Chapter 7

Does hypothalamic-pituitary-adrenal axis activity predict the two-year course of depression and anxiety disorders?
ABSTRACT

Background

There is much evidence that depression and - to a lesser extent - anxiety disorders are associated with hyperactivity of the hypothalamic-pituitary adrenal (HPA) axis. However, lower cortisol levels, possibly due to exhaustion of the HPA axis, have also been observed in (subgroups of) depressed patients. Whether the HPA axis plays a role in the course of depression or anxiety disorders has not been examined in detail. Our objective was to examine whether salivary cortisol indicators at baseline predict the two-year course of depression and anxiety disorders in a large cohort study.

Methods

Longitudinal data with a 2-year follow up are from 837 participants of the Netherlands Study of Depression and Anxiety, with a current DSM-IV based depressive and/or anxiety disorder at baseline, who were recruited from general practice and specialized mental health care. At baseline, seven saliva samples were obtained, determining the 1-hour cortisol awakening response (CAR), evening cortisol level and cortisol suppression after a 0.5 mg dexamethasone suppression test. At follow-up, DSM-IV based diagnostic interviews and Life Chart Assessments integrating diagnostic and symptom trajectories over 2 years were administered to determine chronicity.

Results

41.5% of the respondents had a 2-year chronic course without remission. In multivariable analyses adjusting for demographic and health indicators, a lower awakening response was associated with the risk of chronic course (RR=0.83, p=0.03). No associations were found between evening cortisol and cortisol suppression after dexamethasone ingestion and two-year course outcome.

Conclusion

Among patients with depressive or anxiety disorders, a lower cortisol awakening response—which may be indicative of underlying exhaustion of the HPA axis—predicted a chronic course.

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INTRODUCTION
Depressive and anxiety disorders are prevalent and disabling disorders. The burden of these disorders is in part due to their course, which is often chronic or recurrent. In addition, comorbidity of depression and anxiety disorder frequently occurs and is related to an even poorer outcome. However, little is known about predictors of the course of depressive and anxiety disorders, while such knowledge would greatly improve our understanding of these diseases or could lead to identification of risk groups, which could help prevention.

Hypothalamic-pituitary-adrenal (HPA) axis dysregulation is believed to play an important role in the pathophysiology of depressive and – to a lesser extent – anxiety disorders. Mostly, hyperactivity of the HPA axis has been observed, as reflected by elevated serum, urinary or salivary cortisol levels, in addition to less suppression of cortisol after dexamethasone ingestion or a Dexamethasone/Corticotropin Releasing Hormone (Dex/CRH) test in patients with depression or panic disorder. However, besides HPA axis hyperactivity in part of the patients, there also appears to be a group of patients showing hypocortisolism, which could be a sign of exhaustion of the HPA axis, after chronic and recurrent depressive episodes. Salivary cortisol measures are increasingly used, since they reflect unbound, active cortisol, and their collection is minimally intrusive on HPA axis regulation. The cortisol awakening response reflects the natural response of the HPA axis on awakening, salivary cortisol evening levels reflect basal activity, and the dexamethasone suppression test provides information on the negative feedback system of the HPA axis. When using these measures in a large-scale cohort study, we observed that persons with a remitted or current Major Depressive Disorder (MDD) showed a higher cortisol awakening curve, which was also observed in persons with a current Panic Disorder with agoraphobia.

Whether HPA axis dysregulation predicts the course of depression and anxiety disorders has not been examined extensively. There is some evidence that increased cortisol responses to the Dex/CRH test or DST predict relapse in remitted outpatients with depressive disorder, panic disorder, or in depressed inpatients. Baseline salivary cortisol, cortisol responses on the DST or Dex/CRH test, however, were not found to be related to the treatment response or outcome of depression or panic disorder. However in patients with panic disorder, abnormal DST results or elevated 24-hour cortisol levels at baseline were also found to be associated with more anxiety, phobias and disability 2-4 years later.

