CORTISOL: A POTENTIAL LONG-COVID BIOMARKER IN ADOLESCENTS

by

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The Corona Virus Disease 2019 (COVID-19) pandemic created a public health crisis which, years later, is ongoing yet contained. People are experiencing symptoms of a new condition, termed long-COVID, in which they recover from acute viral distress but continue to have symptoms of fatigue, brain-fog, respiratory distress, changes in taste/smell, and other sickness behaviors for months to years following COVID infection. The latest research shows that patients with long-COVID present very low cortisol concentrations, a stress hormone key in various physiological functions measured in a range of non-invasive and minimally invasive biospecimens. This project examines archival cortisol biospecimens collected before, during, and after the COVID-19 pandemic. The study analyzed data from up to 561 adolescents from the Early Growth and Development Study cohort, with subsamples ranging from 68 to 255 participants depending on COVID-19 diagnosis and symptomatology. We further analyze data from the Early Growth and Development Study, reports of health symptoms, medical records, and a series of assessments throughout the pandemic. Our data analysis shows a moderate negative correlation between the number of reported symptoms and cortisol concentrations ($r(57)= -0.35$, $p= 0.008$), indicating that higher symptom burden is associated with lower cortisol levels. If successful, this study will demonstrate the value of (low) cortisol as a biomarker for long-COVID in adolescents and serve as a template for archived biospecimen projects to inform about long-COVID.

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Introduction

1.1 The COVID-19 Pandemic

The COVID-19 pandemic in 2020 created the worst global public health crisis since the influenza pandemic in 1918, resulting in a catastrophic effect in the world with over 6 million deaths worldwide (Davis et. al., 2023). COVID-19 is a highly contagious disease caused by the respiratory syndrome Coronavirus 2 (SARS-CoV-2) that was first seen in Wuhan, China in late 2019. The World Health Organization (WHO) rapidly called for a world health public emergency in early 2020 as cases continued to rise around the world (Davis, H., et. al., 2023). SARS-CoV-2 is a single-stranded RNA-enveloped virus, which is 29,881 bp in length. Its mechanism of action is characterized by replication of the viral RNA, followed by the synthesis, assemblance, and packaging of structural proteins; after which viral proteins are released to infect other cells (Huang, Y., et. al., 2020).

COVID-19 is characterized by both specific and non-specific clinical manifestations and symptoms, and many similar to the current common cold and flu symptomatology (Baj et. al., 2020). Most patients infected with COVID-19 present with high fever and chills, cough, shortness of breath, sore throat, loss of taste and smell, muscle and body aches, headaches, nausea, dizziness, dyspnea, and diarrhea (Klein, J., et. al., 2023). Critically ill patients differ from those non-critically ill and can present with cases of bilateral pneumonia. In bilateral pneumonia, the interstitial tissue (tissue around your air sacs) presents irritated and fills with pus or other fluids, leaving permanent scars as the condition worsens (Cleveland Clinic, 2022). These manifestations are evident in the computed tomography (CT) scans, as patchy shadows, ground-glass opacities, and hazy areas of increased attenuation that obscures the vascular structure.

The rapid transmission of the novel virus caused distress in the medical system worldwide, and hospital beds were rapidly occupied. The creation of a novel COVID-19 vaccine greatly reduced the impact of the pandemic by reducing the infection rate and decreasing an estimated 14.4 million deaths from COVID-19 in a year (WHO, 2024). In May 2023, the World Health Organization (WHO) declared that COVID-19 no longer constitutes a public health emergency of international concern. According to the WHO, more than 777 million confirmed cases and more than 7 million deaths have been reported by April 2025 (WHO, 2025).

