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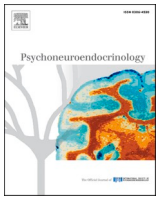

Lower hair cortisol concentration in adolescent and young adult patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Q-Fever Fatigue Syndrome compared to controls

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ABSTRACT

Background: In patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), *momentary* cortisol concentrations in blood, urine, and saliva are lower compared to healthy controls. *Long-term* cortisol concentration can be assessed through hair, but it is unclear whether these concentrations are also lower. Additionally, it is unknown if lower cortisol extends to other patients suffering from persistent fatigue and how hair cortisol concentration (HCC) relates to fatigue levels. Therefore, this study examines HCC in fatigued patients with ME/CFS, Q fever Fatigue Syndrome (QFS), Post-COVID-19 condition (PCC), and Juvenile Idiopathic Arthritis (JIA).

Methods: Adolescent and young adult patients with ME/CFS (n=12), QFS (n=20), PCC (n=8), JIA (n=19), and controls (n=57) were included. Patients participated in a randomized cross-over trial (RCT) targeting fatigue through lifestyle and dietary self-management strategies. HCC was measured pre-post RCT in patients and once in controls, quantified using a LC-MS/MS-based method. Fatigue severity was measured with the Checklist Individual Strength-8. HCC was compared between groups with ANOVAs. Relations between HCC, fatigue severity, and other variables were investigated using linear regression analyses.

Results: The ME/CFS (p=.009) and QFS (p=.047) groups had lower HCC compared to controls. Overall, HCC was negatively associated with the presence of symptoms related to chronic fatigue syndromes (e.g., sleeping issues, often feeling tired, trouble thinking clearly; β=-0.018, p=.035), except in the QFS group (β=.063, p<.001). Baseline HCC did not predict fatigue improvement during the RCT (p=.449), and HCC increased during the trial (M_{dif}=.076, p=.021) regardless of clinically relevant fatigue improvement (p=.658).

Conclusion: Lower cortisol concentration can also be observed in the long-term. Lower HCC is not limited to ME/CFS, as it was also observed in QFS. The role of cortisol may differ between these diagnoses and appears to be unrelated to fatigue levels.

1. Introduction

Adolescent patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) suffer from severe, persistent fatigue and other symptoms such as unrefreshing sleep, post-exertional malaise (PEM), pain, and memory or concentration impairments (guideline NG206 N., 2021). Their symptoms can have an adverse impact on daily functioning, school or work participation, and mental well-being

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(guideline NG206 N., 2021; Roma et al., 2019; Winger et al., 2015; Josev et al., 2021; Afari and Buchwald, 2003; Josev et al., 2017), cumulating developmental challenges for young adulthood and beyond. The aetiology and pathophysiology of ME/CFS is largely unknown even though several theories have been developed (Afari and Buchwald, 2003; Hwang et al., 2023; Noor et al., 2021; Varesi et al., 2021; Walitt et al., 2024; Tomas et al., 2013; Deumer et al., 2021; Armstrong et al., 2014). Some immunological studies suggest that ME/CFS symptoms could be related to changes in the hypothalamic-pituitary-adrenal (HPA) axis, which controls the release of the stress hormone cortisol (Afari and Buchwald, 2003; Tomas et al., 2013; Deumer et al., 2021; Powell et al., 2013; Fries et al., 2005).

Hypofunction of the HPA-axis has frequently been observed in patients with ME/CFS through low cortisol concentrations in blood, urine, and particularly the salivary cortisol awakening response (CAR) when compared to controls (Tomas et al., 2013; Powell et al., 2013; Tak et al., 2011; Papadopoulos and Cleare, 2012; Nijhof et al., 2014). Research has linked more pronounced hypofunction to increased symptom severity (Tomas et al., 2013; Papadopoulos and Cleare, 2012; Torres-Harding et al., 2008), identified moderating factors that lower cortisol concentration (i.e., female sex, early-life stressors, low activity levels, sleep disturbances, depression) (Papadopoulos and Cleare, 2012), and studied the use of hydrocortisone as pharmacological treatment of ME/CFS (Toogood et al., 2021). These studies focused mostly on adult patients. Only one study has investigated cortisol in a large sample of adolescent patients with ME/CFS (Nijhof et al., 2014). This study replicated low cortisol concentration in the salivary CAR, and it observed a normalization of cortisol concentration after psychological therapy successfully alleviated disease burden (Nijhof et al., 2014). In contrast to one adult study (Roberts et al., 2010), the adolescent study did not show that lower pre-treatment cortisol concentration predicted poorer therapy response (Nijhof et al., 2014).

The role of cortisol may differ between adolescent and adult patients, but it is also possible that contrasting findings can be explained by methodological challenges – the measurement of salivary CAR is relatively error prone when participants perform sampling at home (Nijhof et al., 2014; Roberts et al., 2010), and cortisol concentrations in blood, urine, and saliva samples are influenced by time of day and acute stressors as they represent cortisol values *in the moment* (Mirzaian et al., 2024; Noppe et al., 2015 Aug 1). Recent developments have enabled the measurement of cortisol concentration *long-term* in hair samples (Mirzaian et al., 2024; Noppe et al., 2015). Sampling can be performed by a researcher at any time and is therefore less error prone. Hair cortisol concentration (HCC) is also not influenced by time of day and acute stressors, as it represents the average systemic cortisol exposure of a longer period (i.e., the first three centimetres of human scalp hair represent the last three months) (Mirzaian et al., 2024; Noppe et al., 2015). To our knowledge, three studies have been conducted on HCC in ME/CFS. One study found a trend for lower HCC in adult females with ME/CFS when compared to female controls (Roerink et al., 2018). The second study observed similar levels in adults with ME/CFS when compared to adults with atypical depression and to controls (Herane-Vives et al., 2020). The third study pooled women with a diagnosis of ME/CFS, fibromyalgia, or irritable bowel syndrome together, and found that their HCC was higher compared to women with a somatic symptom disorder and equal to controls (Fischer et al., 2022). Clearly, more research is needed to determine HCC status in ME/CFS. This will be the first study to focus on HCC in adolescent and young adult patients.

