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Elucidating the interplay between salivary stress biomarkers and sleep disturbance in shaping the pain experience of youth with chronic pain

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BOSTON UNIVERSITY

ARAM V. CHOBANIAN & EDWARD AVEDISIAN SCHOOL OF MEDICINE

Thesis

**ELUCIDATING THE INTERPLAY BETWEEN SALIVARY STRESS
BIOMARKERS AND SLEEP DISTURBANCE IN SHAPING THE PAIN
EXPERIENCE OF YOUTH WITH CHRONIC PAIN**

by

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DEDICATION

I would like to dedicate this thesis to my parents, sister, and dog Mocha.

“Uống nước nhớ nguồn.”

Ba và Má ~ Khi con ăn mừng thành tựu này, con nhớ đến nguồn gốc của mọi cơ hội mà con có được—Ba và Má. Sự hy sinh, sự kiên nhẫn, tình yêu thương không lay chuyển của ba má chính là gốc rễ giúp con trưởng thành. Luận văn này dành tặng cho ba má với tất cả lòng biết ơn của con.

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JACQUELINE HUA

ABSTRACT

Background:

Chronic pain in youth is a major health concern, with a prevalence of 20.8% worldwide. Salivary biomarkers have been independently linked to chronic pain, where dehydroepiandrosterone (DHEA), a neuroendocrine hormone that plays a role in the physiological stress response, and C-reactive protein (CRP), an inflammatory marker are two biomarkers which will be examined. Sleep disturbances, stress, and stress-related pain outcomes are known to impact pain perception and intensify chronic pain symptoms. While DHEA and CRP in chronic pain are well studied, their combined impact on sleep interference and stress-related pain outcomes in adolescents remains unclear. This study aims to explore how salivary biomarkers of inflammation and stress regulation influence pain experiences and sleep disruption in youth with chronic pain.

Methods:

Participants were recruited from Boston Children's Hospital tertiary pain clinic, presenting with varying chronic pain conditions unrelated to musculoskeletal, pathological inflammation, or tissue injury. They were asked to provide salivary

samples and completed baseline self-reported questionnaires measuring sleep disturbances, stress levels, pain-related outcomes, and pain intensity. Bivariate correlation analyses compared CRP and DHEA to sleep disturbances and self-reported pain-related outcomes of stress and pain catastrophizing. Following descriptive statistics, one-way ANOVAs were done between CRP, psychosocial stressor variables, and pain intensity. T-tests were performed between DHEA, psychosocial stressor variables, and pain intensity.

Results:

The study analyzed 62 participants (ages 10-17; M age=14.5) with chronic pain. Analysis revealed stress was significantly associated with greater sleep disturbances ($r=0.53$, $p=0.001$) and pain catastrophizing ($r=0.41$, $p=0.024$). Further one-way ANOVAs performed demonstrated statistically significant associations between stress and CRP tertiles. CRP showed negative associations with sleep disturbance and stress, but a positive association with pain catastrophizing. Data trends between DHEA and sleep disturbance indicated a negative association. Meanwhile, a positive association between high stress levels and elevated levels of pain catastrophizing. These findings were not statistically significant, which limits definitive conclusions.

Conclusions:

Notable associations were observed when comparing stress with sleep disturbances and pain catastrophizing. Lower CRP tertiles were found to have a significant association with higher stress levels. Pain catastrophizing also demonstrated significant association with usual pain intensity levels. Whereas, CRP did not show significant effects on sleep disturbances, or pain catastrophizing. DHEA did not have a significant influence on sleep disturbances, pain catastrophizing, or stress. These results highlight the impact of the stress-sleep relationship on the chronic pain experience in youth and a potential linkage existing in this relationship with inflammatory biomarker, CRP. This study was limited by a small sample size with minimal racial, ethnic, and gender diversity. Additionally, examining only two salivary biomarkers restricted the ability to fully capture the complexity of the pain experience. Future research is needed in a larger cohort, to clarify the role salivary biomarkers play in the interaction between sleep and stress in adolescents with chronic pain.