Large-scale longitudinal studies examining the role of HPA axis indicators in the naturalistic course trajectory of patients with a current depressive or anxiety disorder are lacking. This study examines whether various salivary cortisol measures (cortisol awakening response, evening level and suppression after dexamethasone ingestion) predict 2-year chronic course in 855 subjects with baseline depression or anxiety disorders, correcting for detailed covariates.
METHODS

Study sample

Data are from the Netherlands Study of Depression and Anxiety (NESDA), a large cohort study on the course of depressive and anxiety disorders among 2981 adults (18-65 years). Respondents were recruited from the community, in primary care through a screening procedure conducted among 65 general practitioners, and in specialized mental health care when newly enrolled at one of the 17 participating mental health organization locations. The overall study sample included persons with psychopathology as well as controls without a psychiatric diagnosis. General exclusion criteria were: a primary diagnosis of psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe addiction disorder and not being fluent in Dutch. For objectives and methods of NESDA see Penninx et al.28 The research protocol was approved by the Ethical Committee of participating universities and all respondents provided written informed consent.

After two years, a face-to-face follow-up assessment was conducted with a response of 87.1% (2596 of the 2981 respondents participated). Non-response was significantly higher among those with younger age, lower educational level, non-North European ancestry and those with major depressive disorder, but was not associated with sex or the presence of anxiety disorder29.

The presence of depressive (Major Depressive Disorder, Dysthymia) or anxiety (Panic Disorder, Social Phobia, Generalized Anxiety Disorder, Agoraphobia) disorders was established using the Composite Interview Diagnostic Instrument (CIDI) according to DSM-IV criteria30. For the present analysis, only subjects who were symptomatic in the month before baseline were included. Consequently, we restricted the sample to the 1456 subjects with a 6-month depressive or anxiety diagnosis who confirmed symptoms in the month prior to baseline at either the CIDI recency questions or the Life Chart Assessment (see below). Of these 1456 subjects, 1185 (81.4%) participated in the 2-year follow-up assessment (median in-between time= 24 months) and had complete data on outcome indicators. We subsequently excluded a total of 7 pregnant or breastfeeding women and 77 participants on corticosteroids, leaving an initial sample of 1101 respondents.

Of these, 837 (76.0%) returned sufficient saliva samples to contribute to at least one of the saliva cortisol analyses (1-hour awakening values, evening value or DST) and therefore constitute the study sample. These 837 persons did not significantly differ from the 270 respondents with missing cortisol indicators in sex, or course outcome, but were older (42.8 versus 38.7 years, $p < 0.001$), more educated (12.0 versus 11.3 years, $p = 0.005$) and differed in baseline psychiatric status (22.2% depression, 42.8% anxiety disorder and 35.0% comorbidity versus 21.2% depression, 34.8% anxiety disorder and 43.9% comorbidity, $p = 0.02$).
Course of depressive and anxiety disorders

Course of depressive and anxiety disorders was determined using two main sources of data collected during the 2-year follow-up assessment: 1) the CIDI interview and the 2) Life Chart assessment (LCA). The CIDI interview determined the presence of DSM-IV classified depressive and anxiety disorders during the time between baseline assessment and 2-year follow-up assessment. Organic exclusion rules were used in defining diagnoses, and hierarchy-free diagnoses were made to allow for research into comorbidity. For all persons with detected depressive or anxiety symptoms in the CIDI interview, the LCA was completed. This assessment uses a calendar method to determine life events during the 2-year follow-up period to refresh memory, and then assessed separately the presence of depressive and anxiety symptoms at each month during this period\textsuperscript{31}. In addition, for each month with reported symptoms, the severity of symptoms was assessed ranging from no or minimal, mild, moderate, severe, or very severe symptoms. Symptoms on LCA were only considered to be present when at least of mild severity. Using both the CIDI and LCA data, distinction was made between those with remission of symptoms - defined as the occurrence of a time-point during follow-up at which no symptoms of depression or anxiety were reported for three consecutive months - versus those with a chronic course – defined as no remission during the 2-year follow-up.