The symptomatology of ME/CFS is very similar to that of Q fever Fatigue Syndrome (QFS) (Ankert et al., 2022; Keijmel et al., 2020; Ledina et al., 2007; Morroy et al., 2016) and post-COVID-19 condition (PCC; also known as post-COVID) (Brodin et al., 2022; Lopez-Leon et al., 2022; Wong and Weitzer, 2021). The three syndromes are differentiated based on which infection preceded symptom onset; *Coxiella burnetii* precedes QFS (Ankert et al., 2022; Keijmel et al., 2020; Ledina et al., 2007; Morroy et al., 2016), *SARS-CoV-2* precedes PCC (Brodin et al., 2022; Lopez-Leon et al., 2022; Wong and Weitzer, 2021), and Epstein-Barr or other (unidentified) infections may precede ME/CFS (Afari and Buchwald, 2003; Noor et al., 2021). To our knowledge, no cortisol research has been conducted in patients with QFS. The first cortisol studies on PCC are emerging, with one study showing that plasma cortisol concentration in adult patients was lower compared to controls more than one year after acute infection (Klein et al., 2023). Based on the similar symptomatology and the findings in PCC, we expect that lower HCC will also be visible in adolescent and young adult patients with QFS and PCC. If confirmed, the question arises whether low cortisol is unique to chronic fatigue syndromes or also present in other chronic diseases with persistent fatigue, such as in the autoimmune disease Juvenile Idiopathic Arthritis (JIA) (Armbrust et al., 2016; Arnstad et al., 2021).

The first aim of this study is to test if lower cortisol concentration can be replicated in hair samples of adolescent and young adult patients with ME/CFS. Second, we investigate if lower HCC extends to patients with QFS and PCC only, or to more patient groups suffering from persistent fatigue. For these two aims, we use baseline HCC data from a randomized cross-over trial (RCT) targeting fatigue severity in patients with ME/CFS, QFS, PCC, and JIA. We compare the baseline data between patient groups and to a control group, also whilst controlling for variables associated with HCC. More RCT data is available to study the relation between cortisol and therapy response (see Nijhof et al., 2014; Roberts et al., 2010). Therefore, the third aim is to test whether baseline HCC predicts fatigue improvement during the RCT. The fourth aim is to explore changes in HCC after clinically relevant fatigue improvement during the trial.

2. Method

2.1. Study setting

The current study is part of a broader research effort on biological disruptions and self-management intervention strategies for QFS at the Wilhelmina Children's Hospital, part of University Medical Center Utrecht (UMC Utrecht) in the Netherlands (Vroegindeweij et al., 2022). The research call was initiated by patient association Q-Support. The research received ethical approval from the Institutional Review Board (IRB) of UMC Utrecht, reference number 20–166. All participants, and legal guardians of those younger than 16, signed informed consent before inclusion. Patients were enrolled in a RCT and adhered to tailored lifestyle advice and generic dietary advice as self-management interventions for persistent fatigue (Vroegindeweij et al., 2023). Each intervention lasted three months, with a one-month wash-out period in-between. Hair samples were collected before and after the interventions in patients, and once in controls. All questionnaires were completed at home before the study visit(s). More information on the RCT can be found in the protocol paper (Vroegindeweij et al., 2022).

2.2. Participants

2.2.1. Patients

Eligible patients (aged 12–29) visited a pediatrician (SN, EP) at the Wilhelmina Children's Hospital for a protocolled screening (Vroegindeweij et al., 2022) between October 2020 and April 2022.

Patients with ME/CFS met adjusted[1] Centers for Disease Control and Prevention (CDC) criteria (Fukuda et al., 1994). Since six months or more, they suffered from severe fatigue, unrefreshing sleep, post-exertional malaise (PEM), and at least two out of six other symptoms: memory or concentration impairment, muscle pain, joint pain,

[1] Note that we deemed unrefreshing sleep and PEM as compulsory symptoms instead of optional symptoms, to align better with other diagnostic criteria for ME/CFS, such as the Canadian Consensus Criteria (Carruthers et al., 2003).

headaches, tender lymph nodes, or frequently recurring sore throat (Fukuda et al., 1994).[2] Patients with QFS or PCC met the same criteria and showed seropositivity for respectively *Coxiella burnetii* or *SARS-CoV-2* during the screening or during a previous hospital visit. In case patients showed seropositivity for more than one infection, the diagnosis was determined by the infection closest to symptom onset. Patients with JIA met the International League of Associations for Rheumatology (ILAR) criteria (Petty et al., 2004) and had to have a stable disease activity, as defined by at least three months without inflammatory flare-ups and unaltered medication (Vroegindeweij et al., 2022).

