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Cortisol and 10-Year Cognitive Decline in Older People From the General Population

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ABSTRACT

Objective: The present study examined bidirectional effects between salivary cortisol and cognitive functioning over time. Furthermore, the role of the APOE-ε4 allele as a moderator of the associations was investigated.

Methods: Using a prospective population-based study, we analyzed data from 752 older adults followed up over 10 years. A random-intercept Cross-Lagged Panel Model was applied to each combination of one cortisol measure (at waking time, 30 min after waking, 11 am, 8 pm, cortisol awakening response, total daily output, and diurnal slope) and one cognitive measure (primary outcome: Clinical Dementia Rating Scale sum of boxes score, CDR-SB; secondary outcome: Mini-Mental State Examination) resulting in 14 (7 × 2) models.

Results: Between-person effects pointed out that a higher cortisol level at 11 am was associated with increased CDR-SB scores, and a higher cortisol awakening response was associated with decreased CDR-SB scores. Within-person effects indicated that cortisol levels at 11 am and 8 pm, and total daily cortisol output were associated with subsequent lower CDR-SB scores. The APOE-ε4 allele did not moderate the relationship between cortisol and cognitive functioning.

Conclusions: Our findings revealed within-person associations between higher cortisol levels and better cognitive functioning at the subsequent follow-up, suggesting cortisol protective effects for cognitive decline.

1 | Introduction

High cortisol levels might exert negative effects on cognition and contribute to cognitive decline and Alzheimer's disease (AD) [1–5]. A recent systematic review with meta-analysis of estimates from cross-sectional studies [6] found that morning cortisol levels were significantly higher in AD patients (in blood, saliva, and cerebrospinal fluids) and in patients with mild cognitive impairment (MCI) (in cerebrospinal fluids only) compared to cognitively normal controls. Moreover, despite not being meta-synthesized, findings from longitudinal studies suggested that high levels of morning cortisol might accelerate cognitive decline in MCI or mild AD patients, whereas results in cognitively healthy adults were contradictory [6]. Indeed, for the latter group, longitudinal studies with large population-based (non-clinical) samples failed to find robust associations so far. Salivary cortisol levels across the day (morning, evening, and diurnal variability) and hair cortisol showed no association

with worsened cognitive functioning and dementia [7–10]. Other studies had more nuanced findings. No association has been shown for cortisol awakening response (CAR) whereas the am:pm cortisol ratio was associated with cognitive functioning at 5 of 9 years' follow-up, even after adjustment for covariates and the baseline score of the outcome was made [11]. Finally, another study about the association between serum cortisol and the incidence of AD reported that cortisol at baseline correlated significantly with probable AD at the 90-month follow-up in adults aged 75 and above [12].

Despite rarely being examined, the direction of the effect between cortisol and cognitive functioning might be more complex, as indicated by previous findings showing that cognitive ability at 20 years of age correlated with the area-under-the-curve cortisol output (AUC) and CAR across 35 years after adjusting for covariates [13].

Therefore, the first aim of the present study was to carry out an in-depth analysis of longitudinal bidirectional associations between cortisol and cognitive functioning to clarify the directionality of effect, if any, and to advance mixed evidence offered by prior studies differentiating between- and within-person effects. Based on research findings discussed above and results from a previous analysis conducted with 5-year follow-up data from the same project (CoLaus|PsyCoLaus) [14], we hypothesized finding associations between morning cortisol (waking cortisol and cortisol 30 min after waking) and diurnal cortisol slope (DCS) (according to previous findings on am:pm cortisol ratio, with high absolute values of both measures indicating high variation in cortisol levels across the day) and cognitive functioning over time. Specifically, we expected that as morning cortisol increases, cognitive functioning at subsequent follow-up decreases, and that as DCS increases, cognitive functioning increases. Furthermore, we expected that as AUC increases, cognitive functioning subsequently decreases, despite previous findings being lacking. Finally, we expected that evening cortisol and CAR are not prospectively associated with cognitive functioning [7, 9]. The primary outcome measure was the Clinical Dementia Rating sum of boxes score (CDR-SB) while the secondary outcome measure was the Mini-Mental State Examination (MMSE) score.

Scholars have previously suggested that the ε4 allele of the apolipoprotein E (APOE-ε4) might moderate the association between cortisol levels and cognitive decline, conferring increased vulnerability, but found only minimal support for this hypothesis (i.e., for verbal memory but not for cognitive functioning and information processing) [7]. The second aim of this study was thus to comprehensively test the moderation effect of the APOE-ε4 allele to evaluate whether it confers increased vulnerability to the potential effects of cortisol on cognitive functioning.

2 | Methods

2.1 | Participants and Procedure

In this study, we used data from CoLaus|PsyCoLaus (www.CoLaus-PsyCoLaus.ch), a prospective population-based cohort study designed to investigate the associations between cardiovascular risk factors, cardiovascular disease, and mental disorders in the community [15–17]. CoLaus|PsyCoLaus included a sample of 6734 adults aged between 35 and 75 years randomly selected among the residents of the city of Lausanne according to the civil register. After the first physical evaluation between 2003 and 2008 [15], the cohort was followed up three times. The first follow-up occurred between 2009 and 2013 [14, 17], the second between 2014 and 2018 [14], and the third one between 2018 and 2021 [18]. The psychiatric evaluations were completed approximately 1 year after the physical evaluations. Cognitive assessments and cortisol measurements were completed from the first follow-up on. Hence, for the present analyses, we used data from the three follow-ups (Figure 1).

