

# Cortisol, Amyloid- $\beta$ , and Reserve Predicts Alzheimer's Disease Progression for Cognitively Normal Older Adults

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**Abstract.** Elevated cortisol as a measure of hypothalamic-pituitary-adrenal-axis hyperactivity has emerged as a predictor of clinical progression of Alzheimer's disease (AD), in conjunction with amyloid- $\beta$  ( $A\beta$ ) abnormalities. Yet factors exist which have the propensity to delay AD symptomatic expression in the face of an AD-type biomarker-based pathological profile. This study sought to determine whether abnormal cerebrospinal fluid (CSF)  $A\beta$  and elevated cortisol levels are associated with clinical transition to mild cognitive impairment (MCI) and AD in cognitively normal (CN) individuals, and if this association is modified by reserve proxies. Data from 91 CN individuals participating in the Alzheimer's Disease Neuroimaging Initiative (ADNI) with available morning CSF cortisol and  $A\beta_{42}$  were evaluated. Reserve was modelled as a latent composite score of standardized intracranial volume and lifetime experience proxies. Cox regressions were used to test associations between baseline CSF cortisol/ $A\beta_{42}$ , reserve score and AD progression, adjusting for age, sex, apolipoprotein E genotype, and depressive symptoms. Individuals with elevated cortisol + abnormal  $A\beta_{42}$  levels at baseline showed highest risk of clinical progression. After a median of 84 months follow-up, significant cortisol/ $A\beta$  reserve interaction for clinical

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30 progression was noted (adjusted HR = 0.15,  $p < 0.001$ ), suggesting a moderating effect of reserve on the association between  
31 cortisol/A $\beta$ + and clinical progression. Our findings indicate that cortisol hypersecretion accelerates clinical progression in  
32 CN individuals presenting with pathological A $\beta$ <sub>42</sub>. High reserve reduces the associated AD progression risk in these high-risk  
33 individuals.

Keywords: Alzheimer's disease, amyloid, cognitive reserve, cortisol

## 34 INTRODUCTION

35 Late onset Alzheimer's disease (AD), by far the  
36 most common form of dementia, is thought to  
37 be of complex and multifactorial etiology, result-  
38 ing from complex interactions of a plethora of  
39 genetic and environmental factors across the lifes-  
40 pan. Cerebral accumulation of amyloid- $\beta$  (A $\beta$ ) and  
41 tau proteins are thought to be key histopathologi-  
42 cal hallmarks and their intracerebral processing may  
43 be an important driver for disease etiology [1–3].  
44 On the other hand, evidence from studies of ani-  
45 mal models and human studies indicate that aberrant  
46 activity of the hypothalamic-pituitary-adrenal (HPA)  
47 system contributes to AD etiopathogenesis, as well  
48 as in the development of cognitive decline and asso-  
49 ciated symptomatology [4, 5]. Indeed hypersecretion  
50 and aberrant receptor-mediated signaling actions of  
51 glucocorticoid (GC), the HPA axis's end-effector  
52 molecule (released as cortisol in man), have been  
53 reported to impede normal A $\beta$  and tau processing  
54 [6–8], promote neurodegeneration [9] and synaptic  
55 dysfunction [10]. Furthermore, they have been shown  
56 to potentially facilitate AD-related cognitive deficits  
57 in animal disease models [4, 11] and human patients  
58 [12–14].

59 The detrimental consequences of a hyperactive  
60 HPA axis have been reported at the prodromal and  
61 clinical stages of AD, with both central [15–17] and  
62 peripheral [18, 19] elevations of cortisol shown to  
63 accelerate disease onset [6, 7, 20] and clinical pro-  
64 gression [16, 18]. Likewise, a combinatory biomarker  
65 exploration of 208 analytes revealed cortisol to be one  
66 of five biomarkers that could reliably predict clinical  
67 progression within a period of 3 years [21]. Experien-  
68 tial data in cognitively normal (CN) older individuals,  
69 though limited, posits abnormal GC secretion as a  
70 predictive marker for rapid cognitive decline in indi-  
71 viduals with excess cerebral A $\beta$  [22]. Yet to date, no  
evidence on clinical translatability of this finding in  
terms of AD clinical progression is available.

