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Hair cortisol levels in women with medically unexplained symptoms

Susanne Fischer [a,*], Nadine Skoluda [b], Nida Ali [b], Urs M. Nater [b], Ricarda Mewes [c,**]

[a] University of Zurich, Institute of Psychology, Clinical Psychology and Psychotherapy, Switzerland
[b] University of Vienna, Department of Psychology, Clinical Psychology, Austria
[c] University of Vienna, Department of Psychology, Outpatient Unit for Research, Teaching and Practice, Austria

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ABSTRACT

Stress has been demonstrated to be involved in the development of medically unexplained symptoms. A key underlying mechanism could be lower levels of cortisol, which can contribute to symptoms such as fatigue or pain. However, the literature is highly equivocal, which may be due to methodological limitations inherent in short-term cortisol assessment. The aim of this case-control study was to investigate, for the first time, whether individuals with different forms of medically unexplained symptoms show altered hair cortisol concentrations, a long-term marker of hypothalamic-pituitary-adrenal functioning. Two groups of women with medically unexplained symptoms were recruited. The first had a functional somatic syndrome, characterised by specific medically unexplained symptoms (i.e., chronic fatigue syndrome, fibromyalgia, or irritable bowel syndrome, n = 33). The second had somatic symptom disorder, characterised by excessive thoughts, feelings, and behaviours devoted to various medically unexplained symptoms (n = 23). These groups were contrasted with healthy controls (n = 30), and women with depression (n = 27). Cortisol representing the previous three months was extracted from hair. Chronic stress and childhood trauma were assessed (retrospectively). Women with somatic symptom disorder had lower hair cortisol than healthy controls and women with functional somatic syndromes. No differences in hair cortisol were found between healthy controls, functional somatic syndromes, and depression. Neither childhood trauma nor chronic stress was correlated with hair cortisol. Provided that our findings are replicated, they may suggest that hypocortisolism is found in a specific subgroup of individuals with medically unexplained symptoms, and potentially in those characterised by excessive thoughts, feelings, and behaviours about symptoms.

1. Introduction

Medically unexplained symptoms are highly prevalent, affecting around a third of patients in primary care settings (Toft et al., 2005), and about half of the patients in secondary care settings (Nimnuan et al., 2001). When these symptoms persist, they are often diagnosed as a functional somatic syndrome according to international research criteria (Barsky and Borus, 1999; Wessely et al., 1999), or as a somatic symptom disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) (APA, 2013). The former category includes individuals with specific constellations of symptoms (e.g., chronic fatigue syndrome, fibromyalgia syndrome, and irritable bowel syndrome) and is often used by medical specialists. The latter category includes individuals with at least one symptom that is distressing or results in impairments together with excessive thoughts, feelings, and behaviours devoted to the symptom(s) and is often used by clinical psychologists/psychiatrists.

As implied by their terminology, the aetiology of medically unexplained symptoms is unclear. However, multiple factors are presumably involved in their development. One of the most frequently discussed aetiopathogenetic factors is stress and subsequent alterations in stress-responsive systems, such as the hypothalamic-pituitary-adrenal axis (Nater et al., 2011a; Tak and Rosmalen, 2010). Indeed, individuals with medically unexplained symptoms are frequently affected by early life stress (Afari et al., 2014), as well as by critical life events and chronic stress before illness onset (Nater et al., 2011a). Furthermore, similar to post-traumatic stress disorder, there is substantial evidence of diminished levels of cortisol in this population (Fries et al., 2005; Heim et al.,

* Corresponding author. University of Zurich, Institute of Psychology, Clinical Psychology and Psychotherapy, Binzmuehlestrasse 14 / Box 26, 8050, Zurich, Switzerland.
** Corresponding author. University of Vienna, Department of Psychology, Outpatient Unit for Research, Teaching and Practice, Renngasse 6, Vienna, Austria.
E-mail addresses: s.fischer@psychologie.uzh.ch (S. Fischer), ricarda.nater-mewes@univie.ac.at (R. Mewes).

