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Hair cortisol change at COVID-19 pandemic onset predicts burnout among health personnel

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ABSTRACT

Background: The COVID-19 pandemic has put chronic pressure on worldwide healthcare systems. While the literature regarding the prevalence of psychological distress and associated risk factors among healthcare workers facing COVID-19 has exploded, biological variables have been mostly overlooked.

Methods: 467 healthcare workers from Quebec, Canada, answered an electronic survey covering various risk factors and mental health outcomes three months after the onset of the COVID-19 pandemic. Of them, 372 (80%) provided a hair sample, providing a history of cortisol secretion for the three months preceding and following the pandemic's start. We used multivariable regression models and a receiver operating characteristic curve to study hair cortisol as a predictor of burnout and psychological health, together with individual, occupational, social, and organizational factors.

Results: As expected, hair cortisol levels increased after the start of the pandemic, with a median relative change of 29% (IQR = 3–59%, $p < 0.0001$). There was a significant association between burnout status and change in cortisol, with participants in the second quarter of change having lower odds of burnout. No association was found between cortisol change and post-traumatic stress disorder, anxiety, and depression symptoms. Adding cortisol to individual-occupational-socio-organizational factors noticeably enhanced our burnout logistic regression model's predictability.

Conclusion: Change in hair cortisol levels predicted burnout at three months in health personnel at the onset of the COVID-19 pandemic. This non-invasive biological marker of the stress response could be used in further clinical or research initiatives to screen high-risk individuals to prevent and control burnout in health personnel facing an important stressor.

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1. Introduction

The COVID-19 pandemic has put high pressure on healthcare systems worldwide and accentuated the healthcare workers' burden (Arshid et al., 2020; World Health Organization, 2021). In this population, burnout rates increased from 30% before the pandemic (Canadian Medical Association, 2018; Poncet et al., 2007) to 50% (Azoulay et al., 2020; Cantu and Thomas, 2020; Cyr et al., 2021; Duarte et al., 2020; Morgantini et al., 2020) per COVID-19 pandemic, while post-traumatic stress disorder (PTSD), anxiety, and depression rates seemed to remain stable (Cai et al., 2020; Chew et al., 2020; Cyr et al., 2021; Du et al., 2020; Magnavita et al., 2020; Wang et al., 2020; Zhang et al., 2020). Studies have revealed that COVID-19 direct care, perceived lack of protection to manage the risks of virus transmission, work interfering with family life, being female and a nurse were associated with higher psychological distress, defined as either burnout, stress, PTSD, anxiety, or depression self-rated symptoms (Morgantini et al., 2020; Sirois and Owens, 2020). In a previous study, our group focused on eight modifiable variables as potential predictors of mental health issues covering individual (resilience), occupational (workload), social (satisfaction of social support), and organizational factors (access to simulation technique, mental health services, accessibility of personal protective equipment [PPE], feeling of security using PPE, perceived organizational support). We found that higher resilience and perceived organizational support were associated with better outcomes regarding burnout, PTSD, anxiety, and depression (Cyr et al., 2021).

While the prevalence of psychological distress and associated risk factors among healthcare workers during the COVID-19 pandemic has been well covered (Pappa et al., 2020; Troglio da Silva and Neto, 2021), biological variables have been mostly overlooked. Moreover, no study has systematically combined biological variables with psycho-socio-organizational factors to predict mental health outcomes in response to COVID-19. This approach is of interest as the pandemic is a significant stressor for many healthcare workers and may therefore impact their stress hormone levels (Thau et al., 2021). In addition to insight into underlying psychopathological mechanisms, biomarkers can be helpful for both risk stratification (e.g., which individual is at increased risk of developing a disease) and treatment response (e.g., which individual has a greater probability of responding to an intervention) (Burke et al., 2005; Holsboer, 2000; Karlen et al., 2011; Luo et al., 2012; Meewisse et al., 2007; Sauve et al., 2007; Steudte et al., 2013, 2011; Vreeburg et al., 2009; Wester and van Rossum, 2015).

The literature regarding the association between the stress hormone cortisol and burnout, or psychopathology, is vast and has yielded inconsistent results. A recent systematic review (Rothe et al., 2020) suggested that the observed heterogeneity was mainly due to the lack of studies that have tested cortisol levels in burnout patients and to the highly disparate methods used to assess cortisol. Although a definite conclusion is difficult to ascertain, results tend to show a decrease in cortisol secretion in patients with burnout (Kakiashvili et al., 2013). A few studies have verified cortisol levels and burnout regarding stressful situations present before the pandemic in healthcare workers. In the following two studies (Fernandez-Sanchez et al., 2018; Wendsche et al., 2020), an increase in cortisol was found in healthcare workers suffering from burnout. These results are surprising since they go against the discussed tendency to decrease cortisol levels in burnout patients and thus further emphasize the heterogeneity of findings. Regarding the psychopathologies, the current state of knowledge points toward higher cortisol levels for depressed patients (Staufenbiel et al., 2013) and levels modulated by time since traumatization for PTSD (Wester and van Rossum, 2015). Results are not as clear regarding patients with anxiety (Elnazer and Baldwin, 2014). Cortisol levels can be measured in blood, urine, saliva, and hair. As opposed to other sample types, hair is not subject to diurnal variation (Russell et al., 2012; Wester and van Rossum, 2015) and provides a picture of long-term exposure to systemic cortisol. As hair grows on average one centimeter (cm) per month, a

3-cm hair measurement represents the accumulation of cortisol over the previous three months (Greff et al., 2019; Wester and van Rossum, 2015).

In more than one thousand published studies on healthcare workers' mental health during the COVID-19 pandemic, we found two that examined cortisol levels. An Argentinian team (Ibar et al., 2021) measured 3-cm hair cortisol concentrations, perceived stress, social support, and burnout in 234 healthcare workers. The 28 participants (12%) with burnout had significantly higher hair cortisol levels than those without burnout. The authors did not measure other mental health endpoints such as PTSD, anxiety, or depression, nor did they measure pre-pandemic baseline cortisol levels, leaving unanswered the impact of change in cortisol levels at the onset of the pandemic. The second study analyzed cortisol concentration accumulated in 6 cm of hair from 67 Slovak female nurses during the pandemic, with sample collection performed approximately three months after the start of the pandemic, from June 8 to July 8, 2020. The researchers found an increase in hair cortisol levels following the onset of the pandemic, but no association with perceived stress, social support, or sleep quality.

We believe it is essential to combine biopsychosocial and organizational variables to gain an integrative view of the complex phenomenon of organizational psychological health during high-stress periods. This approach provides access to knowledge about the relative importance of each factor and the possible interactions between factors, generates more precise theoretical frameworks, and guides future intervention outcomes, in line with personalized medicine (Di Sanzo et al., 2017; Goetz and Schork, 2018; Wium-Andersen et al., 2017). The objectives of the present study were to 1) evaluate the association between hair cortisol (three-month pre-post-pandemic onset, and relative change in cortisol levels), burnout, PTSD, anxiety, and depression in healthcare workers facing the COVID-19 pandemic; and 2) evaluate the impact of adding a biological variable (hair cortisol) to our initial model that included individual, occupational, social, and organizational factors (Cyr et al., 2021). More precisely, we tested whether adding cortisol to our model improves its predictive capacity and/or moderates the associations between the protective factors and the mental health outcomes we reported previously (Cyr et al., 2021).