Research on modifiable factors affecting onset and  
progression of cognitive decline and dementia has

72 received growing attention. A key finding is that high  
73 educational [23–25] and occupational attainment [23,  
74 25], premorbid intelligence [26, 27], as well as cer-  
75 tain anatomical factors including larger pre-morbid  
76 brain size [28–30] are associated with a later onset  
77 and decreased risk of dementia [31, 32] and may even  
78 counteract the detrimental effects of A $\beta$  accumula-  
79 tion on cognitive performance [33].

80 Using data from the Alzheimer's Disease Neu-  
81 roimaging Initiative (ADNI) CN participants [34, 35],  
82 we assess: 1) the impact of cerebrospinal fluid (CSF)  
83 cortisol and A $\beta$  levels on risk of clinical progres-  
84 sion; and 2) the moderating effect of a multi-indicator  
85 reserve composite comprising of maximal adult brain  
86 size, education, occupational complexity and premor-  
87 bid intelligence.

## 88 MATERIALS AND METHODS

### 89 *Participants and data*

90 The data used in this study were obtained from  
91 all stages of ADNI from <http://www.loni.ucla.edu/ADNI> on 31 October 2016. The full list  
92 of inclusion/exclusion criteria can be accessed  
93 through the online ADNI protocol (pages 20–29)  
94 at <http://www.adni-info.org/Scientists/ADNIScientistsHome.aspx>. Written informed consent was  
95 obtained from all participants. Study participants  
96 were between 55 and 90 years old, had a modified  
97 Hachinski score of  $\leq 4$ , and at least 6 years of  
98 education. The dataset included a subset of 91 CN  
99 participants that had measurements of CSF cortisol  
100 and A $\beta$ <sub>42</sub> at baseline (Supplementary Figure 1).  
101 Measurements of Geriatric Depression Scale (GDS),  
102 apolipoprotein E (*APOE*) genotype, education, Intel-  
103 ligence Quotient-IQ (measured by the American  
104 National Adult Reading Test- AMNART score),  
105 intracranial volume (ICV) as a proxy for maximal  
106 adult brain size, and occupation recorded at baseline  
107 were also used for study analyses [36].  
108

### Diagnostic groups

CN participants had Mini-Mental State Examination (MMSE) scores between 24 and 30, a global Clinical Dementia Rating (CDR) score of 0, no evidence of depression and no subjective memory complaints. After the baseline visit, subsequent visits were conducted at 6- or 12-month intervals until a maximum follow-up period of 120 months.

For follow-up diagnostic outcomes, individuals with AD dementia were required to have MMSE scores between 20 and 26 and a CDR score of 0.5 to 1 at baseline [37]. Qualifying individuals with mild cognitive impairment (MCI) had memory concerns but no significant functional impairment. These individuals scored between 24 and 30 on the MMSE, had a global CDR score of 0.5, with a CDR memory score of 0.5 or greater, and had objective memory impairment on the Wechsler Memory Scale-Logical Memory II test [37].

### Biomarker classification

$A\beta_{42}$  and cortisol levels were dichotomized using the previously defined cut offs for  $A\beta_{42}$  (192 pg/ml) [38] and using the mean cortisol level of 15.2 pg/ml [15, 16]. Below cut-off  $A\beta_{42}$  levels were considered abnormal and 'above-mean' cortisol levels are considered high. Thus, four biomarker combination groups were investigated: 1) low cortisol/normal  $A\beta_{42}$ , termed GC/ $A\beta$ -; 2) high cortisol/normal  $A\beta_{42}$ , termed GC+/ $A\beta$ -; 3) low cortisol/abnormal  $A\beta_{42}$ , termed GC-/ $A\beta$ +; and 4) high cortisol/abnormal  $A\beta_{42}$ , termed GC+/ $A\beta$ +

### Generation of reserve composite score

A reserve composite score was generated using exploratory factor analysis (EFA). Education, full-scaled IQ, occupation, and ICV were computed as continuous variables in the factor analysis. All components were standardized to have a mean of 0 and standard deviation of 1. The reserve composite score for each individual was calculated by summing the factor loading of each component multiplied by the standardized component [39]. For exploratory analyses, categorical values of the reserve components were used. Years of formal education completed was dichotomized into low ( $\leq 15$  years) versus high ( $> 15$  years) using a median split of the CN study sample.