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LIST OF ABBREVIATIONS

A- β	Alpha-Beta
A- δ	Alpha-Delta
ACTH.....	Adrenocorticotrophic Hormone
ANOVAs.....	Analysis of Variance Tests
BCH.....	Boston Children’s Hospital
BPSm.....	Biopsychosocial Model
CBT.....	Cognitive Behavioral Therapy
CRP.....	C-Reactive Protein
DHEA.....	Dehydroepiandrosterone
GCT.....	Gate Control Theory of Pain
HPA.....	Hypothalamus-pituitary-adrenal Axis
IASP.....	International Association for the Study of Pain
ICD-11.....	International Classification of Diseases 11 th Revision
IRB.....	Institutional Review Board
PROMIS.....	Patient-Reported Outcomes Measurement Information System
PCS.....	Pain Catastrophizing Scale
REDCap.....	Research Electronic Data Capture
US.....	United States

INTRODUCTION

Chronic pain among youth is a significant public health concern, with prevalence rates increasing globally. In the United States alone, pain affects over 100 million individuals annually, with the estimated cost ranging from \$560 to \$635 billion per year (Smith et al., 2019). Chronic pain not only diminishes one's quality of life but also places substantial burdens on families, including increased parental work loss when caring for affected children (Kitschen et al., 2024). Pain is an inherently complex and phenomenological experience, making it essential to explore both psychosocial and biological factors that contribute to chronic pain.

The experience of stress plays a significant role in chronic pain with related biological, psychological, and social processes. This process in response to the burden of chronic stress is also referred to as allostatic load, where body is required to adapt to adverse physical and psychosocial circumstances (McEwen, 2000; Guidi et al., 2021). Implications of allostatic load have been linked to the development or exacerbation of chronic pain (Nelson et al., 2021). Allostatic load has been found to lead to heightened nervous system sensitization which extensive periods of stress on the nervous system can lead to maladaptive changes resulting in chronicity of pain conditions through the hypothalamus-pituitary-adrenal axis (HPA) (Nelson et al., 2021). Stress biomarkers may underlie the relations between psychological stress and pain. DHEA is a neuroendocrine hormone produced by

the adrenal glands and has been implicated in the modulation of pain pathways, directly impacted by alterations in the HPA axis (Huang et al, 2019). Another salivary biomarker indirectly related to stress is C-reactive protein, is an inflammatory biomarker that serves as a robust indicator of the body's inflammatory response to pain and has previously shown strong associations with chronic pain conditions (Nehring et al., 2023). Knowing that DHEA playing a crucial role in modulating the stress response through its association with the HPA axis, meanwhile CRP is directly linked to inflammation—these biomarkers are essential for advancing our understanding of pain processes.

A critical role in pain perception lies in examining the psychosocial aspects impacting pain and sleep quality. There is strong evidence for a bidirectional relationship between pain and sleep disruption. Poor sleep predisposes individuals augments pain thresholds as a result of disturbance in the GABAergic neurotransmission, thereby altering their pain perception and intensifying the pain experience (Kaczmariski et al., 2023; Oh et al., 2023). This can further lead to physical and mental health comorbidities such as sleep disorders, depression, anxiety, cardiovascular disease, pulmonary disease, post-traumatic stress disorder, diabetes and various other conditions (Andersen et al., 2018; Oh et al., 2023). Pain catastrophizing is another psychosocial factor commonly linked to chronic pain. It is a maladaptive cognitive coping behavior which one is unable to cope with their

pain-related fears and continue to ruminate about their thoughts surrounding pain, thereby magnifying the pain experience (Quartana et al., 2009).

Although the relationship between CRP and chronic pain is well-documented, role DHEA has on chronic pain and the interplay between these biomarkers and psychosocial factors—such as sleep disturbances, stress, pain catastrophizing, and pain intensity—among youth remains poorly understood.

This study aims to investigate the relationship between salivary biomarkers and psychosocial factors in adolescents with chronic pain to either reaffirm existing literature or identify novel relationships. This paper will begin by defining pain and summarizing epidemiological findings on chronic pain in youth. Next, it will outline the modulation and processing framework of pain through the lens of the biopsychosocial model, reviewing existing literature on each variable and its relevance to the study. Statistical models will demonstrate associations between these covariates. Finally, the discussion will interpret the results in detail—highlighting potential linkages between stress biomarkers and pain-related factors. Meanwhile, gaps will also be identified for future research and targeted interventions to deepen understanding of chronic pain in adolescents.