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2000). This aligns well with another frequent observation in these patients, which is of chronic low-grade inflammation (Bashashati et al., 2017; Strawbridge et al., 2019). Together, these alterations have been hypothesised to provide a physiological substrate for flu-like symptoms such as fatigue or pain (Irwin, 2011).

However, the state of research on cortisol concentrations in medically unexplained symptoms is inconclusive. In functional somatic syndromes, a meta-analysis has found that certain subgroups of affected individuals, namely individuals with chronic fatigue syndrome or fibromyalgia syndrome (specifically women), had lower cortisol concentrations when compared to healthy controls, whereas others, namely those with irritable bowel syndrome, did not (Tak et al., 2011). Investigations into somatoform disorder, the DSM-IV predecessor of somatic symptom disorder, are scarce and have yielded contradictory findings: In one study, individuals with an abridged form of somatisation disorder had higher morning cortisol levels than healthy controls (Rief et al., 1998); in a second study by the same authors, neither diurnal nor nocturnal cortisol differed between individuals with abridged somatisation disorder and controls (Rief and Auer, 2000); in a third study, individuals with somatoform disorders had lower diurnal cortisol levels than healthy controls (Pedrosa Gil et al., 2008). This is unfortunate, since a more in-depth understanding of the role of cortisol in these conditions may not only shed light on their pathophysiology, but could also be relevant in the selection and tailoring of existing interventions, and in the development of novel treatments.

One reason for these discrepant findings may be that all these studies have relied on short-term measures of hypothalamic-pituitary-adrenal functioning-using urinary, blood, or saliva sampling. These parameters are subject to a number of state-like confounders (e.g., time of day, day of the week) (Kudielka and Wüst, 2010), which may obfuscate differences between individuals with medically unexplained symptoms and healthy controls. Hair cortisol represents a well-established alternative to determine hypothalamic-pituitary-adrenal functioning (Stalder and Kirschbaum, 2012). It uses one to six centimetres of hair to determine long-term cortisol concentrations. However, no studies have, as of yet, used this methodology in individuals with different functional somatic syndromes or somatic symptom disorder.

The aim of the present case-control study was to investigate to what extent individuals with medically unexplained symptoms differ from healthy controls in hair cortisol concentrations. A further aim of the study was to examine whether hair cortisol could serve as a biological marker that distinguishes individuals with medically unexplained symptoms from those with other mental disorders, such as depressive disorders. This is particularly important since medically unexplained symptoms have sometimes been understood as a form of masked depression (Lipowski, 1990). Interestingly, a meta-analysis of four decades of research has attested to elevated cortisol levels in individuals with depressive disorders as compared to healthy controls (Stetler and Miller, 2011). This suggests that (hair) cortisol could be one marker allowing to distinguish between medically unexplained symptoms and depression. A final aim was to examine to what extent childhood trauma and self-reported chronic stress were associated with cortisol concentrations. Based on the above referenced findings, we hypothesised that women diagnosed with a functional somatic syndrome and those diagnosed with a somatic symptom disorder would exhibit the lowest hair cortisol concentrations, whereas women with depressive disorders would exhibit the highest hair cortisol concentrations, and healthy controls would exhibit intermediate levels. Furthermore, we hypothesised that childhood trauma and self-reported chronic stress would be negatively associated with hair cortisol. Due to the female preponderance in medically unexplained symptoms and to eliminate sex as potential confounder, only women were included in the present study.