Salivary cortisol

As described in more detail elsewhere\textsuperscript{32}, respondents were instructed to collect saliva samples at home on a regular (working) day shortly after the interview at baseline. Instructions concerning saliva sampling prohibited eating, drinking tea or coffee, or brushing teeth within 15 minutes before sampling. Furthermore, no dental work 24 hours prior to sampling was allowed. Saliva samples were obtained using Salivettes (Sarstedt, Germany) at seven time points covering 1-hour awakening cortisol levels, evening cortisol and a dexamethasone suppression test. 1-hour awakening cortisol includes four sampling points; at awakening (T1) and 30 (T2), 45 (T3) and 60 (T4) minutes later. The two evening values were collected at 2200h (T5) and 2300h (T6). Dexamethasone suppression is measured by cortisol sampling the next morning at awakening (T7) after ingestion of 0.5 mg dexamethasone directly after the saliva sample at 2300h (T6). Respondents were instructed to write down the exact sampling times and time of ingestion of dexamethasone, so that compliance could be detected. Samples were stored in refrigerators and returned by mail. After receipt, Salivettes were centrifuged at 2000 x g for 10 minutes, aliquoted and stored at -80°C. Cortisol analysis was performed by competitive electrochemiluminescence immunoassay (E170 Roche, Switzerland). The functional detection limit was 2.0 nmol/l and
the intra- and inter-assay variability coefficients in the measuring range were less than 10%. Data cleaning excluded values >2 SD above the mean.

1-hour awakening cortisol: We calculated the area under the curve with respect to the increase (AUCi) and with respect to the ground (AUCg) using Pruessner’s formulas. The AUCg is an estimate of the total cortisol secretion over the first hour after awakening, whereas the AUCi is a measure of the dynamic of the cortisol awakening response (CAR), more related to the sensitivity of the system, emphasizing changes over time after awakening. If samples were collected outside of a margin of five minutes around the time protocol, values were assigned missing. All persons for whom all four morning samples were available (n=706) could be included in the AUC analyses. In addition, we conducted Linear Mixed Models (LMM) analyses (see statistical analyses section) using all four morning saliva samples, which keeps original values on all four data points, can accommodate for incomplete cases, and takes correlation between repeated measurements into account. All persons with at least two valid morning cortisol values (n = 793) could be included in LMM analyses, thereby reducing the effects of missing values and including more patients in the analyses.

Evening cortisol: Since cortisol levels at 22h00 and 23h00 strongly correlated (Spearman’s rho = 0.8, p < 0.01), we used the mean of both cortisol levels. Data from 832 subjects were available for evening cortisol analyses.

Dexamethasone suppression test (DST): This test provides information on the negative feedback system of the HPA axis, since dexamethasone reduces cortisol level by acting on the pituitary. Of the 800 persons with T1 and T7, 768 (96.0%) subjects had taken the 0.5 mg dexamethasone (indicated by self-report) and were available for the DST analyses. We calculated a cortisol suppression ratio by dividing the cortisol value at T1 by the value at T7 the next morning.

Covariates
Sociodemographics (sex, age, years of education), sampling factors (awakening time and work status on the sampling day) and health indicators (smoking status (current versus no), cardiovascular disease) with effects on salivary cortisol variables in our study and possible effects on the course of psychopathology were included as covariates.

Clinical characteristics
Several clinical characteristics were taken into account, because of an effect on 2-year course of depression and/or anxiety disorders in the NESDA study. Severity of depressive symptoms was measured with the 30-item Inventory of Depressive Symptomatology. Severity of anxiety symptoms was measured using the 15-item Fear Questionnaire. Information on duration of symptoms prior to baseline was derived from the Life Chart
Assessment (LCA)\textsuperscript{31} conducted at baseline, which assessed the percent of time the patient spent with depressive and/or anxiety symptoms in the four years prior to baseline. Age of onset of the index disorder was assessed in the CIDI interview, and earliest age was used for those with comorbid disorders. Finally, baseline disorder status was included (Anxiety disorder, Depression, Comorbid disorders).