All patients in this study had to experience severe fatigue for at least six months. Fatigue severity was measured with the Checklist Individual Strength (CIS)-8 questionnaire, which has a range of 8–56 (Worm-Smeitink et al., 2017). Fatigue was labeled as severe with a total score of >39 in patients with ME/CFS, QFS, and PCC, and a total score of >34 in patients with JIA. Previous research has indicated that fatigue severity is perceived similarly between patients with chronic fatigue syndromes and rheumatic conditions using these cut-offs (Worm-Smeitink et al., 2017; Hewlett et al., 2011). Patients with any additional diagnosis that could fully explain severe fatigue during the pediatrician's screening were excluded, as were JIA patients with an inflammatory flare-up. No patients needed to be excluded due to medication use known to interfere with (hair) cortisol concentration. Ultimately, 59 patients were included (n_{QFS}=20, n_{JIA}=19, $n_{ME/CFS}$=12, n_{PCC}=8) of which 46 completed the full RCT.

2.2.2. Controls

A control group was recruited through included patients. Therefore, most eligible controls were patients' siblings or friends. Controls were included if they were aged between 12 and 29, were not severely fatigued as indicated by a CIS-8 total score of <40, and if they grew up or lived in the same area as the patient within the Netherlands. The latter was intended to increase the likelihood of including controls with equal exposure risk to infectious agents such as *Coxiella burnetii* and *SARS-CoV-2*. Ultimately, hair samples were collected of 57 controls.

2.3. Measurements

2.3.1. Hair cortisol concentration

A sample of approximately 100–150 hairs was acquired from the posterior vertex of each participant during their study visit(s). The hair was cut closely to the scalp and stored in a dark closet at room temperature. The samples were sent to the department of Clinical Chemistry at Erasmus MC (University Medical Center Rotterdam, The Netherlands) for processing and HCC quantification via the liquid chromatography-mass spectrometry method (LC-MS/MS) described in their protocol (Mirzaian et al., 2024).

2.3.2. Fatigue severity

Fatigue severity was self-reported on the computer with the CIS-8 questionnaire before each study visit (Worm-Smeitink et al., 2017). The questionnaire consists of eight items, answered on a 7-point Likert scale. Total scores range from 8 to 56, with higher scores indicating more severe fatigue. Examples of items are "I feel tired", "Physically, I feel exhausted", and "I tire easily" (Worm-Smeitink et al., 2017). Respondents were asked to answer each item based on their experiences in the last two weeks. The CIS-8 questionnaire has strong internal consistency and test-retest reliability (Worm-Smeitink et al., 2017).

2.3.3. Additional baseline measurements

Participants reported their age and sex, and completed a list of self-reported questionnaires on variables that might be associated with HCC. In the PROactive questionnaire (Nap-van der Vlist et al., 2021), participants reported whether they experienced one of the following early-life stressors: parental divorce, death of a parent, long-term sickness of a family member, or being bullied at school. Participants were also asked to think about the previous week and report how many days they were physically active for at least 60 min (e.g., walking at a steady pace or running, cycling, playing a sport), their school or work attendance, and experienced level of pain severity.

Depressive symptoms were measured with the Revised Child Anxiety and Depression Scale (RCADS) subscale 'low mood' on a 4-point Likert scale (Vroegindeweij et al., 2022). Five out of ten items share a relation with core symptoms in chronic fatigue syndromes, namely: "I have trouble sleeping", "I have no energy for things", "I am tired a lot" (all due to fatigue and unrefreshing sleep), "I cannot think clearly" (due to memory and concentration impairment), and "I feel like I don't want to move" (due to fatigue and PEM). Therefore, we decided to split the RCADS low mood scale into two new subscales. The related items will be referred to as "CFS symptoms" whereas the five remaining items ("I feel sad or empty", "Nothing is fun anymore", "I have problems with my appetite", "I feel worthless", and "I feel restless") will be referred to as "depression symptoms". Both subscales have a range of 5–20, with higher scores indicating the presence of more CFS or depression symptoms.

Information on patients' fatigue duration, medication use, and body mass index (BMI) were retrieved from the pediatrician's screening report.

2.4. Statistical analysis

HCC data were first inspected for outliers using the modified Z-score method, which uses the median absolute deviation to compute Z-scores and a threshold of +/- 3.5 to label outliers (Obikee et al., 2014). No outliers were detected. Next, raw HCC values were log10-transformed to achieve normality of the data. Descriptive analyses were used to derive baseline characteristics. Univariable ANOVAs, chi-square tests, and post-hoc group comparisons were used when appropriate to compare baseline characteristics between participant groups. Bonferroni correction was applied to correct for multiple testing.

The first aims were to investigate the presence of low HCC in ME/CFS, QFS, PCC, and JIA compared to controls. Levene's test indicated that the assumption of homogeneity in variance across groups was almost violated (p =.05). Therefore, Welch's ANOVAs were used with Welch's t-tests as post-hoc comparisons tests. We performed the group comparisons stepwise, where at each step, we merged one chronic fatigue syndrome group with another to investigate whether low HCC was unique to ME/CFS or more broadly observed in chronic fatigue syndromes, or even in JIA with persistent fatigue. By merging the groups, the statistical power of the comparisons increased. Next, to test whether group differences were still significant when controlled for relevant variables, we first tested associations between baseline HCC (dependent variable) and age, sex, fatigue duration, fatigue severity, pain severity, CFS symptoms as measured with the RCADS, depressive symptoms as measured with the RCADS, physical activity, z-transformed BMI, school/work participation, and early-life stressors (independent variables) in univariable linear regression analyses. Significant independent variables would then be added as covariates to a multiple linear regression analysis.