1.2 Long-COVID

A subset of the population continued to have symptoms months-to-years after the initial onset of the viral COVID-19 infection. This condition is referred to as long-COVID or "post-acute sequelae of COVID-19," a multisystemic condition with similar symptoms as COVID-19 (Klein, J., et. al., 2023). The most common symptoms, seen in more than 50 percent of cases reported, include fatigue, brain fog, headaches, difficulty in memory, dizziness, difficulty sleeping, dyspnea, confusion, and musculoskeletal weakness (Klein, J., et. al., 2023). Long-COVID is a global health priority given reports suggesting that as many as 41 percent of adults with a history of COVID-19 may be impacted by long-COVID (Klein, J., et. al., 2023). Long-COVID often occurs in patients with prior severe COVID-19 illness, but it is not restricted to those who were previously critically ill or hospitalized; those with mild COVID-19 can also develop long-COVID and might be less aware of it (Yale Medicine, 2023).

Long-COVID shares many similar symptoms with current chronic and complex multisystem medical conditions, including (but not limited to) chronic fatigue symptoms and fibromyalgia. Although long-COVID does not necessarily cause death, it can substantially

worsen an individual's disease state, thus accelerating death (Davis et al, 2023). Currently, there is no test to diagnose a patient suffering from long-COVID, and most differential diagnoses are exclusionary rather than inclusionary. Patients suffering from long-COVID not only experience a physical burden but also face social and economic burden, and it is imperative to develop new techniques to accurately diagnose patients suffering from the disease.

1.3 Cortisol: The Stress Hormone

As researchers seek reliable biomarkers for long-COVID, cortisol has been investigated for its role in the body's stress response and its potential physiological relevance to the condition. Cortisol is a steroid hormone secreted by the adrenal cortex of the adrenal gland, located in the upper abdomen on top of each of the kidneys (Stalder, T. et. al.,). Cortisol is linked to both the body's circadian rhythm and its response to physical and psychological stress; it is regulated by the hypothalamus-pituitary-adrenal (HPA) axis (Stalder, T., et. al., 2013). An imbalance in cortisol levels can cause pathological conditions such as Cushing's and Addison's disease (Kadmiel & Cidlowsky, 2013). Upon experiencing a physical or psychological stressor, corticotropin-releasing hormone (CRH) is released by the paraventricular nucleus of the hypothalamus that acts on the anterior pituitary (Thau, Lauren, et al., 2023). The anterior pituitary then releases the adrenocorticotropic hormone (ACTH) that subsequently acts on the adrenal cortex, forming the HPA axis. Cortisol acts in a negative feedback loop, so high levels of the hormone will inhibit the release of both CRH and ACTH (Thau, Lauren, et al., 2023).

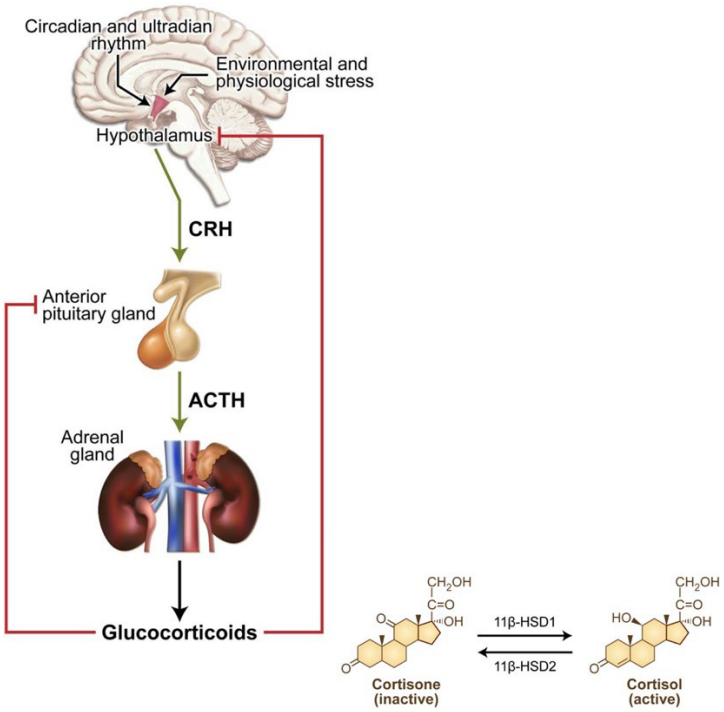

Figure 1: The Hypothalamus-Pituitary-Adrenal pathways for cortisol release upon experience of physical or psychological stress (Kadmiel & Cidlowsky, 2013).

