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# The association between urinary cortisol excretion and cardiovascular risk factors, bone status and quality of life in the population

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ABSTRACT

*Objective:* Patients with glucocorticoid excess have increased cardiovascular risk, decreased bone mineral density and impaired quality of life (QoL). The aim of this study was to evaluate the association between urinary cortisol excretion and cardiovascular risk factors, bone status and QoL in the population. We hypothesized that higher cortisol excretion was associated with adverse cardiovascular risk profile, worse skeletal health and QoL.

*Design, patients and methods:* This was a cross-sectional study including a population sample ($n = 348$), aged 38–77 years. The mean age in women was 64.0 ± 8.5 years ($n = 276$) and 60.3 ± 10.2 years in men ($n = 72$). The metabolic syndrome, body composition measured with bioimpedance, calcaneal quantitative ultrasound, fractures and QoL evaluated with the Nottingham Health Profile, Psychological General Well-Being (PGWB) and the Short Form 36 (SF-36) were studied. Urinary free cortisol (UFC) was measured using radioimmunoassay.

*Results:* UFC was higher in men (230 ± 120 nmol/L) compared to women (153 ± 71; $P < 0.001$) and decreased with increasing age ($P < 0.001$). In a regression analysis, after adjustment for gender, age and body mass index, higher UFC was associated with higher fat-free mass ($P < 0.01$), favourable calcaneal bone measurements ($P < 0.05$), better general health measured with PGWB ($P < 0.01$) and SF-36 ($P = 0.001$) and tended to be negatively associated with the metabolic syndrome ($P = 0.07$).

*Conclusion:* In contrast to our hypothesis, UFC in the upper physiological range was associated with a favourable cardiovascular risk profile, bone measures and QoL.



## 1. Introduction

Cortisol is the main glucocorticoid in humans. Since the glucocorticoid receptor is found in almost all tissues, cortisol has a wide range of action in the human body [1,2]. In fact, cortisol has a major impact on protein, fat and carbohydrate-metabolism, the skeleton, the cardiovascular and immune system as well as the brain [2].

Prolonged glucocorticoid excess as seen in Cushing's syndrome can have devastating effects on health. Patients with Cushing's syndrome have increased cardiovascular risk [3], decreased bone mineral density, increased fracture risk [4,5], cognitive dysfunction and impaired quality of life (QoL) [6,7]. Even mildly, pathologically increased endogenous cortisol production has negative impact on QoL [8], cardiovascular [9] and skeletal health [10,11].

Studies on the relationship between urinary cortisol excretion and cardiovascular risk factors are sparse in the general population. An association between high urinary cortisol and adverse cardiovascular profile has been observed in some, but not in other, small studies of selected subjects [12–15]. Also, cortisol concentration in urine in young women and healthy older men has been associated with decreased bone mineral density and increased fracture risk [16,17]. To our knowledge, the association between urinary cortisol excretion and QoL in the general population has not been studied before.

*Abbreviations:* BMI, body mass index; BUA, broadband ultrasound attenuation; HOMA, homeostatic model assessment; IR, insulin resistance; NHP, Nottingham Health Profile; PGWB, Psychological General Well-Being; QoL, quality of life; SF-36, Short Form 36; SOS, speed of sound; UFC, urinary free cortisol; QUS, Quantitative Ultrasound Measurement; WHO MONICA, World Health Organization MONItoring of trends and determinants in CArdiovascular disease.

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The aim of this study was to analyse the association between urinary cortisol excretion, a surrogate measure of glucocorticoid exposure, and cardiovascular risk factors, bone measures, fractures and QoL in a population sample. We hypothesized that higher cortisol excretion was associated with adverse cardiovascular risk profile, worse skeletal health and QoL.

## 2. Material and methods

### 2.1. Study design and participants

In 1995, a random population sample of 1200 men and 1200 women, aged between 25 years and 64 years, from Gothenburg, Sweden, was invited to participate in the World Health Organization MONItoring of trends and determinants in CArdiovascular disease (WHO MONICA), a project conducted in 38 countries worldwide [18]. The participation rate was 67%, 746 men and 870 women. Extended bone and body composition measurements and hormonal blood sampling were performed on a randomly selected subset of participants ($n$ = 608), including every fourth woman aged between 25– and 44 and every fourth man in all age groups, 25–64 years and all women in the age group 45–64 years. In 2008, these subjects were invited to a re-examination [19]. The participation rate was 67% ($n$ = 412). Non-attendance was due to decease, travelling, living abroad, difficult family circumstances, or unwillingness to participate.

The study group of the current analysis was the individuals who were re-examinated in 2008 [19]. Of 412 subjects, 64 were excluded; 53 did not collect 24-h urine, 8 had inadequate urine samples (<0.75 L/24-h) and three had systematic glucocorticoid therapy. Of the remaining 348 subjects who were included in the study, 276 (79%) were women and 72 (21%) were men.