AMNART was used to estimate premorbid IQ [40, 41] and scores were stratified as low ( $\leq 42$  points) and

high ( $> 42$  points) via median split of the CN study sample.

ICV in ADNI was estimated by the automated MRI method, which combined three tissue classes of segmentation: gray matter, white matter and CSF spaces. ICV ( $\text{cm}^3$ ) data was dichotomized via median split procedure into low ( $\leq 1505.01 \text{ cm}^3$ ) and high ( $> 1505.01 \text{ cm}^3$ ).

Occupation was graded on a scale of 0-3 defined from The National Statistics Socio-economic Classification [42]. Level 0 represented unemployed participants such as housewives; Level 1 represented partly-skilled or unskilled occupations; Level 2 represented skilled occupations; and Level 3 featured professional and managerial occupations.

Inverse probability imputation method was used to deal with the 8 missing values in IQ score [43].

### Statistical analysis

Comparisons of categorical variables including gender, *APOE-ε4* (+ve/-ve) carrier status, and occupation between the four biomarker combination groups were performed using a Chi-squared test. Continuous variables including age, reserve composite, ICV, IQ, education, and GDS were compared using analysis of variance (ANOVA) with Tukey *post-hoc* test, for the four biomarker combination groups.

Time to progression to a more severe diagnostic state (i.e., MCI or AD), based on the most recent diagnostic assessment was inputted as the study outcome within the survival analysis. For individuals that did not progress, final visit time was used as the censoring time.

Kaplan-Meier (KM) curves were employed to compare the risk of progression across the four biomarker groups. Cox proportional hazards models were fitted to explore associations between reserve, cortisol and  $A\beta_{42}$  with risk of progression in separate models. Model 1 was an unadjusted model exploring interaction between  $A\beta_{42}$  and cortisol levels. Model 2 examined the three-way interaction between reserve, cortisol, and  $A\beta_{42}$  by adding the production terms between these variables. Model 3 was further adjusted for baseline measures of age, gender, *APOE ε4*, and GDS. Moreover, interaction between reserve score and the four biomarker combination groups was also tested using the likelihood ratio test. Marginal plots were then used to show the relative risk of progression among these four groups per the reserve score.

In addition, we conducted supplemental analyses to explore the reserve, cortisol, and  $A\beta_{42}$  relationship upon adjusting for established CSF biomarkers known to be associated with high risk for clinical progression, namely total tau [38], fibroblast growth factor-4 (FGF-4), heart-type fatty acid binding protein (hFABP), calcitonin, and tumor-necrosis-factor-related apoptosis-inducing ligand receptor 3 (TRAIL-R3) [21]. We further used separate models to explore associations between the independent reserve proxies and progression to a more severe disease state, as well as their interactions with CSF  $A\beta_{42}$  and cortisol levels. We also tested the possible moderating effect of age, gender, or *APOE*  $\epsilon 4$  on the combination effect of cortisol and  $A\beta_{42}$ .

The statistical analyses were performed using Stata (version 14, Stata). All statistical tests were two-sided, and the statistical significance was defined as  $p < 0.05$ .

## RESULTS

### Population characteristics in relation to CSF cortisol and $A\beta_{42}$

Table 1 summarizes the characteristics of study participants and biomarker-group strata. Differences in sample size for each biomarker group were noted, with the highest number of participants seen in the GC-/ $A\beta$ -, and the lowest being in the GC-/ $A\beta$ +

There were also differences in the mean age between the groups ( $p < 0.05$ ), with significant differences occurring between the GC-/ $A\beta$ -,

GC-/ $A\beta$ +, and the GC+/ $A\beta$ + groups (Tukey HSD test,  $p < 0.05$ ). The proportion of *APOE*- $\epsilon 4$  carriers was also significantly different between groups ( $p < 0.005$ ) with the highest proportion falling into the GC+/ $A\beta$ + group.