2. Methods and materials

2.1. Participants and procedures

The Montreal Heart Institute Ethics Committee approved this observational study on May 14, 2020. We recruited healthcare workers from Quebec, Canada, to complete an electronic survey three months (June 2020) after the COVID-19 pandemic was declared a health emergency in Quebec (March 2020). We also asked participants to provide a hair sample.

2.2. Measures

2.2.1. Psychological questionnaire

Participants responded to an online self-administered validated questionnaire three months after the onset of the pandemic. We assessed the presence of burnout using the two-item Maslach Burnout Inventory criteria (Dyrbye et al., 2014; Loera et al., 2014; West et al., 2009). The severity of depression and anxiety symptoms was measured using the anxiety and depression subscales of the Hospital Anxiety and Depression Scale (Bjelland et al., 2002; Roberge et al., 2013; Zigmond and Snaith, 1983). We used the PTSD Checklist for DSM-5 scale (Ashbaugh et al., 2016; Blevins et al., 2015; Bovin et al., 2016; Wortmann et al., 2016) to score PTSD symptom severity. More detailed information on the questionnaire and scoring can be found in a previous publication (Cyr et al., 2021).

2.2.2. Hair cortisol

We sent participants validated instructions and necessary material to self-collect a hair sample (Ouellet-Morin et al., 2016). We asked participants to collect a 3-cm hair sample, or ideally a 6-cm sample (Lee et al., 2015; Meyer and Novak, 2012; Stalder et al., 2017), between June 7 and 14, 2020. Participants mailed their samples to our research team using a pre-paid envelope, which was then forwarded to the Centre for Studies on Human Stress BioAssay Lab for cortisol analysis. Each 3-cm hair segment was washed in a 15 mL tube with 2.5 mL of isopropanol before mixing. After decanting, the wash cycle was reiterated, and the hair sample was left to dry overnight. Pure methanol (1.5 mL) was added to the sample before the tube was rotated for 24 hours. The samples were then spun down in a microcentrifuge, and 1 mL was aliquoted. The methanol was evaporated at 37 °C under a constant stream of nitrogen. Finally, 0.4 mL of phosphate buffer was injected into the tube before the sample was vortexed for 15 seconds. The reconstituted sample was measured in duplicate using a luminescence immunoassay. The detection range for this assay was between 0.012 and 3.0 µg/dL. The intra- and inter-assay coefficients of variation were 4.69% and 9.34%, respectively. Results are presented in two different concentrations: a concentration per volume (nmol/L, with the multiplication of the results in ug/dL by a factor of 27.59) and a concentration per weight (pg/mg, by applying the following formula: $\frac{[\text{cortisol (µg/dL)}] \times 10\,000 \times \text{volume of reconstitution (µL)}}{\left(\frac{\text{total volume (mL)}}{\text{volume dried down (mL)}}\right) \times \text{sample weight (mg)}}$). All samples were assayed in duplicates, which were later averaged. In the hair collected in mid-June 2020, the distal 3-cm segment reflected cortisol accumulation from mid-December 2019 to mid-March 2020 (three-month pre-pandemic onset), while the proximal 3-cm segment reflected the mid-March to mid-June 2020 period (three-month post-pandemic onset). It was thus possible to calculate the relative change in cortisol between pre- and post-pandemic onset for participants who provided a 6-cm hair sample. We used the following equation: (post-pandemic onset cortisol levels—- pre-pandemic cortisol levels)/(pre-pandemic cortisol levels) multiplied by 100 to report it in percentages. For participants who provided a 3-cm sample, three-month post-pandemic onset cortisol levels could be measured but not pre-pandemic levels (nor change).

Sex, age, ethnicity, body mass index, frequency of hair washing, products in the hair, hair treatments, endocrine disorders, use of endocrine drugs, including the use of hormonal contraceptives, have been reported to potentially modulate hair cortisol levels and different outcomes (Dettenborn et al., 2012; Russell et al., 2012; Stalder and Kirschbaum, 2012; Stalder et al., 2017). Therefore, we collected this information in the same electronic survey as the psychological questionnaire. For details on cortisol-related measures, see Table A1 in the Appendix. For further details on psychological, occupational, and organizational data, refer to Table A1 in our previously published Supplementary Material (Cyr et al., 2021).

2.3. Statistical analysis

Participants' characteristics, including hair cortisol, were summarized using counts and percentages for categorical variables and means +/− SD for continuous variables. For each endpoint (burnout, PTSD, anxiety, and depression), univariable logistic (or linear) regression models were first fitted using cortisol measures (pre-cortisol, post-cortisol or relative change of cortisol) as the independent variable. The unadjusted odds ratio and unadjusted regression coefficients are presented with 95% confidence intervals. Pre-specified adjustment variables (sex, age, ethnicity, body mass index, frequency of hair washing, products in the hair, hair treatments, endocrine disorders, use of endocrine drugs, oral contraceptive or hormone replacement therapy) showing a p-value lower than 0.2 in univariable model with the endpoints were added in the model using the stepwise procedure. The criteria for an adjustment variable to stay in the final model was a significance level of 0.1. This last step with adjustment variables was only considered when there was a statistically significant association between an endpoint and a cortisol measure. The adjusted odds ratio for logistic regressions and adjusted coefficients for linear regressions were presented with 95% confidence intervals. We verified the linearity assumption with the logit of burnout for logistic regression. We categorized variables in case the assumption was not met. In particular, the relative change in cortisol was categorized in four quarters (Q) corresponding to ≤ 3%],]3–29%],]29–59%], and > 59% to satisfy the linearity assumption. For linear regressions, we verified the normality of residuals, and no transformation was needed. Analyses were performed with and without outliers to check if the results were the same.

To evaluate the impact of adding a biological variable (hair cortisol) to our initial model, we first verified that it (Cyr et al., 2021) yielded the same results in the "hair-participant" subsample. We also analyzed the distributions of the variables in the two samples to make sure they were similar. We then added hair cortisol and selected adjustment variables to the initial model using a stepwise procedure and keeping variables with a p-value lower than 0.05. We calculated the area under the receiver operating characteristic (ROC) curve (C-statistic) to measure the predictive capacity of our model. Finally, we tested interactions to verify whether relative change of cortisol moderates our previously reported associations between burnout and individual (resilience) or organizational factors (perceived organizational support).

3. Results

3.1. Participants

Of the 467 participants who answered the three-month survey, 372 (80%) provided a hair sample of the minimum length required (3 cm from the scalp; post-pandemic onset hair growth), with 358 of them providing the ideal 6-cm length (pre- and post-pandemic onset hair growth). The present manuscript will focus on the 372 participants, referred to as the "hair-participant" subgroup, to differentiate them from the complete survey cohort (n = 467). Sociodemographic, hair-related data, and the scores on the psychological questionnaire are shown in Table 1. The mean age of participants was 40 years (SD = 9), and the majority were Caucasian (95%) and female (92%). The main participants' work types were non-physician health professionals (e.g., nutritionists, occupational and respiratory therapists; 30%), followed equally by nurses (24%) and physicians (24%). Thirty-eight percent had been involved in direct COVID-19 patient care, and 33% had been reassigned to another task or hospital during the pandemic. Half of the participants (n = 185; 50%) displayed symptoms of burnout, defined as emotional exhaustion or depersonalization, at least once a week. One hundred twenty-eight different participants (35%) showed severe symptoms of one or multiple psychopathologies (24% PTSD, 23% anxiety and 10% depression) on the validated self-reported questionnaires.