**Statistical analyses**

The associations between salivary cortisol indicators (AUCg, AUCi, evening cortisol and cortisol suppression ratio) and 2-year course outcome (chronic course versus remission) were analyzed using multiple logistic regression analyses. In addition, random coefficient analysis of the four morning cortisol levels was performed using LMM analyses comparing morning cortisol levels between persons with and without chronic course. Two-year outcome (chronic course yes/no), time point (T1, T2, T3, T4) and all covariates were entered as fixed factors, subjects were treated as a random effect and a random intercept was estimated. To examine whether the course of cortisol level after awakening was different for persons with a chronic course versus remission, we added a group by time interaction term.

**RESULTS**

Baseline characteristics are presented in Table 1. In our sample, 65.1% were women and the mean age at baseline was 42.8 years. 186 (22.2%) had a pure depressive disorder (‘Dep’), 358 (42.8%) had a pure anxiety disorder (‘Anx’) and 293 (35.0%) had comorbid depressive and anxiety disorders (‘Comorbid’) at baseline. 490 (58.5%) developed a chronic course compared to 347 (41.5%) persons with remission during the two years of follow-up. 73.5% of respondents showed an increase in cortisol in the first hour after awakening, with a mean increase of 10.4 nmol/l (or 80.3%).

Fully adjusted results illustrated that a lower AUCg as well as a lower AUCi were associated with the risk of a chronic course (RR=0.85, \( p=0.06 \) and RR=0.83, \( p=0.03 \), respectively), as confirmed by LMM results (direct effect: \( F=1.88, p=0.17 \), interaction with time: \( F=3.48, p=0.02 \), Figure 1). Evening cortisol and cortisol suppression after dexamethasone ingestion were not related to a 2-year chronic course. When we tested for quadratic relations, no \( p \)-values below 0.10 were obtained for all the quadratic terms, indicating that no additional non-linear associations could be confirmed.

To further graphically explore the relationship between the AUCg and AUCi with chronic course, we created quintiles of these cortisol measures. Figure 2 depicts the relationship between the cortisol awakening curve and the risk of chronic course across quintiles. Where quintiles of the AUCg were not significantly associated with the risk of chronic course, the lowest quintile of the AUCi was associated with an increased risk of
Table 1 Baseline characteristics

<table>
<thead>
<tr>
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<th>n = 837</th>
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<tbody>
<tr>
<td><strong>Sociodemographics</strong></td>
<td></td>
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<tr>
<td>% Female</td>
<td>65.1</td>
</tr>
<tr>
<td>Age (mean in years, SD)</td>
<td>42.8 (12.3)</td>
</tr>
<tr>
<td>Educational level (mean in years, SD)</td>
<td>12.0 (3.3)</td>
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<tr>
<td><strong>Health indicators</strong></td>
<td></td>
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<tr>
<td>% Smoking</td>
<td>37.5</td>
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<tr>
<td>% Cardiovascular disease</td>
<td>6.6</td>
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<tr>
<td>Baseline diagnosis</td>
<td></td>
</tr>
<tr>
<td>- % Depression only</td>
<td>22.2</td>
</tr>
<tr>
<td>- % Anxiety disorder only</td>
<td>42.8</td>
</tr>
<tr>
<td>- % Comorbid disorder</td>
<td>35.0</td>
</tr>
<tr>
<td>Age of onset (mean, SD)</td>
<td>21.1 (12.7)</td>
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<tr>
<td>Symptom duration (mean %, SD)</td>
<td>57.2 (35.7)</td>
</tr>
<tr>
<td>Depression severity (mean IDS, SD)</td>
<td>29.4 (11.8)</td>
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<tr>
<td>Fear score (mean, SD)</td>
<td>33.3 (19.7)</td>
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<tr>
<td><strong>Sampling factors</strong></td>
<td></td>
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<tr>
<td>Awakening time (mean, SD)</td>
<td>7h32 (1h15)</td>
</tr>
<tr>
<td>% Working on sampling day</td>
<td>58.7</td>
</tr>
<tr>
<td><strong>Salivary cortisol levels</strong></td>
<td></td>
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<tr>
<td>1-hour awakening cortisol*:</td>
<td></td>
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<tr>
<td>- AUCg (mean in nmol/l/h, SD)</td>
<td>19.4 (7.2)</td>
</tr>
<tr>
<td>- AUCi (mean in nmol/l/h, SD)</td>
<td>2.7 (6.5)</td>
</tr>
<tr>
<td>Mean evening level (mean in nmol/l, SD)</td>
<td>5.4 (3.3)</td>
</tr>
<tr>
<td>Dexamethasone suppression test**:</td>
<td></td>
</tr>
<tr>
<td>- Cortisol suppression ratio¹ (mean, SD)</td>
<td>2.8 (1.7)</td>
</tr>
</tbody>
</table>