The third aim was to test whether baseline HCC predicted fatigue improvement during the RCT. Fatigue improvement was computed as the difference score of the CIS-8 at T0 (baseline) minus T4 (after interventions). Baseline HCC was the independent variable and fatigue improvement the dependent variable in univariable linear regression analysis. Next, we added the covariates previously identified to a multiple linear regression model.

The last aim was to explore changes in HCC after clinically relevant

[2] Half of the patients with ME/CFS also met the Canadian Consensus Criteria for ME/CFS (Carruthers et al., 2003). These criteria are stricter, thereby selecting a smaller and more severely impaired group than the CDC criteria.

fatigue improvement (CRFI) during the trial. CRFI was equal to a CIS-8 difference score of ≥6 (Vroegindeweij et al., 2023), utilizing a Reliable Change Index of ≥1.96 to calculate the minimal clinically important difference (Wright et al., 2012). We first tested whether HCC increased in the total sample during the RCT using a paired t-test. Next, we selected all participants who showed CRFI after the first intervention (T2). If HCC started to normalize after achieving CRFI at T2, the increase in HCC should be visible four months later at T4. Therefore, we computed the change in HCC by subtracting the value at T0 from T4 and compared it between participants with and without CRFI at T2 using an independent samples t-test.

Analyses were performed in Rstudio (version 4.2.2) using the "dyplr", "car", "ggstatsplot", "ggplot2", "ggpubr", and "patchwork" packages.

2.5. Statistical power

The number of patients included in this study was predetermined in the RCT protocol paper (Vroegindeweij et al., 2022). In the protocol paper, we calculated that 60 patients (allowing a maximum of 12 dropouts) were required to observe large self-management intervention effects with at least 80 % power. We strived to include 80 controls for the current study (Vroegindeweij et al., 2022) but this target could not be realized due to time constraints. To estimate the power of the current study, we performed a post-hoc power calculation based on our main analysis (i.e., Welch's ANOVA to compare HCC between patients with ME/CFS, QFS, PCC, JIA and controls). The calculation was performed using R-package "pwr". For effect size $\widehat{\omega^2}$=0.18, five subgroups (n=20, n=19, n=12, n=8, n=57), and an alpha-level of 5 %, the calculation yielded a power of 81%.

3. Results

3.1. Description of the total sample

Table 1 presents the baseline characteristics of the total sample (N=116). Compared to the control group, the four patient groups were more often female. Patients with ME/CFS and JIA were also younger than the control group. All patient groups experienced more fatigue, pain, and CFS symptoms compared to the control group. Patients with QFS, PCC, and JIA experienced more depressive symptoms than controls. Patients with QFS, PCC, and ME/CFS reported lower school or work attendance compared to controls. Patients with ME/CFS had been less physically active in the previous week compared to controls.

Between patient groups, the fatigue duration of the PCC group was shortest at baseline. The QFS and PCC groups were significantly older than the ME/CFS group. Three out of eight patients with PCC still tested seropositive on *SARS-Cov-2*, which was not more often compared to other patient groups. Patients with ME/CFS had significantly lower BMI than patients with QFS or PCC. Patients with JIA were more physically active in the previous week compared to patients with ME/CFS. Number of experienced early-life stressors did not differ between any group.

3.2. Group differences in hair cortisol concentration at RCT baseline visit

The difference in HCC between the five groups was significant at baseline and had a large effect size (Welch's ANOVA; F(4,30)=2.91, p=.038, $\widehat{\omega^2}$=0.18, Fig. 1A). The ME/CFS group had significantly lower HCC compared to the control and JIA groups (respectively p=.009 and p=.023). HCC was also lower in the QFS group compared to the control group (p=.047). The difference with the control group remained significant after each merging step (Figs. 1B to 1D). At the final step, the effect size was medium ($\widehat{g}_{Hedges}$=-0.58, Fig. 1D).

Univariable regression analysis confirmed that the ME/CFS and QFS groups had significantly lower HCC compared to the control group (F(4,111)=2.632, β_{QFS}=-.076, $\beta_{ME/CFS}$=-.095, R^2_{adj}=.053, p≤.043). The presence of CFS symptoms (as measured with the RCADS) was associated with lower HCC (F(1,102)=4.563, β=-0.010, R^2_{adj}=.033, p=.035), whereas patients' BMI was associated with higher HCC (F(1,54)=4.146, β=0.044, R^2_{adj}=.054, p=.047). None of the other variables were significantly associated with HCC (e.g., age, sex, fatigue severity, fatigue duration, depressive symptoms, physical activity, early-life stressors).

The multiple linear regression analysis included the groups and CFS symptoms as independent variables. The overall model was significant (F(9,94)=3.222, R^2_{adj}=0.163, p=.002), and showed a trend for lower HCC as the presence of CFS symptoms increased (β=-0.018, p=.076),

Table 1
Descriptive table.

