Archival Report

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Plasma Cortisol, Brain Amyloid-β, and Cognitive Decline in Preclinical Alzheimer's Disease: A 6-Year Prospective Cohort Study

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ABSTRACT

BACKGROUND: Hypothalamic-pituitary-adrenal axis dysregulation, which is typically assessed by measuring cortisol levels, is associated with cognitive dysfunction, hippocampal atrophy, and increased risk for mild cognitive impairment and Alzheimer's disease (AD). However, little is known about the role of hypothalamic-pituitary-adrenal axis dysregulation in moderating the effect of high levels of amyloid-β (Aβ+) on cognitive decline in the preclinical phase of AD, which is often protracted, and thus offers opportunities for prevention and early intervention.

METHODS: Using data from a 6-year multicenter prospective cohort study, we evaluated the relation between Aβ level, plasma cortisol level, and cognitive decline in 416 cognitively normal older adults.

RESULTS: Results revealed that Aβ+ older adults experienced faster decline than Aβ− older adults in all cognitive domains (Cohen's *d* at 6-year assessment = 0.37–0.65). They further indicated a significant interaction between Aβ and cortisol levels for global cognition (*d* = 0.32), episodic memory (*d* = 0.50), and executive function (*d* = 0.59) scores, with Aβ+ older adults with high cortisol levels having significantly faster decline in these domains compared with Aβ+ older adults with low cortisol levels. These effects were independent of age, sex, *APOE* genotype, anxiety symptoms, and radiotracer type.

CONCLUSIONS: In cognitively healthy older adults, Aβ+ is associated with greater cognitive decline and high plasma cortisol levels may accelerate the effect of Aβ+ on decline in global cognition, episodic memory, and executive function. These results suggest that therapies targeted toward lowering plasma cortisol and Aβ levels may be helpful in mitigating cognitive decline in the preclinical phase of AD.

Keywords: Aging, Amyloid, Cognition, Cortisol, Epidemiology, Memory

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Alzheimer's disease (AD) begins with the accumulation of cortical amyloid-β (Aβ), estimated to occur up to 20 years before individuals meet clinical criteria for dementia (1,2). Prospective studies of cognitively normal (CN) older adults with abnormally high levels of Aβ (i.e., Aβ+) show a subtle but persistent decline in cognition, particularly in memory and working memory, which reflect the early downstream neurodegenerative effects of Aβ (3–9). Cognitive decline associated with Aβ continues until individuals meet clinical classification for mild cognitive impairment (MCI) and ultimately AD (1,2). Despite the strong risk for cognitive decline associated with Aβ+ in CN older adults, increasing evidence indicates that the nature and rate of Aβ-related cognitive decline can be moderated by genetic polymorphisms [e.g., *APOE* genotype (10)], sociodemographic [e.g., intelligence or cognitive reserve (11)], and lifestyle [e.g. physical exercise (12)] factors. Consequently, elucidation of the biological processes by which such factors influence Aβ-related neurotoxicity may increase the understanding of AD pathogenesis and inform strategies designed to mitigate Aβ-related neurodegeneration.

Converging data suggest that dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may also moderate Aβ-related cognitive decline in AD. For example, animal studies have observed that early and prolonged exposure to glucocorticoids can promote AD-related neuropathology (13–16) and contribute to the development of cognitive impairment (15). Studies in humans show that HPA axis dysregulation, as evidenced by increased cortisol levels, is associated with reduced hippocampal volume, gray matter, and cognitive function in CN community-dwelling older adults (17,18). Furthermore, cortisol levels are found to be elevated in patients with clinically classified amnestic MCI and AD and are associated with increased cognitive decline (19), as well as increased risk for developing dementia in patients with MCI (20). A recent study observed a strong association between plasma cortisol levels and cortical Aβ levels, with each unit increase in cortisol levels

associated with a 1-unit increase in ^{11}C-Pittsburgh compound B (PiB) standardized uptake value (SUV) ratio (SUVR) values in a sample consisting of CN older adults ($n = 22$) and older adults with MCI ($n = 51$) and AD ($n = 26$) from the Alzheimer Disease Neuroimaging Initiative cohort (21). Further, a recent prospective cohort study (22) from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study observed that Aβ+ CN older adults with increased anxiety symptoms, which are linked to HPA axis dysregulation (23,24), experienced accelerated decline in verbal memory, language, and executive function. Collectively, these data suggest that HPA axis dysregulation may influence relationships between Aβ-related neurotoxicity and cognitive decline in preclinical AD. However, no study of which we are aware has investigated prospectively the relation between an objective biological index of HPA axis function, such as cortisol, Aβ, and cognition, in this phase of AD.