2. Methods

2.1. Participants

The participants of this study were recruited as part of two larger projects: One on functional somatic syndromes (Fischer et al., 2018b, 2019), which also included a sample of healthy controls, and one on somatic symptom disorder and depressive disorder (Mewes et al., 2022). Both projects were conducted at the University of Marburg, Germany, from 2011 to 2016, involved the same PIs (UMN and RM) and included identical assessments regarding the main variables of interest for the current analysis. Moreover, in both projects, the hair sampling procedures were supervised by the same person (NS). The participants of both projects were recruited from the general population as well as from various primary and secondary care services. All were of European geographical ancestry. The inclusion criteria for the clinical groups were: age 18 years or above, female sex, fluency in the German language, fulfilment of research diagnostic criteria for chronic fatigue syndrome (Fukuda et al., 1994), fibromyalgia syndrome (Wolfe et al., 2010), and/or irritable bowel syndrome (Longstreth et al., 2006), or fulfilment of DSM diagnostic criteria for a somatic symptom disorder or a depressive disorder, as detailed below. The exclusion criteria were: pregnancy, lactation, or major physical diseases, such as cancer, hepatic, haematological, neurological, autoimmune, or endocrinological (e.g., thyroid) diseases. In addition, the following major mental disorders were excluded: substance abuse or dependence within the past two years, an eating disorder within the past five years, and a lifetime psychotic or bipolar disorder. Women with a functional somatic syndrome were excluded if they suffered from a comorbid depressive disorder; women with somatic symptom disorder were excluded if they suffered from a comorbid depressive disorder; women with a depressive disorder were excluded if they suffered from a comorbid somatic symptom disorder. It is thus possible that some of the women with a functional somatic syndrome fulfilled criteria for somatic symptom disorder and vice versa.

Applying the eligibility criteria resulted in three groups: $n = 33$ women with a functional somatic syndrome, $n = 23$ women with a somatic symptom disorder, and $n = 27$ women with a depressive disorder. A total of $n = 30$ women were in the control group. The women in the control group were recruited from the general population and were free of any physical or mental illnesses, and did not take any medications. Although the sample sizes of the four groups were not specifically calculated for the purpose of the present study, the number of recruited individuals is similar to previous research on cortisol in individuals with medically unexplained symptoms (Pedrosa Gil et al., 2008; Tak et al., 2011) and was large enough to detect large-sized effects regarding the group comparisons according to a G*Power analysis ($\alpha = .05$, $1\text{-}\beta = 0.80$).

2.2. Protocol

The women with a functional somatic syndrome and the healthy controls were screened for eligibility during an appointment at the University of Marburg. All women with a functional somatic syndrome were diagnosed according to established research diagnostic criteria (Fukuda et al., 1994; Longstreth et al., 2006; Wolfe et al., 2010). In addition, all participants were physically examined and a fasting blood sample was taken to screen for exclusionary physical diseases. The Structured Clinical Interview (SCID) (First et al., 1997) was conducted to screen for exclusionary mental disorders (see previous section). All interviewers were psychologists trained in the SCID.

All participants with a somatic symptom disorder were screened for eligibility via telephone. Somatic symptom disorder was diagnosed according to DSM-5 criteria (APA, 2013) using a structured interview that has been used in previous studies by our group (Rief et al., 2010; Schumacher et al., 2017). Importantly, all participants had to have

symptoms that were medically unexplained rather than explained (as part of a somatic disease). Depressive disorders were diagnosed according to DSM-IV criteria using the SCID (First et al., 1997). All interviewers were trained psychologists. A comprehensive medical history was obtained to screen for exclusionary physical diseases.

Upon fulfilling eligibility criteria, participants were invited to a study appointment at the University of Marburg. All four groups were administered the Questionnaire on Functional Somatic Syndromes (Fischer et al., 2013; Nater et al., 2011b) to obtain a measure of their total somatic symptom load, the Beck Depression Inventory (Beck et al., 1996) to obtain a measure of depression severity during the past two weeks, the Childhood Trauma Questionnaire (Bernstein et al., 2003; Wingenfeld et al., 2010) to assess childhood abuse and neglect, and the Screening Scale of the Trier Inventory for the Assessment of Chronic Stress (Schulz et al., 2004) to obtain a measure of self-reported chronic stress during the past three months.