The institutional Ethics Committee of the University of Lausanne, which afterward became the Ethics Commission of Canton Vaud (www.cer-vd.ch) approved the CoLaus-PsyCoLaus study (project number PB_2018–00038, reference 239/09). The study was performed in agreement with the Helsinki declaration and its former amendments, and in accordance with the applicable Swiss legislation. All participants gave their signed informed consent before entering the study.

2.2 | Measures

2.2.1 | Cognitive functioning

The primary outcome was cognitive and functional impairment as measured by the Clinical Dementia Rating (CDR). It is a scale derived from a semi-structured interview used to evaluate the staging of cognitive impairment and severity of Alzheimer's disease [19] that covers information about six domains: memory, orientation, judgment, and problem solving, community affairs, home and hobbies, and personal care. For each domain, the degree of impairment can be scored using the following categories: 0 = none, 0.5 = questionable, 1 = mild, 2 = moderate, and 3 = severe. The CDR score was derived from neurocognitive and questions on the participants' daily living activities. Participants with a global CDR score ≥ 1 (defining dementia) at the first follow-up (the baseline for the present study) were excluded from the current study to focus on dementia-free older adults. For the purpose of the present analysis, the CDR-SB was used as an outcome. The CDR-SB score is the sum of the six domain scores and can range from 0 to 18 [19].

The secondary outcome was the score at the MMSE [20], which measures global cognitive performance and was completed during the physical evaluation. The MMSE is considered the most widely used screening test for cognitive impairment, especially with the elderly population [21]. Total scores may range from 0 to 30, with higher scores being indicative of a better performance.

2.2.2 | Salivary cortisol and cortisol indices

At the first follow-up, the salivary cortisol was measured during the psychiatric evaluation. At the second and third follow-ups, the salivary cortisol was measured during the physical evaluation. As already described in Ouanes et al. [14],

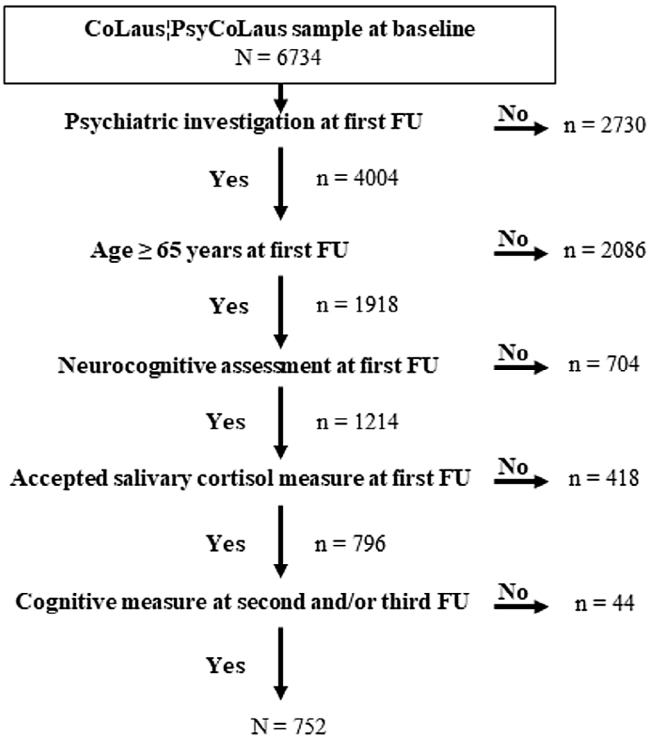

FIGURE 1 | Flow chart of the included participants. FU, follow-up.

salivette sampling devices were used to collect saliva (Sarstedt, Rommeldsdorf, Germany). For each visit, four salivary samples were collected from each participant over one day: upon waking, 30 min after waking, at 11 am and at 8 pm. Participants were instructed not to brush their teeth and to refrain from drinking, eating, smoking, and exercising 30 min before and during the sampling procedure. Participants were also instructed to keep the saliva samples at home in their freezers until all samples had been collected, then return them to the laboratory. In the laboratory, samples were stored at −20°C until biochemical analysis. Salivary cortisol levels were measured using a commercially available chemiluminescence assay (IBL, Hamburg, Germany). Inter- and intra-assay coefficients of variability were < 9%.

The following cortisol indices were calculated: the CAR, the AUC to the ground (AUCg), that is, total daily output, and the DCS. The CAR was calculated as the difference between the cortisol level 30 min after waking and the cortisol level upon waking. The AUCg, defined as the total cortisol output across a day, or total area under the cortisol curve to the ground, was calculated using the trapezoid formula [22]. It captures not only the cortisol levels at the times of sampling but also changes over the day [22]. Finally, the DCS, defined as the linear degree of change in cortisol levels across the day (from morning to evening) was calculated by subtracting the cortisol level value at 8 pm from the value upon waking and dividing the result by the number of hours (i.e., 13) separating both samples [23]. Therefore, high DCS scores represented more negative slopes.