A composite score for the four reserve components was derived using factor analysis, which yielded one common factor with eigenvalue of 1.046. All components loaded well on this factor, and loadings were used to calculate the composite score with the formula:

Composite score =  $0.6625 \times$  education years +  $0.4315 \times$  IQ +  $0.4772 \times$  occupation level +  $0.4395 \times$  ICV (all components were standardized).

No reserve variables or other measures were significantly different between the biomarker groups ( $p > 0.05$ ).

### CSF cortisol evaluation across ADNI diagnostic groups

Since this study is the first to determine an association between a hyperglucocorticoid state/ $A\beta$  interaction and disease progression from the pre-clinical stage, no threshold range of pathological cortisol was available to provide a reference point for cohort stratification. To this end, we sought to compare central cortisol levels for different baseline AD diagnostic groups, given the availability of data from prodromal and clinical AD patients within the ADNI study. The mean CSF cortisol levels for MCI ( $n = 148$ ) and AD ( $n = 69$ ) patients were similar to that of CN ( $n = 91$ ) individuals, with nil significant

Table 1  
Baseline characteristics for the full sample across cortisol and  $A\beta$  groups

Characteristics	Full sample	GC-/ $A\beta$ -	GC+/ $A\beta$ -	GC-/ $A\beta$ +	GC+/ $A\beta$ +	Test of difference ( $p$ )
Sample size	91	31	27	16	17	
Age (y), Mean (SD)	75.65 (5.46)	74.10 (5.73)	76.19 (4.51)	73.85 (5.05)	79.32 (5.09)	0.005*
Male, $n$ (%)	46 (50.55%)	14 (45.16%)	14 (51.85%)	7 (43.75%)	11 (64.71%)	0.565
<i>APOE</i> - $\epsilon 4$ Carrier, $n$ (%)	22 (24.18%)	3 (10%)	3 (11.11%)	7 (43.75%)	9 (52.94%)	0.001*
Education year, Mean (SD)	15.60 (2.95)	15.51 (2.46)	15.70 (3.06)	14.88 (4.03)	16.29 (2.46)	0.587
Full-Scale IQ, Mean (SD)	39.18 (8.60)	35.90 (9.93)	41 (7.81)	40 (7.39)	41.85 (6.47)	0.075
Occupation, $n$ (%)						0.643
0-unemployed	8 (8.79%)	2 (6.45%)	3 (11.11%)	3 (18.75%)	0	
1-unskilled/partly-skilled	9 (9.89%)	2 (6.45%)	4 (14.81%)	2 (12.5%)	1 (5.88%)	
2-skilled	26 (28.57%)	11 (35.48%)	6 (22.22%)	3 (18.75%)	6 (35.29%)	
3-professional/managerial	48 (52.75%)	16 (51.61%)	14 (51.85%)	8 (50%)	10 (58.82%)	
ICV, Mean (SD)	1516.17 (159.11)	1501.55 (165.78)	1516.37 (162.06)	1535.85 (170.18)	1595.24 (177.39)	0.072
GDS total score, Mean (SD)	0.85 (1.05)	0.61 (0.88)	1.07 (1.33)	1.25 (0.86)	0.53 (0.87)	0.080
Reserve score, Mean (SD)	0.02 (1.40)	-0.22 (1.35)	0.06 (1.42)	-0.13 (1.67)	0.64 (1.01)	0.304

SD, standard deviation; IQ, intelligence quotient; ICV, intracranial volume; GDS, Geriatric Depression Scale; *APOE*, apolipoprotein E; GC-/ $A\beta$ -, low cortisol/normal  $A\beta_{42}$ ; GC+/ $A\beta$ -, high cortisol/normal  $A\beta_{42}$ ; GC-/ $A\beta$ +, low cortisol/abnormal  $A\beta_{42}$ ; GC+/ $A\beta$ +, high cortisol/abnormal  $A\beta_{42}$ . \* $p < 0.05$ .