The aim of this study was to evaluate the relationships between plasma cortisol levels, Aβ levels, and cognitive change in a large cohort of CN older adults followed up for 72 months. We hypothesized that Aβ+ would be associated with greater cognitive decline, and that increased cortisol levels would moderate cognitive decline related to Aβ+, such that Aβ+ CN older adults with high cortisol levels would show greater rates of decline in cognitive function compared with Aβ+ CN older adults with low cortisol levels. In light of data suggesting that elevated glucocorticoids have a particularly neurotoxic effect on the hippocampus (18,25–29), we expected that any moderating effect of cortisol on Aβ-related cognitive decline would be greatest for episodic memory.

METHODS AND MATERIALS

CN older adults ($n = 416$) enrolled in the AIBL study (30) underwent Aβ neuroimaging and provided a blood sample to assess plasma cortisol levels. Selection into the full AIBL cohort was controlled to ensure 1) a wide age distribution from 60 years through to 100 years and 2) enrollment of approximately 50% of individuals with subjective memory complaints. Exclusion criteria for the CN older adult cohort were diagnosis of schizophrenia, depression (score ≥6 on the Geriatric Depression Scale Short Form), Parkinson disease, cancer (except basal cell skin carcinoma) within the last 2 years, symptomatic stroke, uncontrolled diabetes, sleep apnea, and current regular alcohol use of more than two standard drinks per day for women or more than four for men. Institutional research committees of Austin Health, St. Vincent's Health, Hollywood Private Hospital, and Edith Cowan University approved the AIBL study; all participants provided written informed consent.

Amyloid Positron Emission Tomography Imaging and *APOE* Genotyping

Aβ imaging with positron emission tomography was conducted using PiB, ^{18}F-florbetapir, or ^{18}F-flutemetamol. A 30-minute acquisition was started 40 minutes after PiB injection, whereas 20-minute acquisitions were performed 50 minutes after florbetapir injection and 90 minutes after flutemetamol injection. For PiB, positron emission tomography SUV data were summed and normalized to the cerebellar cortex SUV, yielding a region to cerebellar ratio termed SUVR. For florbetapir, SUVR was generated using the entire cerebellum as the reference region; for flutemetamol, the pons was used as the reference region for SUVR. In line with previous studies, SUVR was classified dichotomously as either negative or positive (i.e., Aβ− or Aβ+). For PiB, an SUVR threshold ≥1.5 was used. For florbetapir and flutemetamol, SUVR thresholds of ≥1.11 and ≥0.62 were used, respectively. DNA extraction and genotyping were performed as previously described (10,31–33).

Plasma Cortisol Levels

Morning fasted plasma samples were analyzed using a commercial cortisol enzyme-linked immunosorbent assay (IBL International GmbH, Hamburg, Germany). The cortisol enzyme-linked immunosorbent assay was performed as per manufacturer instructions. Briefly, wells are precoated with anticortisol monoclonal antibody, 20 μL of standard; controls and samples were dispensed in duplicate into the desired wells, followed by 200 μL of enzyme conjugate. Wells were then mixed for 10 seconds, incubated for 1 hour at room temperature, and washed three times before the addition of 100 μL of substrate solution and incubation for 15 minutes at room temperature. After incubation, 100 μL of stop solution was added, and the optical density of each well was then measured at 450 nm using a FLUOstar OPTIMA microplate reader (BMG LABTECH GmbH, Ortenberg, Germany). Sample optical density was converted to cortisol concentrations (in nanograms per milliliter) using the established standard curve, calculated using a four-parameter logistic model. The mean plasma cortisol level in the full sample was 143.9 ng/mL (SD = 62.7; range = 19.6–522.6). Because the distribution of raw cortisol values was highly skewed and non-normal (Shapiro-Wilk test = 0.94, $p < 1 \times 10^{-11}$) and could not be corrected to normal using $\log_{10}$ transformation (Shapiro-Wilk test = 0.97, $p < 1 \times 10^{-7}$), they were dichotomized using a median split procedure (17,19,34). Mean cortisol levels in the resultant low-cortisol and high-cortisol groups, stratified by Aβ status, are reported in Table 1.

