

RESEARCH ARTICLE

The effect of plasma cortisol on hippocampal atrophy and clinical progression in mild cognitive impairment

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[†]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (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 listing of ADNI investigators has been submitted with this manuscript.

Abstract

Introduction: Both elevated cortisol and hippocampal volume have been linked to an increased risk for the development of Alzheimer's disease (AD). This longitudinal study assessed the effects of plasma cortisol on hippocampal atrophy and clinical progression rates in patients with mild cognitive impairment (MCI).

Methods: Patients with amnesic MCI ($n = 304$) were selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) based on availability of baseline plasma cortisol and hippocampal volume measures, assessed at baseline and during follow-ups. We investigated associations between plasma cortisol, hippocampal volume, and risk of clinical progression to AD over a study period of up to 100 months (mean follow-up time 36.8 months) using linear mixed models, Cox proportional hazards models, and Kaplan-Meier estimators.

Results: Plasma cortisol predicted greater hippocampal atrophy, such that participants with higher cortisol showed faster decline in hippocampal volume over time (interaction: $\beta = -0.15$, $p = 0.004$). Small hippocampal volume predicted a higher risk of clinical progression to AD (hazard ratio [HR] = 2.15; confidence interval [CI], 1.64–2.80; $p < 0.001$). A similar effect was not found for cortisol (HR = 1.206; CI, 0.82–1.37; $p = 0.670$) and there was no statistical evidence for an interaction between hippocampal volume and cortisol on clinical progression (HR = 0.81; CI, 0.57–0.17; $p = 0.260$).

Discussion: Our findings suggest that higher cortisol predicts higher hippocampal atrophy, which in turn is a risk factor for progression to AD. Regulation of the hypothalamic-pituitary-adrenal axis through stress-reducing lifestyle interventions might be a protective factor against hippocampal degeneration at the prodromal stage of AD.

KEYWORDS

ADNI, cortisol, hippocampus, hypothalamic-pituitary-adrenal axis, MCI, neurodegeneration, risk factor, stress

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1 | INTRODUCTION

Activation and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may accelerate the development and progression of clinical Alzheimer's disease (AD).¹ Animal studies have provided evidence that disturbances of the HPA axis may occur during early stages of disease development. Cortisol, the most important glucocorticoid, was previously shown to be associated with increased brain injury and accelerated progression of AD pathogenesis in animal models.^{2–4}

Several reviews have documented evidence of an adverse effect of HPA axis activation in the development of AD across human studies, as demonstrated using biomarkers of circulating cortisol in blood, saliva, and cerebrospinal fluid (CSF).^{1,5,6} While cortisol appears to be reliably increased in AD patients,^{7–10} recent studies suggest that HPA axis alteration may already occur at the prodromal disease stage in patients with amnesic mild cognitive impairment (MCI).¹¹ This high-risk group is characterized by neural degradation and dysfunction of the hippocampus, which plays a central role in predicting clinical progression to AD dementia.¹² It is proposed that increased cortisol secretion may exacerbate injury in the hippocampus, a brain structure central to HPA axis regulation, and vice versa, which in turn may accelerate development and progression of AD.^{1,6}

In agreement with this notion, there is evidence to suggest that HPA axis dysregulation may play an important role in early stages of AD. In cross-sectional studies, higher plasma cortisol levels have been associated with smaller hippocampal volumes in patients with amnesic MCI¹³ and mild-to-moderate dementia,¹⁴ and with greater β -amyloid ($A\beta$) deposition in a mixed sample of cognitively normal participants and MCI and AD patients.¹⁵ In longitudinal studies, higher plasma cortisol levels have been linked to faster cognitive decline within 2 years and clinical worsening within 4 years in patients with mild dementia.^{14,16} Moreover, higher plasma cortisol levels interact with $A\beta$ deposition to predict faster cognitive decline within 6 years in $A\beta$ -positive cognitively normal older adults.¹⁷ Higher plasma cortisol levels in combination with five other plasma- and CSF-based biomarkers (excluding amyloid- β and tau) optimally predicted disease status in patients with amnesic MCI within 3 years.¹⁸

In the prospect of a potential clinical application, more research is needed to better understand the effects of cortisol measured in blood. To date, longitudinal studies on the predictive properties of circulating cortisol in the progression of AD are rare. This longitudinal study examined the associations of plasma cortisol levels at baseline with hippocampal atrophy and risk of clinical progression to AD dementia over a study period of up to 100 months (mean follow-up time 36.8 months) in amnesic MCI patients from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. We anticipated that higher plasma cortisol levels at baseline would be associated with greater hippocampal atrophy over time and higher risk of clinical progression to AD. Previous reports using overlapping ADNI samples mainly focused on cross-sectional associations between plasma

