Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-181030
IOS Press

Cortisol, Amyloid-β, and Reserve Predicts Alzheimer's Disease Progression for Cognitively Normal Older Adults

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Handling Associate Editor: Julius Popp

Accepted 10 May 2019

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-β (Aβ) 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) Aβ 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/Aβ reserve interaction for clinical

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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

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

INTRODUCTION

Late onset Alzheimer's disease (AD), by far the most common form of dementia, is thought to be of complex and multifactorial etiology, resulting from complex interactions of a plethora of genetic and environmental factors across the lifespan. Cerebral accumulation of amyloid-β (Aβ) and tau proteins are thought to be key histopathological hallmarks and their intracerebral processing may be an important driver for disease etiology [1–3]. On the other hand, evidence from studies of animal models and human studies indicate that aberrant activity of the hypothalamic-pituitary-adrenal (HPA) system contributes to AD etiopathogenesis, as well as in the development of cognitive decline and associated symptomatology [4, 5]. Indeed hypersecretion and aberrant receptor-mediated signaling actions of glucocorticoid (GC), the HPA axis's end-effector molecule (released as cortisol in man), have been reported to impede normal Aβ and tau processing [6–8], promote neurodegeneration [9] and synaptic dysfunction [10]. Furthermore, they have been shown to potentially facilitate AD-related cognitive deficits in animal disease models [4, 11] and human patients [12–14].

The detrimental consequences of a hyperactive HPA axis have been reported at the prodromal and clinical stages of AD, with both central [15–17] and peripheral [18, 19] elevations of cortisol shown to accelerate disease onset [6, 7, 20] and clinical progression [16, 18]. Likewise, a combinatory biomarker exploration of 208 analytes revealed cortisol to be one of five biomarkers that could reliably predict clinical progression within a period of 3 years [21]. Experiential data in cognitively normal (CN) older individuals, though limited, posits abnormal GC secretion as a predictive marker for rapid cognitive decline in individuals with excess cerebral Aβ [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 received growing attention. A key finding is that high educational [23–25] and occupational attainment [23, 25], premorbid intelligence [26, 27], as well as certain anatomical factors including larger pre-morbid brain size [28–30] are associated with a later onset and decreased risk of dementia [31, 32] and may even counteract the detrimental effects of Aβ accumulation on cognitive performance [33].

Using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) CN participants [34, 35], we assess: 1) the impact of cerebrospinal fluid (CSF) cortisol and Aβ levels on risk of clinical progression; and 2) the moderating effect of a multi-indicator reserve composite comprising of maximal adult brain size, education, occupational complexity and premorbid intelligence.

MATERIALS AND METHODS

Participants and data

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

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 cuts 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/Aβ–; 2) high cortisol/normal $A\beta_{42}$, termed GC+/Aβ–; 3) low cortisol/abnormal $A\beta_{42}$, termed GC-/Aβ+; and 4) high cortisol/abnormal $A\beta_{42}$, termed GC+/Aβ+.

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 (≤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 (≤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 (cm^3) data was dichotomized via median split procedure into low (≤1505.01 cm^3) and high (>1505.01 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* ε4 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 Aβ$_{42}$

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–/Aβ–, and the lowest being in the GC–/Aβ+.

There were also differences in the mean age between the groups ($p < 0.05$), with significant differences occurring between the GC–/Aβ–, GC–/Aβ+, and the GC+/Aβ+ groups (Tukey HSD test, $p < 0.05$). The proportion of *APOE*-ε4 carriers was also significantly different between groups ($p < 0.005$) with the highest proportion falling into the GC+/Aβ+ 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× education years +0.4315 × IQ + 0.4772× occupation level +0.4395 × 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/Aβ interaction and disease progression from the preclinical 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 Aβ groups

Characteristics	Full sample	GC–/Aβ–	GC+/Aβ–	GC–/Aβ+	GC+/Aβ+	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
APOE-ε4 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–/Aβ–, low cortisol/normal $A\beta_{42}$; GC+/Aβ, high cortisol/normal $A\beta_{42}$; GC–/Aβ+, low cortisol/abnormal $A\beta_{42}$; GC+/Aβ+, high cortisol/abnormal $A\beta_{42}$. *$p < 0.05$.