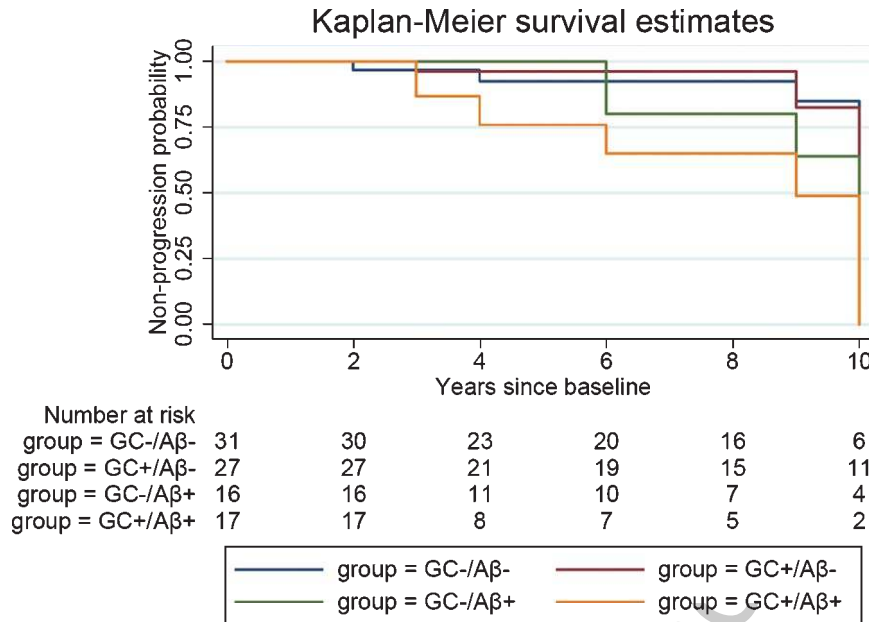


Fig. 1. Kaplan-Meier (KM) survival estimates for the study biomarker groups. Probability of non-progression from cognitive normal stage to clinical AD-dementia, for each glucocorticoid and amyloid biomarker combination group is shown. Estimated number of remaining individuals at risk for disease progression at each time point are also represented. Individuals in the Cortisol High/Aβ<sub>42</sub> Abnormal (GC+/Aβ+) group progressed fastest from the pre-clinical to clinical disease stage, with only 12% non-demented (2 out of 17 at baseline) at time of study censor period. GC-, low cortisol level; GC+, high cortisol level; Aβ-, normal Aβ<sub>42</sub> level; Aβ+, abnormal Aβ<sub>42</sub> level.

266 between-group differences observed (Supplementary  
267 Figure 2).

268 *Reserve, cortisol, Aβ<sub>42</sub>, and stable versus*  
269 *progressive disease stage*

270 After a median follow-up time of 84 months, 19  
271 of the 91 subjects progressed from CN to MCI, and  
272 another 10 subjects progressed to AD. The risk of  
273 progression during follow-up period among the four  
274 biomarker groups is shown in Figure 1. Individuals  
275 in the GC+/Aβ+ group were at higher risk of clinical  
276 progression compared to the GC-/Aβ- group  
277 (HR = 3.67,  $p = 0.017$  in an unadjusted Cox model).

278 The results from the Cox models evaluating the  
279 effect of CSF levels of Aβ<sub>42</sub> and cortisol on time to  
280 progression, and the moderating effect of the reserve  
281 composite on the Aβ<sub>42</sub>/cortisol association are shown  
282 in Table 2. The interaction for cortisol and Aβ<sub>42</sub> on  
283 risk of progression was not statistically significant in  
284 Model 1 and Model 2. However, the three-way inter-  
285 action in Model 3 showed a significant protective  
286 effect of high reserve on those individuals that had  
287 abnormal levels of Aβ<sub>42</sub> and cortisol (HR = 0.153,  
288  $p < 0.001$ ), after adjusting for age, gender, APOE ε4  
289 status, and GDS (Table 2 and Fig. 2). Participants in

290 the GC+/Aβ+ group with high reserve scores had a  
291 relatively lower risk for clinical progression (Supple-  
292 mentary Table 1). Notably, the interaction between  
293 reserve, cortisol, and Aβ<sub>42</sub> remained significant after  
294 controlling for total-tau abnormalities and other CSF  
295 risk biomarkers within an exploratory model (Sup-  
296 plementary Table 2).

