Cortisol in Hair and the Metabolic Syndrome

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Context: Although exposure to supraphysiological levels of glucocorticoids is known to contribute to the development of the metabolic syndrome (MetS), the importance of physiological variation in basal cortisol secretion is less clear. This issue can be addressed by using hair cortisol analysis, which for the first time allows the assessment of long-term integrated hormone levels.

Objective and Design: We used the analysis of cortisol in hair (hairF) to examine associations of long-term cortisol levels with prevalence of MetS and individual cardiometabolic parameters in a large occupational cohort. In additional exploratory analyses, we also studied cardiometabolic associations with hair cortisone levels.

Participants: Participants included 1258 employees of a large aerospace company (aged 16–64 years; 84.8% males) who partook in a voluntary health assessment.

Main Outcome Measures: The first 3 cm of scalp-near hair were analyzed for glucocorticoid concentrations using liquid chromatography tandem mass spectrometry. Relevant cardiometabolic risk factors were assessed and MetS was diagnosed (according to 2009 international task force criteria).

Results: A higher prevalence of MetS was seen in individuals falling into the third (odds ratio 1.71, 95% confidence interval 1.08–2.69) or fourth hairF quartile (odds ratio 2.42, 95% confidence interval 1.55–3.75) compared with the first quartile, in fully adjusted analyses. HairF also showed positive associations with weight-related anthropometric measures (body mass index, waist to hip ratio, waist circumference) and glycated hemoglobin. The exploratory analysis of hair cortisone also indicated relevant associations with cardiometabolic parameters.

Conclusion: Normal physiological differences in long-term cortisol secretion, as assessed in hair, show relevant relationships with MetS and individual cardiometabolic parameters.

The metabolic syndrome (MetS) describes a cluster of cardiometabolic abnormalities, including abdominal obesity, hypertension, hyperglycemia, and dyslipidemia, which together form a central risk factor for type 2 diabetes mellitus and cardiovascular disease. Among other factors, it has been suggested that altered activity of the hypothalamus-pituitary-adrenal (HPA) axis leading to the secretion of glucocorticoid hormones may play an important role in the development of MetS (eg, Reference 1). Glucocorticoids, mainly cortisol in humans, potently affect lipid and carbohydrate metabolism and excess levels have been associated with the development of central ad-
ipositivity, insulin resistance and hyperglycemia, hypertension, and dyslipidemia (see 2). Furthermore, conditions of marked endogenous or iatrogenic hypercortisolism, eg, Cushing’s syndrome, closely resemble the symptom cluster of the MetS (1, 3).

Although these data indicate that supraphysiological glucocorticoid levels contribute to the development of cardiometabolic abnormalities, the importance of physiological variation in basal cortisol levels, as exist in the general population, is less clear. Findings of previous epidemiological research examining associations between MetS components and plasma/serum, salivary, or urinary cortisol have been rather inconsistent, with some studies fully confirming (4–7), partially confirming (8–11), or not confirming (12–14) expected relationships. A potential explanation for these heterogeneous findings may lie in the methodological challenges surrounding the assessment of cortisol (3), ie, it seems likely that the development of MetS is influenced by persistent, long-term elevations in cortisol secretion, whereas the aforementioned methods are particularly sensitive to transient fluctuations (hours to days) in cortisol levels and additionally suffer problems like participant noncompliance during ambulatory assessments.

A recent development that may advance the assessment of long-term glucocorticoid levels is the analysis of human scalp hair. Capitalizing on the continuous incorporation of lipophilic hormones into the growing hair, hair analyses are assumed to provide an easily obtainable index of hormone levels integrated over periods of several months (see 15). Considerable evidence has now supported the validity (16, 17) and test-retest reliability (18) of this method, while its potential value to cardiometabolic research is suggested by associations with central adiposity (19–21) and an increased risk of myocardial infarction (22).