Hair strands were collected from the posterior vertex and 3 cm representing the past three months were cut off each sample. The samples were then washed twice for 3 min in 20 mL glass vials using 3 mL of isopropanol. Next, the samples were dried overnight at room temperature and cut into small pieces. 10 mg of finely minced hair were taken from each sample and incubated for 18 h with 1.8 mL of methanol. After incubation, 1.6 mL of the methanol supernatant was evaporated at 50 °C under a gentle stream of nitrogen. The samples were then reconstituted in ultra-pure water and vortexed for 20 s. To determine cortisol concentrations, a commercially available luminescence immunoassay was used (Tecan, IBL International, Hamburg, Germany). The analyses of the individuals with a functional somatic syndrome and the healthy controls (project one) were identical to the analyses of the individuals with somatic symptom disorder and those with depressive disorders (project two), except for two steps. First, the evaporated samples were reconstituted in 225 μL (project one) vs. 150 μL (project 2) of purified water; however, this was adjusted in the formula for the conversion of cortisol concentrations from μg/dL into pg/mg. Second, the functional sensitivity of the assays was 0.0015 μg/dl (project one) vs. 0.011 μg/dl (project two). The inter- and intra-assay coefficients of variation of both assays were below 10%.

All investigations were carried out on accordance with the latest version of the Declaration of Helsinki, the study protocols were approved by the local ethics committee (University of Marburg), and written informed consent was obtained from all participants.

2.3. Statistical analyses

Data were visually inspected and outliers above three standard deviations were removed (n = 3 with a functional somatic syndrome, n = 1 with a somatic symptom disorder, n = 1 with a depressive disorder). This resulted in a final sample size of N = 108 participants. Data were then tested for normal distribution using the Kolmogorov-Smirnov test. As a result of this, hair cortisol concentrations were log-transformed for statistical analyses, which resulted in a normal distribution. The four groups were first compared regarding sociodemographic, lifestyle, and clinical variables, using Kruskal-Wallis and Chi-squared tests. Next, a univariate ANOVA was conducted to compare the four groups with respect to their hair cortisol concentrations. Age, body mass index (BMI), smoking status, and intake of medication were included as covariates. In addition, previously identified confounders of hair cortisol, namely season, hormonal contraceptives, and heat-based hair treatments (i.e., hair straighteners) (Fischer et al., 2017) were included as covariates. Finally, another univariate ANOVA was conducted to compare the four groups with respect to their hair cortisol concentrations; this time also including the CTQ sum score. A Spearman's correlation was calculated to test whether hair cortisol was associated with levels of childhood trauma and self-reported chronic stress. Missing data was deleted case-wise. The level of statistical significance was set at $\alpha = 0.05$. All analyses were conducted in SPSS 25.

3. Results

3.1. Participant characteristics

All main participant characteristics are listed in Table 1. The median age of the sample was 27 (interquartile range, IQR: 20) and the median BMI was 22 (IQR: 4.5, range: 17–32). A total of 24% of all women indicated that they were smokers. Among the individuals with a functional somatic syndrome, 15 (50%) had chronic fatigue syndrome, 15 (50%) had fibromyalgia syndrome, and 20 (67%) had irritable bowel syndrome. Half of the sample had only one functional somatic syndrome whereas the other half had two or more functional somatic syndromes. Among the individuals with a depressive disorder, 14 (54%) had melancholic depression, 6 (23%) had atypical depression, whereas the remainder did not fulfil criteria for either subtype.

There was a significant difference in age among the four groups ($H(3) = 22.5$, $p < .001$), with post-hoc tests indicating that individuals with a functional somatic syndrome and healthy controls were significantly older than individuals with somatic symptom or depressive disorders (all $p < .031$). By contrast, the four groups did not differ on BMI ($H(3) = 4.3$, $p = .24$), smoking status (X^2 (3, N = 107) = 1.2, $p = .75$), or heat-based treatments (X^2 (3, N = 105) = 0.9, $p = .82$). As expected, the three clinical groups differed in their total somatic symptom load ($H(2) = 11.6$, $p = .003$), with post hoc tests indicating that this difference was driven by the functional somatic syndrome group having significantly higher values than the depressed group ($p = .002$). Likewise, the three groups differed in their depression severity over the past two weeks (*H*

Table 1
Characteristics of individuals with functional somatic syndromes, somatic symptom disorder, depressive disorders, and healthy controls (N = 108). Means and standard deviations as well as absolute and relative frequencies are presented. Group comparisons were conducted using Kruskal-Wallis tests, univariate ANOVAs, and Chi-squared tests.

