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SHORT COMMUNICATION

Anxiety disorders and salivary cortisol levels in older adults: a population-based study

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KEYWORDS
Cortisol;
Anxiety disorder;
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HPA axis;
Awakening response

Summary
Context: The hypothalamic-pituitary-adrenal (HPA) axis is one of the body's main systems that controls response to stress. It acts through the hormone cortisol. While the dysregulation of cortisol has been associated with anxiety disorders, the evidence is inconsistent. Moreover, only a few small studies have assessed this relationship in older adults.
Objective: To determine whether in adults aged 65 years and over there is a difference in daily cortisol pattern between those with and without an anxiety disorder.
Methods: The study population comprised 1788 older adults from a population-based cohort. The Munich version of the Composite International Diagnostic Interview was used to diagnose anxiety disorders (generalized anxiety disorder, social phobia, specific phobia, agoraphobia and panic disorder). The cortisol awakening response and total cortisol secretion over the day were calculated from cortisol levels in four saliva samples taken over the course of one day (at awakening, 30 min after awakening, at 1700 h, at bedtime).
Results: Older adults with an anxiety disorder ($n = 145$, median duration since first symptoms 41 years) had a lower cortisol awakening response ($p = 0.02$) than those without such a disorder ($n = 1643$). This association was most prominent in those with generalized anxiety disorder ($p = 0.008$), but was not associated with the extent of chronicity of anxiety disorders.
Conclusion: Older adults from the general population with long-lasting anxiety disorders had a lower cortisol awakening response than those without. This is consistent with the notion that chronic anxiety may result in downregulation of HPA-axis activity. Longitudinal studies are needed to confirm this mechanism.

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1. Introduction

The hypothalamic-pituitary-adrenal axis (HPA axis) is one of the body's main systems that controls response to stress. It acts through the hormone cortisol, which is produced in the adrenal cortex and affects many tissues including the brain. Cortisol is secreted in a distinct daily pattern whereby cortisol levels rise rapidly after awakening (the cortisol awakening response or CAR) and decrease slowly thereafter. Deregulation of the CAR, and total cortisol secretion over the day have been associated with various disorders, including anxiety disorders (Vreeburg et al., 2010). In addition, age-dependent HPA-axis dysregulation may increase the vulnerability of older adults for psychiatric disorders (Van Cauter et al., 1996).

Although numerous studies have described the relationship between the HPA axis and anxiety disorders, the evidence is inconsistent and only a few studies assessed this relationship in older adults. While one study reported that older adults (mean age 74, $n = 111$) with generalized anxiety disorder (GAD) had higher cortisol levels than those without GAD (Mantella et al., 2008), another study (mean age 76, $n = 48$) reported no association of cortisol levels with an anxiety symptom score (Heaney et al., 2010). A further study of older people (mean age 73, $n = 201$) also reported no difference in total cortisol levels during the day between people with and without lifetime GAD in a non-stressful condition, but the CAR was not assessed (Chaudieu et al., 2008).

In the current study we assessed not only total cortisol secretion, but also the CAR. We jointly analyzed anxiety disorders, but also present data on GAD, social phobia, specific phobia and agoraphobia separately. Furthermore, this study was no convenience sample, but comprised older adults (aged 65 and over) from the general population to minimize selection effects.

2. Methods

2.1. Study setting

This study was set in the Rotterdam Study, a prospective population-based cohort study of older adults designed to assess risk factors for chronic diseases (Hofman et al., 2011). In 1990, all residents in a district in Rotterdam who were aged 55 years and over were invited to participate. Every four years, participants undergo an extensive home interview and physical examination at a research center. The Medical Ethics Committee of the Erasmus MC approved the Rotterdam Study.

The fourth examination round (2002—2004, $n = 3550$) assessed anxiety disorders and salivary cortisol levels. The study population comprised 1788 people after exclusion of people without a valid anxiety assessment ($n = 287$), people without the first two cortisol measurements ($n = 1152$), people using corticosteroids ($n = 287$), and people with dementia ($n = 36$). Almost two thirds of those who were excluded ($n = 1762$) were female against 56.9% of the study participants. The excluded group was significantly older than the study population (mean age 77.3 versus 74.7) and had a lower education.

2.2. Assessment of anxiety disorders

Prevalent anxiety disorders were diagnosed during the home interview. Trained lay interviewers conducted a slightly adapted version of the Munich version of the Composite International Diagnostic Interview (M-CIDI, Wittchen et al., 1998). The following anxiety disorders were assessed with a computerized diagnostic algorithm according to DSM-IV criteria: GAD, panic disorder, agoraphobia, social phobia and specific phobia. Age of symptom onset was recorded. Obsessive compulsive disorder and post-traumatic stress disorder (PTSD) were not assessed, because these disorders are relatively rare in the general population.

2.3. Salivary cortisol protocol

Saliva samples were collected on awakening (T1), 30 min after awakening (T2), at 1700 h (T3), and at bedtime (T4). Cortisol levels in these samples were determined as previously described (Dekker et al., 2008). The multiple measures of cortisol were combined in summary measures to provide valid information about the diurnal pattern of cortisol. We calculated the area under the curve with respect to the ground (AUCg) and the cortisol awakening response (CAR). The AUCg summarizes overall diurnal cortisol exposure. The CAR is a measure of the dynamics of the HPA-axis response upon awakening. The CAR and the AUCg are thought to be regulated differently (Clow et al., 2004). The AUCg was calculated as the total area under the curve from the individual cortisol measures on the *Y*-axis and the time between cortisol measures on the *X*-axis. To not measure the effect of the CAR, we did not include T2 in the calculation. We corrected for total time awake and only calculated the AUCg for those with data on all three time points ($n = 1664$). The CAR was calculated as the difference between cortisol levels at T2 and T1 over two ($n = 1788$, Pruessner et al., 2003). Analyses on the CAR were adjusted for the time between measurements.

2.4. Assessment of other variables

Age, sex, marital status, psycholeptics use, psychoanaleptics use, hormonal drug use, usual sleep duration, and alcohol, coffee and tea consumption were recorded. Education was grouped according to the Standard Classification of Education and rated on a scale from primary education (1) to university level (7). Height and weight were measured at the research center to calculate body mass index (BMI). Smoking was coded according to current smoking status. Cognitive capacity was assessed using the Mini Mental State Examination. A cut-off of 26 indicated adequate cognitive capacity versus impaired cognitive capacity. Disability (Activities of Daily Living) was assessed with the Stanford Health Assessment Questionnaire. The standard cut-off of a mean score of 0.5 indicated no disability versus mild to severe disability. Participants were continuously monitored for occurrence of coronary heart disease. International Classification of Diseases, 10th Revision was used to assign diagnoses of myocardial infarction (I21), percutaneous transluminal coronary angioplasty, coronary artery bypass graft and other forms of acute (I24) or chronic ischemic heart disease (I25). Diabetes