Vascular Risk Factors

A count of vascular risk factors was obtained by summing the following criteria: hypertension (blood pressure ≥ 140/90 mm Hg or currently undergoing treatment with an antihypertensive medication), dyslipidemia (fasting serum total cholesterol ≥ 6.22 mmol/L, fasting serum triglycerides ≥ 2.26 mmol/L, or currently undergoing treatment with statin or fibrate medications), obesity (body mass index > 30 kg/m^2), smoking (ever smoked >20 cigarettes per day for more than 1 year), diabetes (fasting plasma glucose > 7 mmol/L or currently undergoing treatment with diabetes medication), high homocysteine levels (males > 16.2 μmol/L; females > 13.6 μmol/L), or chronic kidney disease (estimated glomerular filtration rate < 45 mL/min (35,36).

Anxiety and Depressive Symptoms

The Hospital Anxiety and Depression Scale (37) was used to assess anxiety and depressive symptoms. Scores ≥8 on each subscale are indicative of clinically significant anxiety and depressive symptoms (37).

Table 1. Sample Characteristics in the Full Sample and Cortisol and Aβ Groups (total *N* = 416)

	Full Sample	Low Cortisol/ Aβ− (1)	High Cortisol/ Aβ− (2)	Low Cortisol/ Aβ+ (3)	High Cortisol/ Aβ+ (4)	Test of Difference		
		n = 158	*n* = 162	*n* = 50	*n* = 46	χ^2 or *F*	*p*	Pairwise Contrasts
Age, Years, Mean (SD)	69.3 (6.6)	67.9 (6.4)	68.5 (5.5)	73.3 (7.9)	72.8 (6.5)	14.85	<.001	3,4 > 1,2
Sex, *n* (%)						1.85	.60	—
Male	186 (44.7)	72 (45.6)	70 (43.2)	26 (52.0)	18 (39.1)			
Female	230 (55.3)	86 (54.4)	92 (56.8)	24 (48.0)	28 (60.9)			
Education, *n* (%)						4.46	.22	—
<15 Years	263 (63.5)	100 (63.3)	95 (59.4)	33 (66.0)	35 (76.1)			
≥15 Years	151 (36.5)	58 (36.7)	65 (40.6)	17 (34.0)	11 (23.9)			
1+ Vascular Risk Factors, *n* (%)	181 (43.5)	73 (46.2)	66 (40.7)	20 (40.0)	22 (47.8)	2.02	.57	—
Full-Scale IQ, Mean (SD)	108.6 (7.1)	107.9 (7.6)	108.5 (6.5)	110.5 (6.6)	109.4 (7.6)	1.95	.12	—
MAC-Q Score, Mean (SD)	25.4 (4.5)	25.2 (4.3)	25.2 (4.5)	25.5 (5.4)	26.3 (4.8)	0.57	.63	—
HADS Depression Score, Mean (SD)	2.6 (2.3)	2.6 (2.2)	2.6 (2.2)	2.8 (2.9)	2.6 (2.5)	0.08	.97	—
HADS Depression Score ≥8, *n* (%)	19 (4.6)	6 (3.8)	5 (3.1)	4 (8.0)	4 (8.7)	4.18	.24	—
HADS Anxiety Score, Mean (SD)	4.3 (2.9)	4.3 (2.8)	4.3 (2.9)	4.2 (3.0)	4.5 (2.8)	0.14	.93	—
HADS Anxiety Score ≥8, *n* (%)	57 (13.7)	22 (13.9)	23 (14.2)	6 (12.0)	6 (13.0)	0.18	.98	—
APOE ε4 Allele Carrier, *n* (%)	115 (27.6)	38 (24.1)	26 (16.0)	26 (52.0)	25 (54.3)	43.14	<.001	3,4 > 1,2
Positive Amyloid Scan (Aβ+), *n* (%)	96 (23.1)	0 (0)	0 (0)	50 (100)	46 (100)	416.00	<.001	3,4 > 1,2
Plasma Cortisol Level, ng/mL, Mean (SD)	143.9 (62.7)	99.2 (25.4)	191.4 (54.2)	91.0 (31.3)	187.8 (47.4)	172.40	<.001	2,4 > 1,3
Baseline Cognition Scores, Mean (SD)								
Global cognition	0.04 (0.03)	−0.04 (0.05)	0.04 (0.05)	0.06 (0.08)	0.11 (0.08)	1.18	.32	—
Episodic memory	0.08 (0.04)	0.12 (0.06)	0.08 (0.06)	0.04 (0.10)	0.07 (0.10)	0.18	.91	—
Executive function	0.01 (0.05)	−0.16 (0.07)	0.06 (0.07)	−0.01 (0.11)	0.14 (0.12)	2.67	.047	2,4 > 1
Language	0.10 (0.05)	−0.03 (0.07)	0.06 (0.07)	0.13 (0.11)	0.22 (0.12)	1.28	.28	—
Attention	−0.01 (0.04)	−0.11 (0.06)	−0.05 (0.06)	0.10 (0.11)	0.01 (0.11)	0.98	.40	—