The steroid hormone is a small primary message molecule derived from cholesterol with a lipophilic nature (Stalder, T., et. al. 2013). Due to its hydrophobicity, cortisol can freely enter the target cells and bind to glucocorticoid receptors in the cytoplasm. The cortisol-receptor complex can enter the nucleus and affects gene expression. The stress biomarker alters glucose metabolism, sculpts immune functioning, and modulates learning and memory (Yale Medicine, 2024). Cortisol, for example, downregulates our body's inflammatory response to boost our immunity (Thau, Lauren, et al., 2023). However, if cortisol levels are high for a long time, our body can get used to the high levels and act as a catalyst for more inflammation (Kadmiel & Cidlowsky, 2013). High levels of glucocorticoids were found to cause a 50 percent reduction in peripheral blood B lymphocytes in mice models, cells important for the adaptive immune

response (Garvy & Fraker, 1991). Elevated glucocorticoid levels caused apoptosis of B-cell precursors from the bone marrow (Garvy, B A, et. al., 1993). In a study from 2016, a change in the cortisol awakening response (CAR) caused by a chronic stressor, was found to be associated with a decrease in CD19+ B lymphocytes (McGregor, B et. al., 2016). Thus, chronic stress such as the case of long-COVID can potentially decrease our body's immune response over time, making us more prone to infections and diseases.

1.4 Hair as a Non-Invasive Biospecimen for Biomarker Collection

Cortisol can be measured in a range of non-invasive (e.g., saliva, hair) and minimally invasive (e.g., blood spots) biospecimens. In recent years, hair has drawn interest in the research community as a non-invasive biomarker to measure steroid hormones. Hair is particularly appealing as a biomarker of stress since it is easy to collect, and it can be transported from remote places without needing any special conditions (for example, saliva needs to be frozen at -20^{o}C when shipped to conserve analytes). Hair is also easy to store, as the only requirement is to be dry and minimally exposed to light to prevent hair degradation. Wang et.al. "Assay validation of hair androgens across the menstrual cycle," released in 2019, validates the use of hair as a steroid hormone measurement biospecimen. The researchers collected hair samples at the end of each menstrual cycle, as well as saliva samples once per week across two menstrual cycles. The results suggested that a one-time collection using hair measurements provides a valid estimate of the average steroid hormones across two months. Thus, our interest in using hair as biospecimen for assessing cortisol concentrations. This research validates the use of hair cortisol as a valid measurement of the average cortisol to assess its relationship with long-COVID.

1.5 Long-COVID Study Highlights Cortisol as a Potential Biomarker in Adults

My project is based on Klein, et. al.'s 2023 paper, "Distinguishing features of long COVID identified through immune profiling," which found that patients experiencing long COVID (LC) symptoms presented hypocortisolemia (low cortisol). Serum cortisol samples were taken from 268 adult participants with mild COVID-19 infection at least one year after acute infection and matched to a control participant using a Gale-Shapley procedure based on demographics, vaccination, and COVID-19 symptoms onset. Cortisol was measured through plasma serum to get a direct snapshot of the hormone levels circulating in the participant's body during the study. Among the long COVID group, participants presented low cortisol levels compared to the control group without previous COVID-19 diagnosis regardless of individual differences in age, sex, BMI samples, or time of collection. Serum cortisol was the most significant predictor of long COVID (AUC 0.96). However, adult populations often experience diverse symptomatology and physiology compared to children. Therefore, the question remains: "Is cortisol a suitable biomarker in the younger population given the results in the adult cohort?"

