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Effects of urinary cortisol levels and resting heart rate on the risk for fatal and nonfatal cardiovascular events

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ABSTRACT

Background and aims: Higher cortisol levels are associated with cardiovascular mortality in the elderly. It is unclear whether this association also exists in a general population of younger adults and for non-fatal cardiovascular events. Likewise, resting heart rate is associated with cardiovascular mortality, but fewer studies have also considered non-fatal events. The goal of this study was to investigate whether twenty-four-hour urinary cortisol (24-h UFC) levels and resting heart rate (RHR) predict major adverse fatal and non-fatal cardiovascular events (MACE) in the general population.
Methods: We used data from a subcohort of the PREVEND study, a prospective general population based cohort study with a follow-up of 6.4 years for 24-h UFC and 10.6 years for RHR. Participants were 3432 adults (mean age 49 years, range 28–75). 24-h UFC was collected and measured by liquid chromatography—tandem mass spectrometry. RHR was measured at baseline in a supine position for 10 min with the Dinamap XL Model 9300. Information about cardiovascular events and mortality was obtained from the Dutch national registry of hospital discharge diagnoses and the municipal register respectively.
Results: 24-h UFC did not significantly increase the hazard of MACE (hazard ratio = 0.999, 95% confidence interval = 0.993–1.006, p = 0.814). RHR increased the risk for MACE with 17% per 10 extra heart beats per minute (hazard ratio = 1.016, 95% confidence interval = 1.001–1.031, p = 0.036) after adjustment for conventional risk factors.
Conclusions: In contrast to 24-h UFC, RHR is a risk marker for MACE in the general population.

1. Introduction

Psychosocial stress is a well-known risk factor for cardiovascular disease (CVD) [1]. Hyperactivation of the hypothalamic-pituitary-adrenal axis (HPA axis) and the sympathetic nervous system (SNS), leading to increased cortisol levels and resting heart rate are postulated to be amongst the mechanisms behind this association [2].

This is plausible as cortisol has a direct effect on various risk factors for CVD. Increased levels of cortisol can affect blood pressure [3], BMI [4], waist circumference [4], fasting glucose levels [4], and HDL levels [4]. Moreover, glucocorticoids may also adversely influence remodeling after myocardial infarction via inhibition of angiogenesis [5], and induction of fibrosis via activation of the mineralocorticoid receptor [6]. An elevated resting heart rate (RHR) in turn might influence cardiovascular outcome by increasing cardiac oxygen demand [7], decreasing coronary blood flow by decreasing the duration of the diastole [8], lowering endothelial shear stress [9], and increasing the risk of plague rupture [10].

Two recent prospective studies showed that elevated levels of cortisol predict cardiovascular death amongst elderly people with [11] and without preexisting CVD [11,12]. To our knowledge, studies in a younger population investigating whether physiological levels of endogenous cortisol are associated with increased incidence in cardiovascular events are lacking. Moreover, the studies in elderly people did not investigate the relationship of cortisol levels with non-fatal cardiovascular events. Regarding the effects of RHR, in populations without known CVD, RHR was found to be a risk factor

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for both cardiovascular death [13–16] and morbidity [14,15,17], although some studies did not find any relationship with non-fatal cardiovascular events [18–20].

In the current study we assessed for the first time in a general population cohort whether higher levels of cortisol are an independent risk factor for major adverse fatal and non-fatal cardiovascular events (MACE). Moreover, we intended to replicate the results of previous studies with regard to higher RHR and the risk for MACE.

2. Materials and methods

2.1. Study population

We used data from a subcohort of the Prevention of REnal and Vascular ENd stage Disease (PREVEND) study. PREVEND is population cohort study originally designed to investigate microalbuminuria as a risk factor for renal disease and CVD. The recruitment of participants for PREVEND has been extensively described elsewhere [21]. In brief, 8592 subjects completed the baseline screening survey in 1997–1998 (T1), rendering the PREVEND study cohort. Subjects with insulin dependent diabetes mellitus and pregnant women were excluded from the study population. The PREVEND study is enriched for albuminuria which is a risk factor for developing renal disease. To obtain a representative random sample of the Groningen general population for the current study, we included all subjects with a urinary albumin concentration (UAC) < 10 mg/L that completed the first screening (N = 2592) and added a random subset (n = 840) from the "over-represented" subjects with an UAC > 10 mg/L proportional to the degree of overrepresentation. This resulted in a group of 3432 subjects with a population representative ratio of albuminuria negative and positive subjects forming the basis for the current study. The average age was 49 years, minimum and maximum were 28–75 years. Follow-up measurements took place between January 2002 and November 2003 (T2). Average time between T1 and T2 was 4.1 years. The study was approved by the local Medical Ethical Committee for human research of the University Medical Center Groningen (UMCG). All participants were aged 18 or older and provided written informed consent for participation in this study.