RESEARCH IN CONTEXT

1. **Systematic Review:** Reviewing the literature about the stress-biomarker cortisol pointed to associations with hippocampal damage and cognitive decline. Longitudinal studies on the predictive properties of plasma cortisol at early stages of Alzheimer's disease (AD) have been rare.
2. **Interpretation:** In our longitudinal study of up to 100 months (mean follow-up time 36.8 months), higher plasma cortisol was specifically related to accelerated hippocampal atrophy over time in 304 older patients with amnesic mild cognitive impairment. Hippocampal atrophy in turn predicted clinical progression to AD dementia. We found no direct influence of plasma cortisol on clinical progression to AD.
3. **Future Direction:** Prospective cohort and intervention studies are needed to substantiate whether interventions that can lower cortisol levels might reduce hippocampal atrophy and protect from or delay AD.

cortisol and brain biomarkers of AD^{13,15,19} or multiple fluid-based biomarkers.¹⁸

2 | METHODS

Longitudinal data used in this study were obtained from the ADNI database and accessed via the ADNIMERGE R package (0.0.1) in October 2022 or directly downloaded from the ADNI data resource webpage (<https://adni.loni.usc.edu>). The primary goal of ADNI has been to test whether neuroimaging, other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of MCI and early AD. For up-to-date information see www.adni-info.org.

2.1 | Study participants

Participants with a diagnosis of amnesic MCI were selected from the ADNI database (ADNI I cohort) with regard to availability of the following assessments: (i) baseline plasma cortisol levels, (ii) at least baseline serial T1-weighted MRI, and (iii) baseline and longitudinal dementia status diagnostics. The final sample included in this study had 304 participants (Figure 1). We included a longitudinal study period of up to 100 months. Of the present sample, approximately 73% of participants completed assessments up to 12 months, 54% completed assessments up to 24 months, 25% completed assessments up to 48 months, and approximately 4.3% of participants completed all assessments up to 96 months following baseline. For the progression

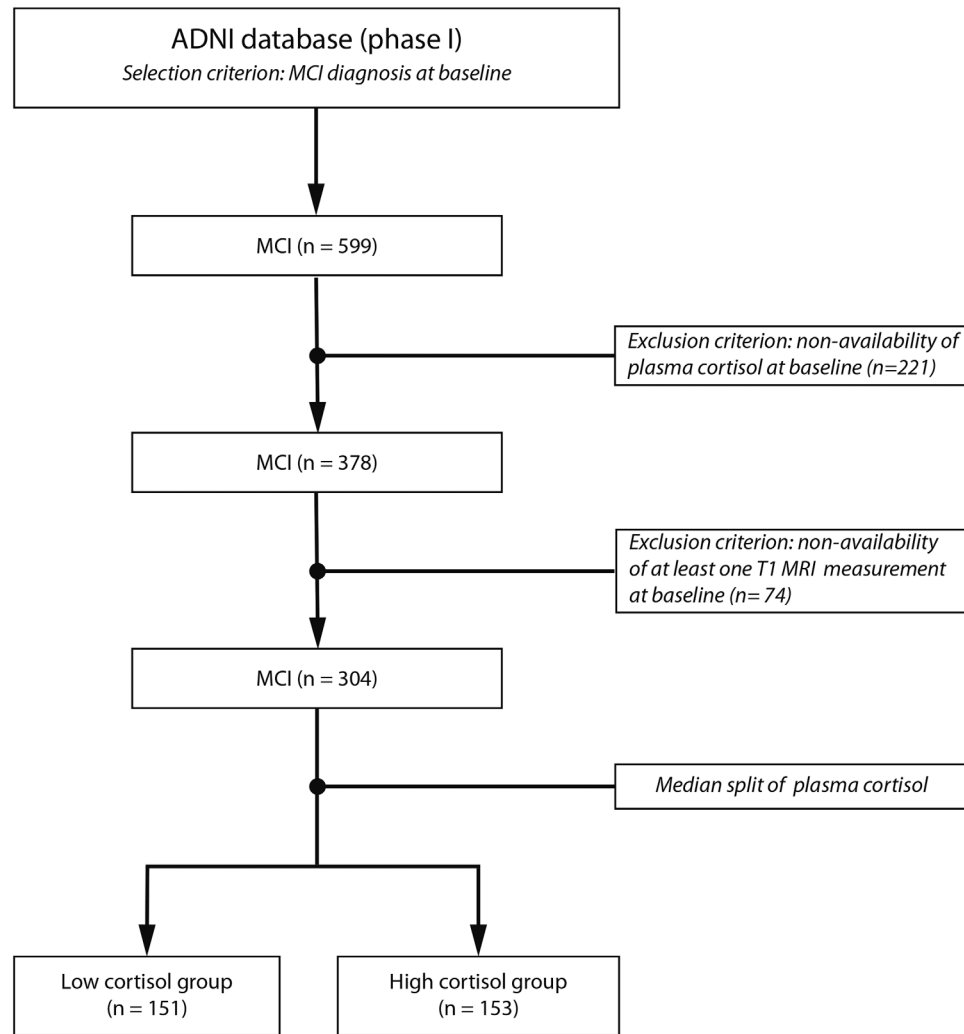


FIGURE 1 Participant selection flowchart, illustrating the selection procedure from the ADNI database. ADNI, Alzheimer's Disease Neuroimaging Initiative; MCI, mild cognitive impairment; MRI, magnetic resonance imaging.

analysis, one participant had to be excluded due to inconsistencies in the dementia diagnosis.