Number of vascular risk factors, full-scale IQ, HADS depression and anxiety scores, plasma cortisol levels, and baseline cognitive test scores are adjusted for age and *APOE* genotype. Numbers in parentheses in column headings for the four groups are used to define group numbers used in pairwise contrasts ($p < .05$). Some frequencies do not sum to total number for group due to missing data.

Aβ, amyloid-β; *APOE* ε4, apolipoprotein epsilon 4; HADS, Hospital Anxiety and Depression Scale; MAC-Q, Memory Complaints Questionnaire.

Subjective Memory Complaints

The Memory Complaint Questionnaire (38) was used to assess subjective memory complaints. The Memory Complaint Questionnaire is a six-item scale that assesses the extent to which an individual experiences memory difficulties in everyday situations (e.g., remembering a telephone number) relative to when she or he was in high school. Scores range from 7 to 35, with scores ≥25 indicative of clinically significant subjective memory impairment.

Neuropsychological Assessment

Comprehensive clinician-administered neuropsychological evaluations were conducted at baseline and 18-, 36-, 54-, and 72-month follow-ups. The Wechsler Test of Adult Reading was used to estimate full-scale IQ (39). Composite measures of cognitive function were derived based on theory and clinical consensus (40). An episodic memory composite score was composed of standardized scores for the California Verbal Learning Test, Second Edition delayed recall, Logical Memory delayed recall, and the Rey Complex Figure Test delayed recall. An executive function composite score was composed of scores on the Letter Fluency and Category Fluency Fruit/Furniture Switching. An attention composite score was composed of scores on the Digit Symbol and Digit Span. A language composite score was composed of scores on the Boston Naming Test and Category Fluency Animals/Boys' Names total score. Factor analyses revealed strong loadings (i.e., all factor loadings ≥ 0.40) of each of the component measures on these composite scores. A global cognition score was also computed by averaging scores across these four cognitive domains at each assessment.

Data Analysis

Simple descriptive statistics were computed to summarize sample characteristics, which were compared between the high- and low-cortisol and Aβ groups using analyses of variance for continuous variables and chi-squared analyses for categorical variables. Linear mixed-effects models were conducted using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY), to evaluate the relation between baseline plasma cortisol and Aβ levels, other risk factors, and cognitive test scores over the 72-month study period. Plasma cortisol level (low vs. high), baseline Aβ level (SUVR-based classification of Aβ− or Aβ+), age, sex, *APOE* genotype (ε4 carrier vs. non-ε4 carrier), Hospital Anxiety and Depression Scale anxiety scores, and radiotracer type were entered as fixed effects/covariates; baseline cognitive test scores as a covariate; and composite cognitive test scores as dependent variables in separate analyses. Cohen's *d* and 95% confidence intervals were computed to estimate effect sizes of group differences at the 72-month assessment.