1.6 Objectives of the Study

In late 2023, research found that patients suffering from long-COVID had very low serum cortisol concentrations. This research, however, specifically focused on the adult population. Long-COVID prevalence rates in children and adolescents are much lower, with ~3% of the total cases (Klein, J., et. al., 2023). This raises the concern that low prevalence in youth may signal under-representation and a high false-negative rate. Hence, it is imperative to screen and create methods to detect long-COVID in the younger population. In this thesis we will analyze archival data from the Early Growth and Development Study (EGDS), an ongoing

longitudinal study of 561 youth which includes hair cortisol and a series of assessments throughout the pandemic. We will also analyze reports of health symptoms and medical records to find 1) if adolescents suffer from long-COVID; 2) if cortisol is related to the number of long-COVID symptoms; and 3) if cortisol is a suitable biomarker to identify long-COVID patients. This study will demonstrate the value of (low) cortisol as a biomarker for long-COVID in adolescents and serve as a template for achieved biospecimen projects to inform about long-COVID.

Methods

Participants

This project analyzes the data from the Early Growth and Development Study (EGDS). The study includes the data collection of 561 adopted children since the early 2000s. For this project, we were interested in the potential number of adolescents with long-COVID symptomatology. To achieve this, we investigated two groups: 1) participants with self-reported COVID-19 testing or medical diagnosis and 2) participants who self-reported having experienced COVID-like symptoms, regardless of testing. Participants were counted in the analysis if they had a clearly documented positive or negative COVID-19 test result or official medical diagnosis. Participants with no confirmed diagnosis or lacking relevant data were excluded. Following the above inclusion/exclusion criteria, final sample numbers for this group were:

- Confirmed COVID-19 positive cases: N = 68
- Confirmed COVID-19 negative cases: N = 255

The second group was to capture the prevalence of long-COVID-like symptoms. To identify participants who belonged to this group, we looked at answers to questions regarding persistent symptoms most commonly reported with long-COVID (e.g., fatigue, brain fog, breathlessness, loss of taste/smell, etc.). Participants were included only if they had answered symptom-related items on the survey. Failure to respond to these items resulted in exclusion from this analysis component. By symptom report, we labeled participants according to the following:

- Participants with long-COVID-like symptoms: N = 200
- Participants who were asymptomatic (no report of long-COVID-like symptoms): N = 123

This dual-criteria approach permitted us to analyze both confirmed infection status and possible markers of long-COVID symptomatology in the adolescent EGDS sample.

Hormone Extraction

Our research used hair samples to measure cortisol concentrations. Hair data corresponded to ages 11, 13, and 15. Samples were collected pre, during, and post the onset of the COVID-19 pandemic. Due to the stability of hair samples, no freezing cycle was needed. Hair, and its hormones, are sensitive to deterioration through light and UV exposure. To prevent exposure, samples were collected and kept in foil packages until further processed. Previous hair hormone validation states that 1 cm of hair growth from the scalp is equivalent to 1 month of hormone concentration. For the EGDS project, hair was segmented 1.5 cm from the scalp, hence cortisol levels were equivalent to the 1.5 months prior to collection. Hair was then weighed to 15 mg as a target weight and put into micro vials, with 10 and 5 mg as alternative options if weight was not sufficient. Three metal beads were added to each vial after weighing. Samples then were ground at 800 Hz for 8 minutes since all hair must be powder for the following chemical extraction for the required hormone.