Details on inclusion/exclusion criteria for ADNI are available in the procedure's manual (<https://adni.loni.usc.edu>). Briefly, at the time of study enrollment, participants are between 55 and 90 (inclusive) years old, have at least a 6th grade education or work history, are fluent in English or Spanish, and have a score of less than 6 on the Geriatric Depression Scale (GDS),²⁰ thus excluding clinical depression. Other exclusion criteria comprise serious neurological disorders apart from possible AD, history of brain lesions or head trauma, and intake of psychoactive medication at baseline. Participants were classified as single- or multi-domain amnesic MCI based on a Mini-Mental State Examination (MMSE)²¹ score between 24 and 30 (inclusive), a Clinical Dementia Rating (CDR) scale²² of at least 0.5, subjective memory complaints, objective memory dysfunction, and preserved general cognition as well as functional performance.²³ Following baseline assessment, participants received serial diagnostic assessments at 6, 12, 18, and 24 months and thereafter annually. At each visit, the clinical and neuropsychological assessments

were carried out in close temporal proximity to the neuroimaging assessments.

2.2 | Consent statement and standard protocol approvals

All study participants provided written informed consent to blood sampling, cognitive and clinical assessments, as well as neuroimaging prior to study inclusion. Ethics approval of the ADNI study were obtained by all institutional review boards of all participating institutions.

2.3 | Clinical data, neuropsychology, and genotyping

For the current analysis, we selected the following individual baseline scores of clinical and neuropsychological measures from the ADNI

database to describe the participant sample: the Alzheimer's disease assessment scale (ADAS13),²⁴ the CDR Sum of Boxes (CDR-SB), the MMSE, the GDS, as well as the Neuropsychiatric Inventory (NPI).²⁵ The Apolipoprotein (APO) ϵ 4 genotype was determined through analysis of blood samples that was carried out by the ADNI Biomarker Core Laboratory at the University of Pennsylvania.²⁶ Systolic and diastolic blood pressure data were selected from the ADNI database, and the participants' body mass index (BMI) was calculated from the downloaded height and weight measurements.

2.4 | Acquisition and analysis of plasma cortisol levels

Baseline plasma cortisol levels, provided by the Biomarkers Consortium Plasma Proteomics Project, were extracted from the ADNI database. Assay documentation and validation methods are described in detail in the data primer²⁷ and are available in the [Supplementary Material](#).

2.5 | Acquisition and analysis of neuroimaging data

Structural T1-weighted magnetic resonance imaging (MRI) scans were acquired on either GE, Siemens, or Philips 1.5T scanners at various ADNI sites using standardized MRI acquisition protocols described in detail elsewhere.²⁸

Anatomical scans (baseline and follow-up measures) were processed using the FreeSurfer software (version 4.3)²⁹ to obtain regional brain volume measures. This atlas-based approach was previously described and validated.³⁰ Right and left hemisphere hippocampal volumes were extracted from the ADNI database and the sum included into our analysis. To investigate whether effects were specific to the hippocampus, or could also be found in other brain regions,¹³ we assessed the following cortical volumes in follow-up analyses: entorhinal, fusiform, lateral, and medial orbitofrontal, and middle temporal regions (bilateral), which were downloaded and calculated as above. Brain region volumes were adjusted for baseline total intracranial volume (ICV) by calculating the ratio between regional brain volume and ICV, multiplied by the overall sample mean of ICV.

2.6 | Acquisition and analysis of CSF $A\beta_{1-42}$ and t-tau levels

Cerebrospinal fluid (CSF) levels (baseline values) of $A\beta_{1-42}$ and t-tau, provided by the Biomarkers Consortium Project, were extracted from the ADNI database. The data described represent the work of the project "Use of Targeted Multiplex Proteomic Strategies to Identify Novel CSF Biomarkers in AD," and procedures are described in detail in the data primer³¹ and are available in the [Supplementary material](#).

We assessed median CSF values of the re-scaled data from the UPENNBIOMK dataset. In accordance with the CSF biomarker signature for MCI in ADNI,³² we used the following cutoff values. The $A\beta_{1-42}$ level was considered "abnormal" for all participants with an $A\beta_{1-42}$ concentration ≤ 192 pg/mL ($A\beta+$). T-tau was considered "abnormal" for all participants with a t-tau concentration ≥ 93 pg/mL (t-tau+).

2.7 | Statistics

Statistical analyses were performed and plots were generated using R Studio (version 1.4.1106 for Mac),³³ including the following R packages: ADNIMERGE (0.0.1), ggplot2 (3.3.6), nlme (3.1-152), survival (3.2-7), and survminer (0.4.9).

