Depressive and anxiety disorders are common and disabling mental disorders. This high burden is in part due to their course, since recurrence and chronicity are frequent for depressive and anxiety disorders. The anxiety disorders with the highest prevalence in combination with a high burden of illness are: generalized anxiety disorders, panic disorder with or without agoraphobia and social phobia, which are examined in this thesis. Depression and anxiety disorders are very heterogeneous and multicausal, a consequence of a complex interplay between genetic and environmental factors of which the pathophysiology is not completely understood yet. It is essential to understand the biological background of these disorders, since this will provide knowledge about possible prevention and treatment. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, one of the most important stress-systems of the body, is thought to play an important role in the pathophysiology of these disorders. One of the reasons for this is that stress is thought to play a role in the onset and course of depressive and anxiety disorders and also sets the HPA axis in motion. The end product of the HPA axis is cortisol, which follows a diurnal rhythm. Levels are highest in the morning during the cortisol awakening response and lowest in the evening. The negative feedback of the system can be measured with the dexamethasone suppression test, which measures cortisol suppression after ingestion of dexamethasone, a synthetic glucocorticoid. Cortisol has increasingly been measured in saliva, since this returns the active unbound form of cortisol and can be obtained during a stress-free method under normal conditions. There have been many studies examining cortisol levels in – especially – depression, but also anxiety disorders. Previous studies were mostly of small sample sizes, thereby limited in the adequate adjustment for possible confounders and examination of the role of disease characteristics in depressive and anxiety disorders. Also, there is debate about whether observed HPA-axis alterations are state or trait dependent, i.e. present only during an episode, or whether it is already present before an episode (vulnerability) or after an episode (‘scar’-effect). Furthermore, no previous studies have examined the role of these salivary measures in the course of depressive and anxiety disorders. Finally, the somatic consequences of differences in salivary cortisol measures are not fully understood. This thesis aims to contribute to our knowledge of the function of the HPA axis in depressive and anxiety disorders, by addressing aspects of this topic which were not covered in previous literature. In Chapter 1, an introduction of the topic is provided and Chapters 2 to 8 report on the results.

In Chapter 2, we examined the influences of sociodemographics, health factors and sampling factors on salivary cortisol measures in 491 persons without lifetime psychiatric disorders. We observed that sex, smoking, physical activity, and season of saliva collection were the most consistent determinants of salivary cortisol indicators. In addition, age, cardiovascular disease and several sampling factors were significant determinants of some
aspects of HPA axis activity. No significant consistent associations were found for: education, weekday, daily alcohol intake, body mass index, pain, diabetes, allergy or lung diseases or other chronic diseases in the main analyses. Therefore, these sociodemographics (sex, age), health factors (smoking, physical activity, cardiovascular disease) and sampling factors (sleep duration, season, awakening time and working on the sampling day) should be considered as covariates when examining salivary cortisol measures.

In Chapter 3, we compared salivary cortisol levels of persons without psychopathology (n= 308) with persons with remitted major depressive disorder (MDD, i.e. in the past but not current, n= 579) and persons with current MDD (n= 701). Remitted as well as current MDD was associated with a modestly but significantly increased cortisol awakening curve as compared to persons without lifetime psychiatric disorders. Second, although not confirmed with 23h00 data, significantly higher 22h00 evening cortisol levels were found for the current MDD group. However, MDD groups did not show more non-suppression after 0.5 mg dexamethasone ingestion; current MDD even seemed to be associated with more suppression. Additional analyses on several depression characteristics revealed no significant associations for most characteristics (e.g. chronicity, symptom severity, childhood trauma), except for a higher cortisol awakening response among depressed subjects with comorbid anxiety. In addition, the use of psycho-active medication was generally associated with decreased cortisol levels and less cortisol suppression after dexamethasone. These results imply that HPA axis activity as measured through salivary cortisol levels is significantly – although modestly - increased in both remitted as well as current depressed outpatients. The latter finding suggests that either the dysregulation was present before the onset of the disorder, perhaps reflecting a biological vulnerability or it is a result of a depressive episode, a ’scar’-effect.

