

# Cortisol, cognition and Alzheimer's disease biomarkers among memory clinic patients

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## ABSTRACT

**Objective** This study aims to investigate the relationship between diurnal cortisol patterns, cognition and Alzheimer's disease (AD) biomarkers in memory clinic patients.

**Method** Memory clinic patients were recruited from Karolinska University Hospital in Sweden (n=155). Diurnal cortisol patterns were assessed using five measures: awakening levels, cortisol awakening response, bedtime levels, the ratio of awakening to bedtime levels (AM/PM ratio) and total daily output. Cognition was measured in five domains: memory, working memory, processing speed, perceptual reasoning and overall cognition. AD biomarkers A $\beta_{42}$ , total tau and phosphorylated tau were assessed from cerebrospinal fluid (CSF). Cognition was measured at follow-up (average 32 months) in a subsample of participants (n=57).

**Results** In assessing the associations between cortisol and cognition, higher awakening cortisol levels were associated with greater processing speed at baseline. No relationship was found between diurnal cortisol patterns and change in cognition over time or CSF AD biomarkers in the total sample. After stratification by CSF A $\beta_{42}$  levels, higher awakening cortisol levels were associated with worse memory performance in amyloid-positive participants. In amyloid-negative participants, higher bedtime cortisol levels and a lower AM/PM ratio were associated with lower overall cognition, greater awakening cortisol levels were associated with better processing speed, and a higher AM/PM ratio was associated with better perceptual reasoning. Additionally, higher awakening cortisol levels were associated with lower CSF A $\beta_{42}$  levels in amyloid-positive participants, while higher bedtime cortisol levels and a lower AM/PM ratio were associated with higher CSF total tau in amyloid-negative participants.

**Conclusions** Our findings suggest that diurnal cortisol patterns are associated with cognitive function and provide new insights into the association between diurnal cortisol patterns and AD-related CSF biomarkers. Further research is needed to examine the complex relationship between cortisol, cognition and brain pathology.

## INTRODUCTION

The global prevalence of dementia is expected to increase sharply over the coming decades.<sup>1</sup> Identifying modifiable risk factors

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Chronic stress alters diurnal patterns of the stress hormone cortisol, which is associated with cognitive performance in healthy adults. Limited research has investigated the associations between diurnal cortisol patterns and cognitive performance in memory clinic patients.

### WHAT THIS STUDY ADDS

⇒ This is the first study to assess the association between diurnal cortisol patterns and Alzheimer's disease biomarkers A $\beta_{42}$  and tau in humans.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights the role of chronic stress as a potential modifiable risk factor for the development of Alzheimer's disease, and promotes tailored interventions that reduce chronic stress and its consequences.

is vital in preventing or postponing cognitive decline and dementia. Approximately 40% of all dementia cases could be delayed or prevented by targeting modifiable lifestyle risk factors.<sup>2</sup> Chronic stress is a potential dementia risk factor. In humans, stress activates the hypothalamic-pituitary-adrenal (HPA) axis, the main end-product of which is the hormone cortisol. Under normal circumstances, cortisol follows a circadian pattern, characterised by a peak shortly after awakening (the cortisol awakening response (CAR)), followed by decreasing cortisol levels throughout the remainder of the day.<sup>3</sup> However, chronic stress has been linked to diurnal pattern dysregulations, specifically with an altered post-awakening peak, increased levels late in the day and reduced diurnal cortisol variation.<sup>4,5</sup> HPA-axis dysregulations are linked to adverse health outcomes, including heart disease, depression<sup>6</sup> and potentially cognitive decline.<sup>7,8</sup> Measuring alterations in the diurnal cortisol pattern

could therefore be an effective method to assess the effects of chronic stress.

The number of published studies on the relationship between cortisol and dementia has increased rapidly in recent years. For instance, a recent meta-analysis found that morning cortisol levels were elevated in Alzheimer's disease (AD), the most common type of dementia, compared with cognitively healthy controls.<sup>9</sup> Additionally, several studies showed that high single-measurement cortisol levels and a flattened diurnal cortisol pattern are associated with reduced cognition, mainly in cognitively healthy populations.<sup>10–12</sup> Cortisol levels even appear to predict cognitive decline, especially among those at elevated genetic risk for AD.<sup>8</sup> This may be due to cortisol-driven neurodegeneration and reduced hippocampal neurogenesis.<sup>13–15</sup> Animal models have shown that glucocorticoid hormone levels are associated with increased brain accumulation of the AD-related biomarkers tau and beta-amyloid (A $\beta$ ).<sup>16–17</sup> However, few studies have assessed the association between cortisol levels and these AD biomarkers in humans,<sup>18–19</sup> and to the best of our knowledge, none have accounted for diurnal cortisol patterns. The present study aims to assess how diurnal cortisol pattern components relate to clinical diagnosis, cognitive function, cognitive decline and AD biomarkers in a memory clinic sample. We hypothesise that cortisol patterns reflecting chronic stress (flattened CAR, higher evening cortisol levels and reduced ratio of morning to evening cortisol levels), are associated with reduced cognitive function, greater cognitive decline and greater AD pathology.