297 A significant role for GDS and APOE ε4 carriage  
298 in increasing the risk of progression for the entire  
299 population was noted, with respective HR of 1.78  
300 ( $p < 0.001$ ) for the former, and 4.30 ( $p < 0.001$ ) for  
301 the latter in Model 3 (Table 2).

302 To further explore the relationship between reserve  
303 and clinical progression, we examined the effect of  
304 the independent reserve variables in four separate  
305 models for ICV, IQ, occupation and education; and  
306 the interaction of each of these variables with CSF  
307 levels of Aβ<sub>42</sub> and cortisol. Differential effects of  
308 the distinct reserve variables were noted (Supple-  
309 mentary Table 3). In the IQ interaction model, a  
310 significant decrease in risk was observed in those  
311 individuals that have high levels of pre-morbid IQ  
312 in the GC+/Aβ+ group (HR: 0.065,  $p = 0.026$ ). Sim-  
313 ilarly, in the ICV and occupation interaction models,  
314 significant decreases in risk were observed for indi-  
315 viduals with high ICV (HR: 0.010,  $p = 0.012$ ), and

Table 2  
Cox regression of interactions between cortisol, A $\beta$ <sub>42</sub>, and reserve score with risk of clinical progression

Indicators	Model 1		Model 2		Model 3	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
High Cortisol	1.42 (0.56–3.60)	0.464	1.30 (0.51–3.31)	0.587	0.68 (0.27–1.74)	0.421
Abnormal A $\beta$	2.33 (0.93–5.82)	0.070	2.24 (0.85–5.92)	0.103	0.76 (0.29–1.98)	0.580
High Cortisol*Abnormal A $\beta$	1.11 (0.33–3.71)	0.862	2.88 (0.80–10.40)	0.107	9.25 (1.97–43.43)	0.005*
Reserve score			1.14 (0.73–1.80)	0.566	1.11 (0.66–1.87)	0.690
High Cortisol*Reserve score			0.97 (0.56–1.68)	0.905	1.10 (0.59–2.04)	0.766
Abnormal A $\beta$ *Reserve score			1.34 (0.71–2.53)	0.003*	2.50 (1.38–4.54)	0.003*
High cortisol*Abnormal A $\beta$ *Reserve score			0.34 (0.14–0.82)	0.017*	0.15 (0.06–0.43)	<0.001*
Female					0.90 (0.35–2.37)	0.838
Age					1.01 (0.91–1.12)	0.856
APOE4 Carrier					4.30 (2.06–8.96)	<0.001*
GDS total score					1.78 (1.32–2.39)	<0.001*

HR, hazard ratio; CI, confidence interval; GDS, Geriatric Depression Scale. \**p* < 0.05.

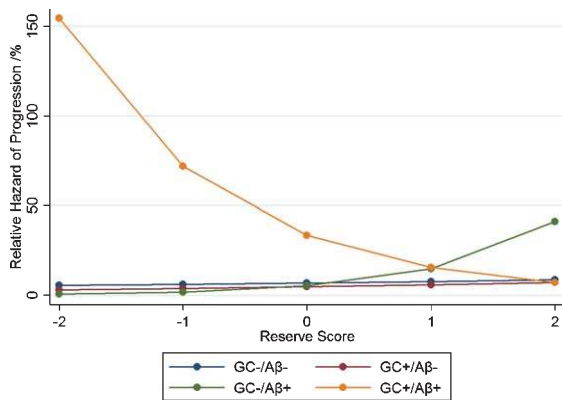


Fig. 2. Marginal plot showing relative hazard of AD clinical progression for biomarker groups in relation to reserve score. Levels of reserve are represented in relation to relative risk of AD clinical progression for each glucocorticoid and amyloid biomarker combination group. Benefit of increasing reserve level in terms of reduction in disease progression risk is most evident for the Cortisol High/A $\beta$ <sub>42</sub> Abnormal (GC+/A $\beta$ +) group. GC-, low cortisol level; GC+, high cortisol level; A $\beta$ -, normal A $\beta$ <sub>42</sub> level; A $\beta$ +, abnormal A $\beta$ <sub>42</sub> level. Model adjusted for age, gender, APOE  $\epsilon$ 4 status, and GDS score. The reference group was Cortisol Low/A $\beta$ <sub>42</sub> Normal group (GC-/A $\beta$ -) at the reserve score of 0.

those who had a professional level occupation (HR: 0.015, *p* = 0.007). No interaction between education level and cortisol/A $\beta$ <sub>42</sub> status was detected (HR = 0.16, *p* > 0.05). In addition, we found no significant interactions between age, gender, or APOE  $\epsilon$ 4 and cortisol/A $\beta$ <sub>42</sub> status (*p* for interaction > 0.05).