BACKGROUND

Defining Pain

Pain is a multifaceted experience, shaped through biological, psychological, and social elements. Its unique construct ensures that no two individuals experience pain in the same way. Inherently complex due to its multidimensional nature, pain extends beyond physical discomfort, influencing emotional well-being, cognitive function, and social dynamics. Its profound impact can shape an individual's quality of life, limit daily functioning, and contribute to broader societal challenges, including healthcare burdens and economic costs. Pain is first categorized into acute and chronic based on the course of symptoms. It can also be categorized into three primary mechanistic types: nociceptive, neuropathic, or nociplastic. Recognizing the form in which pain presents in individuals, provides a deeper understanding of the pain experienced by those facing it.

According to the International Association for the Study of Pain and the International Classification of Diseases (ICD-11), chronic pain is defined as pain which persists or recurs for a duration longer than three months (Treede et al., 2019). Acute pain, by contrast, is defined as pain occurring suddenly that can be a warning to the nervous system of a disease or potential threat to the body (IASP, n.d.). This pain can be a result of injury, illness, trauma, surgery, or other medical procedures. This form of pain can occur from a few seconds to less than six months.

Next, the three primary mechanistic types of pain will be described. Nociceptive pain is a signal of the threat to impending tissue damage due to trauma—an injury yet to be healed, or certain inflammatory processes (Nicolaidis, 2010). This form of pain is usually localized and presents as an aching or sharp sensation. Neuropathic pain, on the other hand, stems from injury to one’s somatosensory system—the neural circuit responsible for touch, sensation, and pain processing (Costigan et al., 2009). This form of pain can manifest as shooting, burning, and tingling shocks to patients. The third type of pain mechanism is nociplastic pain, characterized by pain arising from a disruption of the neural circuit that are involved in pain transmission, processing, and modulation of the nociceptors without any clear signs of tissue damage present which would otherwise explain the pain. By understanding both the mechanism and type of pain an individual experiences, healthcare providers can make more informed decisions about treatment options.

The Epidemiology of Pediatric Chronic Pain

Chronic pain affects an estimated 20-46% of pediatric children in the US, with a prevalence higher among biologically female children (Miró et al., 2023). Among this population, prevalence rates based on areas of pain ranged from 20% of adolescents experiencing general pain, 9% experiencing musculoskeletal pain, 7% with abdominal pain, and 4% experiencing headaches (Liao et al., 2011). The high prevalence of pain comes with a significant economic burden. The United

States spends an estimated \$19.5 billion yearly on adolescents with moderate to severe chronic pain (Groenewald et al., 2014).

In addition to the economic burden of pain, the high rates associate with chronic pain are morbidity and disease burden measures which can further quantify the scale at which chronic pain affects this vulnerable population. Disability-adjusted life years (DALYs) is an epidemiological tool used to quantify the burden of disease, where one DALY is equal to a loss of one healthy year for an individual (GHO, n.d.). A study from 2019 done by The Global Burden of Disease (GBD) examined trends from 1990 to 2019. In which they found the DALYs for low back pain in adolescents and young adults 627.66 years out of 100,000 individuals (Yang et al., 2019). Despite trends of pain prevalences showing a modest decrease in average DALYs worldwide, healthcare expenditures and utilization continue to rise. These findings demonstrate the significant burden pain has on the US population. Further research on adolescents with chronic pain found approximately 57% of adolescents were at high risk for having poor quality of life and health outcomes on the Pediatric Quality of Life Inventory (PedsQL), which is a model measuring the quality of life amongst children and adolescents with acute and chronic pain (Wrona et al., 2021).

The Pain Experience

Pain modulation is a process within the central nervous system that controls the transmission and perception of pain pathways when actual or impending tissue damage is detected (Purves et al., 2001). Pain modulation occurs through the descending pathway, which regulates and inhibits pain signals, while the ascending pathway transmits nociceptive information from peripheral receptors to the central nervous system. The ascending pain pathway begins with nociceptors detecting noxious stimuli and transmitting action potentials to primary afferent neurons. These neurons release excitatory neurotransmitters, such as glutamate and substance P, which activate secondary neurons in the dorsal horn of the spinal cord, ultimately leading to the perception of pain and the initiation of inflammatory responses (Yam et al., 2018). As the pain signals travel through the ascending pathway, descending pathways use neurotransmitters to modulate the signals and later inhibiting it and reducing pain transmission of pain to the brain (Lau et al., 2014). This pain modulation process is what shapes one's distinct sensory experience of pain (Kirkpatrick et al., 2015).