## METHODS

### Study design and participants

This research is based on the Cortisol and Stress in Alzheimer's Disease (Co-STAR) cohort study. Participants were recruited from the Karolinska University Hospital memory clinic in Huddinge, Sweden. Between 2014 and 2017, all patients aged 45+ years were invited to participate at their first memory clinic visit, provided they were physically able to participate and did not suffer from conditions affecting HPA-axis activity (eg, Cushing's disease). Of the patients approached, 280 did not fulfil these inclusion criteria, while a further 136 declined to participate. In total, 233 participants agreed to participate, 188 of whom provided data and did not withdraw their consent to be included. One hundred and fifty-five participants contributed sufficient data for the assessment of the cross-sectional associations between diurnal cortisol patterns, cognitive function and AD biomarkers. Participants diagnosed with subjective cognitive impairment (SCI) or mild cognitive impairment (MCI) at baseline were invited to participate in a follow-up examination. Out of 123 invited participants, 68 completed follow-up assessments between February 2018 and May 2019, after an average follow-up of 32 months. Sufficient data for inclusion in follow-up analysis was provided by 57 participants.

### Clinical assessments

In accordance with standard assessment procedures at the Karolinska University Hospital memory clinic, participants met with neuropsychologists for a comprehensive cognitive assessment, completed physical and neurological examinations and underwent brain imaging (mostly MRI), blood chemistry and cerebrospinal fluid (CSF) examinations. Co-STAR participants were additionally provided a home cortisol sampling kit. Participants were diagnosed based on a consensus meeting, using the International Classification of Diseases 10th Revision (ICD-10) dementia diagnostic criteria,<sup>20</sup> and the Winblad *et al* clinical criteria (including subjective cognitive issues, impairment on cognitive tests and absence of dementia)<sup>21</sup> for MCI diagnoses. A diagnosis of SCI was given if the patient did not fulfil the MCI or dementia criteria, but reported cognitive issues. Participants were excluded if they did not provide cortisol samples or were diagnosed with dementia other than AD.

### Cognitive function

At baseline, all participants underwent an extensive battery of neurocognitive tests. Unadjusted z-scores were calculated for all tests, based on a cognitively healthy reference population of 24 older Swedish adults (12 men and 12 women). This sample of healthy volunteers without major health conditions was similar in age to the study sample (reference: m=63.2, range: 47–75; study sample: m=62.5, range 47–82), but had slightly higher education levels (reference: m=17.0 years, SD=3.1; study sample: m=14.2, SD=3.2). Z-scores for tests related to the same cognitive domain were averaged to create cognition scores. Five cognitive domains were included: memory, working memory, processing speed, perceptual reasoning and overall cognition. The memory score was based on the Rey Auditory Verbal Learning Test (delayed recall),<sup>22</sup> the Rey-Osterrieth Complex Figure (immediate recall),<sup>23–24</sup> the Wechsler Adult Intelligence Scale (WAIS) Digit Symbol Substitution Test (immediate recall)<sup>25</sup> and the Hagman test, developed at the Karolinska University Hospital to assess visual memory (manuscript in preparation). The overall cognition score was obtained using four tests of Wechsler's Abbreviated Scale of Intelligence: WAIS Block Design, WAIS Similarities, WAIS Matrix Reasoning and WAIS Information (instead of WAIS Vocabulary).<sup>25–26</sup> Working memory was calculated using two tests: WAIS Digit Span and WAIS Arithmetic. Processing speed was assessed with the WAIS Digit Symbol Substitution Test. Perceptual reasoning was calculated using WAIS Block Design and WAIS Matrices.<sup>25</sup>

Due to their non-normal distribution, all five cognitive domains were zero-skewness log transformed. At follow-up, participants underwent an abridged test battery including tests sensitive to cognitive change. Memory and processing speed scores were calculated in the same manner as at baseline, based on the same reference population, but tests for overall cognition, working memory and perceptual reasoning scores were not included at