3.2. Hair cortisol levels and change at the onset of COVID-19 pandemic

Table 2 presents pre-pandemic and post-pandemic onset hair cortisol levels in both nmol/L and pg/mg, as well as the relative change between these values. The mean pre-pandemic cortisol level was 3.1 (SD = 6.8) nmol/L [26.8 (SD = 58.1) pg/mg], and 3.7 (SD = 9.8) nmol/L post-pandemic onset [32.4 (SD = 84.2) pg/mg]. As expected, hair cortisol levels were higher after the start of the pandemic and increased by a median of 29% (IQR = 3–59%, p < 0.0001). For statistical purposes, we categorized participants by quarters of relative cortisol change, as summarized in Table 3. The proportion of burnout in each quarter is also presented.

3.3. Hair cortisol, burnout, and psychopathologies

Neither pre- nor post-pandemic onset hair cortisol levels were associated with burnout status (p = 0.4; p = 0.4). However, there was a

Table 1

Participants' sociodemographic, hair-related characteristics, and psychological questionnaire scores.

Variables	n (%) or Mean ± SD	All $n = 372$
Female sex	340 (92.4%)	368
Age (years)	40.3 ± 9.1	369
Ethnicity		368
Caucasian	348 (94.6%)	
Other	20 (5.4%)	
Type of work		371
Administrative agent	13 (3.5%)	
Administrator	14 (3.8%)	
Nurse	89 (24.0%)	
Physician	89 (24.0%)	
Resident physician	6 (1.6%)	
Paramedic	9 (2.4%)	
Other health professional	113 (30.5%)	
Beneficiary attendant	8 (2.2%)	
Laboratory technician/technologist	7 (1.9%)	
Other	23 (6.2%)	
Workload in the last month (hours/week)		363
≤ 34	66 (18.2%)	
[35–44]	207 (57.0%)	
[45–54]	56 (15.4%)	
[55–64]	20 (5.5%)	
≥ 65	14 (3.9%)	
Direct COVID care, yes	142 (38.4%)	370
Reassignment, yes	121 (32.8%)	369
Participation in simulation-type practices related to COVID-19, yes	75 (20.3%)	369
Access to mental health help, yes	337 (91.1%)	370
Access to PPE		366
Never, rarely, or sometimes	30 (8.2%)	
Often	88 (24.0%)	
Always	248 (67.8%)	
PPE perception of security		363
Rather in danger or totally at risk	35 (9.6%)	
Pretty safe	276 (76.0%)	
Totally safe	52 (14.3%)	
Mean body mass index (kg/m^2)	26.8 ± 6.2	365
Frequency of hair washing		371
Every day or more than once a day	94 (25.3%)	
Every two days	150 (40.4%)	
Twice a week	98 (26.4%)	
Once a week or less	29 (7.8%)	
Use of hair products, yes	199 (53.6%)	371
Hair coloration/treatment in the last 6 months, yes	166 (44.9%)	370
Medical data		
Endocrinological disorder, yes	26 (7.0%)	371
Use of endocrinological medication, yes	37 (10.0%)	371
Use of oral contraceptive or hormone replacement therapy, yes	150 (42.3%)	355
Psychological data		
Burnout (MBI-2), yes	185 (50.4%)	367
Post-traumatic stress symptoms (PLC-5 score [0–80])	19.5 ± 14.9	367
≥ 31	89 (24.3%)	
Depressive symptoms (HADS-D score [0–21])	5.1 ± 3.8	361
≥ 11	36 (10.0%)	
Anxiety symptoms (HADS-A score [0–21])	7.9 ± 4.0	362
≥ 11	84 (23.2%)	
Resilience (CD-RISC-10 [0–40])	27.6 ± 6.0	369
Satisfaction of social support (SSQ6 [6–36])	28.8 ± 6.0	367
Perceived organizational support (SPOS8 [0-48])	23.0 ±11.6	367

Abbreviations: MBI-2, Maslach Burnout Inventory; PCL-5, PTSD Checklist for DSM-5; HADS-D, Depression subscale of Hospital Anxiety and Depression Scale; HADS-A, Anxiety subscale of Hospital Anxiety and Depression Scale; CD-RISC-10, 10-item Connor-Davidson Resilience Scale; SSQ, Social Support Questionnaire (satisfaction subscale); SPOS, 8-item Survey of Perceived Organizational Support Scale; SD, Standard deviation.

statistically significant association ($p = 0.008$) between burnout and cortisol relative change, with participants in the second quarter (Q2,]3% – 29%]) having lower odds of burnout (Table 4). Compared to this group, participants who had almost no change in cortisol or decreased levels (Q1, ≤ 3%) after the onset of the pandemic had 2.4

Table 2

Mean, standard deviation, and median of participants' hair cortisol levels pre- and post-pandemic onset as well as absolute and relative change between those measures.

	Mean	SD	Median	All $n = 372$
Pre-pandemic onset hair cortisol				358
(nmol/L)	3.13	6.79	1.50	
(pg/mg)	26.75	58.07	12.89	
Post-pandemic onset hair cortisol				372
(nmol/L)	3.70	9.77	1.96	
(pg/mg)	32.36	84.19	16.87	
Hair cortisol change				358
(nmol/L)	0.22	3.64	0.33	
(pg/mg)	1.91	31.26	2.87	
Hair cortisol relative change				358
(%; nmol/L)	38.42%	66.80%	28.87%	
(%; pg/mg)	38.93%	66.13%	29.48%	

Note: 372 participants provided a hair strand of at least 3 cm. Of these, 358 (96%) participants provided a 6-cm hair strand, which allowed the research team to calculate pre-pandemic hair cortisol levels and the change in pre- and post-pandemic onset cortisol levels. The formula used to convert nmol/L to pg/mg is

$$\frac{[cortisol\ (\mu g/dL)]\ \times\ 10\ 000\ \times\ volume\ of\ reconstitution\ (\mu L)}{\left(\frac{total\ volume\ (mL)}{volume\ dried\ down\ (mL)}\right)\ \times\ sample\ weight\ (mg)}.$$

Abbreviation: SD, Standard deviation.

Table 3

Categorization of participants by quarters of hair cortisol relative change ($n = 358$).

Quarter	Hair cortisol relative change	Frequency	Cumulative frequency	Cumulative percent	Proportion of burnout (n=354)
Q1	≤3%	90	90	25.1	57.3%
Q2	]3–29%]	89	179	50.0	36.0%
Q3	]29–59%]	90	269	75.1	59.6%
Q4	>59%	89	358	100.0	50.6%

Note: The 14 missing data represent participants who provided a strand of hair shorter than 6 cm. Proportion of burnout was assessed with MBI-2, Maslach Burnout Inventory, and there were four additional missing data for this questionnaire.

times more odds of burnout ($p = 0.005$); those with a change between 29% and 59% (Q3), 2.6 times more odds of burnout ($p = 0.002$); and those with cortisol change exceeding 59% (Q4), 1.8 times more odds of burnout ($p = 0.051$). This association remained significant after adjusting for ethnicity, use of hair treatments, and endocrine disorder (Table 4, right columns). We repeated the same analysis using PTSD, anxiety, or depression as the dependent variable rather than burnout. There was no significant association between pre-pandemic, post-pandemic or relative cortisol change and the severity of these psychopathologies (Tables A2 and A3). Tables A4–A6 show unadjusted regression coefficients from linear regression between cortisol relative change and three-month PTSD, anxiety, and depressive symptoms.