2.2.3 | Other variables

Information on age, self-reported sex, education level (categorized as basic, apprenticeship, high school/college, and university), and body mass index (BMI, in kg/m^2) at the first follow-up were considered for the present study. Furthermore, depressive symptoms (as reported at the first follow-up) were examined using the French version [24] of the Center for Epidemiologic Studies-Depression Scale (CES-D) [25]. The scale consists of 20 items measuring the severity of depressive symptoms during the last week on a four-point Likert scale, from 0 = "rarely or none of the time (less than 1 day)" to 3 = "most or all of the time (5–7 days)". A previous study provided support for the validity and efficacy of the French version of the CES-D as a screening instrument among clinical and nonclinical adults [26]. The *APOE* genotype was also determined as previously described [27]. Participants were divided into two groups: APOE-ε4 carriers (having at least one APOE-ε4 allele) and APOE-ε4 non-carriers (those having no APOE-ε4 allele).

2.3 | Statistical Analysis

Participants with available cognitive data for at least two out of three time points were considered for subsequent analysis (i.e., at the first follow-up and at the second or third follow-up).

Missing value analysis was performed benefiting from Little's test for missing completely at random (MCAR). Little's test was applied separately to data from the first follow-up, from all follow-ups, and from subsets including variables of each of the models tested (described below). If the test suggested that the data were MCAR ($p > 0.05$), further examination was dropped. Otherwise, if missingness was not MCAR, a variable based on the presence of at least one missing value per participant was created (no missing value = 0, at least one missing value = 1) and possible associations between missingness and the variables in the dataset at the first follow-up

were examined using logistic regression models to understand whether they could account for missingness supporting the missing at random (MAR) assumption [28]. We similarly performed complete missing data analysis for the outcomes measured at follow-ups. Logistic regression analysis was used to test the association between groups and variables of interest at the first follow-up.

Descriptive statistics (number, frequency, mean, and standard deviation) were computed for the variables of interest. Variable distribution was inspected visually using histograms and Q-Q plots and statistically using skewness and kurtosis values and the Shapiro–Wilk test.

We relied on the random-intercept Cross-Lagged Panel Model (RI-CLPM) to differentiate between intra- and inter-individual effects over time [29, 30]. The RI-CLPM separates the analyzed variables into two latent components, that is, a stable, "trait-like" baseline between-person component (random intercept) and a dynamic, "state" within-person component [31]. Therefore, cross-lagged paths in the RI-CLPM indicate how a change in cortisol level influences a change in cognitive functioning (and vice versa), relative to the individual unique baseline.

Different RI-CLPM (7 cortisol measures × 2 measures of cognition) were tested, including as covariates (time-invariant predictors) age, sex, BMI, education, and depressive symptoms. For each RI-CLPM, the moderation effect of APOE-ε4 was tested by performing a multiple group RI-CLPM using no constraints between groups, with a multiple group RI-CLPM in which the lagged coefficients were constrained to be equivalent across groups [32]. A chi-square difference test was carried out to test the between-model difference in adjustment, with nonsignificant results suggesting no relevant group effects.

Expecting a non-normal distribution of some of the variables, the robust maximum likelihood estimator (MLR) was used for all RI-CLPMs [33, 34]. Before testing RI-CLPMs, we performed multiple imputations (10 datasets) including variables of interest (except CAR, AUCg, and DCS which were directly calculated with data resulting from multiple imputations). In addition, cortisol values 30 min after waking and CAR were linearly rescaled by dividing by 10 and AUCg by dividing by 100. The goodness of fit was examined by inspecting values of the following indicators: Robust Chi-square/df, Robust Root Mean Square Error of Approximation (RMSEA), Robust Comparative Fit Index (CFI), and Robust Standardized Root Mean Square Residual (SMSR). The following cutoff criteria were used to assess the fit index: CFI >0.95, RMSEA <0.06, SMSR <0.08, and chi square/df p value >0.05.

All analyses were performed in RStudio using the packages "tidyverse" [35], "car" [36], "stats" [37], "mde" [38], "naniar" [39], "mice" [40], and "lavaan" [41].

3 | Results

The characteristics of the sample are shown in Table 1 while the results of the missing data analysis are presented in Tables S1 and S2.

3.1 | Results From RI-CLPMs

Table 2 reports the results of the analyses examining the longitudinal associations between cortisol measures and CDR-SB scores. Overall, the tested models adequately fitted the data. There was evidence for autoregressive effects for both cortisol and CDR-SB scores, for which higher values at the second follow-up predicted an increase at the subsequent third follow-up. Between-person effects were supported for cortisol at 11 am and CAR but in opposite directions: high values of cortisol at 11 am were associated with high CDR-SB scores, whereas the higher the CAR, the lower the CDR-SB. Regarding within-person effects, the findings showed negative cross-sectional and longitudinal associations. Specifically, higher cortisol values than usual compared to the person mean at 11 am and 8 pm and higher AUCg predicted lower CDR-SB scores. These results were robust to Bonferroni correction for multiple tests ($p<0.00357$) except cortisol at 8 pm. No significant cross-lagged effects from CDR-SB to cortisol were found.

