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A two-year follow-up study of salivary cortisol concentration and the risk of depression

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Summary Stress is a suspected cause of depression. High cortisol concentration, a biomarker of an activated stress response, has been found in depressed patients. The aim of this study was to determine if a high level of salivary cortisol is a risk factor of depression. In 2007, we enrolled 4467 public employees. Morning and evening salivary cortisol concentration were measured for each participant. Participants reporting high levels of depressive, burnout, or stress symptoms, assessed by questionnaires were assigned to a psychiatric interview. In this interview 98 participants were diagnosed with depression and subsequently excluded. Two years later in 2009, 2920 participants who had provided at least one valid saliva cortisol measurement at baseline participated at follow up. The psychiatric interviews were repeated and 62 cases of newly onset depression were diagnosed. Odds ratios of depression were estimated for every 1.0 nmol/l increase in morning, evening, and daily mean cortisol concentration, as well as for the difference between morning and evening cortisol concentration. The risk of depression decreased by increasing daily mean cortisol concentration and by increasing difference between morning and evening concentrations, while morning and evening cortisol concentrations were not significantly associated with depression. The adjusted odds ratios for 1.0 nmol/l increase in morning, evening, and daily mean cortisol concentration were 0.69 (95% CI: 0.45, 1.05), 0.87 (95% CI: 0.59, 1.28), and 0.53 (95% CI: 0.32, 0.90), respectively. The adjusted odds ratio for 1.0 nmol/l

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increase in difference between morning and evening concentration were 0.64 (95% CI: 0.45, 0.90). This study did not support the hypothesis that high salivary cortisol concentration is a risk factor of depression, but indicate that low mean salivary cortisol concentration and a small difference between morning and evening cortisol concentration may be risk factors of depression.

1. Introduction

Stress and stressful life events are often implicated in the causation of depression and numerous other diseases (Maddock and Pariante, 2001; Risch et al., 2009), although there are unresolved questions about the causal mechanisms (Hammen, 2005). Sudden and intense stressors cause an acute increase in cortisol secretion, while it has been suggested that long-term and less intense stressors may cause a low-level increase as well as a lowered cortisol secretion after several years (Yehuda et al., 1996; Rosmond and Bjorntorp, 2000). Abnormalities in the HPA axis have therefore been speculated to play a key role in the development and recurrence of depression (Hammen, 2005).

Increased cortisol level and thus hyperactivity of the HPA axis has repeatedly been reported in cross-sectional studies of patients diagnosed with depression (Brown et al., 2004; Pariante and Lightman, 2008; Knorr et al., 2010; Stetler and Miller, 2011; Jonsdottir et al., 2012). However, it is unclear whether this reflects a causal mechanism leading to depression or mechanisms that are secondary to the inception of the disease. The few longitudinal studies conducted so far show that different measures of increased cortisol level at baseline predict depression at follow up 1 to 6 years later (Goodyer et al., 2000; Harris et al., 2000; Halligan et al., 2007; Adam et al., 2010; Goodyer et al., 2010; Ellenbogen et al., 2011; Vrshek-Schallhorn et al., 2012). Harris et al. (2000) examined 116 adult women screened to have a high risk of depression and observed that a high morning cortisol concentration was associated with depression during 13 months of follow up, but did not find any association with evening cortisol concentration. Goodyer et al. (2000) and Halligan et al. (2007) found similar results during 1 year and 3 years of follow up that included 180 and 57 adolescents, respectively. Goodyer et al. (2010) in a later study examined 401 adolescents and found high concentrations of morning cortisol to be associated with depression 3 years later. Ellenbogen et al. (2011) showed that a high mean concentration of cortisol across the day among 59 adolescents predicted depression during 1—6 years of follow up. Adam et al. (2010) observed no association between morning-to-evening slope or mean cortisol concentration across the day and depression in 230 adolescents during 1 year of follow up. But the cortisol awakening response was a significant predictor of depression. Vrshek-Schallhorn et al. (2012) examined 270 adolescents and showed that the cortisol awakening response predicted depression up to 2½ year after baseline, but not thereafter. They observed no relation between morning-to-evening slope or mean cortisol concentration across the day and depression.

Thus, results from longitudinal studies are equivocal and based on relatively few observations. Studies are mainly conducted among adolescents and include no healthy adult populations. We recruited a large, healthy working population and measured the HPA activity by saliva cortisol concentration and analysed the risk of new onset depression two years later. We hypothesised that a high level of cortisol increases the risk of depression.

2. Methods

2.1. Design

This follow-up study is based on the Danish PRISME cohort established in 2007 and re-examined in 2009 (Kolstad et al., 2011; Grynderup et al., 2012). The purpose of the PRISME study is to examine to what extent psychological work factors and increased HPA axis activity are risk factors of depression, burnout, or stress symptoms. We measured salivary cortisol in all participants in 2007 and analyzed if morning concentration, evening concentration, mean of morning and evening concentration, or the morning-to-evening slope (difference between morning and evening concentration) predicted new-onset of depression at follow up in 2009. Cases of depression were identified in 2007 and 2009 by a two-step procedure: First, we identified participants reporting mental symptoms (symptoms of depression, perceived stress, or burn-out) in a questionnaire. Second, these participants were invited to a standardized psychiatric interview to identify cases with depression.

2.2. Population

In 2007, we approached 10,036 public employees from the municipal and hospital sector in Aarhus, Denmark for participation in the Danish PRISME cohort. Of these 4467 employees (45%) participated by collecting saliva samples and filling in a short questionnaire on sleep, medication, and alcohol intake the day of sampling. Participants with a clinical diagnosis of depression at baseline according to ICD-10 (n = 98) and pregnant women (n = 138) were excluded leaving 4231 participants for follow up. In 2009, all participants from 2007 were approached, and a total of 3031 participated. A total of 2920 of these participants provided a valid salivary cortisol measurement, as described later, and thus comprised the final study population.

2.3. Collection of saliva samples

All participants received Salivette® cotton swabs that they were instructed to keep in the mouth until thoroughly saturated. The saturated swabs were kept in a tube and stored in a refrigerator until they were returned by mail. The average time from date of sampling to date of receiving the samples at the National Research Centre for the Working Environment were 5 days (SD = 3 days). The samples were then stored at −20 °C and analyzed within 6 months. Participants sampled