**Table 1** Characteristics of study participants in percentages or means and SD, by diagnosis

Means (SD) and percentages	n (155)	SCI (n=60)	MCI (n=63)	AD dementia (n=32)	P value (X <sup>2</sup> /ANOVA)
Age (years, ANOVA)	155	60.2 (6.46)	62.6 (7.92)	67.9 (8.29)	<0.001***
Education (years, ANOVA)	155	14.4 (3.24)	14.0 (3.50)	13.4 (3.07)	0.380
Female (% , X <sup>2</sup> )	155	61.7	54.0	68.8	0.360
Awakening time (hh:mm, ANOVA)	155	07:11	06:58	07:18	0.360
Stress measures					
Perceived Stress Scale (___/40, ANOVA)	145	17.6 (6.25)	19.0 (8.06)	18.0 (7.41)	0.267
Cortisol					
Awakening cortisol (t1) (nmol/L, ANOVA)	155	8.2 (4.48)	9.1 (5.24)	11.0 (5.78)	0.042*
Bedtime cortisol (t6) (nmol/L, ANOVA)	155	2.0 (2.72)	2.7 (4.43)	2.3 (3.60)	0.541
Cortisol awakening response (ANOVA)	155	0.69 (1.41)	0.60 (1.18)	0.27 (1.26)	0.326
Daily cortisol output (ANOVA)	155	75.5 (46.05)	91.0 (79.22)	78.3 (33.30)	0.333
Cortisol AM/PM ratio (t1/t6) (ANOVA)	155	9.45 (8.75)	7.39 (5.39)	10.02 (7.99)	0.166
CSF biomarkers					
Aβ <sub>42</sub> (ng/L, ANOVA)	135	867.4 (172.68)	713.6 (229.81)	426.7 (107.69)	<0.001***
Aβ <sub>42</sub> ≤550 ng/L (% , X <sup>2</sup> )	135	3.8	28.8	87.1	<0.001***
T-Tau (ng/L, ANOVA)	135	279.5 (112.73)	321.8 (183.48)	612.2 (266.71)	<0.001***
T-Tau >400ng/L (% , X <sup>2</sup> )	135	13.5	23.1	83.9	<0.001***
P-Tau (ng/L, ANOVA)	135	41.7 (14.24)	45.4 (21.37)	72.5 (28.84)	<0.001***
P-Tau >80ng/L (% , X <sup>2</sup> )	135	3.8	7.7	29.0	0.001**
Cognition					
Overall cognition (mean z-score, ANOVA)	125	-0.28 (0.86)	-0.91 (0.84)	-1.29 (0.89)	<0.001***
Memory (mean z-score, ANOVA)	134	-0.05 (0.78)	-1.46 (1.18)	-2.77 (0.88)	<0.001***
Processing speed (mean z-score, ANOVA)	124	-0.26 (1.14)	-1.00 (1.26)	-1.52 (1.02)	<0.001***
Working memory (mean z-score, ANOVA)	110	-0.25 (0.82)	-0.83 (1.11)	-1.17 (0.40)	<0.001***
Perceptual reasoning (mean z-score, ANOVA)	127	0.05 (0.84)	-0.61 (0.96)	-0.90 (0.91)	<0.001**

\*Significant at p<0.05; \*\*significant at p<0.01, \*\*\*significant at p<0.001.  
 AD, Alzheimer's disease; ANOVA, analysis of variance; MCI, mild cognitive impairment; P-Tau, phosphorylated tau ; SCI, subjective cognitive impairment; T-Tau, total tau.

follow-up. Change in cognition was calculated as the difference between baseline and follow-up z-score.

### CSF AD biomarkers

Three AD-related CSF biomarkers were included in the study: Aβ<sub>42</sub>, total tau (T-Tau) and phosphorylated tau (P-Tau). The CSF samples were collected through lumbar punctures as part of the memory clinic's standard assessments, using polypropylene tubes. The samples were mixed gently to avoid gradient effects, centrifuged for 10 min at 2000×g and subsequently kept at -80°C until biochemical analysis. Tau and Aβ<sub>42</sub> were assessed by means of sandwich ELISA. This process has previously been described in more detail.<sup>27</sup> T-Tau and P-Tau underwent logarithmic transformation to reduce skewness.

### Cortisol

The diurnal cortisol pattern was assessed at baseline using salivary cortisol, commonly used in stress research,<sup>28</sup> as it reflects physiologically active free cortisol.<sup>29</sup> Salivary

cortisol was measured using home sampling kits, to reflect basal cortisol levels. Due to high day-to-day variability in cortisol levels, participants were asked to collect saliva on two non-consecutive weekdays. Cortisol measurements were taken at six different time points: immediately after awakening (time point (t1), 30 min after awakening (t2), 1 hour after awakening (t3), at 14:00 (t4), at 16:00 (t5) and immediately before bedtime (t6). Participants documented exact sampling times at each measurement and stored the samples in their freezer until sending them back to the memory clinic. From there, the samples were sent to Dresden LabService GmbH (Dresden, Germany), where they were stored at -20°C until analysis. The samples were subsequently thawed and centrifuged at 3000 rpm for 5 min, yielding a supernatant with low viscosity. Cortisol levels were assessed using chemiluminescence immunoassay with high sensitivity (IBL International, Hamburg, Germany), with intra-assay and inter-assay coefficients below 8%.

As cortisol levels shift rapidly during the first hour after awakening, morning measurements taken more than 15 min from their intended measurement time (<15 or >45 min after awakening for t2; <45 or >75 min after awakening for t3) were excluded. Subsequently, the measurements from the 2 days were averaged. Data from each time point were winsorised at three SD from the mean to reduce the effect of outliers.<sup>3 30</sup> Due to the high number of participants who had invalid t3 data for both measurement days, the CAR and total daily cortisol output were calculated without t3.

In the current study, the diurnal cortisol pattern was assessed using five cortisol measures: awakening cortisol (t1) levels, bedtime cortisol (t6) levels, the CAR (increase from t1 to t2), total daily cortisol output (t1, t2, t4, t5 and t6) and the ratio of awakening (t1) to bedtime (t6) cortisol (AM/PM ratio (t1/t6)). All of these measures have been previously used in stress research.<sup>30</sup> The CAR was calculated as the 'area under the curve with respect to increase'<sup>31</sup> for t1 and t2. Total daily cortisol output was calculated as the 'area under the curve with respect to ground'<sup>31</sup> for t1, t2, t4, t5 and t6. Awakening cortisol (t1), bedtime cortisol (t6), total daily cortisol output and the AM/PM ratio exhibited skewness, and underwent logarithmic transformation to increase normality.