The current study aimed to investigate the relationships of hair cortisol levels with MetS and individual cardiometabolic components in a large occupational cohort. In addition to hair cortisol (hairF), we also conducted an exploratory examination of hair cortisone (hairE) levels in relation to cardiometabolic parameters. The rationale for this drew on recent data from salivary research suggesting that under specific circumstances, salivary cortisone (E) may provide a closer and more robust reflection of systemic cortisol (F) levels than salivary F (23). Although hairE has received little attention so far, analogies between glucocorticoids in saliva and hair indicate that hairE may potentially also hold merit as a relevant measure in addition to hairF. Specifically, in both saliva (23) and hair (24), higher levels of E than of F have been found, and in both mediums this unusual ratio has been attributed to local F-to-E conversion by 11β-hydroxysteroid-dehydrogenase type 2 (11β-HSD2) (23, 24). These analogies make it conceivable that hairE levels may also provide a useful and robust marker of long-term systemic F levels. To ensure high-quality hair glucocorticoid data, hair samples were analyzed using a highly specific and sensitive liquid chromatography-tandem mass spectrometry method.

Materials and Methods

Participants

Participants were 1258 employees of a large German aerospace company who partook in a voluntary, company-funded health assessment (84.8% male; mean age 39.1 years, range 16–64 years). Inclusion criteria were hair longer than 3 cm at the posterior vertex region of the scalp, no baldness or obvious hair loss at this region, and no reported use of any glucocorticoid-containing medications. All participants provided written informed consent, and the study protocol was approved by the Ethics Committee of the Mannheim Medical Faculty, University of Heidelberg, and conducted in accordance with the Declaration of Helsinki.

Assessment of health behaviors and hair-related parameters

Regular alcohol use was assessed via self-report [defined as consumption on ≥ 3 d/wk] and serum γ-glutamyltransferase (γGT) was used as an objective marker of excessive alcohol intake. Smoking was defined as self-reported current smoking or having ceased to smoke less than 5 years ago. Regular consumption of fruit, salad, or vegetables was defined as consumption of either component at least once a day. Regular physical activity was assessed by summing 5-point frequency ratings in the areas of mild (eg, walking), moderate (eg, fast walking or cycling), and vigorous (activities causing sweating) activity over the past 6 months. The assessment of hair-related characteristics included the number of hair washes per week and the use of hair treatments (coloration, permanent wave, or hair straightening) during the past 3 months.

Cardiometabolic parameters and MetS diagnosis

Early morning fasting blood samples were drawn for the measurement of low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), triglycerides, glucose, and glycated hemoglobin (HbA1c). All analyses were conducted in the Synlab Laboratories (Augsburg, Germany) according to standard laboratory procedures complying with International Organization for Standardization norms. Specifically, cholesterol and triglycerides were measured enzymatically with reagents from Roche Diagnostics (Mannheim, Germany) on a Cobas 8000 analyzer. HDL-C was measured using a homogeneous assay from Roche Diagnostics, and LDL-C was calculated using the Friedwald equation (25). Anthropometric data [body mass index (BMI), waist to hip ratio (WHR)] and blood pressure (BP) assessments were carried out by trained study personnel. Blood pressure was measured twice within a 20-minute period and mean values were calculated for systolic (SBP) and diastolic BP (DBP). Information on SBP and DBP were combined in a single value of mean arterial BP (MAP) using the following formula: MAP = [(2 × DBP) + SBP]/3.

MetS diagnosis was based on the unified criteria of the 2009 international task force report (26). A diagnosis was given if
individuals exceeded cutoff values in 3 or more of 5 risk factor categories, including elevated waist circumference (males: $\geq 102$ cm; females: $\geq 88$ cm), elevated triglycerides ($\geq 150$ mg/dL or drug treatment for elevated triglycerides), reduced HDL-C (males: $< 40$ mg/dL; females: $< 50$ mg/dL), elevated BP (systolic: $\geq 130$ mm Hg; diastolic: $\geq 85$ mm Hg; or antihypertensive drug treatment), elevated long-term glucose [$HbA_1c$ $\geq 5.7\%$ (based on Reference 27)].