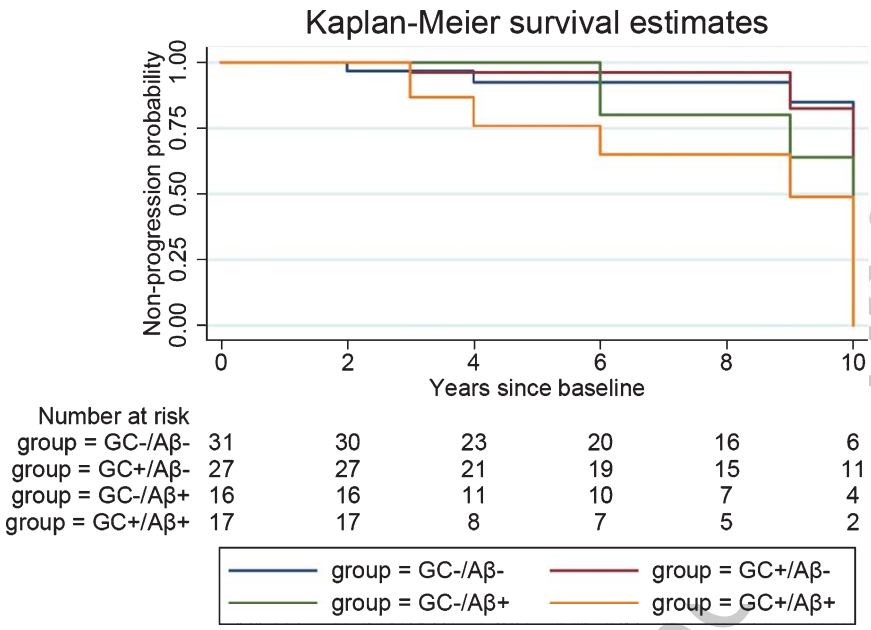

Fig. 1. Kaplan-Meier (KM) survival estimates for the study biomarker groups. Probability of non-progression from cognitive normal stage to clinical AD-dementia, for each glucocorticoid and amyloid biomarker combination group is shown. Estimated number of remaining individuals at risk for disease progression at each time point are also represented. Individuals in the Cortisol High/Aβ_{42} 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_{42} level; Aβ+, abnormal Aβ_{42} level.

between-group differences observed (Supplementary Figure 2).

Reserve, cortisol, Aβ_{42}, and stable versus progressive disease stage

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

The results from the Cox models evaluating the effect of CSF levels of Aβ_{42} and cortisol on time to progression, and the moderating effect of the reserve composite on the Aβ_{42}/cortisol association are shown in Table 2. The interaction for cortisol and Aβ_{42} on risk of progression was not statistically significant in Model 1 and Model 2. However, the three-way interaction in Model 3 showed a significant protective effect of high reserve on those individuals that had abnormal levels of Aβ_{42} and cortisol (HR = 0.153, $p < 0.001$), after adjusting for age, gender, *APOE* ε4 status, and GDS (Table 2 and Fig. 2). Participants in the GC+/Aβ+ group with high reserve scores had a relatively lower risk for clinical progression (Supplementary Table 1). Notably, the interaction between reserve, cortisol, and Aβ_{42} remained significant after controlling for total-tau abnormalities and other CSF risk biomarkers within an exploratory model (Supplementary Table 2).

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

To further explore the relationship between reserve and clinical progression, we examined the effect of the independent reserve variables in four separate models for ICV, IQ, occupation and education; and the interaction of each of these variables with CSF levels of Aβ_{42} and cortisol. Differential effects of the distinct reserve variables were noted (Supplementary Table 3). In the IQ interaction model, a significant decrease in risk was observed in those individuals that have high levels of pre-morbid IQ in the GC+/Aβ+ group (HR: 0.065, $p = 0.026$). Similarly, in the ICV and occupation interaction models, significant decreases in risk were observed for individuals with high ICV (HR: 0.010, $p = 0.012$), and

Table 2
Cox regression of interactions between cortisol, $A\beta_{42}$, and reserve score with risk of clinical progression

Indicators	Model 1		Model 2		Model 3	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
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 Aβ	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 Aβ	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 Aβ*Reserve score			1.34 (0.71–2.53)	0.003*	2.50 (1.38–4.54)	0.003*
High cortisol*Abnormal Aβ*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. $^*p < 0.05$.

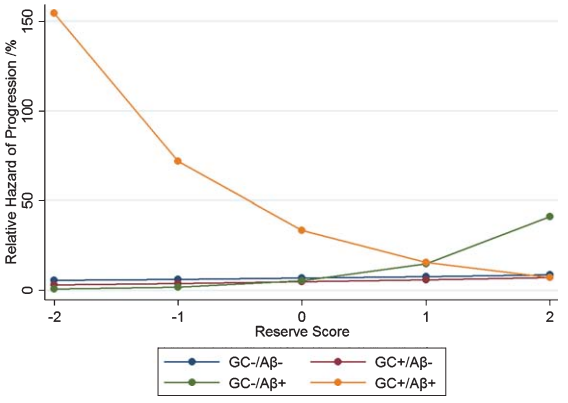

Fig. 2. Marginal plot showing relative hazard of AD clinical progression for biomarker groups in relation to reserve score. Levels of reserve are represented in relation to relative risk of AD clinical progression for each glucocorticoid and amyloid biomarker combination group. Benefit of increasing reserve level in terms of reduction in disease progression risk is most evident for the Cortisol High/$A\beta_{42}$ Abnormal (GC+/Aβ+) group. GC–, low cortisol level; GC+, high cortisol level; Aβ–, normal $A\beta_{42}$ level; Aβ+, abnormal $A\beta_{42}$ level. Model adjusted for age, gender, APOE ε4 status, and GDS score. The reference group was Cortisol Low/$A\beta_{42}$ Normal group (GC–/Aβ–) 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/$A\beta_{42}$ status was detected (HR = 0.16, $p > 0.05$). In addition, we found no significant interactions between age, gender, or *APOE* ε4 and cortisol/$A\beta_{42}$ status (p for interaction >0.05).