### Statistical analysis

Descriptive statistics were calculated for the study sample. The data is displayed separately for the three diagnostic groups (SCI, MCI and AD) (table 1). For a visual representation of the diurnal cortisol patterns in the three diagnostic groups, see figure 1A. Significance levels for the differences between the diagnostic groups were calculated by means of  $\chi^2$  for categorical or analysis of variance for continuous variables. Linear regression analyses were subsequently conducted. All analyses were adjusted for age, sex and education. Age and sex are related to both cognition and AD dementia prevalence, while education

is associated with performance on cognitive tests.<sup>3 32 33</sup>

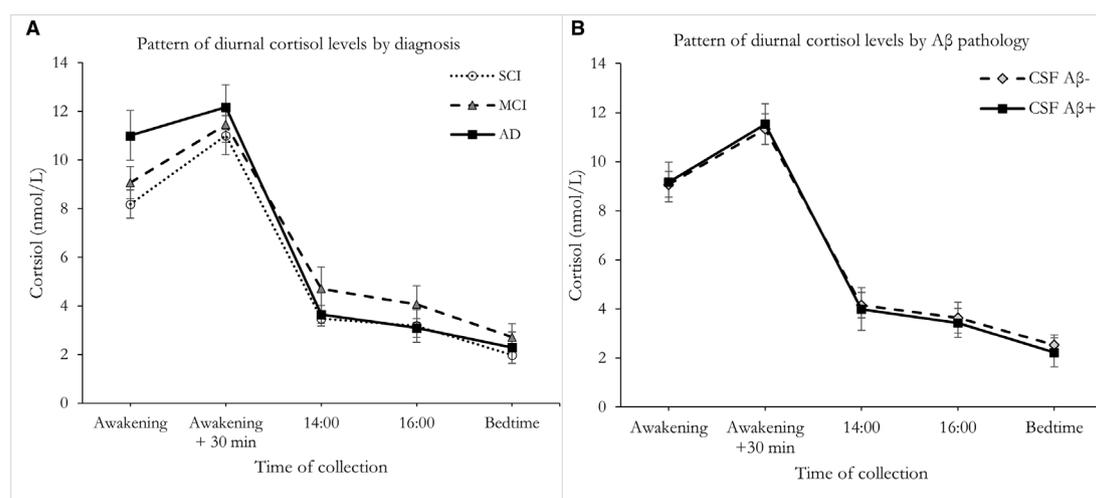
Given that SCI and MCI diagnoses tend to include pathologically heterogeneous groups of people, further linear regressions were run to assess potential statistical interaction between the cortisol measures and CSF A $\beta$ <sub>42</sub> in predicting cognitive function, using a dichotomous measure of CSF A $\beta$ <sub>42</sub> (CSF A $\beta$ <sub>42</sub> levels  $\geq 550$  ng/L vs CSF A $\beta$ <sub>42</sub> levels <550 ng/L, laboratory-recommended cut-off at the Karolinska memory clinic shown to discriminate well between AD and SCI).<sup>34 35</sup> P values of the interactions show whether the coefficients for the associations between the cortisol measures and the cognitive outcomes are statistically different between amyloid-positive and amyloid-negative participants. Additional analyses stratified by amyloid pathology were subsequently conducted.

SPSS Statistics V.27 (IBM, Armonk, New York, USA) was used for all analyses, except the zero-skewness log transformations, which were performed using Stata V.16 (StataCorp, College Station, Texas, USA). Tests were conducted at an  $\alpha$ -level of .05. Unstandardised coefficients or ORs, 95% CIs and p values are reported for the results of the regression analyses.

## RESULTS

### Characteristics of participants

One hundred and fifty-five participants were included at baseline (60 SCI, 63 MCI and 32 AD dementia). Participants were aged 46–85 years, with a mean age of 62.8 years. The majority was women, 60.0%. When examining the characteristics of the study sample by diagnosis, participants with AD dementia were, on average, older (68.1 years) than participants with MCI (62.5) and SCI (60.1, see table 1). CSF A $\beta$ <sub>42</sub> levels were abnormal (<550 ng/L) in 87.1% of patients with AD, in 28.8% of patients with MCI and in 3.8% of patients with SCI. Similarly, abnormal levels of T-Tau (>400 ng/L) were significantly more



**Figure 1** Diurnal patterns of cortisol levels, by (A) diagnostic category and by (B) amyloid pathology status. AD, Alzheimer's disease; A $\beta$ , beta-amyloid; A $\beta$ -, CSF A $\beta$ <sub>42</sub> level above 550 ng/L; A $\beta$ +, CSF A $\beta$ <sub>42</sub> level below 550 ng/L; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; SCI, subjective cognitive impairment.

common in patients with AD (83.9%) than in patients with MCI (23.1%) or patients with SCI (13.5%). Only 29.0% of patients with AD displayed abnormal levels of P-Tau (>80 ng/L), although this proportion was still significantly lower among patients with MCI (7.7%) and SCI (3.8%).