3.4. Burnout logistic regression model

To begin, we confirmed that the distributions of the variables included in the burnout model were similar in the original sample ($n = 467$) and the "hair-participant" subgroup ($n = 372$). Then, we applied the initial multivariable model for burnout (Cyr et al., 2021), consisting of eight independent variables covering individual-occupational-social-organizational factors. The results remained similar. Indeed, resilience and perceived organizational support continued to be significantly negatively correlated with burnout (Table 5, left-hand columns). The initial model was associated with an area under the ROC curve (C-statistic) of 0.67. When we added relative

Table 4

Unadjusted and adjusted odds ratios, 95% confidence intervals, and *p*-values from multivariable logistic regression analysis for the relative change in hair cortisol and burnout among healthcare workers who provided a 6 cm hair sample.

Variables	Unadjusted (n = 354)				Adjusted (n = 349)			
	OR	95% CI		*p*	OR	95% CI		*p*
Relative cortisol change				0.008				0.01
Q1 vs. Q2	2.39	1.31	4.37	0.005	2.34	1.26	4.36	0.007
Q3 vs. Q2	2.62	1.43	4.80	0.002	2.70	1.44	5.06	0.002
Q4 vs. Q2	1.82	0.997	3.33	0.051	1.98	1.06	3.69	0.03
Ethnicity, Caucasian (yes vs. no)					4.42	1.40	14.03	0.01
Hair treatment (yes vs. no)					0.62	0.40	0.97	0.04
Endocrinological disorder (yes vs. no)					2.21	0.90	5.40	0.08

Note: Relative cortisol change quarters correspondence: Q1, ≤ 3%; Q2, between]3–29%]; Q3, between]29–59%]; Q4, > 59%. Abbreviations: CI, Confidence intervals; OR, Odds ratio; Q, Quarter.

Table 5

Unadjusted and adjusted odds ratios, 95% confidence interval, and *p*-values from multivariable logistic regression analysis for burnout among healthcare workers who provided a 6 cm hair sample.

Variables	Initial model (n = 330)				Initial model + cortisol (n = 326)			
	Unadjusted OR	95% CI		*p*	Adjusted OR	95% CI		*p*
Resilience	0.68	0.52	0.87	0.003	0.67	0.51	0.88	0.003
Social support	0.88	0.69	1.13	0.31	0.88	0.68	1.13	0.31
Workload				0.77				0.87
[35–44] h vs. ≤ 34 h	0.90	0.49	1.65	0.73	0.82	0.43	1.55	0.54
[45–54] h vs. ≤ 34 h	0.92	0.42	2.02	0.83	0.85	0.37	1.96	0.70
[55–64] h vs. ≤ 34 h	0.78	0.23	2.57	0.68	0.62	0.16	2.46	0.49
≥ 65 h vs. ≤ 34 h	2.02	0.53	7.72	0.30	1.43	0.34	5.93	0.63
Perceived organizational support	0.78	0.61	0.995	0.045	0.78	0.61	1.01	0.06
Participation in simulation-type practices related to COVID-19 (yes vs. no)	1.28	0.71	2.32	0.41	1.19	0.63	2.24	0.60
Access to mental health help (yes vs. no)	0.73	0.31	1.71	0.47	0.93	0.38	2.29	0.88
Access to PPE[a]				0.36				0.26
Often vs. never, rarely or sometimes	1.99	0.70	5.67	0.20	2.26	0.74	6.88	0.15
Always vs. never, rarely or sometimes	1.48	0.56	3.96	0.43	1.53	0.54	4.37	0.42
PPE perception of security				0.74				0.69
Pretty safe vs. totally safe	0.80	0.41	1.55	0.50	0.83	0.40	1.71	0.61
Rather in danger or totally at risk vs. totally safe	0.98	0.34	2.83	0.97	1.19	0.38	3.67	0.77
Cortisol relative change								0.03
Q1 vs. Q2					2.40	1.19	4.83	0.01
Q3 vs. Q2					2.58	1.29	5.18	0.008
Q4 vs. Q2					1.81	0.90	3.64	0.10
Ethnicity, Caucasian (yes vs. no)					4.78	1.43	15.91	0.01
Hair treatment (yes vs. no)					0.56	0.34	0.92	0.02
Endocrinological disorder (yes vs. no)					3.84	1.38	10.68	0.01

Note: Adjusted ORs are presented for an increase of one standard deviation (*SD*) for continuous variables (resilience; *SD* = 5.9, social support; *SD* = 5.6, and perceived organizational support; *SD* = 11.7). Relative cortisol change quarters correspondence: Q1, ≤ 3%; Q2, between]3–29%]; Q3, between]29–59%]; Q4, > 59%. Abbreviations: CI, Confidence intervals; OR, Odds ratio; PPE, Personal protective equipment.

[a] Due to small n in some of the original categories, this variable was re-categorized as Always; Often; Never, Rarely or Sometimes.

change in hair cortisol and its adjustment variables, the C-statistic increased to 0.74. In other words, an individual with burnout will have a higher predicted probability than an individual without burnout 74% of the time, using this second model.

We were then interested to know whether the effect of resilience or perceived organizational support on burnout differed depending on the extent of cortisol change. Cortisol change did not moderate the association between burnout status and resilience or perceived organizational support (*p* = 0.77 and *p* = 0.35, respectively).

4. Discussion

We studied the relationship between the pre-post COVID-19 pandemic biological marker of stress (hair cortisol) and individual, occupational, social, and organizational factors on burnout, PTSD, anxiety, and depression among healthcare workers. We found a significant association between burnout status and the relative change in hair cortisol levels following the onset of the COVID-19 pandemic, but not with absolute cortisol levels per se. Our data suggest that a slight relative increase in cortisol levels in response to the pandemic is associated with lower burnout odds than a decrease, a moderate, or a large increase in cortisol levels. The capillary cortisol concentrations found in our study (pre-pandemic onset mean: 26.8 pg/mg, median: 12.9 pg/mg; post-pandemic onset mean: 32.4 pg/mg, median: 16.9 pg/mg) are lower compared to a study conducted on healthcare workers that reported a median concentration of 89 pg/mg for healthcare workers in direct

contact with patients, and 70 pg/mg for workers without direct contact (Ibar et al., 2021). In contrast, they are higher than another study on nurses during the pandemic, whose mean capillary cortisol levels before and during the pandemic were 5.5 pg/mg and 6.7 pg/mg, respectively (Rajcani et al., 2021).

In addition to the vast heterogeneity of published hair cortisol levels, most studies only report absolute levels, not relative change, making the comparison with our study challenging. Schaafsma et al. published a scoping review in 2021 assessing the relation of hair cortisol with work-related stressors in healthy workers (Schaafsma et al., 2021). They found five longitudinal and 17 cross-sectional studies, both study types showing mixed results. There were three cross-sectional studies with burnout as an endpoint. Regarding the two subdomains used to classify burnout in the present study (emotional exhaustion and depersonalization), two of these studies showed positive associations between 3-cm hair cortisol level and burnout and one a non-significant effect. Our 3-cm data align with the non-significant findings, with three-month post-pandemic onset hair cortisol not associated with burnout status ($p = 0.4$). One hypothesis for the non-significant associations regarding absolute hair cortisol levels could be that, faced with the clear onset of a stressor, within-individual change in stress hormone response could be more sensitively correlated with burnout than absolute levels. Another hypothesis could be that hair cortisol analysis, influenced by hair product use, washing frequency, and environmental damage, is not precise enough to capture the difference in absolute levels but sufficient for relative change, as each 6-cm sample has its own control. It should also be noted that the 6-cm hair sample cortisol measure is subject to a washout effect; the 3-cm sample being closer to the scalp, and thus having been there for a shorter time, is less subject to degradation of cortisol (Dettenborn et al., 2012; Meyer and Novak, 2012; Russell et al., 2012). A recent meta-analysis recognized an average decrease of 29% between the first 3 cm hair segment to the second 3 cm hair segment (Stalder et al., 2017). However, some studies have also reported washout levels as low as 6% (Kirschbaum et al., 2009). It is, therefore, necessary to consider this potential washout with caution. Also, we consider that the pandemic context could have reduced the washout of our sample, as we collected the sample in early spring, which reduces the potential effect of UV. Furthermore, we have no reason to believe that the washout effect would differ between individuals. In line with this, we checked the variability of the pre-pandemic and post-pandemic cortisol level measurements and found that the standard deviations were not statistically different (*SD* pre- = 6.7, *SD* post- = 9.7; $p = 0.3$). To reduce the limit of the washout effect, it would have been ideal to sample a 3-cm sample in March 2020 (which would have served as the baseline reflecting the January-March 2020 period) and to take another 3-cm sample in June 2020 (to reflect the cortisol secreted during the first three months of the pandemic). However, this study was launched in response to the COVID, and due to delays in getting Institutional Review Board and gaining access to the population, this method was not possible.