Baseline characteristic	Mean (SD) or frequency (%)						
	Total (n=116)	ME/CFS (n=12)	QFS (n=20)	PCC (n=8)	JIA (n=19)	Control (n=57)	Group dif. sig.
Age (in years, range 12–29)	20.19 (4.89)	14.92 (2.15)	22.25 (4.65)	20.25 (6.41)	16.05 (2.68)	21.84 (4.20)	**
Sex (female)	83 (69.2 %)	10 (83.3 %)	16 (80.0 %)	8 (100 %)	17 (89.5 %)	32 (52.5 %)	*
Coxiella Burnetii(seropositive)	28 (23.33 %)	1(8.33 %)	20 (100 %)	3(37.5 %)	0(0 %)	4(6.56 %)	**
SARS-CoV-2 (seropositive)	26 (21.67 %)	2 (16.66 %)	4 (20.0 %)	3 (37.5 %)	7 (63.6 %)	10 (16.39 %)	Ns
BMI (body mass index)	23.72 (5.33)	20.20 (2.65)	24.47 (5.52)	26.30 (6.40)	23.93 (5.19)	*NA*	*
Fatigue duration (in years)	2.08 (3.40)	2.25 (3.09)	6.05 (3.45)	0.81 (0.26)	5.00 (4.01)	.00 (.00)	**
Fatigue severity(CIS-8, range 8–56)	32.77 (14.56)	48.73 (5.31)	47.90 (5.08)	46.29 (5.47)	40.06 (8.15)	21.15 (8.72)	**
Pain severity(VAS, range 1–10)	3.41 (3.29)	5.91 (3.18)	6.53 (2.36)	4.00 (3.51)	4.25 (3.09)	1.67 (2.41)	**
CFS symptoms (RCADS-LM, range 5–20)	9.39 (3.20)	12.17 (2.98)	12.21 (1.99)	11.88 (1.73)	10.93 (2.28)	6.98 (1.89)	**
Depressive symptoms (RCADS-LM, range 5–20)	7.87 (2.50)	8.33 (2.53)	9.63 (1.83)	9.13 (3.09)	8.87 (3.09)	6.69 (1.81)	**
School or work attendance (in %)	87.18 (23.46)	76.00 (24.35)	70.21 (36.31)	56.93 (37.33)	82.92 (14.30)	98.08 (7.47)	**
Physically active days (during last week)	3.36 (2.22)	1.55 (1.51)	3.33 (2.33)	2.00 (1.41)	3.88 (1.71)	3.72 (2.30)	*
≥1 early-life stressors(yes)	54 (47.7 %)	7 (63.6 %)	12 (66.7 %)	4 (57.1 %)	8 (50.0 %)	23 (37.7 %)	Ns

Note. QFS=Q fever Fatigue Syndrome; ME/CFS=Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; PCC=Post-COVID-19 Condition; JIA=Juvenile Idiopathic Arthritis. Group differences were tested for significance in the last column (group dif. sig.). Continuous variables were tested using one-way univariate ANOVAs, whereas categorical variables were tested using chi-square tests. All analyses and post-hoc comparisons were corrected for multiple testing (Bonferroni). Ns = not significant, ** p <.001, * p <.05.