*Adjusted for sex, age, education, smoking, working, awakening time and cardiovascular disease.
**Additionally adjusted for IDS score, Fear score, symptom duration and type of baseline disorder (Dep, Anx, Comorbid).
¹Relative risks for continuous measures are given per SD increase. AUCg: SD=7.2, AUCi: SD=6.5, evening cortisol: SD=3.3, Cortisol suppression ratio: SD=1.7

Table 2 The adjusted risk of having a 2-year chronic course across various salivary cortisol indicators.

<table>
<thead>
<tr>
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<th>2-year chronic course</th>
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<tbody>
<tr>
<td></td>
<td>RR (95% CI)*</td>
</tr>
<tr>
<td>AUCg (nmol/l/h)</td>
<td>0.87 (0.74-1.02)</td>
</tr>
<tr>
<td>AUCi (nmol/l/h)</td>
<td>0.89 (0.76-1.05)</td>
</tr>
<tr>
<td>Evening cortisol (nmol/l)</td>
<td>1.06 (0.91-1.23)</td>
</tr>
<tr>
<td>Cortisol suppression ratio</td>
<td>0.97 (0.84-1.12)</td>
</tr>
</tbody>
</table>

*Adjusted for sex, age, education, smoking, working, awakening time and cardiovascular disease.
**Additionally adjusted for IDS score, Fear score, symptom duration and type of baseline disorder (Dep, Anx, Comorbid).

Abbreviations: SD=standard deviation, IDS=Inventory of Depressive Symptoms, AUCg/i=Area under the curve with respect to the ground/increase.
*n = 706 for AUCs, n = 832 for evening cortisol and n = 768 for DST.
¹Cortisol suppression ratio= cortisol T1/ cortisol T7
Figure 1 Baseline 1-hour cortisol awakening levels for persons with and without a chronic course after two years. Analyses are adjusted for sex, age, education, smoking, working, awakening time, cardiovascular disease, IDS score, Fear score, age of onset, symptom duration and type of baseline disorder (Dep, Anx, Comorbid). LMM results: direct effect: $F=1.88$, $p=0.17$, interaction with time: $F=3.48$, $p=0.02$. Per time-point: Awakening: $p=0.48$, 30 min: $p=0.07$, 45 min: $p=0.08$ and 60 min: $p=0.11$.

chronic course as compared to the middle quintile (Figure 2). The quintiles did not appear to be consistently associated with risk of chronic course, the risk was only increased for the lowest quintile of AUCi (lowest quintile versus all higher quintiles together: RR=1.90, 95% CI=1.24-2.90, $p=0.003$).