Methanol, 1.5 mL, was added to the hair vial and rotated for 21-24 hours. Samples were then centrifuged at 5000 rpc for 5 minutes. The liquid part was transferred to a new clean vial and put into a water bath, 50^{o}C for 10 minutes, and nitrogen (N_2) gas was used to help with evaporation. Once evaporated, samples were reconstituted with assay dilution from the corresponding commercially available Salimetrics' saliva assay kit for cortisol and vortexed at 1000 rpm for 1 minute before starting the assay. The samples were measured using ELISA assay techniques and read through the Gen5 software.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics Version 30.0.0.0 (172). Data were winsorized to minimize the effect of extreme outliers prior to analysis. Group differences between participants with positive versus negative COVID-19 diagnosis and symptom presence versus absence were examined using independent samples *t*-tests. Relationships between continuous variables, such as cortisol levels and symptom count, were assessed using Pearson's correlation coefficients. Additionally, linear regression analyses were conducted to examine whether cortisol levels predicted symptom count, with COVID-19 diagnosis included as a predictor. Assumptions of regression analysis were checked and met. A two-tailed significance level of $p < 0.01$ was applied for all analyses to reduce the risk of type I errors.

Results

In our SPSS analysis to test whether youth suffer from long-COVID, we tested if a COVID-19 diagnosis is correlated with an increase in the number of symptoms in patients across multiple interviews. The results revealed that youth who have had a COVID-19 diagnosis have more, and longer lasting symptoms (M=4.022, SD=2.888) than youth who have not had COVID-19 (M=.184, SD=.393), and t-tests show that this difference is statistically significant, $t(81)=-8.121$, $p<.001$.

In our second analysis to test whether cortisol is related to the number of long-COVID symptoms, first we tested if the number of symptoms was correlated with the natural logarithm of hair cortisol concentrations (HCC). Our correlation analysis revealed that youth who have more covid symptoms have lower cortisol levels, $r(57)=-.350$, $p<.008$. Subsequently, we also tested if the fact that youth had or not symptoms was correlated with the child's HCC. The results revealed that youth who have a history of COVID-19 symptoms have lower cortisol (M=2.146, SD=.825) compared to youth who do not have a history of COVID-19 symptoms (M=2.599, SD=.913), and t-tests revealed that this difference between symptom groups is statistically significant $t(73)=1.81$, $p=.037$. As a follow up analysis, I tested if, within youth who have covid symptom history, do those with more symptoms have lower cortisol. The regression analysis could not be completed because the symptom counts variable, and the interaction of symptom count with symptoms was perfect. That is, there were no youth who had symptoms of COVID without being classified as having COVID symptoms.

Additionally, we found that youth who have had COVID-19 diagnosis have lower cortisol than youth (M=2.033, SD+.888) who have not had COVID-19 (M=2.555, SD=.761), and t-tests reveal that this group difference between COVID positive and negative diagnoses for

youth is statistically significant, t(44)=1.989, p=.026. As a follow up analysis, I tested if, within youth who have had covid, do those with more symptoms have lower cortisol? A regression analysis tested if there was a significant interaction between covid diagnosis and total symptom count. There was not an interaction effect, B=-.302, SD=.502, t=-.601, p=.551, with the interaction explaining only 0.8% of the variance in cortisol (F(1,42)=.36, p=.551 beyond the main effects.

Lastly, we tested if cortisol was by itself a suitable biomarker to identify youth who suffer from long-COVID. For this, we analyzed if HCC and COVID-19 diagnosis was correlated with the number of long-COVID symptoms. Although HCC (ln pg/ml) was, by itself, associated with symptom count, r(57)=-.350, p<.008, regression analysis in which symptom count was predicted by cortisol and a COVID diagnosis revealed that knowing a person's cortisol score did not predict their covid symptoms, B=-.126, SE=.331, t=-.381, p=.705, beyond the prior diagnosis of COVID, B=3.68, SE=.601, t=6.134, p<.001.