**Hair steroid analysis**

Hair strands (~3 mm diameter) were cut as close as possible to the scalp from a posterior vertex position. The proximal 3-cm hair segment was used for analyses. Wash and steroid extraction procedures followed the protocol described in Stalder et al (18, study II) with some changes being made to allow analysis by liquid chromatography-tandem mass spectrometry. Specifically, samples were washed in 2.5 mL isopropanol for 3 minutes, and glucocorticoids were extracted from 10 mg of whole, nonpulverized hair using 1.8 mL methanol in the presence of 50 µL cortisol-d$_4$ and cortisone-d$_7$ as internal standards for 18 hours at room temperature. Samples were spun in a bench top centrifuge (Mikro 22R; Andreas Hettich GmbH and Co. KG, Tuttingen, Germany) at 15 200 $\times$ g relative centrifugal force for 2 minutes, and 1 mL of the clear supernatant was transferred into a new 2 mL tube. The alcohol was evaporated at 65°C under a constant stream of nitrogen and reconstituted with 250 and 1 mL of the clear supernatant was transferred into a new 2 mL tube. The alcohol was evaporated at 65°C under a constant stream of nitrogen and reconstituted with 250 µL double-distilled water, 200 µL of which were injected into a Shimadzu HPLC-tandem mass spectrometry system (Shimadzu, Canby, Oregon) coupled to an AB Sciex API 5000 Turbo-ion-spray triple quadrupole tandem mass spectrometer (AB Sciex, Foster City, California) with purification by on-line solid-phase extraction. The lower limits of quantification of this assay were below 0.1 pg/mg for cortisol and cortisone, and the inter- and intraassay coefficients of variance were between 3.7% and 8.8%. The extraction from whole hair samples has been shown to yield comparable results to pulverized hair extraction, both in terms of absolute concentrations and high inter-method correlations (18) as well as similar chromatographic peak areas of the 2 methods (41).

**Statistical analysis and data exclusion**

Hair glucocorticoid, anthropometric, and physiological data (all except WHR, MAP, and LDL-C) were positively skewed and were thus log10 transformed for inferential analyses. Descriptive data in tables and text are presented in original units. The deletion of extreme values ($> 3$ SD from the mean) resulted in the further exclusion of hairF ($n = 18$), hairE ($n = 13$), BMI ($n = 9$), waist circumference ($n = 4$), HDL-C ($n = 2$), triglycerides ($n = 5$), $HbA_1c$ ($n = 17$), and glucose ($n = 16$) data. In preparatory analyses, hairF and hairE associations with demographic and lifestyle parameters were examined using correlation analyses and partial correlation analyses controlling for sex (continuous variables) or analyses of variance and covariance controlling for sex (dichotomous variables).

A two-part analytical strategy was used for the main analyses. First, hairF and hairE associations with individual anthropometric and cardiometabolic parameters were examined using bivariate Pearson correlation analyses, followed up by partial correlation analyses, controlling for significant variables identified in preparatory analyses. Second, a logistic regression approach was used to examine the predictive value of hairF or hairE levels separately for the prevalence of MetS. Hair glucocorticoid data were first entered into these analyses as a continuous variable. Subsequently, hairF and hairE quartiles were calculated and the second, third, and fourth quartiles were contrasted with the first quartile as the reference category. Analyses were run in 3 blocks, extending a simple logistic regression model (model 1) with adjustments for sociodemographic and hair-related parameters (model 2) and behavioral risk factors (model 3). All analyses were performed using SPSS for Windows, version 19 (IBM, Chicago, Illinois).

