical Characteristics. Demographic information was collected at the baseline assessment. Age, gender and medical history were self-reported. The Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) was used to estimate the premorbid intelligence of participants. Functional ability was rated using the Clinical Dementia Rating scale (CDR; Morris, 1993). The Mini Mental State Examination (MMSE; Folstein *et al.*, 1975) was used to screen global cognitive function. *APOE* genotype was determined using blood genotyping.

Depressive Symptoms. The Geriatric Depression Scale – Short Form (GDS-S; Sheikh & Yesavage, 1986; Yesavage et al., 1982) was used to assess depressive symptoms. The GDS-S consists of 15 questions and uses a yes/no response format enabling ease of use for individuals with cognitive difficulties. The GDS-S is appropriate for use with older adults and is a reliable and valid measure of depressive symptoms in this population (Sheikh and Yesavage 1986; Strauss, et al. 2006; Yesavage et al. 1982). Clinically significant depressive symptoms, and probable clinical depression (hereafter referred to as depression), were

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indicated by scores greater than 5 on the GDS-S. The cut score of 5 on the GDS-S has been reported to have sensitivity of 92.7% and specificity of 65.2% relative to cases identified using the International Classification of Diseases 10th revision (ICD-10) criteria for major depression (Almeida and Almeida 1999).

Neuroimaging. PET neuroimaging in the AIBL study has been described in detail previously (Rowe, et al. 2010; Villemagne, et al. 2014). Briefly, 201 participants were administered Pittsburgh Compound B (PiB) and standardised uptake value (SUV) data were acquired 40-70 minutes post-injection, 79 participants were administered ¹⁸F-florbetapir (FBP) and SUV data were acquired 50-70 minutes post-injection, and 80 participants were administered ¹⁸F-flutemetamol (FLUTE) and SUV data were acquired 90-110 minutes post-injection. Data were summed and normalised to the cerebellar cortex SUV, giving the region-to-cerebellar ratio, termed SUV ratio (SUVR) for PiB (Rowe et al., 2010). The whole cerebellum was used as reference region for FBP, while the pons was used as reference region for FLUTE (Villemagne et al., 2014).

Procedure

Participants attended the research facility at each assessment time point after having fasted overnight. Once written consent to participate in the study was obtained, an 80ml blood sample was then taken; 0.5ml of which was forwarded for *APOE* genotyping at a clinical pathology laboratory. Next, trained research assistants conducted a clinical interview and comprehensive neuropsychological assessment including WTAR, MMSE, CDR, and

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GDS-S. Neuroimaging was acquired on a separate day to the clinical data at each assessment time point.

Data Analysis

Neuroimaging results were coded as a dichotomous categorical variable using a PiB SUVR of 1.5, a FBP SUVR of 1.1, and a FLUTE SUVR of 0.62 as cut-offs for high/low A β level in accordance with previous reports describing the definition of abnormal amyloid levels (Jack et al. 2008; Villemagne et al. 2011). For the GDS-S, performance was classified as a dichotomous categorical variable where a score greater than 5 was used to classify individuals as having depression (Sheikh and Yesavage 1986; Yesavage et al. 1982). Individuals were also classified as to whether or not they carried an *APOE* ϵ 4 allele.

To test the hypothesis that high A β would be associated with increased incidence of depression over 54 months, first chi-square analysis was used to test for an association between A β status and incidence of depression on the dichotomised GDS-S (score >5) at each assessment. Odds ratios with 95% confidence intervals (CI) were then calculated as a measure of effect for all significant associations. Next, a binary logistic regression analysis was conducted to evaluate the relationship between A β status at baseline and incident depression occurring at any assessment other than baseline over the 54 month study period. A β status at baseline (low A β vs. high A β), baseline variables that differed between the incident depression and no incident depression groups in bivariate analyses (i.e., age and *APOE* genotype), and an interaction term of A β status x *APOE* genotype were entered

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as independent variables, and incident depression status (incident depression vs. no incident depression) was entered as the dependent variable.