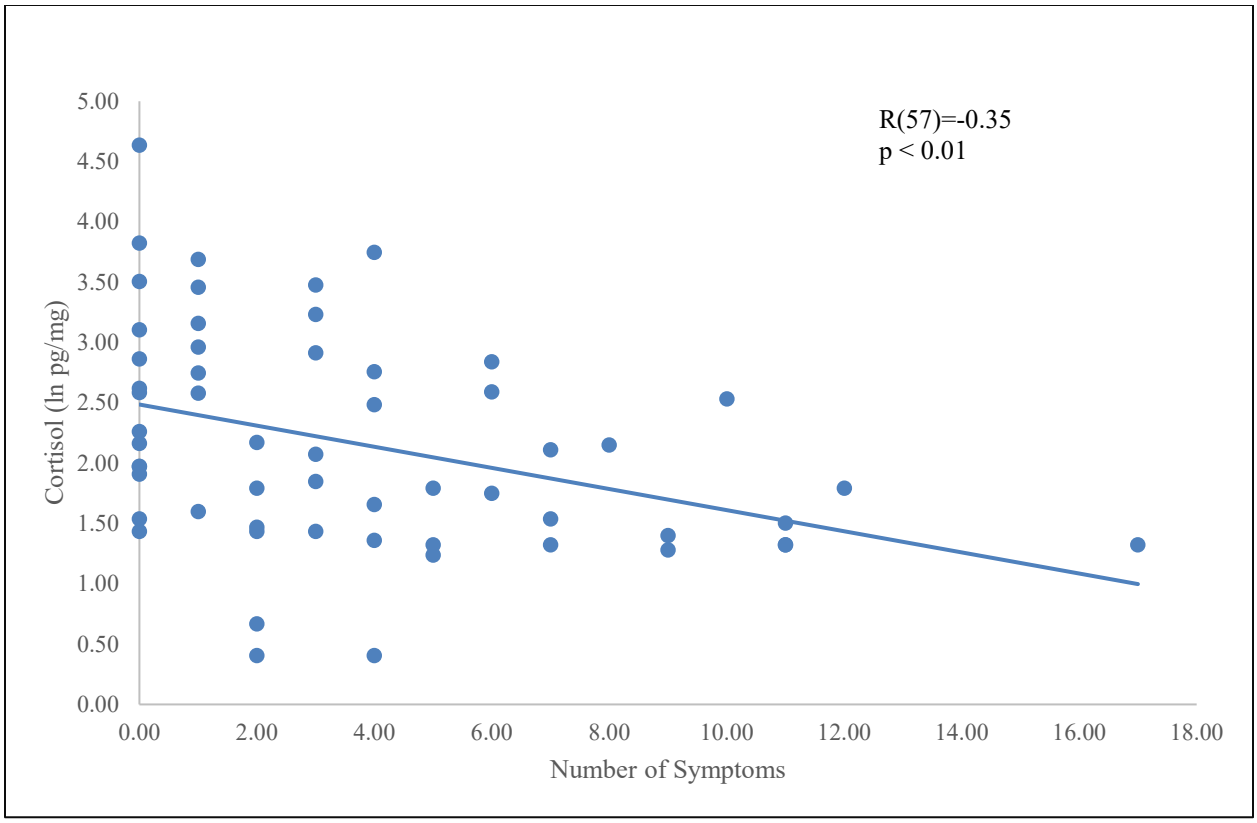

Fig. 2: Relationship between hair cortisol concentrations and the number of reported long-COVID symptoms among adolescents. The x-axis represents the number of symptoms reported, while the y-axis shows the log-transformed hair cortisol concentrations (pg/mg). As the number of symptoms increased, hair cortisol levels decreased, indicating a negative correlation. This inverse relationship was statistically significant, $r(57)=-0.35$, $p<0.01$. These findings suggest that lower cortisol levels may be associated with greater symptom burden in adolescents who have experience COVID-19, potentially reflecting long-term physiological stress.