**Results**

Table 1 shows the descriptive characteristics of the study sample. Analyses revealed a positive correlation between hairF and hairE levels ($r = 0.63, P < .0001$; for a more detailed examination of hairF-hairE association patterns, see Supplemental Data A, published on The Endocrine Society’s Journals Online web site at http://jcem.endojournals.org). HairF and hairE levels both increased linearly with age (hairF: $r = 0.11, P < .0001$; hairE: $r = 0.22, P < .0001$). No sex differences were revealed for hairF [$F_{(1,1216)} = 1.83, P = n.s.$], whereas hairE levels were higher in males than in females [$F_{(1,1221)} = 22.65, P < .0001$, $\eta^2_p = 0.018$]. Alcohol consumption was unrelated to hairF and hairE levels [$F_{(1,1208)} = 0.11, P = n.s.$, and $F_{(1,1211)} = 0.95, P = n.s.$, respectively], but positive associations with $\gamma$GT were seen for both measures (hairF: $r = 0.11, P < .0001$; hairE: $r = 0.158, P < .0001$). HairF and hairE levels were unrelated to smoking status, daily fruit, salad or vegetable intake, or the physical activity level (all $P > .05$).

HairF was found to be unrelated to the number of hair washes per week ($r = -0.046, P = n.s.$), whereas a reduction in hairE levels were seen with increasing hair-washing frequency ($r = -0.096, P = .001$), which remained significant after adjusting for sex ($r_p = -0.122, P < .0001$). Individuals reporting the use of hair treatments exhibited lower hairF [$F_{(1,1217)} = 6.78, P < .009$, $\eta^2_p = 0.006$] and hairE levels [$F_{(1,1223)} = 30.161, P < .0001$, $\eta^2_p = 0.024$], with both effects remaining significant after adjusting for sex [$F_{(1,1199)} = 4.22, P = .04$, $\eta^2_p = 0.004$; $F_{(1,1201)} = 9.245, P = .002$, $\eta^2_p = 0.008$, respectively].

**Hair glucocorticoids and cardiometabolic parameters**

Table 2 shows the results of bivariate correlation and adjusted partial correlation analyses between hair glucocorticoid levels and cardiometabolic measures. In bivariate analyses, hairF levels showed predicted relationships with most examined cardiometabolic measures (all except
LDL-C and triglycerides), whereas hairE was related to each of the examined cardiometabolic parameters. The overall sizes of bivariate associations tended to be numerically stronger for hairE than for hairF levels. After statistical adjustment, the strengths of associations were reduced, even though most relationships with hairF and hairE still met statistical significance levels. Further exploratory analyses of associations of cardiometabolic measures with combined hair glucocorticoid measures (hairF/HairE, hairF to hairE ratio) are provided in Supplemental Data B.

Hair glucocorticoids and MetS diagnosis
Overall, 24.0% of individuals met MetS diagnostic criteria (Table 1). MetS participants exhibited higher hairF levels [mean (±SD), no MetS: 7.70 (±8.12) pg/mg; MetS: 10.78 (±11.37) pg/mg; F(1,1205) = 33.99, P < .0001, ηp² = 0.027] and higher hairE levels [mean (±SD), no MetS: 23.95 (±13.46) pg/mg; MetS: 30.93 (±18.56) pg/mg; F(1,1211) = 43.49, P < .0001, ηp² = 0.035] than individuals without MetS diagnosis.

Table 2. Results of Bivariate Pearson Correlations and Adjusted Partial Correlations Between Hair Glucocorticoid Measures (n Between 1205 and 1236) and Cardiometabolic Parameters

<table>
<thead>
<tr>
<th>HairF</th>
<th>Bivariate</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.161***</td>
<td>0.112***</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.142***</td>
<td>0.076**</td>
</tr>
<tr>
<td>WHR</td>
<td>0.144***</td>
<td>0.069*</td>
</tr>
<tr>
<td>MAP</td>
<td>0.106***</td>
<td>0.047</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-0.065*</td>
<td>-0.037</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-0.008</td>
<td>-0.080**</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.044</td>
<td>-0.015</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.155***</td>
<td>0.116***</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.064*</td>
<td>0.005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HairE</th>
<th>Bivariate</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.215***</td>
<td>0.136***</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.234***</td>
<td>0.127***</td>
</tr>
<tr>
<td>WHR</td>
<td>0.248***</td>
<td>0.110***</td>
</tr>
<tr>
<td>MAP</td>
<td>0.160***</td>
<td>0.061*</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-0.109***</td>
<td>-0.059*</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.074*</td>
<td>-0.037</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.082**</td>
<td>-0.006</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.171***</td>
<td>0.090**</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.159***</td>
<td>0.054</td>
</tr>
</tbody>
</table>

* P < .05; ** P < .01; *** P < .001.