A post-hoc analysis was also conducted to examine the association between the incidence of depression and key clinical characteristics. Unique cases of incident depression occurring at any assessment were identified in the total sample according to categorisation based on the GDS-S score. Depressed and non-depressed participants were then compared on rates of self-reported history of a diagnosed depressive disorder, progression to meet clinical criteria for MCI or AD at the 54-month assessment, classification of high A β , and withdrawal from the AIBL study using Chi-square analysis.

Results

Baseline demographic and clinical characteristics of the high and low A β groups are summarised in Table 1. The high A β group was older and had a significantly greater proportion of *APOE* ϵ 4 carriers than the low A β group. Figure 1 shows the median score and interquartile range on the GDS-S for the high and low A β groups at each of the assessments. For all assessments, the upper value of the interquartile range was less than the standardised cut-off score (GDS-S >5) for classification of probable depression.

Figure 2 summarises the proportion of individuals who scored above 5 on the GDS-S for each of the A β groups across each of the four assessments. Table 2 summarises the number of participants classified with depression in the total sample and within the high and low A β groups across the four assessments. The number of new cases of depression presenting at

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each of the four assessments within each group is also reported in Table 2. Chi-squared analysis was used to compare the proportion of participants classified as depressed between the A β groups at each assessment. No association between A β group and depression was identified at baseline, 18 or 36 months. However, there was a significant association between A β group and depression at the 54 month assessment, $\chi^2(1) = 6.50, p < .05$. The odds-ratio for this relationship indicated that a classification of high A β made it 4.5 (95% CI 1.3-16.4) times more likely to have depression at the 54 month assessment (Table 2). The logistic regression model predicting incident depression (n=14, 4.9%) over the 54-month study period indicated that the interaction of A β status x *APOE* genotype predicted incident depression at a statistically significant level (Wald $\chi^2(1)=6.75, p=0.009$; OR=5.73, 95%CI=1.53-21.38). In this model, age (Wald $\chi^2(1)=0.75, p=0.38$), A β status alone (Wald $\chi^2(1)=0.48, p=0.49$) and *APOE* genotype alone (Wald $\chi^2(1)=1.23, p=0.27$) were not significant predictors of incident depression.

There were 20 unique cases of depression identified in the total sample, of which 6 (4 low A β , 2 high A β) were classified as depressed at least twice in the 54 month study period. Table 3 summarises the clinical characteristics of both the depressed and non-depressed groups. Chi-square analysis (see Table 3) indicated that the depressed group was more likely to self-report a history of a diagnosed depressive disorder, $\chi^2(1) = 4.49, p < .05$, and to progress to meet clinical criteria for MCI or AD at the 54-month assessment, $\chi^2(1) = 15.39, p < .05$. From the depressed group, 30% of participants (n=6) progressed to MCI or AD in the study period. Incidence of depression and progression to MCI or AD occurred at the same assessment for 10% (n=2) of the depressed group. Depressed and non-depressed groups were

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equally likely to be classified as high A β , $\chi^2(1) = 0.67$, $p > .05$ and withdrew from the AIBL study at the same rate, $\chi^2(1) = 0.01$, $p > .05$.

Discussion

The hypothesis that high A β would be associated with increased incidence of clinically significant depressive symptoms, and probable depressive disorder, was supported. Cognitively normal individuals with low levels of depressive symptoms were followed for 54 months. The incidence of clinically significant depressive symptoms occurring after enrolment remained low for the entire sample (1-9%). However, relative to the low A β group, the high A β group was 4.5 times more likely to exhibit clinically significant depressive symptoms by the 54 month assessment. Additionally, high A β and carriage of an *APOE* $\epsilon 4$ was predictive of the incidence of depression over 54 months. These findings suggest that AD-related neuropathology in cognitively normal older adults is associated with an increased incidence of depressive symptoms of clinical severity, particularly for individuals at increased risk of AD due to genetic factors. Importantly, of those who progressed to MCI or AD the incidence of depression and progression to MCI or dementia did not occur at the same time point for most individuals (66%). As such it is unlikely that the observed increase in depressive symptom levels was a reaction to any realisation of cognitive and functional deficits. Instead, the accumulation of cerebral A β may be one biological mechanism that contributes to the pathophysiology of both depression and AD at least in some people (Byers and Yaffe 2011).