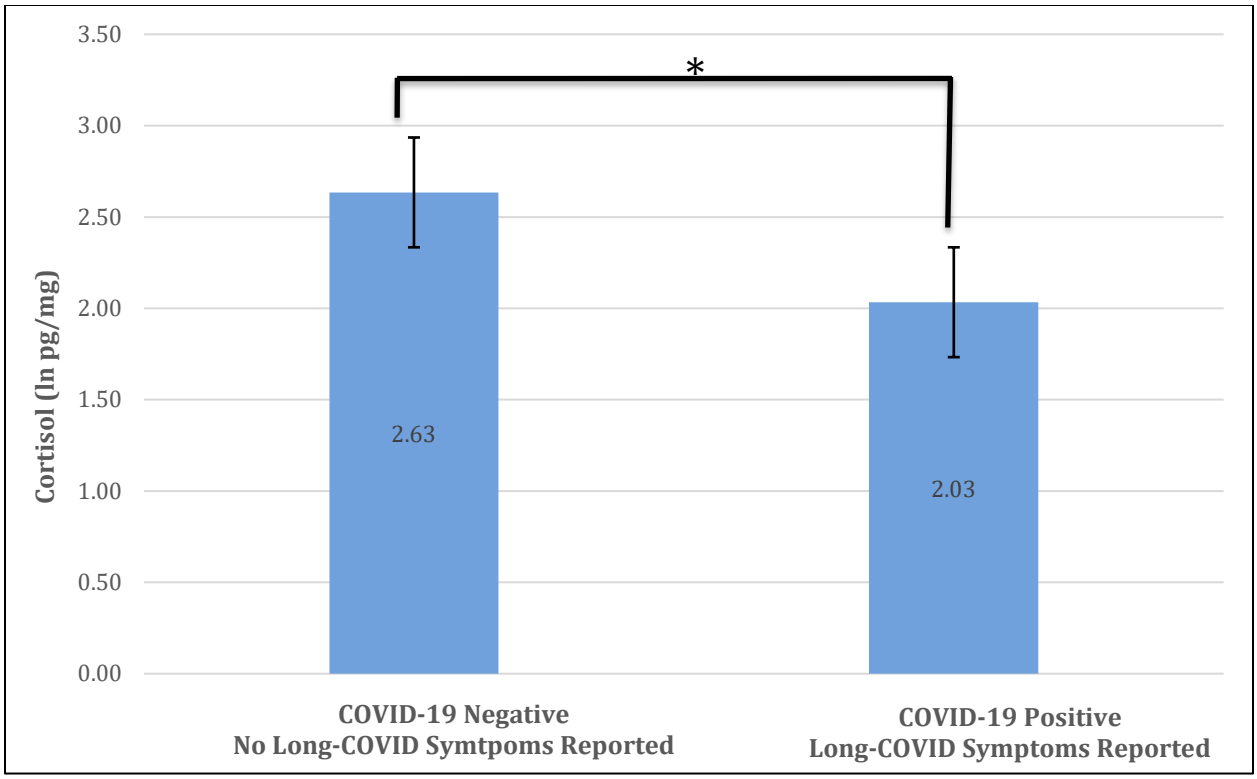

Fig. 3: Bar graph showing mean natural log (ln) cortisol levels in adolescents by COVID-19 status and symptom presence. Group 1 includes adolescents who tested negative for COVID-19 and reported no symptoms (mean ln cortisol = 2.63), and Group 2 includes those who tested positive and reported symptoms (mean ln cortisol = 2.03). Mean ln cortisol levels were significantly higher in the COVID-negative, asymptomatic group compared to the COVID-positive, symptomatic group ($p = 0.028$). Error bars represent the standard error of the mean.

Discussion

The present study investigated the use of hair cortisol concentrations (HCC) as a biomarker for long-COVID in the youth population, using data from the Early Growth and Development Study (EGDS). Our findings indicate that youth with a confirmed COVID-19 diagnosis report significantly more symptoms compared to youth without a history of COVID-19. Additionally, those with a COVID-19 diagnosis or long-COVID symptomatology showed significantly lowed HCC levels, supporting the hypothesis that low cortisol levels may be linked to long-COVID in younger individuals.