The results of the analyses examining the longitudinal associations between cortisol measures and MMSE scores are displayed in Table 3. Again, the tested models adequately fitted the data overall. The results did not point to a close association between cortisol and MMSE. However, significant and negative cross-lagged effects from cortisol at waking time and DCS to subsequent MMSE scores were shown. High cortisol values than usual compared to the person mean at waking time and high DCS (i.e., more negative cortisol slope) predicted a decrease in MMSE scores at follow-up. These results became non-significant when the Bonferroni correction was applied. There was no evidence for reverse effects from MMSE to cortisol.

3.2 | APOEε4 As a Moderator of the Association Between Cortisol and Cognitive Measures

To test if the reciprocal effects between cortisol measures and CDR-SB and MMSE scores were the same for APOEε4 carriers versus non-carriers, we performed multiple group analyses. The results indicated that the lagged effects for APOEε4 carriers versus non-carriers appeared to be the same except for the effects between cortisol at 11 am and MMSE ($p=0.021$; Table S3). However, this result became non-significant when the Bonferroni correction was applied. The fit of the multigroup RI-CLPM exploring the association between cortisol at 11 am and MMSE was satisfactory (Table S4). Further examination using z-test [42] showed that the cross-lagged effect (i.e., standardized coefficients) from cortisol (11 am) at the second follow-up to MMSE at the third follow-up was significantly different between groups ($z=2.197$, $p<0.05$). In APOEε4 carriers, cortisol at 11 am predicted a lower MMSE score at the subsequent follow-up (standardized coefficient $=-0.212$, standardized standard error (SE) $=0.115$) while the effect was not significant in APOEε4 non-carriers (standardized coefficient $=0.074$, standardized standard error (SE) $=0.061$).

Furthermore, the autoregressive effect from cognition at the first follow-up to the second follow-up was significantly different between groups ($z=-2.251$, $p<0.05$). In APOEε4 non-carriers, a higher MMSE score at the first follow-up predicted a lower

TABLE 1 | Characteristics of the sample ($N = 752$).

Variable	First follow-up M (SD)	Second follow-up M (SD)	Third follow-up M (SD)
Age	71.34 (4.47)		
Sex (female) (%)	61.17		
Level of education (%)			
Basic	16.89		
Apprenticeship	46.94		
High school/college	23.40		
University	12.77		
BMI	26.76 (4.61)		
Depressive symptoms	10.33 (8.09)		
APOEε4 carrier (%)	20.08		
MCI (CDR = 0.5) (%)	47.74		
Cortisol (nmol/L)			
Waking time	19.0 (9.6)	27.2 (14.9)	26.5 (14.7)
30 min after waking	25.5 (12.4)	38.8 (20.5)	36.3 (16.6)
At 11 am	11.0 (6.9)	15.7 (10.0)	16.3 (8.7)
At 8 pm	4.3 (4.9)	7.0 (10.3)	6.7 (9.6)
CAR	6.5 (12.1)	11.6 (18.9)	9.8 (17.5)
AUCg	143.9 (65.2)	214.3 (106.4)	211.3 (53.6)
DCS	1.1 (0.8)	1.6 (1.3)	1.5 (1.3)
MMSE	29.25 (1.48)	28.91 (1.92)	28.76 (1.83)
CDR-SB	0.90 (0.65)	0.91 (0.77)	0.88 (0.79)

Abbreviations: AUCg, area under the curve to the ground or total daily output; BMI, body mass index; CAR, cortisol awakening response; CDR-SB, Clinical Rating Scale Sum of Boxes score; DCS, diurnal cortisol slope; MCI, mild cognitive impairment (questionable dementia according to the CDR); MMSE, Mini-Mental State Examination score.

MMSE score at the subsequent follow-up (standardized coefficient = −0.233, standardized standard error (SE) = 0.126) while the effect was not significant in APOEε4 carriers (standardized coefficient = 0.191, standardized standard error (SE) = 0.140).

Finally, in APOEε4 carriers, cortisol at 11 am predicted further cortisol increases at subsequent time points.

4 | Discussion

We carried out an in-depth investigation of the longitudinal association between cortisol and cognitive functioning and decline, considering the diurnal variations in cortisol. Indeed, four measurement occasions of saliva samples were analyzed across each wave of the study. As previously suggested [43], we focused on both between- and within-person associations using a series of RI-CLPM. Our results showed associations between cortisol levels and impairment in cognitive functioning measured by the CDR-SB in a population-based sample of older adults. Individuals who secreted higher levels of cortisol (at 11 am) than other persons experienced larger impairment in cognitive functioning (i.e., high CDR-SB scores). Despite not reaching statistical significance, standardized estimates of random intercepts from other models for cortisol (at waking time, 8 pm, AUCg, and DCS) and CDR-SB were positive and exceeded 0.100. Conversely, individuals who showed greater CAR than other persons experienced better average cognitive functioning. Considering that previous research found positive associations between cortisol levels and cognitive decline (i.e., the higher the cortisol levels, the higher the cognitive decline) [10–12, 44] except for CAR [7, 9], our findings suggest that the positive association refers to a trait-like association or between-person difference that might be related to common causes and/or risk factors. In other words, this positive association does not implicate causation or the influence of one factor on the other. Potential common causes or risk factors at work might be stressful life events or chronic stress, neuroticism, depression, sleep disturbances, and cardiovascular risk factors [1]. Additionally, an early supportive and responsive social environment fostering secure attachment and affective reserve may represent protective factors for both cortisol and cognitive decline [45].

