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Associations between hypothalamic–pituitary–adrenal axis function and peak bone mass at 20 years of age in a birth cohort

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ABSTRACT

In older adults, high-normal circulating cortisol levels are associated with lower bone mass, but relationships between hypothalamic–pituitary–adrenal axis function and peak bone mass in young adults have not been examined. We studied 411 male and 390 female participants in the Western Australia Pregnancy Cohort (Raine) Study. At 18 years of age, participants underwent a Trier Social Stress Test (TSST) with measurement of plasma and salivary cortisol at baseline and at multiple time points after stress. Cortisol responses were classified as anticipatory responder (significant fall in cortisol during the test), reactive responder (significant increase) or non-responder. At 20 years, total body bone mineral content (BMC) and density (BMD) were measured by DXA. In males, after adjustment for weight, height (for BMC and bone area only), alcohol and smoking, there was a significant inverse relationship between both plasma and salivary cortisol measured at baseline in the TSST and each of BMC and BMD, such that each additional 10% of salivary cortisol was associated with reductions of 6.9 g (95% CI −11.7, −2.2) in BMC, and 1.8 mg/cm^2 (95% CI −3.3, −0.4) in BMD. Males classified as anticipatory responders in the TSST had 3.2% lower BMC (adjusted mean ± SE: 3131 ± 28 vs. 3233 ± 18 g, P = 0.006) and 2.5% lower BMD (1108 ± 9 vs. 1136 ± 6 mg/cm^2, P = 0.022) than reactive responders. In females, there were no significant relationships between baseline cortisol or TSST responses and BMC or BMD in covariate-adjusted analyses. We conclude that in young males (but not females), higher circulating cortisol at the baseline of the stress test and an anticipatory responder pattern on the TSST are associated with lower total body bone mass.

1. Introduction

It is well-recognized that glucocorticoid treatment is a risk factor for osteoporosis [1], and excessive endogenous cortisol production in Cushing's syndrome leads to significant reduction in bone mineral density (BMD) and increased fracture risk [2]. Less is known on the effects of endogenous cortisol within the physiological range on bone health, but there is evidence from epidemiological studies in older adults that high-normal cortisol levels may be associated with lower BMD [3–6] or increased rate of bone loss [3,7].

Analysis of the relationships between endogenous cortisol and bone health is challenging because of the complexity of hypothalamic–pituitary–adrenal (HPA) axis physiology, including diurnal variation, stress responses, and interactions between obesity and cortisol secretion and metabolism. In previous studies of older adults, a range of measures of HPA axis function have been used, including integrated 24-h cortisol level and trough cortisol concentration [3], morning and evening salivary cortisol levels [4], post-dexamethasone cortisol level [5,6], and peak plasma cortisol following tetracosactrin stimulation [7]. The Trier Social Stress Test (TSST), a psychosocial stress protocol, has been shown to reliably and consistently produce HPA axis stimulation and elicit the highest endocrine responses of any laboratory stressor [8,9], therefore may be more physiologically relevant than pharmacological stressors in the evaluation of HPA axis activity. However, the association between the HPA axis response to TSST and bone density has not been studied. In addition, there have been no studies examining the relationships between HPA axis function and peak bone mass in young

Abbreviations: AUC, area under the curve; BMI, body mass index; BMC, bone mineral content; BMD, bone mineral density; CV, coefficient of variation; DXA, dual-energy x-ray absorptiometry; HPA, hypothalamic–pituitary–adrenal; TSST, Trier Social Stress Test.

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adults. This is potentially important, as attainment of optimal peak bone mass in early adult life is considered the best protection against osteoporosis in later life [10].

In the Western Australia Pregnancy Cohort Study, a well-characterized community-based cohort study, HPA axis function was evaluated by the Trier Social Stress Test at late adolescence (18 years of age). In this analysis, we examined relationships between HPA function at late adolescence and bone mass measured at 20 years of age in participants, when peak bone mass is generally attained [11].