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The synergistic relationship observed between high A β and *APOE* ϵ 4 carriage with increased incidence of depression observed in the present study is consistent with reports from an earlier study (Metz, et al. 2013). Furthermore, previous studies have reported that *APOE* ϵ 4 carriage is associated with increased risk of depression in late life (Sureshkumar, et al. 2012; Yen, et al. 2007), and that this relationship is maintained even when controlling for vascular disease factors, indicating that the association is unlikely the result of vascular pathology (Yen et al. 2007). The current sample was selected specifically so as not to have significant vascular risk factors and therefore the relationship between depressive symptoms and A β observed here is unlikely to have been mediated by any cerebral vascular disorder. Individuals with depression and high A β , who also carry an *APOE* ϵ 4 allele have also been reported to be at a greater risk (40% v. 4%) of developing dementia than non-carriers (Qiu, et al. 2015). Taken together these data suggest that in cognitively normal older adults, the major risk factors for AD, and in particular their combination, also increase substantially the risk of depression.

The clinical and demographic characteristics of the incident cases of depression occurring at any assessment within the total sample of the current study were also explored. Results of these analyses indicated that the incident depression group was more likely to self-report a history of depressive episodes. Given that risk for recurrence of depression increases with multiple episodes (American Psychiatric Association 2013; Gonzales, et al. 1985; Kessing, et al. 2000), the finding that individuals with current depression were also more likely to report a history of depressive episodes suggests that the current classification of depression based on the GDS-S is valid. Importantly, rates of prior history of depressive

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episodes did not differ significantly between the high and low A β groups (see Table 1).

Consequently, the difference in incidence of depression between groups is unlikely to have been due to the effects of any prior history of depression. The incident depression group was also more likely to progress to MCI or AD over the course of the study. This finding accords with results of an earlier study which also observed that depressive symptoms accelerated cognitive decline and increased risk of progression to AD in MCI patients with high A β burden (Brendel, et al. 2015). Importantly though, depressed and non-depressed individuals were equally likely to be classified as having high levels of A β . This indicates that the increased rate of AD progression was not driven by increased rates of high levels of A β within the depressed group, but rather that the combined presence of high levels of A β and depression may have enhanced the rate of disease progression. This suggests that there is an interaction between the two conditions that increases an individual's risk of progressing into the later stages of AD.

From a clinical perspective, the identification and validation of a profile indicating preclinical AD would be useful in informing diagnosis, formulation, and prognosis of individuals with late life depressive disorders. The results of this study indicated that non-demented individuals with high A β appear to be at a higher risk of developing a late life depressive disorder, which subsequently results in an accelerated rate of disease progression. Thus we believe that it is important for clinicians to monitor closely patients at risk of dementia for increases in depressive symptoms, particularly in the context of an individual with prior depressive episodes. The emergence of such a depressive disorder late in life, in

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addition to progressive cognitive decline, may herald the onset of the AD process, as well as indicating a potentially increased rate of AD progression.

The current study is limited in several ways. While, the data here provide insight into the relationship between $A\beta$ and depression, it is important to highlight that the AIBL sample is an experimental sample and hence is not be representative of the broader population. Further investigation in community-based samples of older adults is required to ensure the generalizability of the relationship between $A\beta$ and depression.

Another limitation of the current study is that it did not consider the interaction of the relationship between depressive symptoms and $A\beta$ with the cognitive and functional symptoms of AD. Due to the low incidence of depression within the AIBL sample, the current study did not have sufficient statistical power to evaluate this interaction. It is well established that $A\beta$ -related cognitive decline occurs in the preclinical stage of AD and it would be important to consider how the trajectory of this decline is influenced by the presence of a depressive disorder.