Controlling for sex, age, hair-washing frequency, hair treatment, and γGT.
respectively. HairF or hairE levels, respectively, entered as continuous variables showed MetS predictive effects, and these remained significant after adjusting for sociodemographic and hair-related variables (model 2) and behavioral risk factors (model 3). When hairF quartiles were considered as a categorical variable, individuals falling into the third and fourth hairF quartiles exhibited a significantly higher MetS prevalence than those in the first hairF quartile, and this effect was also robust to statistical adjustments (models 2 and 3). When considering hairE quartiles, only individuals in the fourth quartile exhibited increased MetS prevalence, also after statistical adjustments (models 2 and 3). Figure 1 depicts the MetS odds ratios and 95% confidence intervals based on hair glucocorticoid quartiles for the final, fully adjusted model.

### Table 3. Logistic Regression Results Predicting MetS Prevalence Based on HairF and HairE Quartiles

<table>
<thead>
<tr>
<th>MetS, %</th>
<th>Model 1 OR (95% CI)</th>
<th>Model 2 OR (95% CI)</th>
<th>Model 3 OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HairF</td>
<td>Continuous&lt;sup&gt;a&lt;/sup&gt; n/a</td>
<td>3.27 (2.15–4.96)</td>
<td>2.92 (1.89–4.52)</td>
</tr>
<tr>
<td></td>
<td>First quartile 15.9</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td></td>
<td>Second quartile 21.9</td>
<td>1.47 (0.96–2.23)</td>
<td>1.37 (0.89–2.11)</td>
</tr>
<tr>
<td></td>
<td>Third quartile 24.3</td>
<td>1.73 (1.14–2.61)</td>
<td>1.60 (1.04–2.44)</td>
</tr>
<tr>
<td></td>
<td>Fourth quartile 33.8</td>
<td>2.69 (1.81–4.01)</td>
<td>2.47 (1.64–3.72)</td>
</tr>
<tr>
<td>HairE</td>
<td>Continuous&lt;sup&gt;a&lt;/sup&gt; n/a</td>
<td>7.49 (3.98–14.10)</td>
<td>4.75 (2.48–9.13)</td>
</tr>
<tr>
<td></td>
<td>First quartile 18.0</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td></td>
<td>Second quartile 16.9</td>
<td>0.84 (0.54–1.29)</td>
<td>0.72 (0.46–1.14)</td>
</tr>
<tr>
<td></td>
<td>Third quartile 22.5</td>
<td>1.34 (0.90–2.00)</td>
<td>1.12 (0.74–1.70)</td>
</tr>
<tr>
<td></td>
<td>Fourth quartile 37.8</td>
<td>2.70 (1.85–3.95)</td>
<td>1.95 (1.31–2.91)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; n/a, not available.

Model 1 was a simple logistic regression. Model 2 was adjusted for sex, age, hair-washing frequency, and use of hair treatments. Model 3 was adjusted for sex; age; hair-washing frequency; use of hair treatments; smoking; γGT; daily fruit, salad, and vegetable consumption, and physical activity level. Only significant variables were kept in the model. This resulted in the exclusion of hair-washing frequency; use of hair treatments (block 2); and daily fruit, salad, and vegetable consumption (block 3).

<sup>a</sup> Note that ORs and 95% CIs refer to log10-transformed hairF and hairE data.