We did not find any significant relation between cortisol change and the severity of the three psychopathologies studied (PTSD, anxiety, and depression). It must be stated that the temporality between cortisol dysregulation and psychological manifestation remains largely misunderstood and may take longer than three months to associate fully. However, other teams also reported no prediction of depressive symptoms through hair cortisol levels (Dowlati et al., 2010; Gerritsen et al., 2019; Herane-Vives et al., 2020a, 2018, 2020b, 2020c; Kuehl et al., 2015; Mayer et al., 2018; Psarraki et al., 2021; Steudte-Schmiedgen et al., 2017). Another explanation for the absence of association between cortisol change and PTSD, anxiety, and depression can be that cortisol may not be an important pathophysiological mechanism underlying these disorders. A recent review summarized six possible biological mechanisms responsible for variations in resilience in healthcare workers facing the COVID-19 pandemic (Rajkumar, 2021a). In addition to the hypothalamic-pituitary-adrenal axis studied in the present paper,

they identified brain neurotransmitters, immune system, neuropeptides, epigenetic and environmental factors as possible mediators. Another lead would be heart rate variability, as it is a known measure of the autonomous nervous system balance (Rajkumar, 2021b), and is reduced in anxiety disorders (Chalmers et al., 2014). Finally, while we did not study the downstream effects of changes in cortisol levels on burnout, Onen Sertoz et al. did, and their results suggest that the serum brain-derived neurotrophic factor circulating biomarkers may be involved (Onen Sertoz et al., 2008).

The area under the ROC curve is a good indicator of the model's reliability and predictive capacity. A C-statistic range from 0.5 to 1, with 0.5 indicating a random model prediction and a C-statistic of 1, representing a perfect concordance (Pencina and D'Agostino, 2015). Adding hair cortisol and the adjustment variables in the new model presented in this study, the C-statistic increased from 0.67 to 0.74, implying a better prediction of burnout when introducing this biomarker in the model. This reinforces the importance of integrating biological to psychosocial and organizational variables in the same study to better understand critical factors driving psychological health during high-stress periods.

We tested for moderation between resilience, perceived organizational support, and cortisol but did not find any effect. In other words, the strength of the established associations was similar for all degrees of cortisol change among participants. By contrast, a study on 45 undergraduate psychology course students examined pre-pandemic salivary cortisol indices on the psychological impact of strict social confinement during the COVID-19 pandemic (Baliyan et al., 2021). They showed that 41% of the variance in during-confinement perceived stress was predicted by total diurnal cortisol release, resilience score, and their interaction. The effect of cortisol was positive for subjects with high resilience and negative for subjects with low resilience. They stated that it "could suggest that an inverted-U shape relationship between cortisol indices and distinct mental health outcomes (…) may emerge under stressful situations", which is in line with our findings on hair cortisol relative change and burnout.

4.1. Limits

Since this study was launched after the onset of the pandemic, we cannot rule out or ascertain that some participants had prior medical or psychiatric conditions (anxiety disorders, major depression, PTSD) which could be associated with altered cortisol release patterns. In our previous paper (Cyr et al., 2021), psychiatric antecedent was included in the pre-specified list of adjustment variables potentially associated with burnout. Although statistically associated with burnout in univariable analysis, it ended up not being statistically significant in our multivariable model (called the "initial" model). Because we are presenting an extension of this initial model in the current manuscript, psychiatric antecedent was not considered a potential adjustment variable. However, we conducted a post-hoc analysis adding psychiatric antecedent as an adjustment variable to our final model and found no association with burnout ($p = 0.29$). We also added the interaction between psychiatric antecedent and relative change in hair cortisol, and again, found that the interaction was not statistically significant ($p = 0.96$). Moreover, by looking at the pre-pandemic literature in a similar population, anxiety and depression rates were surprisingly similar to those we found (Canadian Federation of Nurses Unions, 2020; Canadian Medical Association, 2018). We collected at baseline history of endocrine disorders (7%), use of endocrine medication (10%), and/or hormonal contraceptives (42%). Because we recognize that these variables may affect cortisol levels, we have considered these as adjustment variables in our model to take their effect into account. As per our stepwise regression methodology (adjustment variables which had a p-value < 0.2 were added to our model), taking endocrine medication was the only of these three variables that affected burnout ($p = 0.19$) and relative cortisol change ($p = 0.12$), and was thus added to our model.

We needed a 3- to 6-cm hair sample to measure and calculate cortisol

relative change from the onset of the pandemic. Consequently, female participants may have been more overrepresented in our analyses considering the basal length of their hair compared to men. However, our whole cohort is predominantly female and representative of the local healthcare worker population (Ministère de la Santé et des Services sociaux, 2011). Secondly, sex was not associated with burnout and was not included in our model. Thus, over-representation of females does not seem to be a factor limiting our results' internal or external validity. Otherwise, our sample appears representative in terms of age and marital status compared to local nurses, who accounted for one-quarter of our sample (Canadian Federation of Nurses Unions, 2020). Any external application of our results should be made with caution, particularly in countries where Caucasians are not a majority of healthcare workers. Finally, "non-physician health professionals," including nutritionists, occupational and respiratory therapists, seemed overrepresented in our study. Since work type was not significantly associated with burnout, we do not expect this to mitigate the external validity of our study.

Adding cortisol with its adjustment variables (ethnicity, hair treatment, and endocrine disorder) slightly modified our previously published model, with perceived organizational support only reaching a trend level ($p = 0.06$). A known limit of stepwise multivariable regression models is that as more variables are included, the more likely it is that fortuitous statistical associations can be found (Smith, 2018). To mitigate this limitation, we made sure to limit and pre-specify our independent and adjustment variables. Forcing pre-specified predictors into the models allowed the model to consider predictors based on knowledge rather than mathematical criteria alone.

5. Conclusion and future directions

Change in hair cortisol levels predicted burnout at three months in health personnel at the onset of the COVID-19 pandemic. This emerging non-invasive biological marker of the stress response could be used in further clinical or research initiatives to screen high-risk individuals to prevent and control burnout in health personnel facing an important stressor. To prevent burnout, healthcare organizations may benefit from providing an optimal work environment that promotes healthcare workers' resilience, particularly for those with at-risk cortisol changes. More studies, ideally longitudinal ones, integrating bio-psycho-socio-organizational factors are needed to better understand the complex phenomenon of psychological health of workers facing high-stress periods.