To note, our findings related to the within-person effects showed that high cortisol levels (at 11 am and 8 pm, and AUCg) were associated with better cognitive functioning at follow-up

TABLE 2 | Results from random-intercept Cross-Lagged Panel Models examining the association between cortisol measures and cognitive decline as measured using the CDR-SB (controlling for the effect of age, sex, BMI, education, and depressive symptoms).

	Waking time		30 min after waking		At 11 am		At 8 pm		CAR		AUCg		DCS	
Parameters	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***
Cross-lagged effects														
CDR-SB t1 → COR t2	−2.062 (2.091)	−0.068	−0.289 (0.290)	−0.067	−0.224 (1.565)	−0.011	2.291 (1.706)	0.099	−0.008 (0.282)	−0.002	0.024 (0.146)	0.011	−0.393 (0.212)	−0.142
COR t1 → CDR-SB t2	0.004 (0.006)	0.045	0.034 (0.047)	0.069	−0.010 (0.008)	−0.108	0.000 (0.008)	0.003	0.029 (0.047)	0.048	−0.047 (0.085)	−0.044	0.013 (0.059)	0.015
CDR-SB t2 → COR t3	−0.206 (0.966)	−0.009	−0.023 (0.133)	−0.009	0.251 (0.630)	0.018	−0.112 (0.578)	−0.007	0.031 (0.161)	0.011	−0.004 (0.055)	−0.003	0.033 (0.090)	0.015
COR t2 → CDR-SB t3	0.000 (0.002)	0.011	−0.003 (0.014)	−0.008	−0.015 (0.003)	−0.244***	−0.006 (0.002)	−0.107**	−0.006 (0.015)	−0.018	−0.117 (0.026)	−0.198***	0.037 (0.022)	0.075
Stability paths														
COR t1 → COR t2	−0.232 (0.206)	−0.121	−0.164 (0.194)	−0.081	0.108 (0.113)	0.069	0.042 (0.108)	0.019	−0.241 (0.146)	−0.132	0.150 (0.132)	0.081	−0.159 (0.148)	−0.089
CDR-SB t1 → CDR-SB t2	−0.116 (0.114)	−0.089	−0.153 (0.125)	−0.118	−0.089 (0.110)	−0.070	−0.134 (0.116)	−0.103	−0.146 (0.127)	−0.113	−0.100 (0.111)	−0.078	−0.135 (0.116)	−0.104
COR t2 → COR t3	0.182 (0.055)	0.185**	0.011 (0.045)	0.014	0.164 (0.054)	0.192**	0.031 (0.020)	0.034	0.043 (0.046)	0.047	0.107 (0.038)	0.141**	0.202 (0.063)	0.196**
CDR-SB t2 → CDR-SB t3	0.188 (0.060)	0.181**	0.172 (0.060)	0.165**	0.181 (0.061)	0.177**	0.203 (0.060)	0.196**	0.167 (0.059)	0.161**	0.201 (0.059)	0.195**	0.197 (0.060)	0.189**
Correlated change														
t1	0.127 (0.246)	0.042	0.055 (0.028)	0.136	−0.339 (0.232)	−0.123	0.052 (0.130)	0.026	0.050 (0.030)	0.122	−0.003 (0.019)	−0.014	−0.002 (0.023)	−0.006
t2	−0.772 (0.499)	−0.103	−0.079 (0.068)	−0.076	0.012 (0.384)	0.002	1.371 (1.026)	0.241	0.011 (0.058)	0.011	0.045 (0.060)	0.079	−0.176 (0.085)	−0.263*
t3	0.325 (0.283)	0.043	−0.106 (0.037)	−0.130**	−0.859 (0.204)	−0.193***	−0.009 (0.194)	−0.002	−0.148 (0.038)	−0.162***	−0.081 (0.019)	−0.190***	0.015 (0.026)	0.021
Random intercept														

(Continues)

TABLE 2 | (Continued)

	Waking time		30 min after waking		At 11 am		At 8 pm		CAR		AUCg		DCS	
Parameters	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***
Random intercept	0.376 (0.235)	0.129	−0.044 (0.028)	−0.118	0.540 (0.208)	0.409**	0.153 (0.105)	0.222	−0.088 (0.028)	−0.259**	0.031 (0.017)	0.197	0.024 (0.020)	0.129
Fit indices														
No. of parameters	68		68		68		68		68		68		68	
Scaled chi-square (df)	0.715 (1)		11.735 (1)		6.627 (1)		0.917 (1)		18.946 (1)		1.247 (1)		0.039 (1)	
p value	0.40		0.001		0.010		0.34		0.001		0.26		0.84	
Scaling correction factor Yuan-Bentler correction	0.995		0.804		1.521		0.551		0.780		1.475		0.920	
Robust CFI	1.000		0.989		0.989		1.000		0.981		1.000		1.000	
Robust RMSEA	0.000		0.107		0.107		0.000		0.136		0.022		0.000	
Robust SRMR	0.003		0.010		0.012		0.003		0.013		0.005		0.001	

Abbreviations: *B*, unstandardized estimate; CDR-SB, Clinical Dementia Rating Scale Sum of Boxes score; CFI, Robust Comparative Fit Index; COR, cortisol; df, degree of freedom; RMSEA, Robust Root Mean Square Error of Approximation; SE, standard error; SRMR, Robust Standardized Root Mean Square Residual; *β*, standardized estimate.