### Discussion

This study examined associations between long-term glucocorticoid levels, as assessed in hair, and the metabolic syndrome within a large occupational cohort. Our results show a dose-response increase in MetS prevalence with higher hairF levels (1.7- and 2.4-fold raised odds for individuals in the third or fourth hairF quartiles compared with the first quartile, respectively) as well as relationships between hairF and different cardiometabolic parameters. Interestingly, hairE was also found to be related to individual cardiometabolic measures, even though a MetS-predictive effect was seen only for the highest hairE quartile (1.9-fold raised OR) but not for intermediate quartiles. The present hair glucocorticoid ORs for MetS stand in contrast to most previous research in nonclinical popula-

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**Figure 1.** Odds ratios (95% confidence intervals) for MetS diagnoses based on hair glucocorticoid quartiles. Data are shown for the fully adjusted model 3, controlling for sex, age, smoking, and γGT. *P < .05; ***, P < .001.
tions, which has shown no or only relatively weak associations between basal cortisol levels and the prevalence of the MetS (28–31). This may reflect methodological advantages of hair analyses, which are assumed to allow a more reliable assessment on long-term cortisol levels than previous methods (15). Importantly, the current ORs for high hairF levels are similar to or even higher than previously reported odds for conventional MetS risk factors. For example, research on larger cohorts has reported cross-sectional MetS ORs for current or past smoking (OR 1.2–1.8), high carbohydrate intake (OR 1.1–1.7), or being physically inactive (OR 1.2–1.4) (32). Our data thus indicate a sizable relationship between chronically elevated glucocorticoid levels, as assessed in hair, and prevalence of the MetS.

In addition to associations with MetS diagnosis, our findings revealed relationships between hair glucocorticoid levels and individual cardiometabolic measures, even though effect sizes tended to be relatively small. As part of this, the present study is the first to reveal consistent hair glucocorticoid relationships with HbA1c as an index of long-term glucose levels (27). This is particularly interesting as the respective associations with glucose levels were weaker than those for HbA1c and not robust to statistical adjustments. This may reflect the fact that both hair glucocorticoids and HbA1c are assumed to provide integrated long-term information, ie, they assess a corresponding time frame. On the other hand, glucose levels are more likely to be affected by acute fluctuations, which may have resulted in a weaker relationship with long-term hair glucocorticoid data.

In addition to HbA1c, consistent positive relationships of hair glucocorticoid levels with anthropometric measures (BMI, WHR, waist circumference) were also observed, which is in line with previous research (19–21). These data add to the previous literature showing complex links of HPA axis activity and body fat-related processes and obesity. Specifically, the present data could be seen as concurring with findings suggesting hypercortisolism in obesity, ie, evidence showing increased adrenal cortisol secretion, acute cortisol hyperresponsivity, and elevated urinary cortisol excretion in obese individuals as well as local cortisol production in adipose tissue (3, 33, 34). Conversely, these effects have been shown to be counteracted by increased metabolic clearance and cellular cortisol uptake in obesity (34) and this, in turn, corresponds with data showing normal or even decreased plasma or salivary cortisol levels in obesity (eg, References 35 and 36). It is difficult to determine how the present hair cortisol findings integrate into this literature. Future enquiries applying additional HPA axis assessments besides hair analyses may help to further elucidate underlying mechanisms.

In addition to associations with long-term glucose levels and anthropometric measures, bivariate analyses also revealed associations of hair glucocorticoids with mean arterial BP and blood lipid measures (mainly for hairE). However, these relationships were reduced in adjusted analyses, mostly missing significance levels. It is unclear whether this reduction was due to the removal of confounding influences or whether statistical adjustments (eg, for age) may have resulted in artificial variance restriction, thus making the detection of associations more difficult. Surprisingly, the results of adjusted analyses even revealed a small inverse relationship between hairF and LDL-C, which is at variance with previous evidence (2) and needs to be treated with caution until corroborated by future research. Overall, the present results suggest that relationships between long-term glucocorticoid levels and blood lipid measures or mean arterial BP, if existent, are likely to be weak, which is in line with previous evidence (eg, 37).