2.7.1 | Sample characteristics

For the present analyses, groups with low and high cortisol levels were defined using a median split, since distribution of cortisol values was strongly skewed (Shapiro-Wilk test $W = 0.8067$, $p < 2.2e-16$) and to avoid any a priori assumptions. Dichotomization of cortisol measures was similarly incorporated in previous studies.^{11,17,34,35} The entire sample, as well as the cortisol groups were characterized using baseline demographic, clinical, and biological markers. Cortisol groups (low, high) were compared using t-tests for continuous variables or chi-squared statistics for categorical variables. In follow-up analyses, we assessed the associations between plasma cortisol and age as well as APO ϵ 4 status.

2.7.2 | Linear mixed effects models

Linear mixed effects (LME) analysis was conducted to assess the association between baseline plasma cortisol and change in hippocampal volume over the 100 months study period. For all models, relative change in hippocampal volume since baseline was entered as response and random intercepts and slopes were confirmed. The LME model included baseline hippocampal volume, baseline plasma cortisol, time from baseline, and the interaction term plasma cortisol*time as independent variables. In follow-up analyses, we assessed whether a possible effect of plasma cortisol on brain structure is specific for the hippocampus, a key region in prodromal AD stages. For this, we calculated the same LME models to compare the effect of baseline plasma cortisol on relative change in other selected brain regions, as mentioned above. In another follow-up analysis, only participants with a positive CSF signature of AD ($A\beta+/t\text{-tau}+$) were considered, based on the NIA-AA Research Framework recommendations.³⁶

2.7.3 | Survival analysis

Cox proportional hazards models were carried out to assess the risk of longitudinal clinical progression from MCI to AD dementia

associated with hippocampal volume (large/small; stratified at baseline with a median split), baseline plasma cortisol (high/low), and their interaction. Risk groups were defined for all four possible combinations of hippocampal volume (large/small) and cortisol (high/low) groups.

First, we calculated a forest plot to visualize the difference in the risk of clinical progression across the four risk groups. The plot provides hazard ratios (HR) and 95% confidence intervals based on a Cox model, setting the group with large hippocampus and low cortisol (low risk group) as reference. Next, the overall Cox proportional hazards model was calculated. The model included baseline hippocampal volume (large/small), baseline cortisol (high/low), and the interaction term hippocampal volume*plasma cortisol. Time was calculated from baseline to the first visit, when AD dementia was diagnosed (event) or to the most recent visit for censored cases. Additionally, Cox proportional hazards models were calculated for the $A\beta+/t\text{-tau}+$ subsample.

Kaplan-Meier curves were computed to visualize the survival (i.e., non-progression) probability of the risk groups over the 100-month study period. Groups were compared using log rank tests with Bonferroni corrections, and median survival probabilities were displayed.

2.7.4 | Adjustment for co-variables

Statistical analyses were conducted using models with and without adjustment for co-variables of no interest. In-line with existing literature, in the models including co-variables, we adjusted for age, sex, systolic blood pressure, APO $\epsilon 4$ status, and the GDS.^{13,19,35} We report adjusted and unadjusted outcomes in the respective results tables.

3 | RESULTS

3.1 | Characteristics of participants

Descriptive demographic, clinical, and biomarker characteristics at baseline are shown in Table 1 for the entire sample of MCI patients and for groups stratified by plasma cortisol. Compared to the low cortisol group, the high cortisol group was older and had a lower hippocampal volume at baseline. The groups were comparable in other demographic, clinical, or biological markers. The number of longitudinal assessments per participants ranged from 1 to 10 visits, with an average of 4.7 visits per participant.

Follow-up analyses showed that there was an overall positive relationship between baseline age and plasma cortisol in the total sample ($\rho = 0.107$, $p = 0.006$). There were no significant baseline correlations between plasma cortisol and APO $\epsilon 4$ status in the total sample ($\rho = 0.073$, $p = 0.123$) (Table S1, Figure S1).

3.2 | Plasma cortisol and hippocampal volume at baseline and over time

We evaluated the effect of plasma cortisol (low/high) on hippocampal volume. Results are shown in Figure 2 and Table 2. Compared to the low cortisol group, the high cortisol group showed lower hippocampal volume at baseline ($\beta = -0.15$, $p = 0.007$, unadjusted, Figure 2A). This group difference was reduced to trend level, when adjusting for covariates ($\beta = -0.10$, $p = 0.08$, adjusted). Baseline plasma cortisol predicted change in hippocampal volume over time, such that the high cortisol group showed a faster decline in hippocampal volume compared to the low cortisol group (Figure 2B). This interaction between plasma cortisol and time on hippocampal atrophy was significant in unadjusted ($\beta = -0.15$, $p = 0.004$, Table 2, Model 1) and adjusted models ($\beta = -0.15$, $p = 0.004$, Table 2, Model 2). Baseline hippocampal volume had no influence on decline in hippocampal volume over time. The interaction was maintained in the $A\beta+/t\text{-tau}+$ subsample ($n = 64$, $\beta = -0.25$, $p = 0.002$, Table S2, adjusted model).