*$p < 0.05$.

**$p < 0.01$.

***$p < 0.001$.

TABLE 3 | Results from random-intercept Cross-Lagged Panel Models examining the association between cortisol measures and overall cognition as measured using the MMSE (controlling for the effect of age, sex, BMI, education, and depressive symptoms).

	Waking time		30 min after waking		At 11 am		At 8 pm		CAR		AUCg		DCS	
Parameters	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***
Cross-lagged effects														
MMSE t1 → COR t2	0.038 (0.635)	0.003	−0.036 (0.083)	−0.022	0.046 (0.668)	0.005	0.197 (0.409)	0.022	−0.003 (0.087)	−0.002	0.001 (0.049)	0.001	0.008 (0.053)	0.007
COR t1 → MMSE t2	−0.051 (0.020)	−0.219*	−0.205 (0.106)	−0.113	−0.003 (0.013)	−0.014	0.004 (0.016)	0.011	0.130 (0.104)	0.075	−0.173 (0.136)	−0.058	−0.395 (0.187)	−0.166*
MMSE t2 → COR t3	−0.024 (0.338)	−0.003	0.030 (0.053)	0.035	0.323 (0.294)	0.065	−0.052 (0.171)	−0.009	0.021 (0.057)	0.022	0.026 (0.019)	0.056	−0.030 (0.032)	−0.040
COR t2 → MMSE t3	−0.005 (0.006)	−0.046	−0.009 (0.033)	−0.011	−0.000 (0.009)	−0.001	−0.009 (0.009)	−0.062	0.028 (0.038)	0.033	−0.062 (0.079)	−0.042	−0.014 (0.061)	−0.011
Stability paths														
COR t1 → COR t2	−0.204 (0.205)	−0.108	−0.223 (0.192)	−0.109	0.167 (0.097)	0.111	0.057 (0.106)	0.026	−0.252 (0.135)	−0.138	0.166 (0.127)	0.090	−0.133 (0.145)	−0.075
MMSE t1 → MMSE t2	−0.200 (0.139)	−0.138	−0.166 (0.141)	−0.115	−0.202 (0.143)	−0.139	−0.188 (0.137)	−0.130	−0.192 (0.138)	−0.132	−0.186 (0.139)	−0.129	−0.184 (0.138)	−0.127
COR t2 → COR t3	0.184 (0.057)	0.188**	−0.002 (0.046)	−0.002	0.174 (0.053)	0.205**	0.028 (0.024)	0.031	0.031 (0.046)	0.034	0.114 (0.039)	0.151	0.215 (0.067)	0.208**
MMSE t2 → MMSE t3	−0.015 (0.070)	−0.017	−0.012 (0.068)	−0.013	−0.025 (0.072)	−0.027	−0.043 (0.083)	−0.048	−0.025 (0.070)	−0.027	−0.026 (0.072)	−0.029	−0.018 (0.076)	−0.020
Correlated change														
t1	−0.186 (0.582)	−0.023	−0.011 (0.077)	−0.010	−0.258 (0.495)	−0.036	−0.136 (0.255)	−0.026	0.041 (0.073)	0.039	−0.027 (0.042)	−0.044	0.018 (0.045)	0.023
t2	1.332 (1.373)	0.064	0.309 (0.180)	0.104	−0.223 (0.937)	−0.015	−5.908 (3.916)	−0.361	0.227 (0.121)	0.083	−0.210 (0.196)	−0.130	0.585 (0.320)	0.305
t3	−1.403 (0.750)	−0.073	0.342 (0.104)	0.164**	0.380 (0.561)	0.032	−1.416 (0.910)	−0.103	0.496 (0.107)	0.214***	0.015 (0.063)	0.014	−0.020 (0.089)	−0.011
Random intercept														
Random intercept	0.313 (0.516)	0.054	0.091 (0.055)	0.121	−0.554 (0.336)	−0.236	−0.221 (0.217)	−0.167	0.030 (0.050)	0.043	−0.015 (0.028)	−0.050	0.031 (0.041)	0.088

(Continues)

TABLE 3 | (Continued)

Parameters	Waking time		30 min after waking		At 11 am		At 8 pm		CAR		AUCg		DCS	
	B **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***	***B*** **(SE)**	***β***
Fit indices														
No. of parameters	68		68		68		68		68		68		68	
Scaled chi-square (df)	14.397 (1)		11.552 (1)		3.038 (1)		2.280 (1)		0.095 (1)		0.063 (1)		5.547 (1)	
p value	0.000		0.001		0.081		0.131		0.758		0.803		0.019	
Scaling correction factor Yuan-Bentler correction	0.742		0.545		1.391		0.601		0.718		0.939		0.732	
Robust CFI	0.979		0.987		0.993		0.998		1.000		1.000		0.992	
Robust RMSEA	0.115		0.087		0.061		0.032		0.000		0.000		0.067	
Robust SRMR	0.011		0.008		0.007		0.004		0.001		0.001		0.007	

Abbreviations: *B*, unstandardized estimate; CFI, Robust Comparative Fit Index; COR, cortisol; df, degree of freedom; MMSE, Mini Mental State Examination; RMSEA, Robust Root Mean Square Error of Approximation; SE, standard error; SRMR, Robust Standardized Root Mean Square Residual; *β*, standardized estimate.

