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Cortisol serum levels in familial longevity and perceived age: The Leiden Longevity Study

Raymond Noordam [a], David A. Gunn [b], Cyrena C. Tomlin [b], Maarten P. Rozing [a], Andrea B. Maier [a,d], P. Eline Slagboom [c,d], Rudi G.J. Westendorp [a,d], Diana van Heemst [a], Anton J.M. de Craen [a,*]

On behalf of the Leiden Longevity Study group

[a] *Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands*
[b] *Unilever Discover, Colworth House, Sharnbrook, Bedfordshire, UK*
[c] *Section of Molecular Epidemiology, Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands*
[d] *Netherlands Consortium of Healthy Ageing (NCHA), The Netherlands*

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Summary
Background: Cortisol levels are strongly associated with a person's health. Familial longevity and age assessment of facial photographs (perceived age) are both associated with morbidity and mortality. The present study aimed to investigate morning cortisol levels in familial longevity and the association of these levels with perceived age.
Methods: Perceived age and serum morning cortisol levels were measured for 138 offspring from long-lived families and 138 partners from the Leiden Longevity Study. Considered confounding factors were chronological age, gender, body mass index, current smoking habits, antidepressant drug use, antihypertensive drugs and diabetes medication.
Results: In the fully adjusted model, which was restricted to participants who did not use antidepressant drugs, offspring had similar serum cortisol levels compared to their partners (0.54 and 0.55 μmol/L, respectively; $p = 0.54$). Using a similar model taking offspring and partners together, an increase of 0.1 μmol/L in morning cortisol levels was associated with an 0.42 (95% CI 0.0—0.84, $p = 0.048$) year increase in perceived age. This association was significantly attenuated in the offspring group (0.01, 95% CI −0.58 to 0.59, $p = 0.98$) compared to the partner group (0.81, 95% CI 0.20—1.41, $p = 0.009$ year increase in perceived age per 0.1 μmol/L increase in cortisol respectively) (p for interaction = 0.042).

* Corresponding author at: Department of Gerontology and Geriatrics, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands.
E-mail address: craen@lumc.nl (A.J.M. de Craen).

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Conclusion: This study demonstrates that high levels of cortisol are associated with a higher perceived age. This association was attenuated in offspring from long-lived families compared to their partners, suggesting enhanced stress resistance in these subjects. Future research will be aimed at elucidating potential mechanisms underlying the observations in this study.

1. Introduction

Chronic psychological stress has a major effect on a person's health, as it is associated with both an increased incidence of cardiovascular morbidity and mortality (Kiecolt-Glaser and Glaser, 1999; Ohlin et al., 2004) and with a poorer immune response (Kiecolt-Glaser et al., 1996; McEwen et al., 1997; Vedhara et al., 1999). One of the hormones secreted under acute stress is the glucocorticoid cortisol. Cortisol secretion is tightly regulated by the hypothalamus–pituitary–adrenal axis (HPA axis) (Lundblad and Roberts, 1988). Moreover, cortisol itself inhibits upstream HPA signaling by a negative feedback mechanism, resulting in a diminished secretion of cortisol (Beyer et al., 1988). Chronically high serum cortisol levels are frequently observed in patients with Cushing syndrome (Boscaro et al., 2001), depression (Tafet et al., 2001), and obesity (Bjorntorp and Rosmond, 2000). Subjects having chronically high levels of cortisol have a higher prevalence of muscle weakness, osteoporosis, hypertension and diabetes mellitus type 2 and have a higher mortality risk (Walker et al., 1998; Manelli and Giustina, 2000; Schoorlemmer et al., 2009). Thus, high levels of cortisol are potentially damaging for tissues over time and, conversely, low levels might be indicative of healthy aging.

The Leiden Longevity Study was set up to study biological mechanisms associated with familial longevity and healthy aging. Families were included in this study when at least two siblings had reached the age of 89 years (men) or 91 years (women) (Schoenmaker et al., 2006). The middle aged offspring of these long-lived siblings have a lower prevalence of diabetes mellitus type 2, myocardial infarction, and hypertension compared to their partners (married and cohabitating), who were not part of a long-lived family (Westendorp et al., 2009). It is unknown, however, whether cortisol associates with familial longevity and, therefore, whether it could be partly responsible for the beneficial profile of the offspring.

Another marker of health aging is how old individuals look in facial photographs (their, so-called, "perceived age"). A higher perceived age (*i.e.* an older looking facial appearance) associates with both morbidity and mortality (Christensen et al., 2009). In addition, environmental factors known to influence health also associate with perceived age. For example, smoking and low body mass index both associate with an older looking appearance, whereas a high social class and high education associate with a younger looking appearance (Rexbye et al., 2006). Research on identical twins suggests also a genetic contribution to perceived age (Shekar et al., 2005; Gunn et al., 2009). However, specific genes associated with perceived age have yet to be described. Furthermore, biological mechanisms associated with an older (or younger) looking appearance still need to be elucidated. Previous research has hinted toward an association between cortisol and perceived age, as depression is associated with both (Tafet et al., 2001; Rexbye et al., 2006), but a direct associative relationship has yet to be investigated.

In this study we aimed to investigate whether cortisol levels are associated with familial longevity and perceived age. To assess this, three research questions were addressed. First, we assessed whether offspring from long-lived families have lower levels of serum morning cortisol compared to their partners. Second, we determined whether higher levels of serum morning cortisol levels were associated with a higher perceived age. And third, we assessed whether the association between morning cortisol levels and perceived age was different between offspring from long-lived families and their partners. To answer these research questions we measured morning cortisol levels and assessed perceived age in a sample of 276 middle aged subjects (138 offspring and 138 partners thereof) from the Leiden Longevity Study.

2. Materials and methods

2.1. Study design

The Leiden Longevity Study was designed to find phenotypic and genetic markers related to familial longevity. An extended description about the longevity phenotype and inclusion strategy has been published previously (Westendorp et al., 2009). In short, a total of 421 families were recruited consisting of long-lived Caucasian siblings together with their offspring and the partners thereof. Inclusion was only performed when at least two long-lived siblings were still alive and fulfilled the age criteria of 89 years in case of males and 91 years for females. The siblings were not selected on health conditions or demographics. Because proper controls at high age are lacking, the offspring from these nonagenarian siblings were asked to participate along with their partners who act as age-matched controls (Schoenmaker et al., 2006) who did not come from a long-lived family. Partners are hereafter called controls.

In total, 190 couples (an offspring living with a control), who were living in the near district of the research center (less than 45 min by car), were asked to come fasted at 0830 h to the research center for fasted blood sampling and an oral glucose tolerance test. In total 140 couples approved and participated in this study. Four subjects (2 offspring and 2 controls) were excluded because of use of oral corticosteroids at the time this study was conducted, leaving 276 subjects (138 offspring and 138 controls) for analyses. The study was approved by the Medical Ethical Committee of the Leiden University Medical Center and written informed consent was obtained from all subjects.