Plasma cortisol, amyloid-β, and cognitive decline in preclinical Alzheimer's disease: A 6-year prospective cohort study

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Introduction

Hypothalamic-pituitary-adrenal (HPA) 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 disease (AD). However, little is known about the role of HPA axis dysregulation in predicting cognitive decline or 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. We aimed to evaluate the independent and interactive effect of plasma cortisol levels and Aβ status in predicting cognitive changes in the preclinical phase of AD.

Results

High plasma cortisol levels at baseline were associated with 2.2 times the risk of Aβ+. Furthermore, high levels of cortisol were associated with greater decline in global cognition generally and were also found to increase the effect of Aβ+ on decline in global cognition, episodic memory, and attention. Specifically, compared to Aβ+ older adults with low cortisol, Aβ+ older adults with high cortisol had significantly faster decline on these measures, with Cohen's d values of 0.69 for episodic memory, 0.42 for global cognition, and 0.31 for attention. These effects were independent of age, education, premorbid intelligence, *APOE* and *BDNF* genotype, subjective memory complaints, vascular risk factors, and depression and anxiety symptoms.

Table 1: Demographic & clinical characteristics

	Aβ- low cortisol	Aβ- high cortisol	Aβ+ low cortisol	Aβ+ high cortisol	*p*
N	158	162	50	46	
Age	69.3 (6.6)	67.9 (6.4)	68.5 (5.5)	73.3 (7.9)	< .001
N (%) Female	86 (54.4%)	92 (56.8%)	24 (48.0%)	28 (60.9%)	.60
N (%) *APOE* Ɛ4	38 (24.1%)	26 (16.0%)	26 (52.0%)	25 (54.3%)	< .001
Premorbid IQ	107.9 (7.6)	108.5 (6.5)	110.5 (6.6)	109.4 (7.6)	.12
MAC-Q	25.2 (4.3)	25.2 (4.5)	25.5 (5.4)	26.3 (4.8)	.63
HADS depression	2.6 (2.2)	2.6 (2.2)	2.8 (2.9)	2.6 (2.5)	.97
HADS anxiety	4.3 (2.8)	4.3 (2.9)	4.2 (3.0)	4.5 (2.8)	.93
Plasma cortisol	99.2 (25.4)	191.4 (54.2)	91.0 (31.3)	187.8 (47.4)	< .001

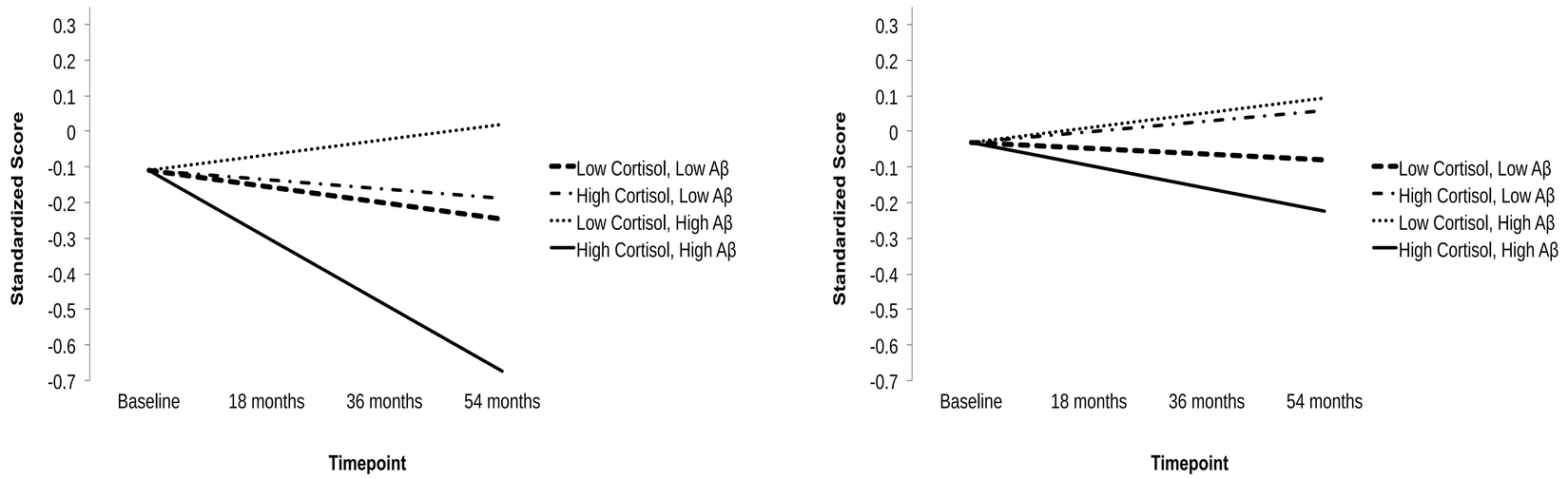
Methods

Cognitively normal older adults (n=416) enrolled in the AIBL study underwent Aβ neuroimaging at a single timepoint. Fasted blood samples were collected at baseline and analysed using a commercial cortisol ELISA, performed according to manufacturer instructions. Because the distribution of raw cortisol values was highly skewed and non-normal, and could not be corrected to normal using $\log_{10}$ transformation, they were dichotomized using a median split procedure.

Five cognitive composites were derived: Episodic Memory, Executive Function, Attention, Language and Global Cognition

Latent growth curve models were conducted to evaluate the relation between baseline plasma cortisol and Aβ levels, other risk factors, and cognitive composite scores over the 72-month study period.

Figure 1: Group mean differences at 18-months, after accounting for baseline, for each outcome measure



Summary

In cognitively healthy older adults, high plasma cortisol levels are associated with greater decline in global cognition, and accelerate the effect of Aβ+ on decline in global cognition, episodic memory, and attention over a 54-month period. These results suggest that therapies targeted toward lowering plasma cortisol and Aβ levels may help mitigate cognitive decline in the preclinical phase of AD.

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