RESULTS

Of the 416 CN older adults who completed the baseline assessment, 402 (96.6%), 389 (93.5%), 379 (91.1%), and 347 (83.4%) completed 18-, 36-, 54-, and 72-month follow-ups, respectively. Table 1 shows characteristics of the full sample and the sample stratified according to cortisol and Aβ status at the baseline assessment. Compared with the low-cortisol/Aβ− and high-cortisol/Aβ− groups, the low-cortisol/Aβ+ and high-cortisol/Aβ+ groups were older and more likely to be *APOE* ε4 allele carriers. No differences between the cortisol/Aβ groups were observed on the Hospital Anxiety and Depression Scale scores. Analyses of baseline cognitive test scores revealed a significant between-group difference in executive function scores, with the high-cortisol/Aβ− and high-cortisol/Aβ+ groups scoring higher than the low-cortisol/Aβ− group. None of the other baseline cognitive test scores differed.

Table 2 shows results of models evaluating the effect of Aβ and plasma cortisol values on changes in global cognition and individual cognitive domains over the 72-month study period. Results of these analyses revealed a significant interaction of Aβ × time on all composite scores (Cohen *d* values comparing cognitive test scores in Aβ+ vs. Aβ− CN older adults at the 72-month assessment = 0.52 for global cognition, 0.65 for episodic memory, 0.51 for executive function, 0.42 for language, and 0.37 for attention). They further revealed a significant interaction of plasma cortisol × Aβ × time on global cognition, episodic memory, and executive function composite scores. Inspection of this interaction revealed that compared with Aβ+ CN older adults with low cortisol levels, those with high cortisol levels had moderately lower episodic memory ($d = 0.50$) and executive function ($d = 0.59$) and a small magnitude reduction in global cognition ($d = 0.32$) scores at the 72-month assessment (Figure 1). Neither the level of depression nor anxiety symptoms moderated cortisol × Aβ × time interactions, all $F < 2.56$, all $p > .05$. Further, incorporation of depressive symptoms and vascular risk factors into the linear mixed-effects models did not change the results.

DISCUSSION

Results of this study supported our hypothesis that Aβ+ would be associated with greater cognitive decline, and that high plasma cortisol levels would moderate cognitive decline related to Aβ+, such that Aβ+ CN older adults with high plasma cortisol levels would have greater rates of decline in cognitive function compared with Aβ+ CN older adults with low plasma cortisol levels. By convention (41), the combined effect of high cortisol level and Aβ+ was moderate in magnitude for episodic memory and executive function and small in magnitude for global cognition. The increased rate of decline in Aβ+ CN older adults with high cortisol levels was independent of the effects of known risk factors for cognitive decline, including age, sex, *APOE* genotype, and anxiety symptoms. Taken together, these findings replicate and extend results from prior studies in animals (13–16) and humans (17–22,26,27,42), which implicate dysregulation of the HPA axis in cognitive dysfunction and suggest that increased plasma cortisol levels may interact with Aβ+ to accelerate cognitive decline in the preclinical stages of AD.

The finding that high cortisol level and Aβ+ interacted to accelerate decline in episodic memory is consistent with the well-known neurotoxic effects of cortisol on the hippocampus (8,25,29,43), which has a key role in facilitation of episodic memory processes. Because HPA axis activity is inhibited

Table 2. Results of Linear Mixed-Effects Models Evaluating Relation Between Plasma Cortisol Levels, Aβ, and Cognitive Change Over a 72-Month Period in Healthy Older Adults