The negative correlation between symptom counts and hair cortisol suggests that lower cortisol levels may be associated with increased physiological burden due to long-COVID. These findings are consistent with prior research in adults by Klein et al. (2023), who reported a significant decrease in plasma cortisol concentrations in participants with long-COVID. This project extends prior literature by demonstrating a similar relationship when using non-invasive hair cortisol analyses in adolescent samples. Our findings provide new insights into how long-COVID may manifest across younger age groups and be tracked over time using HCC.

Cortisol is a key component of the HPA axis and plays an essential role in modulating our body's stress response, immunological function, and metabolism. A disruption in cortisol production, and particularly in chronic infections such as long-COVID, may reflect a prolonged activation of the stress response, an eventual fatigue of the HPA axis, or a maladaptation following viral infection. Prior research has shown that chronic stress or illness can reduce circulating cortisol levels, leading to a weaker immune system and fatigue (Kadmiel & Cidlowsky, 2013; McGregor et al., 2016). Our findings that lower HCC is associated with an increased number of symptoms supports the idea that long-COVID may involve a chronic stress

response or immune dysregulation that continues months-to-years after the acute onset of COVID-19.

Our data also revealed that lower HCC, while negatively correlated to the number of symptoms, was not a statistically significant predictor of long-COVID symptoms when controlled by a prior COVID-19 diagnosis. These results may be linked to the limited number of participants reporting a COVID-19 diagnosis in the EGDS data. It is possible that in larger data sets these results may show HCC as a statistically significant predictor of long-COVID symptoms. Our results suggest that cortisol alone may not be sufficient as the only biomarker for identifying youth with long-COVID. Rather, it may serve as a complementary measurement when used in conjunction with clinical history, reported-symptomatology, and other long-COVID criteria. The non-invasive nature of hair cortisol, however, makes it an appealing approach for longitudinal monitoring in pediatric and isolated populations where other more invasive procedures may not be feasible.

Our findings carry several implications for the research in long-COVID in pediatric population. First, they support the idea that younger populations are also impacted by long-COVID in a similar pattern as it affects adults, including the decrease response of the HPA axis. Second, this project highlights the promise of using a non-invasive biospecimen and its biomarkers–as hair cortisol–to study long-term health outcomes in chronic diseases. Lastly, this project demonstrates the value of (low) cortisol as a biomarker for long-COVID in adolescents and serves as a template for archived biospecimen projects to inform about long-COVID.

Despite the contributions, our study presents several limitations. The relatively small sample size of COVID-19 positive participants and those meeting long-COVID symptom criteria limits the statistical power. Additionally, symptom data relied on self– or parent–reported

questionnaires, which may be subject to bias or underreporting. The timing of biospecimen collection may also not perfectly align with the onset or duration of symptoms, thus our choice to use hair as a cumulative measure of cortisol concentrations over time. This project also did not control for other stress-related or environmental factors (i.e., social isolation, trauma) that may influence cortisol levels independently of COVID-19 infection, although prior research contributes to this factor finding cortisol concentrations historically minimal in adults suffering from long-COVID.

Future research should aim to replicate these findings in a larger adolescent sample and explore other potential biomarkers such as cytokine profiles, immune cells, or metabolic markers, to better analyze the physiological consequences of long-COVID. Longitudinal studies should also track long-COVID symptomatology and investigate if low cortisol concentrations are a cause or consequence of long-COVID symptoms. Finally, future studies should investigate if salivary cortisol concentrations might be an indicative of the body's circadian rhythm response and correlate this to long-COVID symptoms.

Conclusions

This study provides preliminary evidence that hair cortisol is reduced in adolescents with prior COVID-19 infection and a greater number of long-COVID symptoms. While HCC alone does not appear to predict whether a patient has higher numbers of long-COVID symptoms, it offers promising support for biomarker in long-COVID research and surveillance in youth. As public health efforts shift to manage post-pandemic consequences in our population, this project helps to pave the way for more accurate and accessible measurements of long-COVID in the younger population.

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