At follow-up, 57 participants were included (38 SCI at baseline, 19 MCI at baseline; 58% women). Participants were followed-up for an average of approximately 2.7 years. To assess potential selection bias in the follow-up sample, characteristics of SCI and MCI participants included at follow-up were compared with those not included. No differences were found in demographic factors, cortisol patterns or perceived stress levels, but participants who were included in the follow-up had higher CSF A $\beta_{42}$  levels (889.1 vs 712.2 ng/L;  $p < 0.001$ ) and a better memory score (-0.33 vs -1.09;  $p = 0.001$ ) at baseline (online supplemental table 1).

### Comparisons of the diurnal cortisol pattern

Only awakening cortisol levels differed significantly between the diagnostic groups ( $F = 3.23$ ,  $p = 0.042$ , figure 1A); participants with AD dementia had the highest while participants with SCI had the lowest levels. There were no differences in cortisol measures between participants with normal and abnormal CSF A $\beta_{42}$  levels (figure 1B).

### Associations between cortisol measures and cognition

Linear regressions showed that high awakening cortisol levels were associated with greater processing speed ( $b: 0.28$ ; 95% CI: (0.01 to 0.54), table 2). At a 90% confidence level, a greater cortisol AM/PM ratio (t1/t6) was related to better overall cognition, while lower awakening cortisol levels and a greater CAR were related to better memory performance, but these associations did not reach statistical significance ( $0.1 > p > 0.05$ ). None of the cortisol measures were associated with working memory or perceptual reasoning in the full sample. Baseline cortisol measures were not associated with memory or processing speed at follow-up (table 3).

### Associations between cortisol measures and CSF biomarkers

There were no significant associations between the cortisol measures and the AD biomarkers (A $\beta_{42}$ , T-Tau and P-Tau) in the full sample. Participants with higher T-Tau levels appeared to have greater daily cortisol output, but this association did not reach significance ( $b = 0.11$ ; 95% CI: (-0.02 to 0.23), table 4).

### Associations between cortisol measures and cognition, stratified by amyloid pathology

Analyses of the interactions between the cortisol measures and A $\beta_{42}$  on the cognitive outcomes showed that there was evidence for interactions between the cortisol AM/PM ratio and A $\beta_{42}$  in predicting overall cognition ( $p = 0.016$ , see table 2) and between awakening cortisol and A $\beta_{42}$  in predicting memory ( $p = 0.024$ ). Further exploratory analyses stratified by amyloid pathology were subsequently

conducted. For amyloid-negative participants, higher awakening cortisol levels remained significantly associated with better processing speed ( $b: 0.35$ ; 95% CI: (0.01 to 0.70)), lower bedtime cortisol levels were associated with greater overall cognition ( $b: -0.19$ ; 95% CI: (-0.34 to -0.04)) and a higher AM/PM ratio was associated with greater overall cognition ( $b: 0.38$ ; 95% CI: (0.17 to 0.59)) and better perceptual reasoning ( $b: 0.26$ ; 95% CI: (0.02 to 0.50)). In amyloid-positive participants, lower awakening cortisol levels were associated with better memory ( $b: -0.78$ ; 95% CI: (-1.19 to -0.36)). The associations between awakening cortisol and processing speed seen in the full sample was not significant in amyloid-positive participants, although there was no evidence for interaction between awakening cortisol levels and A $\beta_{42}$  in predicting processing speed.

## DISCUSSION

This study investigated associations between diurnal cortisol patterns, cognition and CSF AD biomarkers among memory clinic patients. Diurnal cortisol pattern comparisons showed that participants with AD dementia had significantly higher awakening cortisol levels than those with SCI. Interestingly, there was no difference in awakening cortisol levels between participants with normal and abnormal CSF A $\beta_{42}$  levels. Afternoon and evening cortisol measures did not differ between clinical diagnostic groups. In assessing the associations between cortisol and cognition, higher awakening cortisol levels were associated with better processing speed at baseline. No other significant associations between cortisol patterns and cognition were found. Similarly, no associations were found between cortisol patterns and CSF AD biomarkers.

Further analyses were conducted after stratification for amyloid pathology status. In participants without amyloid pathology, the association between higher awakening cortisol levels and better processing speed remained significant. Furthermore, lower bedtime cortisol levels and a greater AM/PM ratio were associated with better overall cognition and a greater AM/PM ratio was associated with better perceptual reasoning. Together, these findings suggest that a more pronounced cortisol pattern (higher morning and lower evening cortisol levels), is associated with better cognition. In those with amyloid pathology, lower awakening cortisol levels were associated with better memory. This association is in line with the finding that awakening cortisol levels were highest in patients with AD, but contradicts the association between high awakening cortisol levels and better processing speed in the full sample. There was evidence for interactions between the cortisol AM/PM ratio and A $\beta_{42}$  in their association with overall cognition, and between awakening cortisol levels and A $\beta_{42}$  in their association with memory, but not for other interactions. Care must be taken in interpreting differences in stratified results between subgroups without evidence for interaction.