	Healthy control (n = 30)	Functional somatic syndrome (n = 30)	Somatic symptom disorder (n = 22)	Depressive disorder (n = 26)
Age (years)[a]	32 (25.3)	40 (31)	25 (5.5)	24 (5)
Body mass index (kg/m^2)	22.1 ± 2.5	23.5 ± 3.3	21.9 ± 3	22.4 ± 3
Smoking (yes)	6 (20%)	6 (20%)	6 (27%)	8 (31%)
Somatic symptom load (FFSS)[b]	0 (3.25)	21.5 (23.8)	18.5 (14)	13.5 (15.3)
Depression severity (BDI)[c]	1 (2.5)	7 (11.5)	8.5 (9.5)	25 (14.8)
Chronic stress (SSCS)[c]	3.5 (6.75)	15.5 (7.5)	22.5 (10.5)	34 (9.5)
Childhood trauma (CTQ)	50 (13)	50 (11.5)	51 (15.75)	56 (24.5)
Medication (yes)				
Antihypertensives	0	2 (7%)	0	0
Analgesics	0	7 (23%)	5 (23%)	1 (4%)
Antidepressants	0	4 (13%)	0	4 (15%)

BDI = Beck Depression Inventory (21 depressive symptoms rated by severity, possible score range from 0 to 63) referring to the past two weeks.
CTQ = Childhood Trauma Questionnaire (25 items rated by frequency of occurrence; score range from 25 to 125).
FFSS = Questionnaire on Functional Somatic Syndromes (52 somatic symptoms rated by frequency of occurrence; possible score range from 0 to 104).
SSCS=Screening Scale of the Trier Inventory for the Assessment of Chronic Stress (12 items rated by frequency of occurrence; possible score range from 0 to 48) referring to the past three months.
[a] Healthy controls and individuals with functional somatic syndromes were older than individuals with somatic symptom or depressive disorder ($p < .05$).
[b] Individuals with functional somatic syndromes had higher scores than individuals with depressive disorder ($p < .01$).
[c] Individuals with depressive disorder had higher scores than individuals with functional somatic syndromes and somatic symptom disorder ($p < .001$).

(2) = 37.6, $p < .001$), with the depressed group having significantly higher values than both the functional somatic syndrome and somatic symptom disorder groups (both $p < .001$). Furthermore, the three groups differed on self-reported chronic stress over the past three months (H (2) = 37.1, $p < .001$), such that the depressed group reported significantly higher levels than the functional somatic syndrome and somatic symptom disorder group (both $p < .001$). The three groups did not differ with respect to childhood trauma (H (2) = 2.2, $p = .33$) or the intake of antihypertensive, analgesic, or antidepressant medications (X^2 (2, N = 78) = 0.9, $p = .63$).

3.2. Hair cortisol concentrations

As evident from Fig. 1, the four groups differed significantly in their hair cortisol concentrations when controlling for age, BMI, smoking, intake of medication, and confounders of hair cortisol (F (3, 87) = 3, $p = .036$, partial eta^2 = 0.09). The main results did not change when excluding the four individuals with cortisol values below the more conservative functional sensitivity threshold of 0.011 μg/dl (n = 2 healthy controls, n = 2 individuals with somatic symptom disorder; F (3, 83) = 3.6, $p = .016$, partial eta^2 = 0.12). Post-hoc tests of the total sample indicated that individuals with somatic symptom disorder had significantly lower hair cortisol concentrations than healthy controls and individuals with a functional somatic syndrome (both $p < .012$), whereas there was no difference between individuals with a functional somatic syndrome and healthy controls ($p = .935$) and individuals with a depressive disorder and healthy controls ($p = .161$). Subgroup analyses within the depressed group did not indicate any differences between individuals with melancholic vs. atypical depression (F (1, 11) = 1.6, $p = .230$).