CRediT authorship contribution statement

Marie-Joelle Marcil: Data curation, Funding acquisition, Visualization, Writing – review & editing. **Samuel Cyr:** Data curation, Funding acquisition, Methodology, Visualization, Writing – review & editing. **Marie-France Marin:** Conceptualization, Funding acquisition, Writing – review & editing. **Camille Rosa:** Data curation, Formal analysis, Funding acquisition, Validation, Writing – original draft, Writing – review & editing. **Jean-Claude Tardif:** Conceptualization, Funding acquisition, Writing – review & editing. **Stéphane Guay:** Conceptualization, Funding acquisition, Writing – review & editing. **Marie-Claude Guertin:** Formal analysis, Funding acquisition, Methodology, Writing – original draft, Writing – review & editing. **Christine Genest:** Funding acquisition, Writing – review & editing. **Jacques Forest:** Funding acquisition, Writing – review & editing. **Patrick Lavoie:** Funding acquisition, Writing – review & editing. **Mélanie Labrosse:** Funding acquisition, Writing – review & editing. **Alain Vadeboncoeur:** Funding acquisition, Writing – review & editing. **Shaun Selcer:** Funding acquisition, Writing – review & editing. **Simon Ducharme:** Funding acquisition, Writing – review & editing. **Judith Brouillette:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision,

Validation, Visualization, Writing – original draft, Writing – review & editing.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2021.105645.

References

Arshid, M.A., Mumtaz, M., Nazir, R., 2020. Unforeseen challenges to global health system, in particular context to COVID-19 pandemic and health care personnel. Arab J. Basic Appl. Sci. 28, 145–153.

Ashbaugh, A.R., Houle-Johnson, S., Herbert, C., El-Hage, W., Brunet, A., 2016. Psychometric validation of the English and French versions of the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5). PLoS One 11, e0161645.

Azoulay, E., Waele, De, Ferrer, J., Staudinger, R., Borkowska, T., Povoa, M., Iliopoulou, P., Artigas, K., Schaller, A., Hari, S.J., Pellegrini, M.S., Darmon, M., Kesecioglu, M., Cecconi, J., Esicm, M., 2020. Symptoms of burnout in intensive care unit specialists facing the COVID-19 outbreak. Ann. Intensive Care 10, 110.

Baliyan, S., Cimadevilla, J.M., de Vidania, S., Pulopulos, M.M., Sandi, C., Venero, C., 2021. Differential susceptibility to the impact of the COVID-19 pandemic on working memory, empathy, and perceived stress: the role of cortisol and resilience. Brain Sci. 11.

Bjelland, I., Dahl, A.A., Haug, T.T., Neckelmann, D., 2002. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J. Psychosom. Res. 52, 69–77.

Blevins, C.A., Weathers, F.W., Davis, M.T., Witte, T.K., Domino, J.L., 2015. The Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5): development and initial psychometric evaluation. J. Trauma Stress 28, 489–498.

Bovin, M.J., Marx, B.P., Weathers, F.W., Gallagher, M.W., Rodriguez, P., Schnurr, P.P., Keane, T.M., 2016. Psychometric properties of the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (PCL-5) in veterans. Psychol. Assess. 28, 1379–1391.

Burke, H.M., Davis, M.C., Otte, C., Mohr, D.C., 2005. Depression and cortisol responses to psychological stress: a meta-analysis. Psychoneuroendocrinology 30, 846–856.

Cai, Q., Feng, H., Huang, J., Wang, M., Wang, Q., Lu, X., Xie, Y., Wang, X., Liu, Z., Hou, B., Ouyang, K., Pan, J., Li, Q., Fu, B., Deng, Y., Liu, Y., 2020. The mental health of frontline and non-frontline medical workers during the coronavirus disease 2019 (COVID-19) outbreak in China: a case-control study. J. Affect. Disord. 275, 210–215.

Canadian Federation of Nurses Unions, 2020. Mental Disorder Symptoms Among Nurses in Canada.

Canadian Medical Association, 2018. CMA NATIONAL PHYSICIAN HEALTH SURVEY: A National Snapshot. Canadian Medical Association.

Cantu, L., Thomas, L., 2020. Baseline well-being, perceptions of critical incidents, and openness to debriefing in community hospital emergency department clinical staff before COVID-19, a cross-sectional study. BMC Emerg. 20, 82.

Chalmers, J.A., Quintana, D.S., Abbott, M.J., Kemp, A.H., 2014. Anxiety disorders are associated with reduced heart rate variability: a meta-analysis. Front. Psychiatry 5, 80.

Chew, N.W.S., Lee, G.K.H., Tan, B.Y.Q., Jing, M., Goh, Y., Ngiam, N.J.H., Yeo, L.L.L., Ahmad, A., Ahmed Khan, F., Napolean Shanmugam, G., Sharma, A.K., Komalkumar, R.N., Meenakshi, P.V., Shah, K., Patel, B., Chan, B.P.L., Sunny, S., Chandra, B., Ong, J.J.Y., Paliwal, P.R., Wong, L.Y.H., Sagayanathan, R., Chen, J.T., Ying Ng, A.Y., Teoh, H.L., Tsivgoulis, G., Ho, C.S., Ho, R.C., Sharma, V.K., 2020. A multinational, multicentre study on the psychological outcomes and associated physical symptoms amongst healthcare workers during COVID-19 outbreak. Brain Behav. Immun. 88, 559–565.

Cyr, S., Marcil, M.J., Marin, M.F., Tardif, J.C., Guay, S., Guertin, M.C., Rosa, C., Genest, C., Forest, J., Lavoie, P., Labrosse, M., Vadeboncoeur, A., Selcer, S., Ducharme, S., Brouillette, J., 2021. Factors associated with burnout, post-traumatic stress and anxio-depressive symptoms in healthcare workers 3 months into the COVID-19 pandemic: an observational study. Front. Psychiatry 12, 668278.

Dettenborn, L., Tietze, A., Kirschbaum, C., Stalder, T., 2012. The assessment of cortisol in human hair: associations with sociodemographic variables and potential confounders. Stress 15, 578–588.

Di Sanzo, M., Cipolloni, L., Borro, M., La Russa, R., Santurro, A., Scopetti, M., Simmaco, M., Frati, P., 2017. Clinical applications of personalized medicine: a new paradigm and challenge. Curr. Pharm. Biotechnol. 18, 194–203.

Dowlati, Y., Herrmann, N., Swardfager, W., Thomson, S., Oh, P.I., Van Uum, S., Koren, G., Lanctot, K.L., 2010. Relationship between hair cortisol concentrations and depressive symptoms in patients with coronary artery disease. Neuropsychiatr. Dis. Treat. 6, 393–400.

Du, J., Dong, L., Wang, T., Yuan, C., Fu, R., Zhang, L., Liu, B., Zhang, M., Yin, Y., Qin, J., Bouey, J., Zhao, M., Li, X., 2020. Psychological symptoms among frontline healthcare workers during COVID-19 outbreak in Wuhan. Gen. Hosp. Psychiatry 67, 144–145.

Duarte, I., Teixeira, A., Castro, L., Marina, S., Ribeiro, C., Jacome, C., Martins, V., Ribeiro-Vaz, I., Pinheiro, H.C., Silva, A.R., Ricou, M., Sousa, B., Alves, C., Oliveira, I., Silva, P., Nunes, R., Serrao, C., 2020. Burnout among Portuguese healthcare workers during the COVID-19 pandemic. BMC Public Health 20, 1885.