**Table 2** Associations between diurnal cortisol patterns and cognitive performance—in the full sample, and stratified by normal/abnormal CSF Aβ<sub>42</sub> levels (laboratory-recommended cut-off), plus p values for interactions cortisol\*Aβ<sub>42</sub> for each of the cortisol measures

	Overall cognition			Memory			Working memory			Processing speed			Perceptual reasoning							
	b	95% CI	p	P value (interaction)	b	95% CI	p	P value (interaction)	b	95% CI	p	P value (interaction)	b	95% CI	p					
All		(n=125)			(n=134)				(n=110)				(n=124)			(n=127)				
Awakening cortisol (t1)	0.01	-0.22 to 0.25	0.919	0.070	-0.24	-0.50 to 0.02	0.070	0.498	0.11	-0.21 to 0.42	0.498	0.042*	0.28	0.01 to 0.54	0.042*	0.03	-0.23 to 0.27	0.845		
Bedtime cortisol (t6)	-0.11	-0.24 to 0.02	0.102	0.381	-0.07	-0.21 to 0.08	0.381	0.750	0.03	-0.15 to 0.20	0.750	0.991	0	-0.15 to 0.15	0.991	-0.09	-0.23 to 0.06	0.230		
Cortisol awakening response	-0.02	-0.13 to 0.10	0.751	0.080	0.11	-0.01 to 0.23	0.080	0.660	-0.03	-0.19 to 0.12	0.660	0.552	0.04	-0.09 to 0.16	0.552	0.01	-0.11 to 0.13	0.900		
Daily cortisol output	-0.07	-0.27 to 0.13	0.479	0.456	-0.08	-0.31 to 0.14	0.456	0.666	0.06	-0.21 to 0.33	0.666	0.277	0.12	-0.10 to 0.35	0.277	-0.03	-0.24 to 0.18	0.770		
Cortisol AM/PM ratio (t1/t6)	0.18	0.00 to 0.36	0.052	0.939	-0.01	-0.22 to 0.21	0.939	0.978	0	-0.24 to 0.25	0.978	0.212	0.14	-0.08 to 0.35	0.212	0.14	-0.05 to 0.34	0.151		
Aβ <sub>42</sub> ≥550 ng/L		(n=75)			(n=80)				(n=68)				(n=76)			(n=76)				
Awakening cortisol (t1)	0.12	-0.18 to 0.42	0.439	0.271	-0.17	-0.49 to 0.14	0.271	0.024*	0.12	-0.27 to 0.52	0.543	0.468	0.35	0.01 to 0.70	0.047*	0.08	-0.25 to 0.41	0.622	0.229	
Bedtime cortisol (t6)	-0.19	-0.34 to -0.04	0.016*	0.291	-0.09	-0.25 to 0.08	0.291	0.841	-0.06	-0.26 to 0.14	0.546	0.297	-0.02	-0.21 to 0.17	0.855	-0.13	-0.30 to 0.04	0.123	0.884	
Cortisol awakening response	0.01	-0.12 to 0.14	0.919	0.228	0.08	-0.05 to 0.22	0.228	0.493	-0.02	-0.20 to 0.16	0.801	0.778	-0.03	-0.19 to 0.12	0.662	0.03	-0.11 to 0.17	0.673	0.678	
Daily cortisol output	-0.1	-0.34 to 0.14	0.418	0.575	-0.07	-0.33 to 0.19	0.575	0.59	-0.05	-0.38 to 0.29	0.773	0.575	0.03	-0.26 to 0.32	0.854	-0.06	-0.33 to 0.21	0.636	0.784	
Cortisol AM/PM ratio (t1/t6)	0.38	0.17 to 0.59	<0.001***	0.481	0.09	-0.16 to 0.33	0.481	0.147	0.15	-0.14 to 0.44	0.310	0.128	0.19	-0.08 to 0.46	0.157	0.26	0.02 to 0.50	0.035*	0.397	
Aβ <sub>42</sub> <550 ng/L		(n=36)			(n=37)				(n=29)				(n=32)			(n=36)				
Awakening cortisol (t1)	-0.41	-0.93 to 0.11	0.114	<0.001***	-0.78	-1.19 to -0.36	<0.001***	0.718	-0.13	-0.87 to 0.61	0.718	0.797	0.06	-0.44 to 0.57	0.797	-0.26	-0.80 to 0.27	0.320	0.320	
Bedtime cortisol (t6)	-0.02	-0.33 to 0.29	0.895	0.484	-0.09	-0.36 to 0.18	0.484	0.257	0.23	-0.18 to 0.64	0.257	0.961	0.01	-0.27 to 0.28	0.961	-0.11	-0.42 to 0.19	0.460	0.460	
Cortisol awakening response	-0.09	-0.37 to 0.19	0.512	0.067	0.2	-0.02 to 0.42	0.067	0.482	-0.13	-0.50 to 0.24	0.482	0.063	0.19	-0.01 to 0.40	0.063	-0.06	-0.34 to 0.22	0.677	0.677	
Daily cortisol output	-0.18	-0.57 to 0.21	0.352	0.204	-0.25	-0.63 to 0.14	0.204	0.692	0.11	-0.44 to 0.65	0.692	0.265	0.21	-0.17 to 0.58	0.265	-0.18	-0.57 to 0.22	0.368	0.368	
Cortisol AM/PM ratio (t1/t6)	-0.18	-0.59 to 0.22	0.365	0.166	-0.28	-0.68 to 0.12	0.166	0.181	-0.36	-0.90 to 0.18	0.181	0.961	0.01	-0.40 to 0.42	0.961	0.02	-0.39 to 0.43	0.926	0.926	