In follow-up analyses, we assessed the specificity of the predictive effect of baseline plasma cortisol on change in brain volumes over time by targeting other brain regions. There were no significant effects of plasma cortisol on fusiform, lateral, and medial orbitofrontal and middle temporal volumes (all $p > 0.1$, Table S3 and S4).

3.3 | Plasma cortisol, hippocampal volume, and clinical progression

We evaluated the effects of hippocampal volume and plasma cortisol on the risk of clinical progression to AD dementia. Results from the Cox models are shown in Figure 3 and Table 3. Survival curves as determined by the Kaplan-Meier-estimator are shown in the supplements (Figure S2). The forest plot provides the risk of clinical progression to AD dementia across the four risk groups (Figure 3). Compared to the low-risk reference group (large hippocampal volume/low cortisol), the risk of clinical progression to AD dementia was increased in the other groups (all HR ratios > 1) and differed significantly for the two high-risk groups with small hippocampal volumes (Figure 3; Figure S2 C+D).

In the overall Cox proportional hazards models, baseline hippocampal volume was associated with clinical progression to AD dementia, such that small hippocampal volume predicted a higher risk of clinical progression in unadjusted (HR = 2.10; CI, 1.62–2.71; $p < 0.001$; Table 3, Model 1; Figure S2 A+D) and adjusted (HR = 2.15; CI, 1.65–2.81; $p < 0.001$; Table 3, Model 2) models. There was no significant effect of baseline plasma cortisol on clinical progression in unadjusted (HR = 1.06; CI, 0.83–1.37; $p = 0.634$; Table 3, Model 1; Figure S2 B+D) or adjusted (HR = 1.07; CI, 0.82–1.39; $p = 0.615$; Table 3, Model 2) models. There was no significant interaction between hippocampal volume and plasma cortisol on clinical progression in unadjusted (HR = 0.84; CI, 0.59–1.20; $p = 0.327$; Table 3, Model 1) and adjusted (HR = 0.81; CI, 0.56–1.16; $p = 0.245$; Table 3, Model 2) models. In the $A\beta+/t\text{-tau}+$

TABLE 1 Baseline demographics, clinical, and biomarker characteristics

		Cortisol groups			
	Total sample (n = 304)	Low (n = 151)	High (n = 153)	Test statistic	p-Values
Demographics					
Age (years)	74.1 ± 7.3	73.1 ± 7.2	75 ± 7.3	-2.26	0.025
Education (years)	15.5 ± 3.1	15.6 ± 3.1	15.4 ± 3.1	0.54	0.593
Gender: females	113 (37.2%)	61 (40.4%)	52 (34%)	1.08	0.299
Clinical markers					
ADAS13	18.8 ± 6.4	18.2 ± 6.3	19.3 ± 6.4	-1.57	0.117
CDR-SB	1.6 ± 0.8	1.6 ± 0.8	1.6 ± 0.8	0.11	0.910
MMSE	27 ± 1.8	27.1 ± 1.8	26.8 ± 1.8	1.35	0.179
GDS	1.6 ± 1.4	1.7 ± 1.5	1.5 ± 1.3	1.00	0.318
NPI	1.9 ± 2.8	1.7 ± 2.2	2.1 ± 3.3	-1.29	0.197
Blood-based biomarkers					
APO ε4 status: ε4+	175 (57.6%)	83 (55%)	92 (60.1%)	0.63	0.427
Plasma cortisol (ng/mL)	150.1 ± 55.3	113.5 ± 17.2	186.3 ± 56.1	-15.35	<0.001
CSF markers					
	n = 148	n = 73	n = 75		
Aβ+	110 (74.3%)	50 (68.5%)	60 (80%)	1.99	0.157
t-tau+	66 (44.6%)	28 (38.4%)	38 (50.7%)	1.80	0.180
Neuroimaging markers					
Hippocampal volume (mm³), normalized	6427.2 ± 1061.5	6591.2 ± 1144.0	6265.3 ± 949.4	2.70	0.007
Vascular markers					
Systolic BP (mmHg)	134.7 ± 17.1	134.3 ± 17.8	135.2 ± 16.5	-0.45	0.655
Diastolic BP (mmHg)	74.9 ± 9.6	75 ± 9.5	74.8 ± 9.9	0.15	0.878
BMI (kg/m²)	26.2 ± 4	26.5 ± 4.2	26 ± 3.8	1.00	0.316
Follow-up assessments					
Follow-up time (months)	36.8 ± 26.1	35.0 ± 26.5	38.6 ± 25.7	-1.21	0.228
Follow-up visits (n)	4.7 ± 2.6	4.4 ± 2.7	4.9 ± 2.5	-1.57	0.117

Note: Numbers are given as mean ± standard deviation, where applicable or as count (percentage). The actual sample size for a variable is given, if different from sample size specified in column header. Hippocampal volumes were normalized to baseline intracranial volume as described above. The statistical difference between cortisol groups was calculated using t-test and chi²-test for continues and categorical variables, respectively.