2.2. 24-h urinary free cortisol

24-h urinary free cortisol (24-h UFC) was measured at T2. Participants were asked to collect urine samples in a polypropylene container on two consecutive days prior to the visit to the outpatient clinic. They were carefully instructed to urinate into the container during the 24-h collection period and refrigerate the sample until delivery to the laboratory. 24-h urine collection was available on at least one day for 2761 people and at both days for 2710 people. Urinary creatinine was measured to assess completeness of the 24-h urine collection. We used the following formula to assess completeness: incomplete urine $\leq$ 0.7 of [mmol urinary creatinine $\times$ 113]/[21 $\times$ kilograms of body weight] [22], as this has been proven to be the most sensitive method to detect incompleteness [23]. Only samples which were complete according to the above formula were used for the current study. Urinary free cortisol (UFC) was measured by liquid chromatography—tandem mass spectrometry (LC—MS/MS) analysis. The lower detection limit of the assay was 0.3 nmol/l. At low, middle, and high concentrations, intra-assay variation ranged from 1.3 to 2.4% while inter-assay variation ranged from 3.8 to 7.8%. 24-h UFC was calculated by multiplying urinary volume with cortisol concentration and is expressed in nmol per 24-h. We used the mean of the two samples on two consecutive days to reflect HPA axis function. In the case when values of only one day were available we used this value instead of the mean.

2.3. Resting heart rate

RHR and blood pressure Blood pressure was measured, in supine position, every minute for 10 min, with an automatic device (Dinamap XL Model 9300, Johnson–Johnson Medical, Tampa, FL, USA).

2.4. Follow-up and outcomes

Information about cardiovascular events was obtained from the Dutch national registry of hospital discharge diagnoses (PRISMANT). Information about mortality was obtained from the municipal register. Information on the cause of death was acquired by linking the number of death certificates to the primary cause of death as coded by the Dutch Central Bureau of Statistics. The outcome of interest was a combined end-point of fatal and non-fatal major adverse cardiovascular events (MACE). MACE was defined as acute myocardial infarction (ICD-code 410), acute and subacute ischemic heart disease (411), occlusion or stenosis of the precerebral (433) or cerebral arteries (434) and the following procedures: coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, and other vascular interventions namely percutaneous transluminal angioplasty or bypass grafting of aorta and peripheral vessels. Mortality from any other cause was censored.

2.5. Medication use

Medication (antihypertensive, lipid-lowering, antidiabetic) was self-reported and substantiated with information of drug-use from the IADB.nl, which contains dispensing information from 55 community pharmacies in the Northern part of the Netherlands, covering on average 500 000 persons annually (www.IADB.nl) and almost the entire population of PREVEND study participants [24]. The database's pharmacy information includes, among others, name of the drug, anatomic–therapeutic–chemical (ATC) classification and date of prescription. Medication records of patients are virtually complete because of high patient pharmacy commitment in the Netherlands [25] We extracted information on drug prescriptions from 100 days prior until 100 days after the date of the visit to our research facilities.

2.6. Covariates

Each survey in the PREVEND study consisted of one to two visits to an outpatient unit. Participants completed a questionnaire on demographics, CVD history, lifestyle and medication use before the visit. Height and weight were measured and a fasting blood sample was drawn. Body mass index was calculated as the ratio between weight and height squared. Smoking status was assessed by self-report. Participants were considered smokers if they had smoked in the previous year and previous smokers if they had quit smoking more than one year ago. Hypertension was defined as systolic blood pressure $\geq$ 140 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg following the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure criteria, or use of antihypertensive medication. Hyperlipidemia was defined as cholesterol level >6.5 mmol/L when a history of hyperlipidemia was absent, or use of lipid-lowering drugs. Diabetes was defined as fasting glucose level 7.0 mmol/L, nonfasting glucose level 11.1 mmol/L, or use of antidiabetic medication. Prior history of CVD at inclusion of the study was defined as self-report of