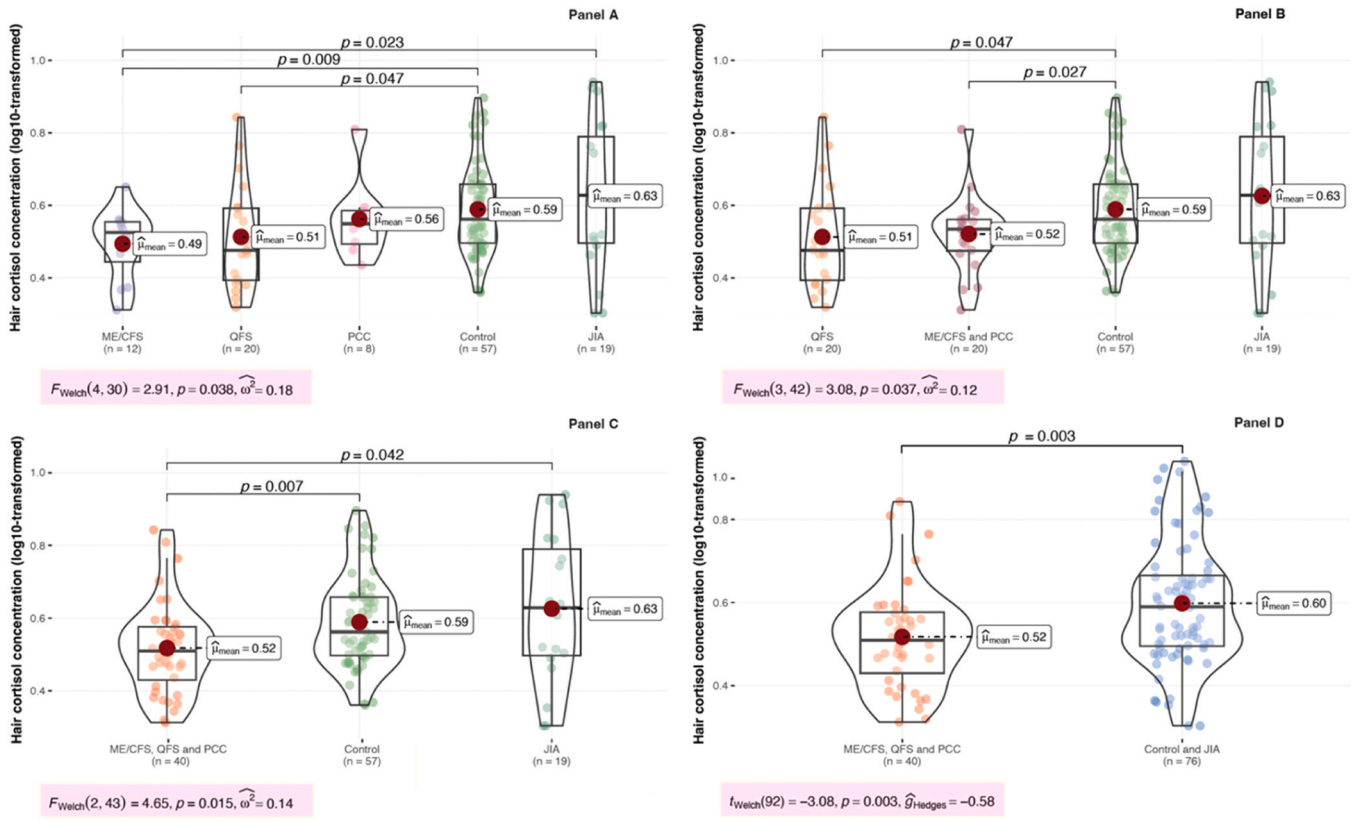

Fig. 1. Group comparisons of hair cortisol concentration at baseline visit. *Note. Presented are the distributions of hair cortisol concentration (log10-transformed) per subgroup at RCT baseline visit. The shape of the violin plots indicates the density of the data distribution, with longer tails suggesting skewness. Symbol $\widehat{\omega^2}$ represents the effect size for ANOVAs, especially useful with relatively small sample size comparisons. Values around 0.01 are low, around 0.06 are medium, and around 0.14 are large (Field, 2013). Symbol $\hat{g}_{Hedges}$ represents the effect size for Welch's t-test, with values around 0.2 as small, around 0.5 as medium, and around 0.8 as large (Cohen, 2013).*

except in the QFS group (β=.063, *p*=.001). This interaction effect is presented in Fig. 2.

3.3. Baseline HCC as predictor of fatigue improvement

Fatigue severity improved significantly during the RCT (M_{dif}=-4.25, $CI_{95\,\%}$=-6.70 to −1.80, paired *t*=-3.49, *p*=.001). Baseline HCC was not associated with fatigue improvement during the RCT, either in univariable regression analysis (*p*=.449) or in multiple linear regression analysis controlling for group, BMI, and CFS symptoms (*p*=.431).

3.4. Changes in HCC after clinically relevant fatigue improvement at T2

The RCT was completed by 46 patients, of which 44 had no missing

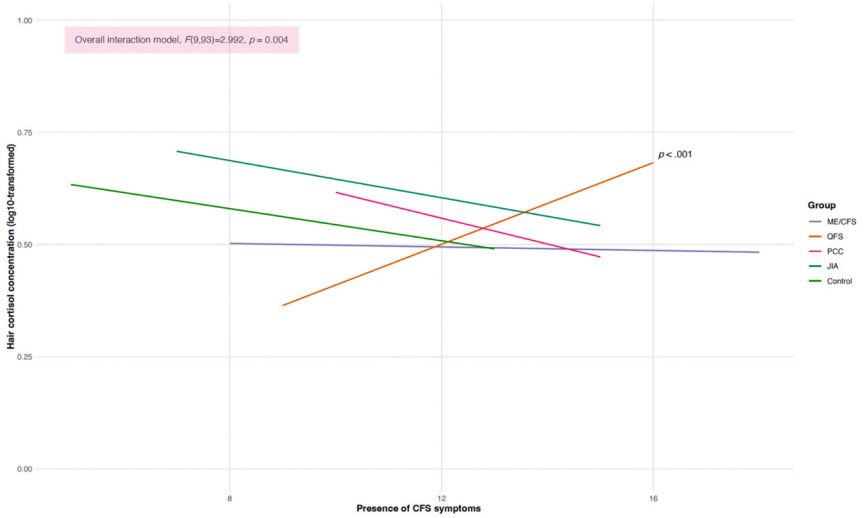

Fig. 2. Interaction effect between diagnosis and fatigue syndrome symptoms on HCC. Note. Chronic fatigue syndrome (CFS) symptoms were measured with five items from the RCADS 'low mood' subscale. The relation between CFS symptoms against HCC was plotted per group. Except for the QFS group, there was a trend for lower HCC as the presence of CFS symptoms increased. The increase in HCC was significant in the QFS group as compared to the control group (p<.001).

HCC data. Clinically relevant fatigue improvement (CRFI) was observed in 10 out of 44 patients (22.73 %) after the first intervention (T2). HCC increased significantly during the trial (M_{dif}=.076, *paired* t=-2.388, p=.021). The HCC increase was equal in patients with and without CRFI (t=.450, p=.658, Fig. 3A). HCC at baseline (T0) and after the interventions (T4) did not differ between the two groups (respectively p=.094 and p=.130). HCC increase and HCC at T4 also did not differ between patient groups (respectively p=.098 and p=.100, Fig. 3B).

4. Discussion

Previous research has observed lowered cortisol concentration in blood, urine, and saliva samples of patients with ME/CFS compared to controls (Tomas et al., 2013; Powell et al., 2013; Tak et al., 2011; Papadopoulos and Cleare, 2012; Nijhof et al., 2014), implying that patients with ME/CFS might be exposed to less cortisol *in the moment*. The current study found that cortisol concentration was lower in hair samples as well, suggesting that cortisol exposure is also lowered in the *long-term*. Lower HCC might not be unique to ME/CFS, as lower concentration was also observed in patients with QFS. Although HCC increased and fatigue severity improved during the RCT, we did not observe an association between the two in patients with ME/CFS, QFS, PCC, and JIA.