### 2.2. Anthropometry and blood pressure

Body height was measured to the nearest 0.5 cm. Body weight was measured to the nearest 0.1 kg in the fasting state with the subject in light clothes. Body mass index (BMI) was calculated as weight/height$^2$ (kg/m$^2$). Waist circumference was measured with a soft tape midway between the lowest rib margin and the iliac crest in the standing position. The hip circumference was measured over the widest part of the gluteal region and the waist/hip circumference ratio was calculated. A single operator performed all the anthropometric measurements.

Blood pressure was measured with a random-zero sphygmomanometer (Hawksley & Sons) and reported as the mean of three consecutive measurements in a sitting position.

### 2.3. Body composition and bone measurement

Fat-free mass and body fat were estimated using impedance measurements (SEAC Multiple frequency bioimpedance meter, model SFB 2, UniQuest Ltd, Queensland, Australia), based on total body resistance and reactance [20].

Bone measurements were performed by using Quantitative Ultrasound Measurement (QUS; LUNAR Achilles, Madison, WI, USA) on the right calcaneus with the subject in a sitting position [19]. High-frequency ultrasound waves were used to measure the velocity of the ultrasound signal [speed of sound (SOS)] and the frequency attenuation [broadband ultrasound attenuation (BUA)], and stiffness index, expressed as a percentage of the result from young adults, calculated. The standard error for SOS was 3.7 (0.3%), 2.2 (2.2%) for BUA and 1.9 (2.8%) for stiffness [21].

### 2.4. Questionnaires

Self-reported health related QoL was evaluated by three questionnaires; the Nottingham Health Profile (NHP) [22,23], Psychological General Well-Being (PGWB) [24] and the Short Form 36 (SF-36) [25,26]. The NHP includes 38 statements, answered by yes or no, that are divided into six dimensions: pain, energy, sleep, emotional reactions, social isolation, and physical mobility. The scores range between 0 and 100 where low score indicates a good QoL. The PGWB contains 22 items, with a six-grade response format, divided into six dimensions: anxiety, depressed mood, positive well-being, self-control, general health, and vitality. Also, all the questions are summarized into an overall well-being score, i.e. total score. The maximum PGWB score is 132 where a high score indicates a good QoL. The Short Form 36 (SF-36) includes 36 questions that are divided into eight scales; physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health that can be summarized further into two measures; physical and mental health [25]. A high score indicates a good QoL.

Psychological stress was asked for where 1 = no stress, 2 = some stress experience at some points, 3 = some stress periods during the last 5 years, 4 = several stress periods during the recent 5 years, 5 = continuous stress during the last year and 6 = continuous stress during the last 5 years. Stress was defined as feeling tense, irritated, and anxious or having sleep disturbances due to problems at home or at work.

Physical activity during work and leisure time, graded 1–4 (low–high), were assessed with a self-administered validated questionnaire [27].

### 2.5. Other measurements

X-ray-verified fractures were retrieved from the Gothenburg hospital registers and via the National Board of Health and Welfare, Stockholm, Sweden. Osteoporotic fractures were registered according to ICD 10 codes S32, S42, S52, S62, S72, S82, S92 and T08 (wrist, upper arm, hip, ankle, lower leg and vertebrae).

Ongoing pharmacological treatment was asked for and coded according to the Anatomical Therapeutic Chemical (ATC) Classification System.

Metabolic syndrome was defined according to the criteria published in 2005 by the International Diabetes Foundation [28]. This included waist circumference $\geqslant$80 cm for women and $\geqslant$94 cm for men and two of the following: (a) triglycerides $\geqslant$1.7 mmol/l or lipid-lowering treatment; (b) HDL-cholesterol <1.29 mmol/l for women, <1.03 for men; (c) blood pressure $\geqslant$130/85 mmHg or antihypertensive treatment; (d) f-glucose $\geqslant$5.6 mmol/L or diabetes mellitus type 2.

Insulin resistance (IR) was calculated according to the homeostatic model assessment (HOMA-IR) as: (fasting plasma insulin concentration (mU/l) $\times$ f-plasma glucose (mmol/l))/22.5, where the output of the model was calibrated to give a normal IR of 1 [29].

Menstruations and age at menopause (the last bleeding) were asked for and serum follicle stimulating hormone FSH was analysed.

### 2.6. Biochemical analyses

Venous blood samples were drawn between 8 and 10 am after an overnight fast, in menstruating women on cycle day 7–9. For measurement of urinary free cortisol (UFC), 24-h urine was sampled from 355 subjects of whom 325 had two adequate samples (>0.75 L/24-h) and 23 had one sample. For patients with two samplings the mean UFC was calculated.