	Global Cognition		Episodic Memory		Executive Function		Attention		Language	
	F	*p*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*
Plasma Cortisol Level	1.77	.18	1.81	.18	0.44	.51	4.31	.038	1.36	.24
Aβ	3.61	.058	0.05	.81	4.92	.027	2.74	.098	0.18	.67
Time	32.93	<.001	5.21	.023	14.05	<.001	13.06	<.001	10.11	.002
Plasma Cortisol Level × Aβ	5.37	.021	1.67	.20	4.80	.029	5.20	.023	1.74	.19
Plasma Cortisol Level × Time	2.37	.12	3.15	.076	1.80	.18	0.13	.71	4.77	.029
Aβ × Time	28.36	<.001	15.11	<.001	8.70	.003	9.34	.002	5.36	.021
Plasma Cortisol Level × Aβ × Time	4.41	.036	4.25	.039	7.21	.007	0.27	.60	2.65	.104

Models are adjusted for age, sex, *APOE* genotype, baseline anxiety symptoms, radiotracer type, and baseline cognitive test scores.
Aβ, amyloid-β.

by hippocampally mediated corticosteroid feedback (44–46), greater age-related hippocampal atrophy could itself result in reduced inhibition of cortisol production, which may in turn lead to further hippocampal degeneration and reduced episodic memory function. In the current study, we also observed that high plasma cortisol levels accelerated Aβ+-related decline in global cognition and executive function. Although previous studies have focused on the effects of HPA axis dysregulation on hippocampal volume and hippocampally mediated aspects of cognition such as memory (18,25–29), corticosteroid receptors are expressed widely throughout the brain (47). This finding, coupled with results of the current study indicating the strongest magnitude interaction of cortisol and Aβ levels in predicting decline in executive function, suggests that increased cortisol levels and Aβ+ may interact to produce more widespread deleterious effects on cognitive function, particularly executive function, in preclinical AD. Clinically, these findings underscore the potential importance of assessing and monitoring cortisol levels in CN older adults. One hypothesis arising from results of the current study is that therapeutic strategies designed to reduce plasma cortisol levels [e.g., 11β-hydroxysteroid dehydrogenase type 1 inhibitors (48); cognitive-behavioral stress management (49,50)] may also be useful in forestalling cognitive decline in Aβ+ older adults.

Several mechanisms may account for the observed association between increased plasma cortisol levels and greater cognitive decline. First, prolonged exposure to elevated glucocorticoid levels has been linked directly to hippocampal neurodegeneration (25,28,29,43), as well as cerebral Aβ formation and induction of tau hyperphosphorylation in the hippocampus and prefrontal cortex in animal models (13,14,51,52). Thus, long-term hyperactivation of the HPA axis may contribute to the hallmark neuropathological changes associated with AD, which in turn negatively affect cognitive function over time. Longitudinal studies with serial measurements of cortisol and Aβ will be useful in better understanding the interrelation between cortisol and Aβ levels, as well as other markers of AD-related neuropathology (e.g., tau) and how they relate to cognitive changes in very early to preclinical stages of AD.

High cortisol levels were not associated with the severity of symptoms or positive screens for anxiety and depression in either the Aβ+ or Aβ− groups when considered cross-sectionally at the baseline assessment or prospectively as potential moderators of cortisol and Aβ-related cognitive changes. The effect of cortisol and Aβ levels on cognitive decline observed in the current study was thus independent of and not moderated by these symptoms. The absence of any relationship between anxiety and depression and cortisol levels in this sample aligns with the broader literature showing that relationships between cortisol levels and symptoms of anxiety and depression are inconsistent (24,53). The equivocal nature of this relationship in different studies has been attributed to the small sample sizes studied, differences in cortisol assessment methodologies, and lack of consideration of the phenotypic heterogeneity of anxiety and depression symptoms (24,53–55). Given that CN older adults with anxiety