To our knowledge, only three studies on HCC in adult patients with ME/CFS had been conducted. The findings of these former studies combined are inconclusive, with the first study finding a trend for lower HCC in patients with ME/CFS (Roerink et al., 2018) and the others finding no difference (Herane-Vives et al., 2020; Fischer et al., 2022). We did find a significant difference with large effect size in our study, possibly because our study differed in multiple ways from the previous studies. The average age of our ME/CFS sample was 15 compared to respectively 33, 41, and 40 (Roerink et al., 2018; Herane-Vives et al., 2020; Fischer et al., 2022). Half of our sample also met the Canadian Consensus Criteria (CCC) criteria on top of the CDC criteria, whereas the other studies only mention the CDC criteria (Roerink et al., 2018; Herane-Vives et al., 2020; Fischer et al., 2022). Therefore, it is unclear whether all samples are comparable in terms of disease severity. Our study also included males and females, rather than females only (Roerink et al., 2018; Fischer et al., 2022), and we did not pool any diagnoses together before presenting HCC values per subgroup (Fischer et al., 2022). In addition, our hair measurement did not reflect the last month of cortisol exposure (Roerink et al., 2018), but the last three months of exposure.

As the symptomatology of ME/CFS shares a large overlap with diagnoses QFS and PCC, we wondered if lower HCC would also be visible in these patient groups. The current study confirmed this for QFS. Thus far, research has found that several inflammatory markers are more expressed in patients with QFS and ME/CFS compared to controls, that their blood metabolite profiles are different compared to controls, and that their microbiome taxonomies are strikingly similar (Raijmakers et al., 2020). The current study now adds lower HCC as similarity between these syndromes. Yet, the role of cortisol might differ between the two diagnoses. We observed different cortisol values in response to CFS symptoms (as measured with the RCADS subscale). When the presence of CFS symptoms increased, the value of HCC decreased in ME/CFS but increased in QFS. As the RCADS was not validated for this measurement purpose, future research should re-examine the relation between HCC and symptoms or behaviours and cognitions related to core symptoms of chronic fatigue syndromes with validated tools. Based on Fig. 3B, readers might also suspect that HCC increased more in patients with ME/CFS compared to QFS. The difference was not statistically significant but might have been with larger sample sizes.

Lower HCC did not extend to patients with PCC or to patients with JIA who also suffered from persistent fatigue. It is possible that we would have observed lower HCC in patients with PCC if we had the opportunity to include more than eight patients, as studies have shown that cortisol concentration is lower in groups *on average* but not in all individual patients (Papadopoulos and Cleare, 2012). In addition, the average fatigue duration of the PCC group was approximately 10 months. This was significantly shorter compared to the other patient groups. Moreover, patients could be diagnosed with PCC after six months of disease duration. As HCC values reflected the average exposure to cortisol in the last three months, it means that in some patients with PCC, baseline measurement reflected their cortisol exposure in a period before the official diagnosis. If cortisol lowers in PCC, like the plasma cortisol study one year after acute infection by Klein et al. suggests (Klein et al., 2023), it is the question if it already happens before the six months mark. As the JIA group was one of the largest groups (n=19) that also had a long fatigue duration of five years on average, these explanations do not hold for this patient group, making it more likely that lower cortisol concentration does not extend to all patients suffering from persistent fatigue.

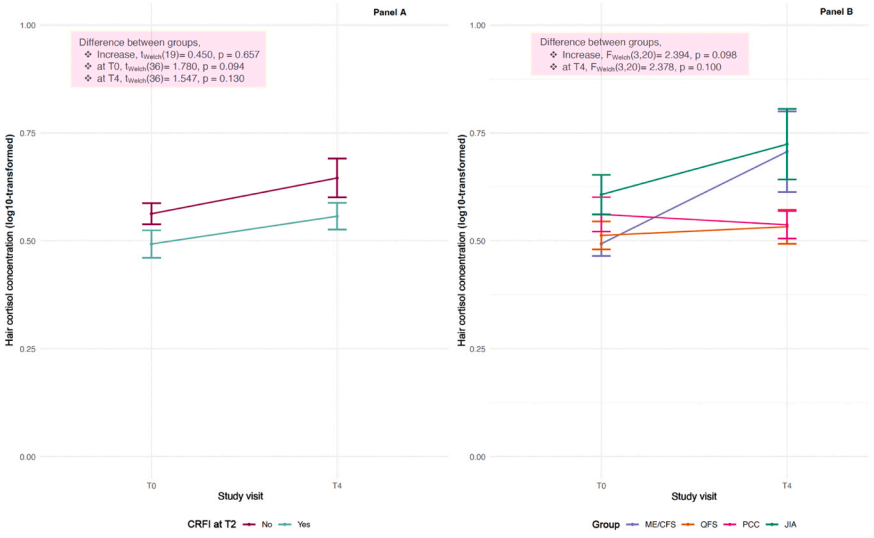

Fig. 3. HCC increase during the RCT. *Note. Presented are the average increases in hair cortisol concentration (HCC) from study visit T0 (baseline visit RCT) to T4 (final study visit RCT) with standard error. Panel A shows the comparison of HCC increase in patients with (n=10) and without (n=34) clinically relevant fatigue improvement (CRFI), including cross-sectional comparisons at T0 and T4. Panel B shows the same comparisons between the patient groups ME/CFS (n=9), QFS (n=15), PCC (n=7), and JIA (n=13).*