Dyrbye, L.N., West, C.P., Satele, D., Boone, S., Tan, L., Sloan, J., Shanafelt, T.D., 2014. Burnout among U.S. medical students, residents, and early career physicians relative to the general U.S. population. Acad. Med. 89, 443–451.

Elnazer, H.Y., Baldwin, D.S., 2014. Investigation of cortisol levels in patients with anxiety disorders: a structured review. Curr. Top. Behav. Neurosci. 18, 191–216.

Fernandez-Sanchez, J.C., Perez-Marmol, J.M., Blasquez, A., Santos-Ruiz, A.M., Peralta-Ramirez, M.I., 2018. Association between burnout and cortisol secretion, perceived stress, and psychopathology in palliative care unit health professionals. Palliat. Support Care 16, 286–297.

Gerritsen, L., Staufenbiel, S.M., Penninx, B., van Hemert, A.M., Noppe, G., de Rijke, Y.B., van Rossum, E.F.C., 2019. Long-term glucocorticoid levels measured in hair in patients with depressive and anxiety disorders. Psychoneuroendocrinology 101, 246–252.

Goetz, L.H., Schork, N.J., 2018. Personalized medicine: motivation, challenges, and progress. Fertil. Steril. 109, 952–963.

Greff, M.J.E., Levine, J.M., Abuzgaia, A.M., Elzagallaai, A.A., Rieder, M.J., van Uum, S.H. M., 2019. Hair cortisol analysis: an update on methodological considerations and clinical applications. Clin. Biochem. 63, 1–9.

Herane-Vives, A., Arnone, D., de Angel, V., Papadopoulos, A., Wise, T., Alameda, L., Chua, K.C., Young, A.H., Cleare, A.J., 2020a. Cortisol levels in unmedicated patients with unipolar and bipolar major depression using hair and saliva specimens. Int. J. Bipolar Disord. 8, 15.

Herane-Vives, A., de Angel, V., Papadopoulos, A., Wise, T., Chua, K.C., Strawbridge, R., Castillo, D., Arnone, D., Young, A.H., Cleare, A.J., 2018. Short-term and long-term measures of cortisol in saliva and hair in atypical and non-atypical depression. Acta Psychiatr. Scand. 137, 216–230.

Herane-Vives, A., Papadopoulos, A., de Angel, V., Chua, K.C., Soto, L., Chalder, T., Young, A.H., Cleare, A.J., 2020b. Cortisol levels in chronic fatigue syndrome and atypical depression measured using hair and saliva specimens. J. Affect Disord. 267, 307–314.

Herane-Vives, A., Young, A.H., Wise, T., Aguirre, J., de Angel, V., Arnone, D., Papadopoulos, A., Cleare, A.J., 2020c. Comparison of short-term (saliva) and long-term (hair) cortisol levels in out-patients with melancholic and non-melancholic major depression. BJPsych Open 6, e41.

Holsboer, F., 2000. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology 23, 477–501.

Ibar, C., Fortuna, F., Gonzalez, D., Jamardo, J., Jacobsen, D., Pugliese, L., Giraudo, L., Ceres, V., Mendoza, C., Repetto, E.M., Reboredo, G., Iglesias, S., Azzara, S., Berg, G., Zopatti, D., Fabre, B., 2021. Evaluation of stress, burnout and hair cortisol levels in health workers at a University Hospital during COVID-19 pandemic. Psychoneuroendocrinology 128, 105213.

Kakiashvili, T., Leszek, J., Rutkowski, K., 2013. The medical perspective on burnout. Int. J. Occup. Med. Environ. Health 26, 401–412.

Karlen, J., Ludvigsson, J., Frostell, A., Theodorsson, E., Faresjo, T., 2011. Cortisol in hair measured in young adults - a biomarker of major life stressors? BMC Clin. Pathol. 11, 12.

Kirschbaum, C., Tietze, A., Skoluda, N., Dettenborn, L., 2009. Hair as a retrospective calendar of cortisol production-Increased cortisol incorporation into hair in the third trimester of pregnancy. Psychoneuroendocrinology 34, 32–37.

Kuehl, L.K., Hinkelmann, K., Muhtz, C., Dettenborn, L., Wingenfeld, K., Spitzer, C., Kirschbaum, C., Wiedemann, K., Otte, C., 2015. Hair cortisol and cortisol awakening response are associated with criteria of the metabolic syndrome in opposite directions. Psychoneuroendocrinology 51, 365–370.

Lee, D.Y., Kim, E., Choi, M.H., 2015. Technical and clinical aspects of cortisol as a biochemical marker of chronic stress. BMB Rep. 48, 209–216.

Loera, B., Converso, D., Viotti, S., 2014. Evaluating the psychometric properties of the Maslach Burnout Inventory-Human Services Survey (MBI-HSS) among Italian nurses: how many factors must a researcher consider? PLoS One 9, e114987.

Luo, H., Hu, X., Liu, X., Ma, X., Guo, W., Qiu, C., Wang, Y., Wang, Q., Zhang, X., Zhang, W., Hannum, G., Zhang, K., Liu, X., Li, T., 2012. Hair cortisol level as a biomarker for altered hypothalamic-pituitary-adrenal activity in female adolescents with posttraumatic stress disorder after the 2008 Wenchuan earthquake. Biol. Psychiatry 72, 65–69.

Magnavita, N., Tripepi, G., Di Prinzio, R.R., 2020. Symptoms in health care workers during the COVID-19 epidemic. A cross-sectional survey. Int. J. Environ. Res. Public Health 17, 20.

Mayer, S.E., Lopez-Duran, N.L., Sen, S., Abelson, J.L., 2018. Chronic stress, hair cortisol and depression: a prospective and longitudinal study of medical internship. Psychoneuroendocrinology 92, 57–65.

Meewisse, M.L., Reitsma, J.B., de Vries, G.J., Gersons, B.P., Olff, M., 2007. Cortisol and post-traumatic stress disorder in adults: systematic review and meta-analysis. Br. J. Psychiatry 191, 387–392.

Meyer, J.S., Novak, M.A., 2012. Minireview: Hair cortisol: a novel biomarker of hypothalamic-pituitary-adrenocortical activity. Endocrinology 153, 4120–4127.

Ministère de la Santé et des Services sociaux, 2011. Emplois selon la catégorie professionnelle - Statistiques de santé et de bien être selon le sexe – Tout le Québec – Professionnels de la santé. Gouv.qc.ca.

Morgantini, L.A., Naha, U., Wang, H., Francavilla, S., Acar, O., Flores, J.M., Crivellaro, S., Moreira, D., Abern, M., Eklund, M., Vigneswaran, H.T., Weine, S.M., 2020. Factors contributing to healthcare professional burnout during the COVID-19 pandemic: a rapid turnaround global survey. PLoS One 15, e0238217.

Onen Sertoz, O., Tolga Binbay, I., Koylu, E., Noyan, A., Yildirim, E., Elbi Mete, H., 2008. The role of BDNF and HPA axis in the neurobiology of burnout syndrome. Prog. Neuropsychopharmacol. Biol. Psychiatry 32, 1459–1465.

Ouellet-Morin, I., Laurin, M., Robitaille, M.P., Brendgen, M., Lupien, S.J., Boivin, M., Vitaro, F., 2016. Validation of an adapted procedure to collect hair for cortisol determination in adolescents. Psychoneuroendocrinology 70, 58–62.

Pappa, S., Ntella, V., Giannakas, T., Giannakoulis, V.G., Papoutsi, E., Katsaounou, P., 2020. Prevalence of depression, anxiety, and insomnia among healthcare workers during the COVID-19 pandemic: a systematic review and meta-analysis. Brain Behav. Immun. 88, 901–907.