*$p < 0.05$.

**$p < 0.01$.

***$p < 0.001$.

TABLE 4 | Graphical synthesis of cross-lagged within-person associations from cortisol levels to cognitive measure scores at any subsequent follow-up (green: better cognitive functioning, red: worse cognitive functioning).

Cortisol	CDR-SB	MMSE
Waking time	=	↓*
30 min after waking	=	=
At 11 am	↓	=
At 8 pm	↓*	=
CAR	=	=
AUCg	↓	=
DCS	=	↓*

Note: ↓: association of negative sign.
*Finding not significant if Bonferroni correction for multiple tests is applied (significant p value < 0.00357).

with medium to large effects [46] (see also Table 4). This finding is in line with initial evidence on the protective effects of cortisol on mental health, regulating affect in the short term (i.e., in the next hour) in everyday life [47]. However, this does not necessarily reflect alterations in the basal diurnal cortisol rhythm, as assessed in the present study. A previous analysis of a 5-year follow-up CoLaus|PsyCoLaus data [14] demonstrated that higher cortisol levels were associated with a decreased cognitive decline (Table 1 of the original study). A potential explanation for our findings is that increased cortisol levels could represent efficacious daily stress (phasic) responses. A previous study showed that stress-induced cortisol increases were associated with increased attentional performance but not reasoning abilities [48]. Furthermore, the role of increased cortisol levels in the improvement of cognitive performance and explicit memory has been previously emphasized [49]. Similarly, another study suggested a protective or compensatory effect of cortisol on working memory performance [50]. Those studies focused on cortisol reactivity to an acute stressor, not regulation of the basal cortisol rhythm, which is examined in this study. However, it was previously shown that cortisol reactivity is associated with AUC but not CAR and cortisol slope [51]. Our findings could thus indicate that those participants whose reaction to stress is substantial and more dynamic would show a decreased risk of worsened cognitive function over time. Additionally, these findings may point to the importance of life-phase-related changes in cortisol excretion. A recent study demonstrated that older age was associated with an upward trajectory in cortisol excretion from age 60 onward [52]. This study also found individual differences in cortisol excretion levels and within-individual change over time. It is thus possible that lack or tenuous increases in cortisol excretion—when it would be expected and around 75 years in our sample—may increase the risk of subsequent impairment in cognitive functioning, that is, cortisol increases playing the role of a protective factor. These are intriguing aspects to be addressed in future research separating within-person effects from between-person effects.

The apparent discrepancy between our findings and those from other previous studies showing that higher cortisol levels might predict faster cognitive decline [53–55] may be due to several factors. Indeed, most previous studies did not clearly separate between-person from within-person effects. Participants were at different stages of cognitive decline at baseline, and the exact nature of cortisol measurements varied from study to study. Furthermore, it is likely that the relationship between cortisol and cognitive decline is very complex and may involve cortisol's effects on metabolism, the cardiovascular system, and the immune system, in addition to its direct effects on the brain [1].

Regarding the relationship between cortisol levels and MMSE scores, we found no evidence of a trait-like association and stability over time for MMSE scores only. After accounting for between-person effects, we found that high cortisol levels at waking time and high DCS (i.e., more negative cortisol slope) predicted worse cognitive performance over time. However, these associations between MMSE and cortisol were not robust and do not hold if Bonferroni correction is applied. This may be explained by the fact that the MMSE is usually less sensitive than the CDR, especially in dementia-free individuals [56, 57].

The findings from our study highlight that cognitive functioning does not influence cortisol levels over time, contrary to findings from a previous study [13]. The effect of cognitive functioning on cortisol levels has rarely been examined, and additional research is required.

Finally, we also tested whether the APOE-ε4 allele could confer increased vulnerability to the potential effects of cortisol on impaired cognitive functioning over time. Our findings showed that bidirectional longitudinal associations between cortisol levels and cognitive functioning did not vary for APOE-ε4 carriers versus non-carriers (except cortisol levels at 11 am and MMSE but whose significance did not hold to Bonferroni correction). This result is in line with those of a previous longitudinal study testing the role of the APOE-ε4 allele as a moderator of the association between cortisol and cognition in which the authors found an increased risk for memory decline but no decline in global cognitive function and information processing speed for carriers versus non-carriers [7]. Those findings were interpreted as primarily due to the close association between the APOE-ε4 allele and atrophy in brain structures related to memory performance. A prior cross-sectional study highlighted the possibility that the distinct association between cortisol and cognitive functioning according to APOE-ε4 becomes evident when the presence of two ε4 alleles is considered [58]. However, the risk of positive findings by chance needs to be considered since a high number of tests were carried out in both previous studies. Future research might consider examining the role of two APOE-ε4 alleles compared to heterozygotes and non-carriers.