2. Subjects and methods

2.1. Subjects

The study participants were from the Western Australian Pregnancy Cohort (Raine) Study, which recruited 2900 pregnant women from the public antenatal clinic at King Edward Memorial Hospital and surrounding private clinics in Perth, Western Australia between May 1989 and November 1991, and has subsequently followed the offspring as a birth cohort study. Inclusion criteria were a gestational age between 16 and 20 weeks, English language skills sufficient to understand the study demands, an expectation to deliver at King Edward Memorial Hospital, and an intention to remain in Western Australia to enable future follow-up of their child [12]. Compared with the general Western Australian population, the Raine cohort at birth was characterized by higher proportions of high-risk births and fathers employed in managerial and professional positions, but comparison of participants remaining in the study at the 14-year follow-up suggested attrition resulted in a cohort comparable with the general population [13]. Of the 2868 children born, 1306 participated in the physical examination component of the 20-year cohort follow-up, of whom 1183 had valid whole body dual-energy x-ray absorptiometry (DXA) scans [14]. Of these, 872 underwent the TSST at 18 years. Excluding 24 participants who were taking medications such as exogenous steroids, neuroactive or anti-depressant medications at the time of TSST, 33 participants who did not complete the test or had diurnal disturbances (worked night shifts or had little sleep), and 14 participants displayed unusual patterns which could not be categorized (it was unclear if this was due to physiological or technical reasons), data from 411 males and 390 females were included in this analysis (Fig. 1). The study at both 18 and 20 years of age was approved by the Human Research Ethics Committee of University of Western Australia. Written informed consent was obtained from each participant.

2.2. Trier Social Stress Test (TSST)

A TSST was conducted at the 18-year follow-up visit. Participants were instructed to refrain from physical exercise, smoking, medication, eating and drinking anything besides water for 1 h before the test, which was conducted in the afternoon between 1200 h and 1600 h. This time of day was selected in order to minimise the effect of HPA

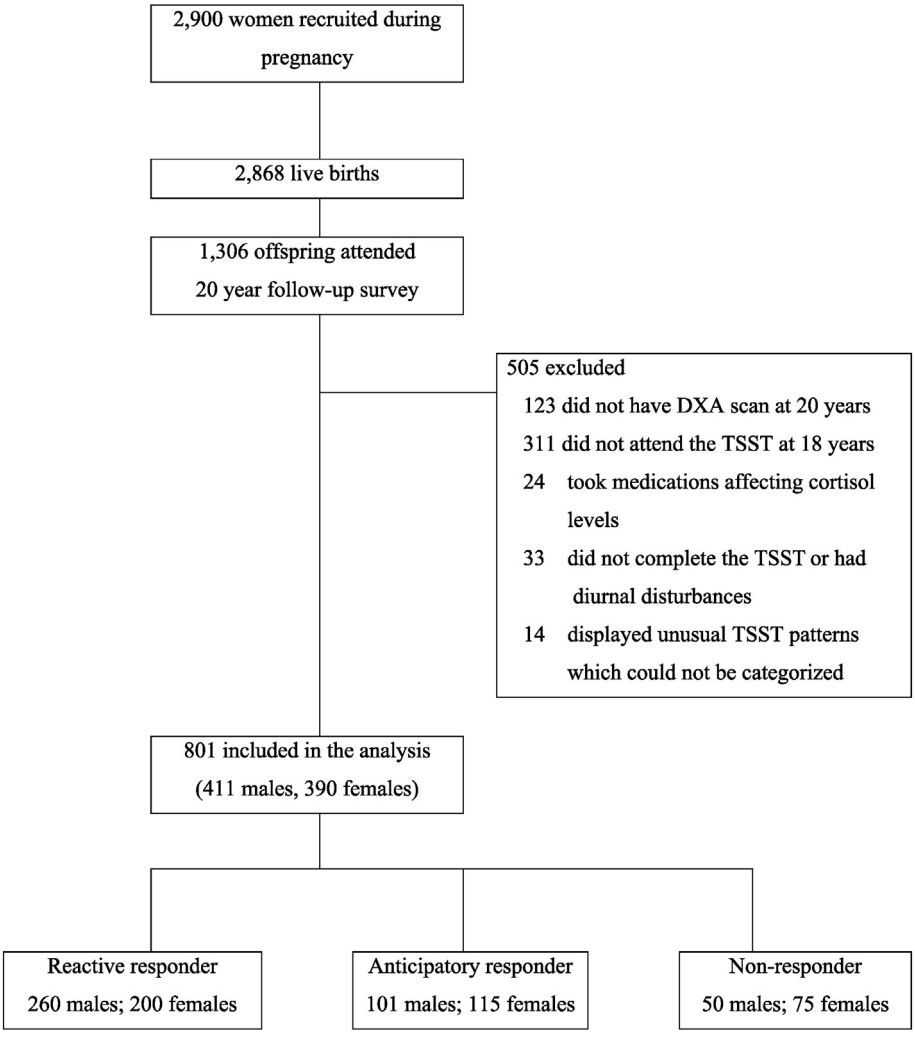

Fig. 1. Participant disposition chart showing how the study population was derived. DXA, dual-energy x-ray absorptiometry; TSST, Trier Social Stress Test.