Hair cortisol was not correlated with childhood trauma ($r_s = 0.01$, $p = .90$) or self-reported chronic stress over the past three months ($r_s = -0.06$, $p = .539$) in the total sample. Including childhood trauma as a covariate in the group comparison led to the exclusion of two individuals with missing values on the Childhood Trauma Questionnaire and reduced the statistical significance of our group comparison to a trend level (F (3, 84) = 2.66, $p = .053$, partial eta^2 = 0.09). The previously identified post-hoc group differences remained significant (both $p < .019$).

4. Discussion

The present study yielded two main findings. First, there was no evidence for altered hair cortisol levels in individuals with a functional somatic syndrome or depressive disorder. Second, individuals with somatic symptom disorder had lower hair cortisol concentrations than healthy controls.

The first finding appears contradictory to previous meta-analyses on cortisol, which have suggested a hypocortisolaemic and hypercortisolaemic pattern in individuals with functional somatic syndromes (Tak et al., 2011) and depression (Stetler and Miller, 2011), respectively. However, regarding functional somatic syndromes, the meta-analysis found that the hypocortisolaemic pattern was only present in individuals with chronic fatigue syndrome and in women with fibromyalgia syndrome (Tak et al., 2011). It thus seems as if our null-finding might be explained by the fact that our mixed, multi-syndrome sample contained a large proportion of women with irritable bowel syndrome, which had not been found to present with altered cortisol levels in previous studies (Tak et al., 2011). Notably, however, more recent studies using hair as a tissue to determine cortisol levels paint a somewhat different picture: Two case-control studies in chronic fatigue syndrome yielded null-findings (Herane-Vives et al., 2020; Roerink et al., 2018), whereas one study in irritable bowel syndrome found that patients were characterised by lower hair cortisol than controls (Norlin et al., 2017). As with urinary, blood, and salivary cortisol, the individual syndromes thus seem to differ in the degree to which they are associated with lower hair cortisol concentrations. Similarly, the fact that we were not able to detect any differences in hair cortisol between depressed individuals and healthy controls may have been due to our sample being composed of different subtypes of depression (half of the sample had melancholic depression, whereas the remainder had atypical or unspecified depression). Indeed, in the meta-analysis of Stetler and Miller (2011), melancholic depression was the main form of depression that was linked to hypercortisolaemia. Large-scale research with sufficient power to allow for more nuanced subgroup investigations will likely shed light on these as of yet unclear issues. Ideally, such studies would integrate both short- and long-term markers of the hypothalamic-pituitary-adrenal axis and cut across multiple levels of the system (i.e., include measures of gene expression as well as of the