Additional analyses were conducted on the association of AUCi and chronic course to examine whether the found association was consistent across disorders. We tested the presence of an interaction between AUCi and baseline disorder status (Anx, Dep, Comorbid), but this was not significant ($p>0.6$), suggesting that the finding appears to be robust across baseline disorder groups. Although the receipt of medication treatment at baseline was not associated with course outcome in multivariable analyses and only tricyclic antidepressant (TCA) use was associated with baseline CAR levels, we conducted additional analyses in which we adjusted for use of TCAs, selective serotonin reuptake inhibitors and other antidepressants. These analyses indeed yielded similar results. Finally, to investigate whether childhood trauma could explain the association found, we adjusted for childhood trauma. We used a cumulative childhood trauma index using the NEMESIS childhood trauma interview, which summarizes the frequency of four reported traumata before the age of 16 – emotional neglect, psychological abuse, physical abuse and sexual abuse – resulting in an index score between 0 and 8. Adjustment for this trauma index produced very similar results.
DISCUSSION

The present study is the first to examine extensive salivary cortisol measures and 2-year course of depressive and anxiety disorders. Results indicate that a lower cortisol awakening response is associated with an increased risk of a chronic course of depression and/or anxiety disorders over two years. Evening cortisol and cortisol suppression after dexamethasone ingestion were not associated with 2-year course of depression and anxiety.

Most prior studies reported no relationship between baseline HPA axis indicators and treatment response or outcome among patients with depression or panic disorder. None of these studies, examining HPA axis activity as predictor for course outcome, included the CAR. We observed that a lower CAR was associated with the risk of a chronic course, independent of important covariates including important clinical course predictors. The CAR showed to be unrelated to diurnal cortisol rhythm and to be under genetic control, which is in contrast to the other diurnal cortisol measures. Therefore, it represents a distinct measure of HPA axis activity.

How can we explain our finding of a lower CAR to be predictive of a chronic 2-year course? A low CAR is potentially indicative of hypocortisolism. It has been hypothesized that...
after long periods of (psychological or physical) stress the HPA axis becomes less responsive through down-regulation, resulting in low cortisol levels. Results supporting this theory come from studies in depressed older persons where hypocortisolism in depression showed to be associated with chronic and recurrent depressive episodes and physical frailty. In addition, Miller et al. conducted a meta-analysis on chronic stress and HPA axis activity and reported that morning cortisol is especially lowered when time has passed since the occurrence of the stressor and the stressor is no longer present, and when the stressor concerns an uncontrollable threat to the physical self, or traumatic stressor. However, these results were mainly based on cross-sectional studies examining one morning cortisol sample. Therefore, longitudinal studies are warranted to examine the temporal associations between chronic stress and HPA axis activity, including the CAR.

Down-regulation after chronic stress could also be reflected in the CAR, since several studies have reported a relationship between chronic or severe stress exposure and a blunted CAR. Although the predictive effect of the CAR for the course of depressive and anxiety disorders in our sample was independent of symptom duration at baseline and childhood trauma, chronic stress exposure could be of importance, since we did not actually assess chronic stress and only captured symptoms of the few years before baseline and not lifetime exposure.

A possible mechanism for hypocortisolism is down-regulation of corticotrophin-releasing-factor (CRH) receptors in the pituitary, following a longer period of stress-induced hypothalamic CRH secretion, resulting in lower adrenocorticotropic hormone (ACTH) and reduced cortisol levels. Alternatively, reduced biosynthesis or depletion of CRH, ACTH and/or cortisol or increased sensitivity of the HPA axis to negative feedback could play a role in hypocortisolism. This latter mechanism might be less important in explaining our findings, since we did not observe an association between the DST and chronic course.

However, it is unclear whether these mechanisms also apply to the CAR, since this is a distinct feature of HPA axis activity. It has been suggested that the CAR is under regulatory control of the hippocampus. Although the hippocampus has an inhibitory effect on HPA axis activity in general, the integrity of the hippocampus appears to be necessary for the CAR. A reduced hippocampus – found especially among the chronically depressed - has been associated with a blunted CAR. Therefore, the hippocampus might play an important role in explaining our result. A reduced hippocampus may contribute to a chronic course through a permanent vulnerability, possibly mediated by lower cortisol levels. However, longitudinal studies are warranted to entangle the relationship between hippocampus, HPA axis activity and the onset and course of depressive and anxiety disorders. Taken together, chronic stress exposure may have lead to down-regulation of the receptors of the HPA axis system and reduction of hippocampal volume, thereby resulting in a lower CAR. These underlying
mechanisms could explain why a lower CAR was found to be associated with a chronic course trajectory.