## DISCUSSION

Elevated levels of central cortisol and abnormal A $\beta$  have been linked to the symptomatic expression of AD [15, 16, 44–46]; yet it is not known whether this

originates from an earlier time-point and if reserve factors help to offset disease progression trajectory associated to HPA axis hyperactivity and A $\beta$  abnormalities, from pre-clinical disease stages. Addressing the latter was a primary objective of our study, and we sought to investigate whether reserve moderates the adverse influence of CSF cortisol elevations and A $\beta$  abnormalities on AD clinical progression from the preclinical stage.

Using data from the ADNI, we show that risk of clinical progression was highest in CN individuals exhibiting both abnormal A $\beta$  and HPA axis hyperactivity. To our knowledge, this is the first report on the impact of combined central A $\beta$  abnormalities/higher cortisol levels on AD clinical progression from the preclinical stage, and suggests that cortisol may act in concert with A $\beta$  to progress symptom onset. Our results are in line with a recent report from the Australian Imaging Biomarkers and Lifestyle Study of Ageing (AIBL) [22], showing rapid cognitive decline from baseline for CN individuals with high cerebral A $\beta$  load presenting with elevated plasma cortisol levels [22]; however, that study did not address progression to disease states and the CSF cortisol levels were not considered.

Cortisol has been shown to be upregulated in prodromal and clinical AD [16, 18], and differences between AD patients and controls have been reported particularly at the morning time-point [47]. The finding of comparable hormone levels for baseline CN individuals and MCI/AD patients lends credence to the possibility that the elevated cortisol levels seen in CN individuals may have been brought about by pathogenic mechanisms occurring prior to symptom onset.

HPA axis activity is enhanced by time-of-day, stress, anxiety, and depression [48–52]. Individuals

364 included in this study had no reported depression  
365 and were relatively healthy, with no chronic diseases  
366 that may have increased central glucocorticoid levels.  
367 Additionally, all samples were taken in the morning,  
368 thereby reducing circadian bias.

369 Other known predictors of clinical AD progres-  
370 sion, including *APOE*  $\epsilon 4$  status [17] and subclinical  
371 depression [53], were assessed as independent pre-  
372 dictors in our study. Nevertheless, increased risk of  
373 progression was evident in the GC+/A $\beta$ + group even  
374 after controlling for these risk factors.

375 This study is strengthened by the use of cen-  
376 tral glucocorticoid measures which provides a useful  
377 indicator of brain exposure to hormone levels, par-  
378 ticularly for regions such as the hippocampus and  
379 frontal cortex that are front-line targets for mani-  
380 festation of AD pathology and highly responsive to  
381 glucocorticoids given enriched localization of hor-  
382 mone receptors [54, 55]. Indeed, a Phase II trial  
383 into the modulation of central glucocorticoid lev-  
384 els via inhibition of the enzyme 11 $\beta$ -Hydroxysteroid  
385 dehydrogenase type 1, also known as cortisone  
386 reductase (which acts within the CNS to convert  
387 cortisone to the biologically active cortisol), is cur-  
388 rently underway, and aimed at exploring a possible  
389 ‘cognition-protective’ effect of GC hormone reduc-  
390 tion in an AD-pathology-sensitive area [56].

391 Our results provide further support to the hypoth-  
392 esis of a moderating effect of high levels of reserve  
393 on the observed risk associated with the GC+/A $\beta$ +  
394 profile. Determination of individual variable contri-  
395 bution to risk reduction observed with the composite  
396 score showed that the effects in this sample were  
397 primarily driven by IQ, premorbid brain size, and  
398 occupation. The lack of an education effect may be  
399 explained by the bias toward higher educated partic-  
400 ipants in the ADNI sample.