Nevertheless, the overall association pattern emerging from the current hair glucocorticoid results corresponds to previous findings from animal glucocorticoid-administration research (eg, Reference 38) and mirrors known cardiometabolic aberrations in patients suffering from hypercortisolism due to Cushing’s syndrome (1, 3). Similarly, some (4–7) but not all (12–14) prior correlational studies using short-term cortisol measures have shown analogous relationships with cardiometabolic measures. However, most of this research was conducted in rather specialized samples, eg, overweight children and adolescents (4, 10) or elderly individuals (5, 7). The present results thus extend these data by showing relevant links between long-term glucocorticoid levels and cardiometabolic measures in an age-heterogeneous sample of normal working individuals.

An interesting aspect of the current findings concerns the exploratory analysis of hairE data, which mostly revealed numerically stronger relationships with cardiometabolic measures for hairE than for hairF. On the other hand, hairE quartiles were found to be less predictive of MetS (showing a nonlinear association) than those for hairF. Still, the present results provide a first indication for a potential merit of hairE as an additional measure besides hairF. Interestingly, in line with previous evidence (24), our data showed that median hairE levels were 3.8-fold raised compared with hairF levels, which is analogous to salivary data (23) but opposite to a positive F-to-E ratio in blood. Despite these differences in absolute concentrations, individual patterns of hairF and hairE levels were closely associated. A more detailed exploration of hairF-hairE association patterns (Supplemental Data B) suggested that these measures were highly correlated except for a subclass of hairF-hairE pairs characterized by dis-
proportionately increased hairF values. One interpretation of these data is that hairF and hairE may generally convey similar information but that, for some individuals, hairF could be more prone to yet unexplained variation. Mechanistically, it is conceivable that a particular fraction of systemic cortisol is locally converted to cortisone by 11β-HSD2 and incorporated into hair (24), resulting in the high observed hairE levels. If this is a local process, hairE levels (or the hairF to hairE ratio) should not be reflective of 11β-HSD activity in other relevant areas, eg, adipose tissue (see 3). In line with this, considering the hairF-to-hairE ratio did not yield improved association patterns with cardiometabolic measures, and this was also the case for an additive hairF+E measure (Supplemental Data B). In summary, based on the current data, it is conceivable that the assessment of hairE could provide a useful addition to hairF for obtaining information on long-term systemic F levels. However, the present knowledge concerning hairE is still very limited, and future methodological research is clearly required to allow a more informed interpretation of hairE results. Such research should also strive to elucidate the present finding that hairE but not hairF levels were related to participants’ sex or frequency of hair washing.

A limitation of the current study relates to its cross-sectional nature, which prevents making causal inferences. Future research should aim to study the predictive value of hair glucocorticoid levels for incident MetS in longitudinal designs. On a practical level, more comprehensive assessments of confounding influences may be used in future research, eg, participants’ accuracy of reporting the use of glucocorticoid-containing medications may be enhanced by referring to specifying examples, such as inhalation or dermal glucocorticoids. Future enquiries may further be extended to include other determinants of net glucocorticoid action at the cellular level, in addition to circulating glucocorticoid levels. Previous research has indicated that glucocorticoid-mediated effects on MetS may be influenced by genetic variants affecting sensitivity of the glucocorticoid receptor (see Reference 39) or by local regeneration of cortisol from inactive cortisone by the enzyme 11β-HSD type 1 (3, 39). Likewise, circadian and stress-responsive changes in cortisol secretion may also be of importance for MetS development (40) in addition to long-term basal cortisol levels. It will be a fascinating task to examine whether combined consideration of these factors and hair glucocorticoid levels will yield even stronger associations with MetS.

In summary, the present results indicate that individual patterns of long-term cortisol secretion are related to the MetS and its components. The analysis of glucocorticoids in hair may provide a particularly well-suited and easily obtainable measure to assess chronically altered glucocorticoid levels in MetS-related research and can thus help to further advance understanding in this area.

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