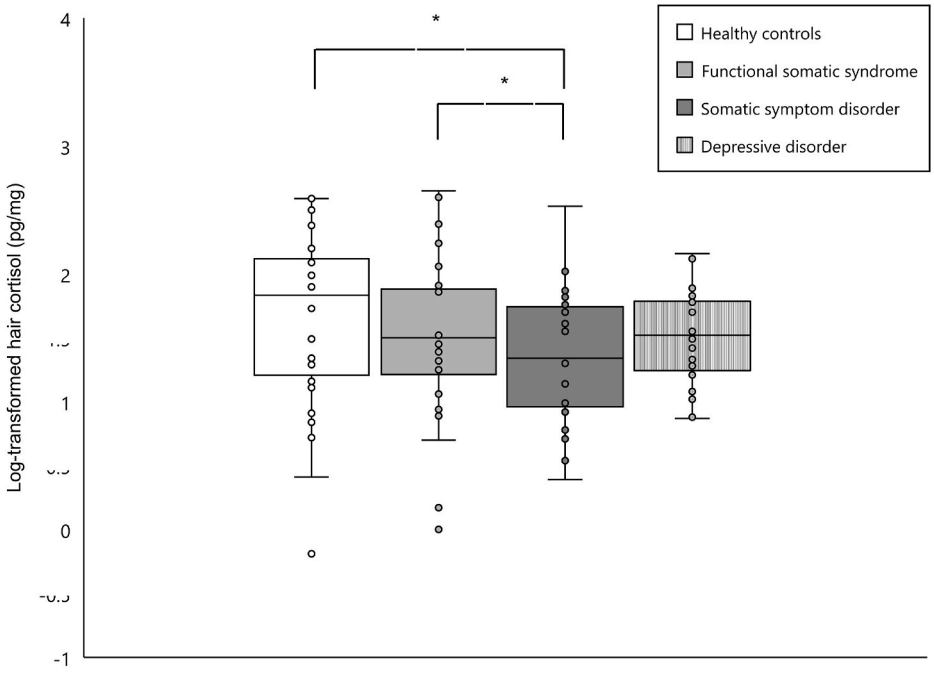

Fig. 1. Hair cortisol concentrations in healthy controls (n = 30), individuals with functional somatic syndromes (n = 30), somatic symptom disorder (n = 22), and depressive disorder (n = 26). Bars represent mean values and standard errors of cortisol values (unadjusted for covariates). Group comparisons indicated significant differences between individuals with somatic symptom disorder and healthy controls as well as between individuals with somatic symptom disorder and those with functional somatic syndromes (both p < .012).

epigenetic and genetic make-up). This approach will allow to identify which individuals with functional syndromes are affected by hypocortisolism and to pinpoint the exact underlying mechanism.

The second finding is in line with one previous study in individuals with somatoform disorders, the DSM-IV antecedent of somatic symptom disorder, which reported a reduced diurnal salivary cortisol output over the course of two days in this group, compared to healthy controls (Pedrosa Gil et al., 2008). It is, however, at odds with two other studies reporting comparably elevated cortisol levels in the morning (Rief et al., 1998) and equal cortisol levels during the day and during the night (Rief and Auer, 2000) in individuals with an abridged version of DSM-IV somatisation disorder. Notably, in the first of these studies, salivary cortisol was assessed once on a morning before participants underwent a mental stress test in the afternoon. In the second study, salivary cortisol was measured once in the morning and once in the late afternoon, before and after a series of mental tasks. These specific contexts render any comparison with hair cortisol, a cumulative, long-term measure of hypothalamic-pituitary-adrenal axis activity, difficult. However, the fact that the clinical and healthy control groups did not differ in their urinary cortisol secretion during sleep (10.30 p.m.–8 a.m.) is puzzling when contrasted with the present findings. One explanation may be that, since hair cortisol is integrating total secretion over time, the concentrations are primarily shaped by the magnitude of the morning rise and the slope of decline across the day than by overnight secretion. These, in turn, are shaped by central drive and the timing of the initiation of the morning rise, which is under neural control and related to day-to-day state factors. An alternative explanation lies in changes in diagnostic criteria from the DSM-IV to the DSM-5, which purports that patients need to dedicate an excessive amount of thoughts, feelings, and behaviours to the symptoms they experience. It is thus possible that only individuals with these psychological characteristics exhibit altered hypothalamic-pituitary-adrenal functioning. This could also explain why individuals with somatic symptom disorder had even lower cortisol concentrations than individuals with functional syndromes, who do not necessarily exhibit these features. Given that this is the first ever study in the literature to examine cortisol in somatic symptom disorder, it will be important that further research into hypothalamic-pituitary functioning in this condition is undertaken.