Results based on linear regressions. All analysis adjusted for age, sex, education. \*p<0.05; \*\*p<0.01; \*\*\*p<0.001. Aβ, beta-amyloid; CSF, cerebrospinal fluid.

**Table 3** Associations between cortisol and change in cognition over time

	Memory (n=49)			Processing speed (n=45)		
	b	95% CI	p	b	95% CI	p
Awakening cortisol (t1)	0.02	-0.31 to 0.34	0.918	-0.05	-0.39 to 0.30	0.792
Bedtime cortisol (t6)	-0.03	-0.21 to 0.14	0.693	-0.02	-0.20 to 0.15	0.795
Cortisol awakening response	-0.02	-0.18 to 0.15	0.840	0.03	-0.14 to 0.19	0.760
Daily cortisol output	-0.09	-0.36 to 0.19	0.528	-0.02	-0.30 to 0.26	0.862
Cortisol AM/PM ratio (t1/t6)	0.09	-0.17 to 0.34	0.510	-0.02	-0.28 to 0.24	0.895

Results based on linear regressions. All analysis adjusted for age, sex and education. \*p<0.05, \*\*p<0.01; \*\*\*p<0.001.

Our results align with a recent meta-analysis which found that patients with AD dementia, but not MCI, had significantly higher morning salivary cortisol levels than cognitively healthy controls.<sup>9</sup> While the reason for the increased morning cortisol levels among patients with AD dementia remains unclear, damage to the hippocampus, HPA axis negative feedback loop dysregulations and low-grade inflammation in AD are suggested pathways.<sup>9</sup>

The relationship between cortisol levels and cognition has been studied extensively in healthy older-aged and middle-aged populations. While results depend on the specific cortisol and cognitive measures used, flattened diurnal cortisol patterns are generally associated with poor cognition.<sup>10 12 36</sup> This is consistent with the findings of the current study; among participants without amyloid pathology, greater awakening cortisol, lower bedtime cortisol and a greater AM/PM ratio were significantly associated with better baseline cognition. In the full sample, high awakening cortisol levels were associated with better processing speed. Conversely, patients with AD displayed higher awakening cortisol levels than patients with MCI or SCI. The association between awakening cortisol and processing speed may be driven by participants with MCI or SCI. Previous studies in healthy older adults on awakening cortisol and cognition have yielded mixed results, with higher awakening cortisol associated with greater working memory,<sup>7 37</sup> but also with worse delayed recall.<sup>38</sup> Korten *et al*, and Ennis *et al*, found no association between awakening cortisol and processing

speed.<sup>7 37</sup> The different associations may reflect multiple potential causes of high awakening cortisol levels. High awakening cortisol levels may reflect normal function in those without/limited AD pathology, while also reflecting greater sleep disturbance or HPA dysregulation in those with AD. This study did not find significant associations between diurnal cortisol patterns and cognitive decline over time, possibly due to limited statistical power. Additionally, participants included at follow-up had better baseline memory and CSF A $\beta_{42}$  compared with those not included, suggesting that they may have been healthier and less likely to decline.

Few studies in humans have examined the association between cortisol levels and AD biomarkers. The current literature suggests that high cortisol levels are associated with greater AD pathology,<sup>16–18</sup> although results vary depending on methodological differences and participants' disease stage. For instance, one study, using morning serum cortisol levels, found high cortisol levels to be associated with lower CSF T-Tau, P-Tau and T-Tau/A $\beta$  among patients with AD dementia.<sup>19</sup> None of the aforementioned studies assessed diurnal cortisol patterns. This is the first study to investigate the associations between diurnal measures of salivary cortisol (a more sensitive measure than plasma, serum or urine cortisol) and biomarkers of amyloid (CSF A $\beta_{42}$ ), tau pathology (CSF P-Tau) and neurodegeneration (CSF T-Tau). This study found no significant association between cortisol patterns and these biomarkers. Further research should examine

**Table 4** Associations between cortisol and CSF AD biomarkers

	A $\beta_{42}$			T-Tau			P-Tau		
	b	95% CI	P	b	95% CI	p	b	95% CI	p
All (n=135)									
Awakening cortisol (t1)	2.96	-68.57 to 74.49	0.935	0.06	-0.09 to 0.21	0.439	0.01	-0.11 to 0.14	0.818
Bedtime cortisol (t6)	21.67	-17.67 to 61.01	0.278	0.05	-0.04 to 0.13	0.272	0.02	-0.05 to 0.08	0.620
Cortisol awakening response	-3.22	-34.11 to 27.68	0.837	0.01	-0.06 to 0.07	0.778	0.01	-0.04 to 0.06	0.681
Daily cortisol output	12.23	-47.61 to 72.07	0.687	0.11	-0.02 to 0.23	0.089	0.07	-0.04 to 0.17	0.200
Cortisol AM/PM ratio (t1/t6)	-27.05	-83.17 to 29.07	0.342	-0.03	-0.15 to 0.08	0.585	-0.01	-0.11 to 0.08	0.798

Results based on linear regressions. All analysis adjusted for age, sex and education.