Statistical difference for plasma cortisol was driven by median split.

Cutoff thresholds: Aβ+ ≤ 192 pg/mL, t-tau+ ≥ 93 pg/mL. APO ε4 carrier status: ε4+ one or two copies of APO ε4 allele.

Abbreviations: Aβ, amyloid beta; ADAS13, Alzheimer's Disease Assessment Scale; APO, apolipoprotein; bl, baseline; BP, blood pressure; CDR-SB, Clinical Dementia Rating Sum of Boxes; CSF, cerebral spinal fluid; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; t-tau, total tau.

subsample, the null results for plasma cortisol were maintained, while the effect of hippocampal volume on clinical progression was not (n = 64, Table S5).

4 | DISCUSSION

4.1 | Summary of results

This longitudinal study in ADNI data assessed effects of baseline plasma cortisol on change in hippocampal volume over a study period of up to 100 months (mean follow-up time 36.8 months) and clinical progression in amnesic MCI patients. We found that higher baseline plasma cortisol was associated with a greater rate of hippocampal atrophy over time. Small baseline hippocampal volume predicted a higher

risk of clinical progression to AD dementia. A similar effect was not found for plasma cortisol. We did not detect statistical evidence for an interaction between hippocampal volume and plasma cortisol on clinical progression. Taken together, our findings suggest that low plasma cortisol levels are related to less hippocampal degradation over time in prodromal AD.

4.2 | Plasma cortisol and hippocampal atrophy

As an important novel finding, our results show that high plasma cortisol levels are associated with faster hippocampal atrophy over time in patients with amnesic MCI. Previous studies found a worsening effect of high baseline cortisol, measured in plasma and serum, on hippocampal volume over time in older adults.^{37,38} More specifically, higher

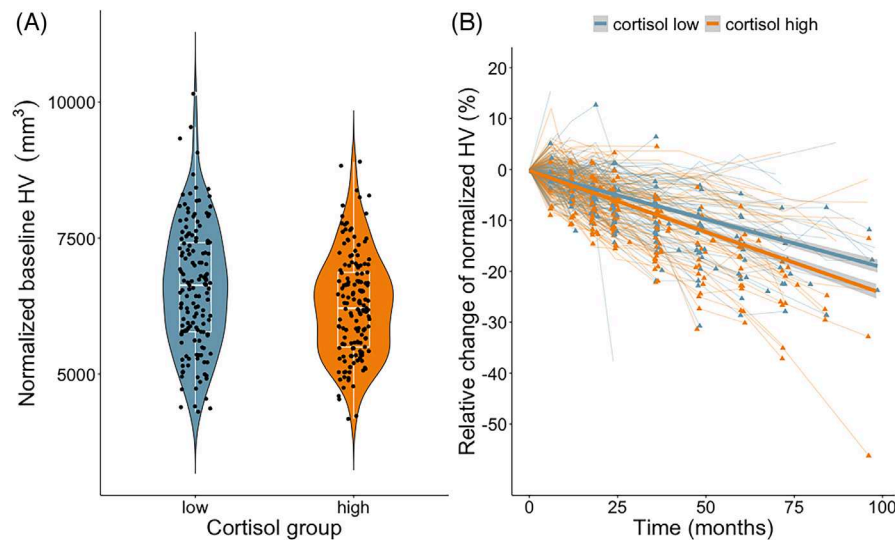


FIGURE 2 Association between plasma cortisol and hippocampal volume. (A) Violin plots show the baseline relationship between low (blue, on the left) and high (orange, on the right) cortisol groups with hippocampal volume. Boxplot with median and upper/lower quartiles are shown in white and individual data points are shown as black circles. (B) Line plots illustrate the association between low (blue) and high (orange) cortisol groups on relative change of hippocampal volume over time. Each thin line represents one participant, dots mark the time point that the participant has been diagnosed with dementia, thick lines indicate linear regression lines within each group. HV, hippocampal volume.

TABLE 2 Effects of baseline plasma cortisol on relative change of hippocampal volume over time

Variables	Model 1			Model 2		
	Estimates (95% CI)	β	p-Value	Estimates (95% CI)	β	p-Value
Intercept	1.14 (−0.19–2.47)	−0.01	0.092	−0.28 (−3.87–3.32)	−0.04	0.879
Baseline HV (mm ³)	−0.00 (−0.00–0.00)	−0.03	0.103	−0.00 (−0.00–0.00)	−0.02	0.308
Plasma cortisol (low)	0.06 (−0.25–0.38)	−0.13	0.695	0.06 (−0.25–0.38)	−0.14	0.686
Time (months)	−0.24 (−0.26–0.21)	−0.75	<0.001	−0.24 (−0.26–0.21)	−0.75	<0.001
Plasma cortisol (low)*time	−0.05 (−0.08–0.01)	−0.15	0.004	−0.05 (−0.08–0.02)	−0.15	0.004
Age				0.01 (−0.02–0.04)	0.01	0.602
Sex (male)				0.49 (0.03–0.95)	0.07	0.037
Systolic BP				0.00 (−0.01–0.01)	0.00	0.890
APO ε4 (ε4+)				−0.19 (−0.64–0.26)	−0.03	0.411
GDS				0.06 (−0.09–0.22)	0.01	0.425

Note: Results of linear mixed effects models, quantifying the effect of baseline hippocampal volume and plasma cortisol on relative change in hippocampal volume over time. Hippocampal volume was normalized to baseline total intracranial volume.