401 The fact that the reserve composite moderates  
402 the A $\beta$ /cortisol-related risk for clinical progression  
403 lends credence to the importance of accounting for  
404 reserve factors in clinical studies. For example, the  
405 Finnish Geriatric Intervention Study to Prevent Cog-  
406 nitive Impairment and Disability (FINGER) provides  
407 evidence for the benefit of promoting reserve via  
408 interventions with a social element such as physical  
409 activity and cognitive training [57]. Such activities  
410 are known to affect HPA axis by altering stress  
411 hormone levels [58, 59]. Further studies assess-  
412 ing psychological/ lifestyle strategies to normalize  
413 GC levels may prove beneficial in delaying dis-  
414 ease onset and progression in individuals with A $\beta$   
415 pathology.

Our study has several limitations. All CSF 416  
samples in ADNI were collected in the morning 417  
before breakfast to avoid circadian bias ([http://adni.](http://adni.loni.usc.edu/methods/documents/) 418  
[loni.usc.edu/methods/documents/](http://adni.loni.usc.edu/methods/documents/)). However, no 419  
exact time of collection was provided, thus limiting 420  
our ability to further control for the cortisol variation 421  
related to ultradian rhythmicity [21]. 422

Sample size in this study was limited as only indi- 423  
viduals with available CSF cortisol and A $\beta$  data were 424  
included. Since some individuals had missing data 425  
for IQ score, imputation methods were employed 426  
to account for missing data which allowed robust 427  
statistical explorations utilizing the entire data set 428  
available. 429

Another known limitation in studies on HPA-axis 430  
hyperactivity and association with clinical indices 431  
of AD includes an absence of ample HPA-axis acti- 432  
vators including pro/anti-inflammatory cytokines, as 433  
well as other risk biomarkers that are associated 434  
with clinical progression within analyses. Recent 435  
evidence from ADNI have provided a combina- 436  
tory biomarker signature made up of CSF and 437  
plasma markers for the prediction of clinical pro- 438  
gression, from the prodromal stage [21]. The authors 439  
found that plasma apolipoprotein A-II and cortisol 440  
levels as well as FGF-4, hFABP, calcitonin, and 441  
TRAIL-R3 in CSF allowed for reliable prediction 442  
of disease status within a 3-year period [21]. In 443  
light of this evidence, and given the availability 444  
of the CSF components of the biomarker compos- 445  
ite within the ADNI dataset, we introduced these 446  
CSF biomarkers as covariates within an exploratory 447  
model; also adjusting for total tau given the estab- 448  
lished clinical progression-predictive attribute of this 449  
risk biomarker [38]. In this set of analysis, we found 450  
that observed results with the cortisol/ A $\beta$  inter- 451  
action on its own and in the presence of reserve 452  
were independent of the effect of the exploratory 453  
risk biomarkers (Supplementary Table 2). In sum- 454  
mary, we report that cortisol elevations are predictive 455  
of faster clinical progression in individuals with 456  
A $\beta$  abnormalities. Interestingly, reserve indicators 457  
ameliorate the observed risk. Our data suggests an 458  
enhanced risk for AD clinical onset and progres- 459  
sion in individuals presenting with abnormal CSF 460  
levels of A $\beta$  and elevated glucocorticoid levels and, 461  
importantly, that this combined effect can be moder- 462  
ated by presence of reserve factors. These findings 463  
necessitate further research into HPA axis hyper- 464  
activity as a co-identifier with amyloid abnormalities, 465  
for high AD risk, and highlight the importance of 466  
accounting for lifetime exposures and factors in the 467

468 interpretation of results from longitudinal aging and  
469 dementia studies.

470 The findings presented further provide a rationale  
471 for lifestyle intervention studies looking into later-  
472 life promotion of reserve and brain maintenance and  
473 the potential use of high cortisol levels as selection  
474 or stratification criterion. At-risk for AD individuals,  
475 based on abnormal A $\beta$  status, with high cortisol lev-  
476 els may benefit from closer monitoring and lifestyle  
477 interventions.

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## SUPPLEMENTARY MATERIAL 526

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