\*P<0.05, \*\*p<0.01; \*\*\*p<0.001.

AD, Alzheimer's disease; A $\beta$ , beta-amyloid; CSF, cerebrospinal fluid; P-Tau, phosphorylated tau; T-TAU, total tau.

whether diurnal cortisol patterns are differentially associated with cognition and AD biomarkers in patients with different amyloid/tau/neurodegeneration biomarker profiles.<sup>39</sup> The present study found limited evidence for interactions between cortisol measures and A $\beta$  in their association with cognitive function. This supports the findings of Udeh-Momoh *et al*, who showed that morning CSF cortisol and A $\beta$  interacted in predicting clinical progression to MCI or AD among cognitively normal older adults.<sup>40</sup> However, due to the high number of non-significant interaction results in the present study, care must be taken in interpreting the stratified results.

The strength of this study was the detailed characterisation of participants, including comprehensive cognitive assessments, CSF AD pathology biomarkers and diurnal cortisol measures, allowing us to examine associations seldomly studied in memory clinic samples. Presented results are uncorrected for multiple testing and should be interpreted with caution. As a relatively high number of participants had invalid t<sub>3</sub> cortisol data, the cortisol measures had to be calculated without t<sub>3</sub>, reducing their robustness.<sup>3</sup> The generalisability of these results may be reduced as more than half of memory clinic patients attending the memory clinic within the recruitment period failed to meet the inclusion criteria or declined to participate, and because at follow-up, only approximately half of the invited participants returned. Additionally, to reduce the burden on the participants, a shortened cognitive tests battery was conducted at follow-up, reducing them to two cognitive domains.

Our findings strengthen the evidence that diurnal cortisol patterns and cognitive impairment are associated, and provide new insights into the association between diurnal cortisol patterns and AD-related CSF biomarkers. This study was based on a memory clinic sample, and care must be taken when generalising these results to other populations. Further longitudinal research should focus on the complex relationship between cortisol, cognition and brain pathology.

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**Supplemental Table 1.** Characteristics of study participants in percentages or means (and standard deviations), for participants included at follow-up (FU) and SCI/MCI participants not included at follow-up (No FU).

<i>Means &amp; Percentages, t-tests unless otherwise indicated</i>	<b>n</b>	<b>Follow-Up</b>	<b>No Follow-up</b>	<i>p (X<sup>2</sup>/ t)</i>
	(FU/No FU)	(n=57)	(n=66)	
Age (years)	(57/66)	60.98 (6.39)	61.84 (8.05)	.517
Education (years)	(57/66)	14.10 (3.39)	14.21 (3.38)	.857
Female (% , X <sup>2</sup> )	(57/66)	59.6	56.1	.688
Stress measures				
Perceived Stress Scale ( __ /40)	(54/60)	18.89 (7.13)	17.85 (7.40)	.448
Cortisol				
Awakening Cortisol (t1) (nmol/l)	(57/66)	8.76 (4.91)	8.53 (4.90)	.797
Bedtime Cortisol (t6) (nmol/l)	(57/66)	2.48 (3.79)	2.24 (3.64)	.718
Cortisol Awakening Response	(57/66)	.53 (1.17)	.75 (1.39)	.347
Daily Cortisol Output	(57/66)	3.92 (.70)	4.04 (.69)	.340
Cortisol AM/PM ratio (t1/t6)	(57/66)	2.04 (.75)	2.00 (.70)	.792
CSF Biomarkers				
Aβ <sub>42</sub> (ng/l)	(46/58)	889.13 (153.80)	712.19 (227.94)	< .001 ***
T-Tau (ng/l)	(46/58)	286.67 (105.27)	311.76 (182.41)	.382
P-Tau (ng/l)	(46/58)	41.78 (13.63)	44.88 (21.10)	.368
Cognition				
Overall cognition (mean z-score)	(47/54)	-.54 (.91)	-.61 (.90)	.688
Memory (mean z-score)	(51/58)	-.33 (.91)	-1.09 (1.35)	.001 **
Processing Speed (mean z-score)	(48/53)	-.54 (1.16)	-.66 (1.33)	.654
Working Memory (mean z-score)	(43/48)	-.37 (.84)	-.66 (1.12)	.169
Perceptual Reasoning (mean z-score)	(49/54)	-.15 (.87)	-.38 (1.03)	.234
Currently taking cortisone (% , X <sup>2</sup> )	(57/66)	12.3	10.6	.771

\* significant at p &lt; .05; \*\* significant at p &lt; .01, \*\*\* significant at p &lt; .001