Pencina, M.J., D'Agostino Sr., R.B., 2015. Evaluating discrimination of risk prediction models: the C Statistic. JAMA 314, 1063–1064.

Poncet, M.C., Toullic, P., Papazian, L., Kentish-Barnes, N., Timsit, J.F., Pochard, F., Chevret, S., Schlemmer, B., Azoulay, E., 2007. Burnout syndrome in critical care nursing staff. Am. J. Respir. Crit. Care Med. 175, 698–704.

Psarraki, E.E., Kokka, I., Bacopoulou, F., Chrousos, G.P., Artemiadis, A., Darviri, C., 2021. Is there a relation between major depression and hair cortisol? A systematic review and meta-analysis. Psychoneuroendocrinology 124, 105098.

Rajcani, J., Vytykacova, S., Solarikova, P., Brezina, I., 2021. Stress and hair cortisol concentrations in nurses during the first wave of the COVID-19 pandemic. Psychoneuroendocrinology 129, 105245.

Rajkumar, R.P., 2021a. Harnessing the neurobiology of resilience to protect the mental well-being of healthcare workers during the COVID-19 pandemic. Front. Psychol. 12.

Rajkumar, R.P., 2021b. Harnessing the neurobiology of resilience to protect the mental well-being of healthcare workers during the COVID-19 pandemic. Front. Psychol. 12, 621853.

Roberge, P., Dore, I., Menear, M., Chartrand, E., Ciampi, A., Duhoux, A., Fournier, L., 2013. A psychometric evaluation of the French Canadian version of the Hospital Anxiety and Depression Scale in a large primary care population. J. Affect Disord. 147, 171–179.

Rothe, N., Steffen, J., Penz, M., Kirschbaum, C., Walther, A., 2020. Examination of peripheral basal and reactive cortisol levels in major depressive disorder and the burnout syndrome: a systematic review. Neurosci. Biobehav Rev. 114, 232–270.

Russell, E., Koren, G., Rieder, M., Van Uum, S., 2012. Hair cortisol as a biological marker of chronic stress: current status, future directions and unanswered questions. Psychoneuroendocrinology 37, 589–601.

Sauve, B., Koren, G., Walsh, G., Tokmakejian, S., Van Uum, S.H., 2007. Measurement of cortisol in human hair as a biomarker of systemic exposure. Clin. Invest. Med. 30, E183–E191.

Schaafsma, F.G., Hulsegge, G., de Jong, M.A., Overvliet, J., van Rossum, E.F.C., Nieuwenhuijsen, K., 2021. The potential of using hair cortisol to measure chronic stress in occupational healthcare; a scoping review. J. Occup. Health 63, e12189.

Sirois, F.M., Owens, J., 2020. Factors associated with psychological distress in health-care workers during an infectious disease outbreak: a rapid systematic review of the evidence. Front. Psychiatry 11, 589545.

Smith, G., 2018. Step away from stepwise. J. Big Data 5, 32.

Stalder, T., Kirschbaum, C., 2012. Analysis of cortisol in hair–state of the art and future directions. Brain Behav. Immun. 26, 1019–1029.

Stalder, T., Steudte-Schmiedgen, S., Alexander, N., Klucken, T., Vater, A., Wichmann, S., Kirschbaum, C., Miller, R., 2017. Stress-related and basic determinants of hair cortisol in humans: a meta-analysis. Psychoneuroendocrinology 77, 261–274.

Staufenbiel, S.M., Penninx, B.W., Spijker, A.T., Elzinga, B.M., van Rossum, E.F., 2013. Hair cortisol, stress exposure, and mental health in humans: a systematic review. Psychoneuroendocrinology 38, 1220–1235.

Steudte-Schmiedgen, S., Wichmann, S., Stalder, T., Hilbert, K., Muehlhan, M., Lueken, U., Beesdo-Baum, K., 2017. Hair cortisol concentrations and cortisol stress reactivity in generalized anxiety disorder, major depression and their comorbidity. J. Psychiatr. Res. 84, 184–190.

Steudte, S., Kirschbaum, C., Gao, W., Alexander, N., Schonfeld, S., Hoyer, J., Stalder, T., 2013. Hair cortisol as a biomarker of traumatization in healthy individuals and posttraumatic stress disorder patients. Biol. Psychiatry 74, 639–646.

Steudte, S., Stalder, T., Dettenborn, L., Klumbies, E., Foley, P., Beesdo-Baum, K., Kirschbaum, C., 2011. Decreased hair cortisol concentrations in generalised anxiety disorder. Psychiatry Res. 186, 310–314.

Thau, L., Gandhi, J., Sharma, S., 2021. Physiology, Cortisol, StatPearls. StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC., Treasure Island (FL).

Troglio da Silva, F.C., Neto, M.L.R., 2021. Psychiatric disorders in health professionals during the COVID-19 pandemic: a systematic review with meta-analysis. J. Psychiatr. Res. 140, 474–487.

Vreeburg, S.A., Hoogendijk, W.J., van Pelt, J., Derijk, R.H., Verhagen, J.C., van Dyck, R., Smit, J.H., Zitman, F.G., Penninx, B.W., 2009. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. Arch. Gen. Psychiatry 66, 617–626.

Wang, L.Q., Zhang, M., Liu, G.M., Nan, S.Y., Li, T., Xu, L., Xue, Y., Zhang, M., Wang, L., Qu, Y.D., Liu, F., 2020. Psychological impact of coronavirus disease (2019) (COVID-19) epidemic on medical staff in different posts in China: a multicenter study. J. Psychiatr. Res. 129, 198–205.

Wendsche, J., Ihle, A., Wegge, J., Penz, M.S., Kirschbaum, C., Kliegel, M., 2020. Prospective associations between burnout symptomatology and hair cortisol. Int. Arch. Occup. Environ. Health 93, 779–788.

West, C.P., Dyrbye, L.N., Sloan, J.A., Shanafelt, T.D., 2009. Single item measures of emotional exhaustion and depersonalization are useful for assessing burnout in medical professionals. J. Gen. Intern. Med. 24, 1318–1321.

Wester, V.L., van Rossum, E.F., 2015. Clinical applications of cortisol measurements in hair. Eur. J. Endocrinol. 173, M1–M10.

Wium-Andersen, I.K., Vinberg, M., Kessing, L.V., McIntyre, R.S., 2017. Personalized medicine in psychiatry. Nord. J. Psychiatry 71, 12–19.

World Health Organization, 2021. The impact of COVID-19 on global health goals, in: Who.int (Ed.).

Wortmann, J.H., Jordan, A.H., Weathers, F.W., Resick, P.A., Dondanville, K.A., Hall-Clark, B., Foa, E.B., Young-McCaughan, S., Yarvis, J.S., Hembree, E.A., Mintz, J., Peterson, A.L., Litz, B.T., 2016. Psychometric analysis of the PTSD Checklist-5 (PCL-5) among treatment-seeking military service members. Psychol. Assess. 28, 1392–1403.

Zhang, W.R., Wang, K., Yin, L., Zhao, W.F., Xue, Q., Peng, M., Min, B.Q., Tian, Q., Leng, H.X., Du, J.L., Chang, H., Yang, Y., Li, W., Shangguan, F.F., Yan, T.Y., Dong, H.Q., Han, Y., Wang, Y.P., Cosci, F., Wang, H.X., 2020. Mental health and psychosocial problems of medical health workers during the COVID-19 epidemic in China. Psychother. Psychosom. 89, 242–250.

Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67, 361–370.