Another explanation for our findings could be that underlying chronic conditions are associated with a low CAR which further determines poor course trajectory. For instance, a blunted CAR has been observed in post-traumatic stress disorder\(^{49}\) and chronic fatigue syndrome\(^{50}\). Alternatively, these disorders may share a common pathophysiology with chronic depression.

Antidepressants also increase expression of glucocorticoid and mineralocorticoid receptors\(^{51}\), which after prolonged usage could also change HPA axis reactivity. However, we only observed an effect of TCAs on the CAR\(^{12}\) and exclusion of TCA users did not affect the results.

We previously observed that a higher CAR was associated with the presence of MDD and panic disorder with agoraphobia\(^{12, 13}\). In contrast, among current patients it appeared to be a low CAR that was predictive of an unfavourable course over time. Possibly, a higher cortisol awakening curve is associated with the onset of depressive disorder and/or panic disorder with agoraphobia and a lower CAR with the chronic course of these disorders. The observations that a higher cortisol awakening curve is associated with parental history of depression or anxiety in unaffected offspring\(^{52, 53}\) and with the incidence of depression in adolescents,\(^{54}\) support the idea that a higher cortisol awakening curve is associated with the onset of depression. Possibly, there are two distinct pathways: 1) a (genetic) biological vulnerability of depressive or anxiety disorders via high (morning) cortisol levels; and 2) a ‘scar’- effect as a result of high allosteric load during life resulting in a lower CAR and chronicity of depression. Future longitudinal studies are warranted to entangle these pathways. Possibly, these different pathways can explain some of the inconsistencies reported in the previous literature on HPA axis activity in depressive and anxiety disorders.

Most previous studies reported no relationship between basal HPA axis indicators or the DST and outcome of depression\(^{17, 21, 23-25}\). Although no studies specifically examined the development of a chronic course over two years, previous results appear to be in keeping with our negative findings with evening cortisol and the DST. Possibly, the diurnal rhythm and negative feedback system are not of importance in the development of a chronic course. However, since associations were present in e.g. panic disorder studies\(^{26, 27}\), it could be that in specific subgroups these HPA axis indicators are associated with course trajectory.

Our study had several strengths, including a large representative sample of outpatients who were longitudinally examined for two years. In addition, we obtained several salivary cortisol measures at baseline, and were able to take several important covariates as well as clinical characteristics into account. Also some limitations have to be acknowledged. The effect we found was similar across different types of baseline disorder (depression only,
anxiety disorder only and comorbid disorders), since interactions were not significant. However, our subsamples of specific depressive or anxiety disorders, such as social phobia or GAD, were not sufficiently large to examine the role of salivary cortisol measures in their course. Systematic bias seemed to be present, since persons who provided saliva samples were older, more educated and less likely to have anxiety disorders or comorbidity. The latter disorders had a more chronic course than depression only. However, participants did not differ in sex or course outcome. Therefore, the influence on the results is expected to be small. Non-compliance with the sampling instructions could have resulted in a measurement error and could have confounded our results. However, it should be noted that even when closely monitoring awakening, still at least 15% of all persons are not responding with a morning cortisol rise. Finally, salivary cortisol samples were only measured on one day. Sampling on multiple days could have increased the reliability of the measurements. However, the large sample size of our study may have (partly) compensated for this.

To conclude, this study is the first to longitudinally examine the relationship between (salivary) cortisol measures and a chronic course of depressive and/or anxiety disorders. Findings further add to the importance of the CAR in mental health, since we found a lower CAR among depression and anxiety patients to be predictive of a more chronic course trajectory over two years.
References