4.1 | Strengths and Limitations

Our study is one of the rare longitudinal studies that assessed the link between cortisol and cognitive functioning. The population-based design and the 10-year follow-up period are considerable strengths. Regarding results generalizability, the sample of elderly considered for the present analysis ($N = 725$) did not differ in sample characteristics such as age, gender, education level, BMI, CES-D, and MCI from all adults aged 65 and over participating in CoLaus|PsyCoLaus ($N = 1126$) at the first follow-up (i.e., the

baseline for our study). Therefore, the analyzed sample was representative of Lausanne residents aged 65 years and above. The use of RI-CLPM also allowed us to distinguish between-person from within-person effects. Nevertheless, certain limitations need to be mentioned. The first limitation is the use of cortisol measures from only one day upon each visit. It has previously been recommended to conduct cortisol measurements on at least two different days to obtain better estimates of diurnal cortisol profiles [43]. However, in population-based studies, this may not be feasible for reasons such as participants' burden and analysis costs. Furthermore, we focused not only on cortisol levels at specific times of the day but also on indicators of change. While the participants recorded the time of sampling using a specific form, no objective measure (e.g., actigraphy, alarm clock, calling participants) [43] was available to verify the exact time the participants collected the saliva samples. Second, salivary cortisol measurement is less precise compared to hair and serum cortisol but has the advantage of being easily collected from participants. Third, although we controlled for some relevant covariates, we did not consider other factors (e.g., stress, sleep disturbances/quality, physical activity, and cardiovascular risk factors) that could have influenced the observed associations [43]. Finally, at the first follow-up, the MMSE was assessed 1 year before the salivary cortisol, and at the second and third follow-ups, the salivary cortisol was measured 1 year before the CDR-SB.

5 | Conclusions

Robust associations were found between cortisol levels and cognitive functioning and decline, as measured with the CDR-SB. On the one hand, cortisol levels and cognitive decline may share common causes or risk factors. On the other hand, at the within-person level, higher cortisol levels at 11 am and 8 pm and higher AUCg were associated with better cognitive functioning at the subsequent follow-up, suggesting a possible protective effect of cortisol on cognitive decline. Future research needs to separate within- from between-person effects to improve our understanding of the relationship between these factors.

Author Contributions

Simone Amendola: conceptualization, formal analysis, visualization, writing – original draft. **Sami Ouanes:** conceptualization, visualization, writing – original draft, supervision. **Leonardo Zullo:** supervision, visualization, writing – review and editing. **Miriam Rabl:** supervision, visualization, writing – review and editing. **Giorgio Pistis:** supervision, visualization, writing – review and editing. **Enrique Castelao:** data curation, funding acquisition, investigation, project administration, resources, supervision, visualization, writing – review and editing. **Pedro Marques-Vidal:** data curation, writing – review and editing, supervision, visualization, project administration, resources, funding acquisition, methodology, investigation. **Julien Vaucher:** methodology, supervision, project administration, writing – review and editing, visualization, data curation, funding acquisition, resources, investigation. **Armin von Gunten:** data curation, funding acquisition, investigation, methodology, project administration, resources, supervision, visualization, writing – review and editing. **Martin Preisig:** data curation, visualization, project administration, supervision, investigation, methodology, writing – review and editing, funding acquisition, resources. **Julius Popp:** conceptualization, supervision, writing – original draft, visualization.

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Conflicts of Interest

Dr. Miriam Rabl received speaker honoraria from OM Pharma, unrelated to the present work. Prof. Julius Popp received consultation and speaker honoraria from Schwabe Pharma, OM Pharma, Lilly, Eisai, Biogen, and Roche, all unrelated to the present work. All other authors report no financial relationships with commercial interests.

Data Availability Statement

The data of the CoLaus|PsyCoLaus study used in this article cannot be fully shared as they contain potentially sensitive personal information on participants. According to the Ethics Committee for Research of the Canton of Vaud, sharing these data would be a violation of Swiss legislation with respect to privacy protection. However, coded individual-level data that do not allow researchers to identify participants are available upon request to researchers who meet the criteria for data sharing of the CoLaus|PsyCoLaus Datacenter (CHUV, Lausanne, Switzerland). Any researcher affiliated with a public or private research institution who complies with the CoLaus|PsyCoLaus standards can submit a research application to research.colaus@chuv.ch or research.psycolaus@chuv.ch. Proposals requiring baseline data only will be evaluated by the baseline (local) Scientific Committee (SC) of the CoLaus and PsyCoLaus studies. Proposals requiring follow-up data will be evaluated by the follow-up (multicentric) SC of the CoLaus|PsyCoLaus cohort study. Detailed instructions for gaining access to the CoLaus|PsyCoLaus data used in this study are available at www.colaus-psycolaus.ch/professionals/how-to-collaborate/.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

No generative AI technology was used to write this manuscript.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.