This study presents with a number of strengths. It is the first to investigate hair cortisol in individuals with different types of medically unexplained symptoms, and the first to include both a healthy and a clinical comparison group. Furthermore, all participants underwent extensive, state-of the art diagnostic assessments and a number of important confounders (e.g., comorbid somatic and mental illnesses) were excluded a priori. However, some limitations also need to be mentioned. First, due to the female preponderance in medically unexplained symptoms, the present study was restricted to women, which means that our findings cannot be generalised to the general population. Second, there was a significant difference in age between the four groups, which could have impacted on our findings. However, in line with a meta-analysis on determinants of hair cortisol (Stalder et al., 2017), age was unrelated to hair cortisol in the present sample, which suggests that age differences did not affect our findings in a profound manner. Third, we did not measure physical activity, which could affect cortisol levels (Tak et al., 2011). However, all BMIs (except for one) were in the normal range and the four groups did not differ in their BMI, which renders it unlikely that any of our participants were characterised by an extreme sedentary lifestyle. Fourth, our research question demanded that we excluded comorbidities with major mental disorders, including depression. However, such "monomorbid" conditions are a rare occurrence in clinical practice and it is thus important for further research to investigate hair cortisol in individuals with comorbid somatic symptom disorder/depression in comparison to healthy controls. Fifth, it was not assessed whether women with a functional somatic syndrome fulfilled criteria for somatic symptom disorder and vice versa. It would certainly be interesting if future research with mono-morbid samples could shed further light on which clinical features in particular are responsible for the herein observed group differences. Sixth, two different immunoassays were used in the present study, which, although manufactured by the same company, differed in the extent to which they were able to detect cortisol concentrations in the very low range. Given that our findings did not change when excluding the four values below the more conservative functional sensitivity threshold of 0.011 μg/dl, it is unlikely for this to have impacted our findings. Related to this, different people were involved in hair sampling and our groups were not equally distributed between the two assays. Although identical sampling protocols were used, the same person supervised the hair sampling, and the intra- and inter-assay sensitivities were below 10%, this could have affected our results and highlights the import of an independent replication of this study. Finally, our cross-sectional study design did not allow us to establish the temporal order between hypocortisolism and somatic symptom disorder and further research is required to determine whether hypocortisolism precedes the development of somatic symptom disorder or vice versa.

In sum, this study provided initial evidence that individuals with somatic symptom disorder, a disorder characterised by excessive thoughts, feelings, and behaviours about physical symptoms, are characterised by lower levels of hair cortisol. Interestingly, our findings also suggest that hypocortisolism is not found in all individuals with medically unexplained symptoms. This is an important observation since this field has witnessed extensive scientific debates as to whether functional somatic syndromes should be understood as one single or several distinct syndromes (Wessely and White, 2004). Provided our findings will be replicated in the future, they can be considered in favour of the notion that somatic symptom disorder is part of a spectrum of mental disorders that present with hypocortisolism (Fries et al., 2005; Heim et al., 2000), which may have direct links to the increased levels of inflammation that are often associated with some of their core symptoms (Irwin, 2011). Notably, childhood trauma and chronic stress, although likely implicated in the aetiopathogenesis of medically unexplained symptoms (Nater et al., 2011a; Tak and Rosmalen, 2010), were not related to hair cortisol. These findings are in line with the general literature on long-term markers of the hypothalamic-pituitary-adrenal axis (Duncko et al., 2019; Fischer et al., 2018a, 2020; Khoury et al., 2019; Stalder et al., 2017) and may suggest that stressors closer to the onset of medically unexplained symptoms that were not captured by our measures may have triggered the hypocortisolaemic pattern. Further, large-scale research is warranted to replicate our findings. Ideally, such studies would extend the present research by including multiple levels and layers of the hypothalamic-pituitary-adrenal axis system (including gene expression, epigenetic, and genetic correlates) and by examining it both in the resting state and under conditions of challenge. Moreover, given that the present study found that hypocortisolaemia featured in a subgroup of individuals exhibiting specific changes in cognition, emotions, and behaviour in relation to bodily symptoms, it would certainly be valuable to gain more insight into the extent to which these psychological features map onto changes in the hypothalamic-pituitary-adrenal system.

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Author statement

RM and UN conceived and designed the studies. SF analysed the data and RM, UN, SF, NS, and NA interpreted the data. SF drafted the article and RM, UN, SF, NS, and NA revised it critically for important

intellectual content. All authors have approved the final article.

Conflicts of interest

None.

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