DISCUSSION

Elevated levels of central cortisol and abnormal Aβ 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 Aβ 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 Aβ 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 Aβ and HPA axis hyperactivity. To our knowledge, this is the first report on the impact of combined central Aβ abnormalities/higher cortisol levels on AD clinical progression from the preclinical stage, and suggests that cortisol may act in concert with Aβ 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 Aβ 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

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

Other known predictors of clinical AD progression, including *APOE* ε4 status [17] and subclinical depression [53], were assessed as independent predictors in our study. Nevertheless, increased risk of progression was evident in the GC+/Aβ+ group even after controlling for these risk factors.

This study is strengthened by the use of central glucocorticoid measures which provides a useful indicator of brain exposure to hormone levels, particularly for regions such as the hippocampus and frontal cortex that are front-line targets for manifestation of AD pathology and highly responsive to glucocorticoids given enriched localization of hormone receptors [54, 55]. Indeed, a Phase II trial into the modulation of central glucocorticoid levels via inhibition of the enzyme 11β-Hydroxysteroid dehydrogenase type 1, also known as cortisone reductase (which acts within the CNS to convert cortisone to the biologically active cortisol), is currently underway, and aimed at exploring a possible 'cognition-protective' effect of GC hormone reduction in an AD-pathology-sensitive area [56].

Our results provide further support to the hypothesis of a moderating effect of high levels of reserve on the observed risk associated with the GC+/Aβ+ profile. Determination of individual variable contribution to risk reduction observed with the composite score showed that the effects in this sample were primarily driven by IQ, premorbid brain size, and occupation. The lack of an education effect may be explained by the bias toward higher educated participants in the ADNI sample.

The fact that the reserve composite moderates the Aβ/cortisol-related risk for clinical progression lends credence to the importance of accounting for reserve factors in clinical studies. For example, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) provides evidence for the benefit of promoting reserve via interventions with a social element such as physical activity and cognitive training [57]. Such activities are known to affect HPA axis by altering stress hormone levels [58, 59]. Further studies assessing psychological/ lifestyle strategies to normalize GC levels may prove beneficial in delaying disease onset and progression in individuals with Aβ pathology.

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

Sample size in this study was limited as only individuals with available CSF cortisol and Aβ data were included. Since some individuals had missing data for IQ score, imputation methods were employed to account for missing data which allowed robust statistical explorations utilizing the entire data set available.

Another known limitation in studies on HPA-axis hyperactivity and association with clinical indices of AD includes an absence of ample HPA-axis activators including pro/anti-inflammatory cytokines, as well as other risk biomarkers that are associated with clinical progression within analyses. Recent evidence from ADNI have provided a combinatory biomarker signature made up of CSF and plasma markers for the prediction of clinical progression, from the prodromal stage [21]. The authors found that plasma apolipoprotein A-II and cortisol levels as well as FGF-4, hFABP, calcitonin, and TRAIL-R3 in CSF allowed for reliable prediction of disease status within a 3-year period [21]. In light of this evidence, and given the availability of the CSF components of the biomarker composite within the ADNI dataset, we introduced these CSF biomarkers as covariates within an exploratory model; also adjusting for total tau given the established clinical progression-predictive attribute of this risk biomarker [38]. In this set of analysis, we found that observed results with the cortisol/ Aβ interaction on its own and in the presence of reserve were independent of the effect of the exploratory risk biomarkers (Supplementary Table 2). In summary, we report that cortisol elevations are predictive of faster clinical progression in individuals with Aβ abnormalities. Interestingly, reserve indicators ameliorate the observed risk. Our data suggests an enhanced risk for AD clinical onset and progression in individuals presenting with abnormal CSF levels of Aβ and elevated glucocorticoid levels and, importantly, that this combined effect can be moderated by presence of reserve factors. These findings necessitate further research into HPA axis hyperactivity as a co-identifier with amyloid abnormalities, for high AD risk, and highlight the importance of accounting for lifetime exposures and factors in the

interpretation of results from longitudinal aging and dementia studies.

The findings presented further provide a rationale for lifestyle intervention studies looking into later-life promotion of reserve and brain maintenance and the potential use of high cortisol levels as selection or stratification criterion. At-risk for AD individuals, based on abnormal Aβ status, with high cortisol levels may benefit from closer monitoring and lifestyle interventions.

ACKNOWLEDGMENTS

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (http://www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

No sponsor had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Data used in preparation of this article were obtained from the ADNI database. As such, the investigators within the ADNI contributed to the design and implementation of ADNI or provided data but did not participate in the analysis or writing of this report.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/18-1030r2).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-181030.

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