Abbreviations: ApoE, apolipoprotein E; BP, blood pressure; CI, confidence interval; GDS, Geriatric Depression Scale; HV, hippocampal volume.

baseline plasma cortisol has been associated with smaller volume of the left hippocampus at a 7-year follow-up time point ($n = 70$).³⁸ The present study expands these reports by indicating that higher levels of circulating plasma cortisol may accelerate hippocampal degeneration in patients with MCI, at a prodromal disease stage with high risk of clinical progression. The fact that higher plasma cortisol is linked to lower hippocampal volume at baseline in patients with MCI¹³ and greater hippocampal atrophy in older adults^{37,38} might suggest that cortisol begins to assert its effects before the stage of MCI.

We further demonstrate that the detrimental effect of plasma cortisol on brain volume is specific for the hippocampal region of the brain. While a recent review highlighted the detrimental effects of

high cortisol on the hippocampus,⁶ previous work from our lab has shown that associations between plasma cortisol and gray matter volume can be found outside of the hippocampus.¹³ In the current study, there was no significant influence between baseline plasma cortisol and volumetric change over time in other regions, including entorhinal, fusiform, lateral, and medial orbitofrontal as well as middle temporal areas. Memory function is affected early on in the course of AD dementia, indicating a key role of hippocampal injury in the prodromal disease stage.¹² Future studies should investigate, whether efforts to lower perceived stress and HPA-axis activation could help decelerate neural degradation in the hippocampus in MCI patients.

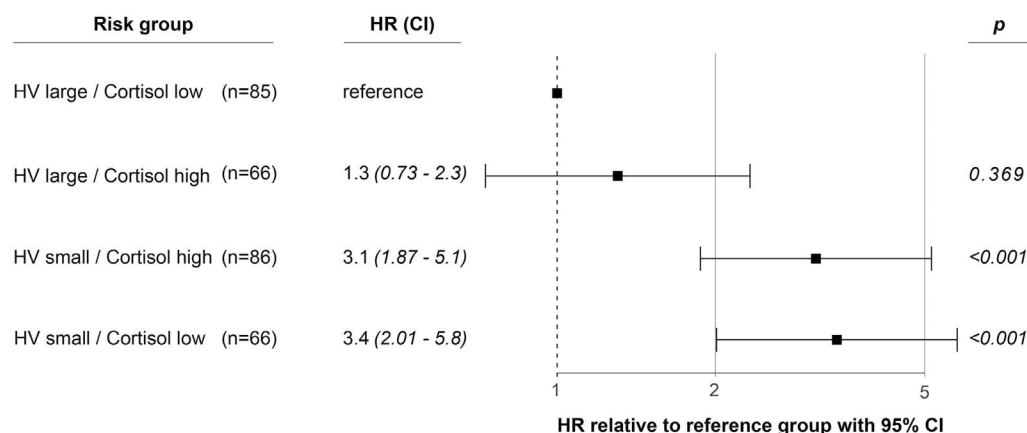


FIGURE 3 Forest plot of the Cox proportional hazards model, illustrating the risk on clinical progression to AD dementia for the four hippocampus-cortisol groups. X-axis shows the hazard ratio. Bars indicate 95% confidence intervals. *p*-Values indicate the significance of the difference in hazard ratio compared to the reference group (HV large/cortisol low). CI, confidence interval; HR, hazard ratio; HV, hippocampal volume.

TABLE 3 Effects of baseline hippocampal volume and plasma cortisol on clinical progression

	Cox model 1		Cox model 2	
	HR (95% CI)	<i>p</i> -Value	HR (95% CI)	<i>p</i> -Value
Hippocampus (small)	2.10 (1.62–2.71)	<0.001	2.15 (1.65–2.81)	<0.001
Cortisol (high)	1.06 (0.83–1.37)	0.634	1.07 (0.82–1.39)	0.615
Hippocampus (small)*cortisol (high)	0.84 (0.59–1.20)	0.327	0.81 (0.56–1.16)	0.245
Age			0.98 (0.96–1.01)	0.164
Sex (male)			0.83 (0.58–1.19)	0.313
Systolic BP			1.00 (0.99–1.01)	0.969
APO ε4 (ε4+)			1.67 (1.14–2.44)	0.009
GDS			1.03 (0.91–1.16)	0.693

Note: Results of the overall Cox proportional hazards models, quantifying the effect of baseline hippocampal volume and plasma cortisol on risk of clinical progression from MCI to AD dementia ($n = 303$). For categorical variables, the group that is compared to the respective reference group is given in parentheses. Hazard ratios are given as value (95% confidence interval). Hippocampal volume was normalized to baseline total intracranial volume.