In Chapter 4, we compared salivary cortisol levels of persons with a remitted (n= 311) or current anxiety disorder (generalized anxiety disorder, social phobia and/or panic disorders with or without agoraphobia, n= 774) to those of persons without psychopathology (n= 342). After adjustment for relevant covariates, we observed a higher cortisol awakening response for persons with a current anxiety disorder. The cortisol awakening curve for remitted anxiety held the intermediate position between current anxiety and controls. Additional analyses on type of disorder and presence of MDD revealed that persons with panic disorder with agoraphobia and persons with a comorbid MDD exhibited higher cortisol awakening responses as compared to persons with other anxiety disorders and no MDD. No differences were found in evening cortisol or cortisol suppression after dexamethasone ingestion between persons with anxiety disorders and controls.
To further examine state versus trait effects and analyze whether a higher cortisol awakening curve could already be observed in unaffected persons at high risk of depressive or anxiety disorders, we conducted a study on parental history of depressive and anxiety disorders in a sample without lifetime psychiatric disorders (Chapter 5). Results showed that CIDI-diagnosed parental history \((n= 74)\) was associated with a higher cortisol awakening curve as compared to persons without parental history \((n= 180)\), independent of neuroticism, childhood trauma and life events. However, self-reported parental history \((n= 114)\) was not associated with a higher cortisol awakening curve. Furthermore, the cortisol awakening curve was similar to that of patients with MDD or panic disorder with agoraphobia. These results suggest that an increased cortisol awakening curve might represent a trait and a biological vulnerability for the development of depressive and/or anxiety disorders.

In Chapter 6, we examined whether psychological traits (associated with psychopathology), such as personality and cognitive reactivity, were associated with the cortisol awakening curve, to further investigate whether the increased cortisol awakening curve in persons without psychopathology represents a trait rather than a state effect. This was done in a sample consisting of 381 persons without a lifetime psychiatric history. No traits were significantly associated with the cortisol awakening response, except for a positive association with hopelessness. Higher scores on hopelessness – a trait associated with depression and suicidality – were associated with a higher cortisol awakening response.

Chapter 7 describes a longitudinal study on the association between salivary cortisol measures at baseline and the course of psychopathology in 837 patients with depressive and/or anxiety disorders. We observed that compared to persons experiencing remission during the two-year follow up, persons with a lower CAR were at a higher risk of developing a chronic course. Evening cortisol and cortisol suppression after dexamethasone intake were not associated with a chronic course. The association appeared to be similar across baseline disorders (anxiety disorder only, depressive disorder only or comorbid disorders). A lower CAR could be the result of a longer underlying activation of the HPA axis due to chronic or severe stress exposure, finally resulting in exhaustion of the system resulting in down-regulation of receptors of the HPA axis.

In Chapter 8, the association between salivary cortisol measures and the metabolic syndrome was examined in 1883 NESDA participants. In addition, measures of the autonomic nervous system (ANS) were related to the metabolic syndrome as well as salivary cortisol measures. Components of the metabolic syndrome included: waist circumference, triglyceride levels, high-density lipoprotein levels, systolic blood pressure and glucose levels, and were also separately analyzed. Results showed that ANS measures were strongly associated with (components of) the metabolic syndrome, whereas salivary cortisol measures were not. Furthermore, ANS measures and HPA axis measures were not
correlated. These results indicate that salivary cortisol levels are not associated with cardiovascular risk as measured through the metabolic syndrome and that basal HPA axis activity is independent of ANS activity.

In **Chapter 9**, the main findings are discussed. In short, the results presented in this dissertation show that salivary cortisol levels, although influenced by many factors are on average slightly higher in persons with psychopathology. More specifically, the cortisol awakening curve is modestly but significantly higher in persons with a remitted or current MDD or a current panic disorder with agoraphobia. Furthermore, evidence was gathered that this higher cortisol awakening curve is more of a trait than a state characteristic, since it is also present in unaffected persons with parental history of depression or anxiety, and with higher scores on hopelessness reactivity. When exploring consequences, we found that the cortisol awakening response at baseline was inversely associated with the risk of a chronic course over two years, but was not associated with the metabolic syndrome.

So, the HPA axis indicator associated with *presence* of depression and anxiety disorders was completely different from the one predicting *course* of depression and anxiety disorders. Possibly, these results reflect two distinct pathways. First, a higher cortisol awakening curve (AUCg) was found to reflect a biological vulnerability marker for depression and panic disorder. Second, among patients with depression and anxiety disorders, a lower CAR (AUCi) – possibly reflecting a high allosteric load during life – was found to predict a chronic course trajectory.