Although previous research on cortisol in blood, urine, or saliva has identified multiple moderators of cortisol concentration in ME/CFS (Papadopoulos and Cleare, 2012), the present study found that only the diagnoses ME/CFS and QFS, BMI, and CFS symptoms (as measured with the RCADS) were associated with HCC. Perhaps some of the previously identified variables are only relevant to ME/CFS, rather than ME/CFS, QFS, PCC and JIA combined, or only to cortisol *in the moment* instead of *long-term*. In addition, we did not find that baseline HCC values predicted fatigue improvement during the trial, which is in line with the adolescent study by Nijhof et al (Nijhof et al., 2014). Unlike in the adolescent study, HCC did not increase after clinically relevant fatigue improvement in our RCT – as HCC increased regardless of fatigue improvement. Perhaps other aspects of the disease improved (e.g., sleep, pain, physical or mental activity, mental well-being) or situational aspects changed (i.e., part of this study was conducted during the COVID-pandemic in which societal restrictions enforced by the government were fluctuating). Nevertheless, more research is needed to explain increases in HCC.

This study faced a couple of limitations, of which some have already been mentioned such as the relatively small PCC group, and our measurement of CFS symptoms. However, dividing the RCADS subscale 'low mood' into two new subscales to measure CFS symptoms and depressive symptoms separately might also be considered a strength, given that types of depression have been linked to lower or higher cortisol concentration (Papadopoulos and Cleare, 2012; Herane-Vives et al., 2020). Part of this study was also limited by the fact that we did not have access to BMI data of the control group. As BMI was associated with HCC in patients, it remains the question whether this association would have sustained with control data included. Another limitation is the lack of an additional HCC measurement. As HCC values represented the average cortisol exposure in the last three months, our final measurement at T4 only depicted HCC in the months after the first intervention. It is possible that we would have observed significant differences between patients with and without clinically relevant fatigue improvement (CRFI) (Fig. 3A) or between patient groups (Fig. 3B) if we had an additional measurement at least three months after the entire RCT had finished. The final limitations concern statistical power. We did not conduct an a priori power calculation and instead relied on a post-hoc power calculation, a limitation that could have been avoided by pre-registering this study. However, as the current study was part of a larger research project (Vroegindeweij et al., 2022), it would not have been possible to recruit a larger sample size. The sample size prevented us from considering a greater number of covariates in all analyses and may have resulted in missed effects, particularly in the CRFI analyses with data from 44 patients.

Ultimately, the role of cortisol in ME/CFS remains unclear. Many studies are required to establish consensus on the presence or absence of lower HCC in patients with ME/CFS compared to controls, preferably with more replicated study designs. If the presence can be established, research needs to focus on the meaning of lower HCC in ME/CFS (e.g., is it a symptom, a consequence of the disease, or a biomarker indicating disease subtype). In addition, future research should continuously include other chronic fatigue syndromes like QFS and PCC. Thus far, the aetiology and pathophysiology of ME/CFS, QFS, and PCC is largely unknown. The large overlap in symptomatology has led to a generalized approach to viewing and managing the diagnoses and if we continue to find similarities between the diagnoses, that might be the best fitting approach. However, if differences can be established, we create the opportunity to derive a more detailed understanding of each diagnosis on its own.

To conclude, this study found that HCC was lower in adolescent to young adult patients with ME/CFS and QFS as compared to controls. Overall, there was a negative association between HCC and the presence of CFS symptoms, except in the QFS group. HCC increased significantly during the RCT, regardless of fatigue improvement. To understand the role of lower cortisol in chronic fatigue syndromes like ME/CFS, QFS, and possibly PCC, more research is required.

CRediT authorship contribution statement

Nico M. Wulffraat: Writing – review & editing, Validation, Supervision, Funding acquisition, Conceptualization. **Elise M. van de Putte:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Sanne L. Nijhof:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization. **Joost F. Swart:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization. **Sjoerd A. A. van den Berg:** Writing – review & editing, Software, Resources, Data curation. **Niels Eijkelkamp:** Writing – review & editing, Validation, Methodology. **Anouk Vroegindeweij:** Writing – original draft, Project administration, Methodology, Investigation, Formal analysis.

Declaration of Competing Interest

The authors have no conflict of interest to report.

Data availability

With publication, all data collected in the present study will be made available to others upon reasonable request, including (deidentified) individual participant data and a data dictionary defining each field in the data set. Requests should be directed to both JFS (j.f.swart@umcutrecht.nl) and SLN (s.l.nijhof@umcutrecht.nl). The data will be shared after approval of a proposal, with a signed data access agreement.

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Author contributors

The study was conceptualised by JFS, SLN, EMP, and NMW. AV conducted the research, supervised by JFS, SLN, EMP, and NMW. SVDB was responsible for laboratory hair sample assessments and provided the HCC data. AV wrote the analytical code and performed the analyses with the HCC data. AV wrote the manuscript under supervision of/revision by all co-authors. All authors could access the underlying data of the study, interpreted data, provided critical review of the manuscript, approved the final version, and were responsible for the decision to submit for publication.

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