Abbreviations: APO, apolipoprotein; BP, blood pressure; CI, confidence interval; GDS, Geriatric Depression Scale; HR, hazard ratio.

4.3 | Plasma cortisol, hippocampal volume, and clinical progression

We did not detect statistical evidence for an effect of plasma cortisol on clinical progression to AD dementia. We first reproduced established findings, showing that a large hippocampus protects the brain significantly longer from clinical symptoms than a small hippocampus.¹² A similar effect was not found for baseline plasma cortisol, and there was no significant interaction between hippocampal volume and plasma cortisol on clinical progression. In previous studies, higher plasma cortisol predicted clinical worsening in patients with AD, but not in non-demented older adults.¹⁶ Higher cortisol levels measured in CSF have been associated with faster cognitive decline and clinical worsening across the AD continuum³⁹ and in patients with amnesic MCI¹¹ and mild dementia.^{14,16} The present lack of an effect of plasma cortisol on clinical progression is surprising. It appears that, in our sample,

higher plasma cortisol is related to higher hippocampal atrophy in MCI patients, which in turn is a risk factor of accelerated disease progression. Another reason might be the limited sample size at follow-up assessments, warranting further investigation. Overall, our study highlights the role of plasma cortisol as a potentially modifiable risk factor of hippocampal degeneration in prodromal AD.

To conclude, our results show an exacerbating influence of high circulating cortisol on hippocampal atrophy over time. Hippocampal atrophy in turn accelerates clinical progression to AD in patients with MCI. Our findings may point toward a protective effect of lower cortisol at the early disease stage. Future studies should assess, whether stress-reducing lifestyle interventions could have a decelerating effect on hippocampal atrophy, which in turn may influence clinical progression to AD dementia. It is important to implement these targeted interventions as early as possible before neural damage becomes too severe.

4.4 | Study strengths and limitations

The present study has both strengths and limitations. Making use of the ADNI cohort, we had access to one of the biggest, well documented, and open access study databases on AD. The availability of longitudinal study data enabled the evaluation of temporal associations of the cortisol-brain-function.

A limitation of our study is the high inter-, as well as diurnal intra-, individual variability of cortisol levels. Even though plasma cortisol had been collected in the same manner in all participants (i.e., as morning fasting blood samples), a one-timepoint cortisol measurement, as used in the present study, could represent long-term levels or merely a same-day spike. Also, blood plasma levels reflect both bound and unbound cortisol. Since this has been shown to lead to an overestimation of adrenal dysfunction, it might introduce a positive bias to our cortisol-brain function analysis.^{40,41} Analysis of prevalently unbound cortisol might provide a better estimate of stress related pathways. For overcoming both these limitations, we suggest analysis of hair cortisol for future studies. Hair samples provide an approximation of long-term retrospective cortisol levels,⁴² and extraction methods are thought to yield mostly unbound cortisol. Finally, our study sample was both relatively small and included a number of incomplete longitudinal assessments. A larger, more completely assessed cohort will most likely support and strengthen our findings.

AUTHOR CONTRIBUTIONS

Silke White: data analysis, R scripting, interpretation of study results, and manuscript drafting/revision; René Mauer: statistical consultation, R scripting; Catharina Lange: data analysis; Olga Klimecki: manuscript editing and revision; Willem Huijbers: study concept and design, data analysis, interpretation of study results; Miranka Wirth: study concept and design, data analysis, interpretation of study results, and manuscript drafting/revision.

ACKNOWLEDGMENTS

The authors sincerely thank the ADNI research group and participants for their contributions to this research work. A complete list of ADNI investigators can be found at https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf. 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). The 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 (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.

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

Silke White reports nothing to disclose. Dr. René Mauer reports nothing to disclose. Dr. Catharina Lange reports nothing to disclose. Dr. Olga Klimecki reports nothing to disclose. Dr. Willem Huijbers is an employee of Biogen and was previously employed by Philips. The study was not funded by Biogen or Phillips. Dr. Miranka Wirth reports nothing to disclose. Author disclosures are available in the [supporting information](#).

DATA AVAILABILITY STATEMENT

The data that support findings of this study are openly available through the ADNI database at adni.loni.usc.edu. All R scripts used for analysis, as well as the originally downloaded datasets, are available via the open science framework (OSF, <https://osf.io/6n7up/>).

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How to cite this article: White S, Mauer R, Lange C, Klimecki O, Huijbers W, Wirth M. The effect of plasma cortisol on hippocampal atrophy and clinical progression in mild cognitive impairment. *Alzheimer's Dement*. 2023;15:e12463. <https://doi.org/10.1002/dad2.12463>