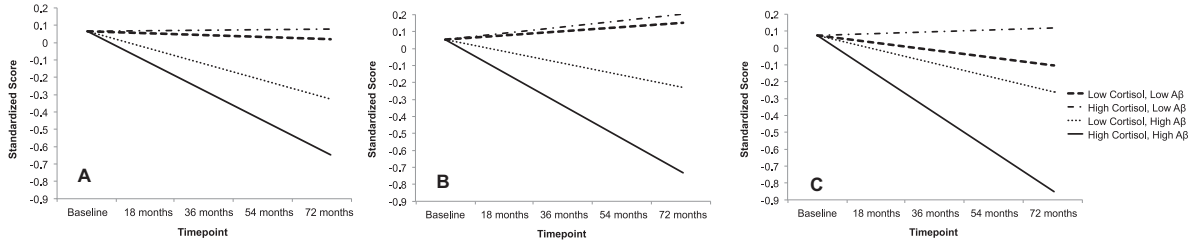

Figure 1. Slopes of **(A)** global cognition, **(B)** episodic memory, and **(C)** executive function scores in plasma cortisol and amyloid-β (Aβ) groups over the 72-month study period. Groups were operationalized as follows: baseline plasma cortisol level (low vs. high based on median split), baseline Aβ level (standardized uptake value ratio–based classification of Aβ− or high Aβ level [Aβ+]). Age, sex, *APOE* genotype (ε4 carrier vs. non-ε4 carrier), Hospital Anxiety and Depression Scale anxiety scores, and radiotracer type were entered as fixed effects/covariates; baseline cognitive test scores as a covariate, and global cognition scores as the dependent variable.

and mood disorders were excluded from the AIBL study, additional research is needed to assess whether these disorders, or dimensions of them [e.g., anhedonic depression (54)], may modify risk for cognitive decline in Aβ+ CN older adults with high cortisol levels.

This study has some methodological limitations. First, the AIBL cohort of CN older adults has relatively high levels of education and premorbid intelligence and was enriched to include approximately 30% of older adults who were *APOE* ε4 allele carriers. Thus, it is unclear whether results of the current study may generalize to general population–based samples of older adults in which the prevalence of ε4 allele carriers is 14% (56). Second, given the skewed and non-normal distribution of plasma cortisol levels, a median split procedure was used to dichotomize the sample into older adults with low and high plasma cortisol levels. Further research will be useful in determining specific threshold ranges of plasma cortisol levels that are directly and interactively with Aβ+ associated with cognitive changes in preclinical AD, and how fluctuations in cortisol levels throughout the course of the day, as well as other factors implicated in the stress response system, such as corticotropin-releasing factor, relate to these outcomes. Of note, only 13 CN older adults in the AIBL sample had plasma cortisol levels higher than the normal range of 70 to 280 ng/mL (57), although sensitivity analyses revealed that results did not change when data for these individuals were excluded. Results of the current study therefore suggest that increased cortisol levels within the normal range can directly and interactively with Aβ+ predict cognitive decline in preclinical AD. Third, although plasma cortisol levels evidenced a moderately strong interactive effect with Aβ+ in predicting cognitive decline, p values for these interactions were only borderline significant, albeit $p < .05$, and were not adjusted for multiple comparisons. Further, other blood-based biomarkers associated with HPA axis dysregulation [e.g., inflammatory cytokines (58)], which were not assessed in the current study, may additionally contribute to risk prediction models of cognitive decline in preclinical AD. Further, emerging findings from the Alzheimer Disease Neuroimaging Initiative suggests that a combination of plasma and cerebrospinal fluid markers other than Aβ and tau, including cortisol, apolipoprotein A-II, and fibroblast growth factor 4, reliably predict progression from MCI to AD (59). Additional research is needed to evaluate how levels of cortisol and other plasma and cerebrospinal fluid markers, alone and interactively with Aβ+, may predict cognitive decline in preclinical AD.

Notwithstanding these limitations, results of this study indicate that increased plasma cortisol levels in combination with Aβ+ are associated with accelerated decline in global cognition, episodic memory, and executive function in preclinical AD. These findings suggest that the combination of cortisol and Aβ assessments may be useful biomarkers in predicting cognitive decline in preclinical AD. Further research is needed to attempt to replicate these results in general population–based samples and evaluate longitudinal interrelationships among cortisol and Aβ levels and cognitive changes; characterize neurobiological mechanisms underlying HPA axis dysregulation, Aβ, and other AD-related neuropathological markers; and evaluate the efficacy of HPA axis–targeted therapies in mitigating cognitive decline in the early to preclinical phase of AD.

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RHP had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

The authors report no biomedical financial interests or potential conflicts of interest.

A list of the AIBL Research Team is available at https://aibl.csiro.au/about/aibl-research-team/.

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