Additionally, the present study only considered the total score on the GDS-S, which is known to be a relatively coarse screening measure, as an indicator of overall depressive symptom severity. There may be a particular depressive symptom profile related more specifically to cerebral $A\beta$ burden, or to other AD-related pathology such as neurodegeneration, which may show progressive changes over time. For example, Donovan, et al. (2015) reported that dysphoria and apathy-anhedonia depressive symptoms, but not anxiety-concentration symptoms, were associated with reduced hippocampal volume independent of $A\beta$ in cognitively normal older adults without clinical depression. Thus, the

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possibility of specific subsets of depressive symptoms that relate more strongly to AD pathology warrants further investigation. By considering these factors, a profile of symptoms associated with preclinical AD can begin to be developed in order to enhance clinical identification of the disease in its earliest stages.

Nevertheless, results of the present study begin to contribute to the establishment of this profile by indicating that non-demented older adults with high A β are at increased risk of a late life depressive disorder, which may be associated with increased risk of progression to AD dementia.

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Conflict of Interest

KH and EG report no disclosures. C.L.M. is an advisor to Prana Biotechnology Ltd and a consultant to Eli Lilly. R.H.P. is a scientific consultant to Cogstate Ltd. P.M. is a full-

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time employee of Cogstate Ltd. D.A. has served on scientific advisory boards for Novartis, Eli Lilly, Janssen, and Pfizer Inc. R.N.M. is a consultant to Alzhyme. C.C.R. has served on scientific advisory boards for Bayer Pharma, Elan Corporation, GE Healthcare and AstraZeneca; has received speaker honoraria from Bayer Pharma and GE Healthcare; and has received research support from Bayer Pharma, GE Healthcare, Piramal Lifesciences and Avid Radiopharmaceuticals. V.L.V. served as a consultant for Bayer Pharma; and received research support from a NEDO grant from Japan.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Table 1.

Mean (SD) of baseline demographic and clinical characteristics for the Low A β and High A β groups.

	Low A β (n = 278)	High A β (n = 81)	<i>p</i>
Age	68.70 (6.08)	73.47 (7.33)	.00
Gender	53% Female	53% Female	.98
Premorbid IQ (WTAR)	108.26 (7.01)	109.65 (6.84)	.12
APOE4 carriers	23%	60%	.00
MMSE	28.96 (1.17)	28.75 (1.19)	.16
CDR Total*	0 (0.5)	0 (0.5)	.16
CDR-SOB*	0 (1.5)	0 (0.5)	.99
Self-reported history of depression	19%	14%	.29
GDS*	0.00 (8.00)	0.00 (2.00)	.11

*Median (range) reported

WTAR = Wechsler Test of Adult Reading, APOE4 = Apolipoprotein ϵ 4, CVRF = Cardiovascular Risk Factor, MMSE = Mini Mental State Examination, CDR = Clinical Dementia Rating, CDR-SOB = Clinical Dementia rating Sum of Boxes score, GDS – Geriatric Depression Scale

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Table 2.

Number (%) of cases of clinically significant depressive symptoms at each assessment time point for the Low A β and High A β groups.

	Total Sample		Low A β		High A β		p
	Total	New	Total	New	Total	New	
Baseline	5 (1.4%)	-	5 (1.8%)	-	0 (0%)	-	.23
18 months	7 (2.1%)	7	4 (1.5%)	4	3 (4.3%)	3	.15
36 months	7 (2.1%)	3	5 (1.9%)	3	2 (3.1%)	0	.55
54 months	10 (3.2%)	5	5 (1.9%)	2	5 (8.3%)	3	.01

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Table 3.

Characteristics of incident cases of clinically significant depressive symptoms (GDS-S >5)

	Depressed	Non-depressed
Unique cases	20	339
Self-reported history of depressive disorder	7 (35%)	55 (16%)*
MCI/AD Progression	6 (30%)	21 (6%)*
AIBL Withdrawal	2 (10%)	35 (10%)
High A β Classification	6 (30%)	75 (22%)

* $p < 0.05$

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Figure Captions

Figure 1. Box plots indicating the median and interquartile range for total GDS-S scores at each time point for Low A β (dark grey bars) and High A β groups (light grey bars).

Figure 2. Proportion of individuals with clinically significant depressive symptoms (GDS-S >5) at each assessment point for the Low A β (dark grey bars) and High A β groups (light grey bars).

** Indicates statistical significance, $p < 0.05$

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