To understand the physiological basis of pain, the neurophysiological mechanisms illustrated in Figure 1 depict how pain is processed in the spinal cord, as explained by the Gate Control Theory of Pain (GCT), first proposed by Ronald Melzack and Patrick Wall in 1965. The Gate Control Theory of Pain describes pain processing from a neurobiological perspective, proposing that a pain signal travels

through three distinct regions of the spinal cord—substantia gelatinosa, transmission cells within the dorsal horn, and fibers in the dorsal column—before reaching the brain (Mendell, 2013). The dorsal horn of the spinal cord functions as a gate that regulates the transmission of the pain signals sent to the brain. When the gate is closed, the pain signals are inhibited, prevention perception of pain by the brain. Conversely, when the gate opens, these pain signals are transmitted, allowing pain to be processed and later perceived by the brain. (Trachsel et al., 2023).

The Gate Control Theory of Pain

Pain is Perceived

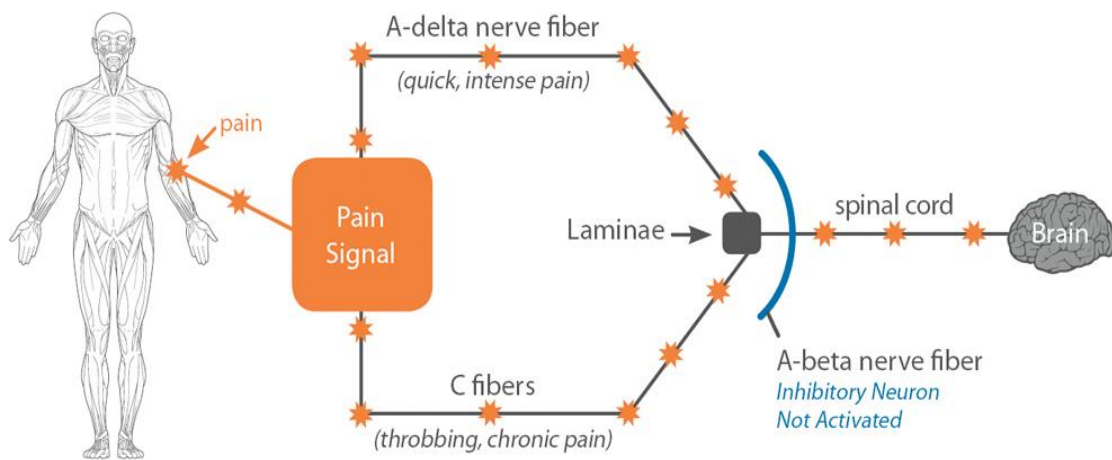


Figure 1: The Gate Control Theory of Pain (Grunch, n.d.)

This diagram illustrates the Gate Control Theory of Pain by depicting the mechanism through which pain signals are processed, traveling from the brain to the spinal cord and then transmitted via A- β , A- δ , or C nerve fibers to generate a pain response.

According to the Gate Control Theory of Pain, pain perception is modulated at the spinal cord level through the interaction of one large and two small afferent sensory fibers—where non-nociceptive information is processed through large, while small nerve fibers conduct nociceptive pain information (Kirkpatrick et al., 2015). Large nerve fibers, such as A- β (A-beta) fibers, are myelinated and function to close the gate, thereby decreasing pain perception (Ward, 2014) These fibers primarily process sensory information such as touch, pressure, and vibration (Ward, 2014). In contrast, small nerve fibers, such as A- δ (A-delta) and C fibers open the gate and increase pain perception. A- δ nerve fibers are small and myelinated, producing sharp, localized pain (Woessner, 2011). Whereas, C-fibers are the smallest and unmyelinated fiber types, which is typically dull, burning, and long-lasting (Weise et al., 2015). C-fibers often are the primary contributor to chronic pain.

This original model explores the neurobiological approach to the pain process. It examines nociception—the process of neural feedback within the nervous system that processes harmful stimuli (Armstrong et al., 2023).

While it briefly acknowledges the role cognition and emotional state have on nociception with psychological factors such as stress, anxiety, and pain catastrophizing amplifying pain, later discussed models such as the biopsychosocial model, will bring clarity to the supratentorial processing of nociception—which is better known as the pain experience.

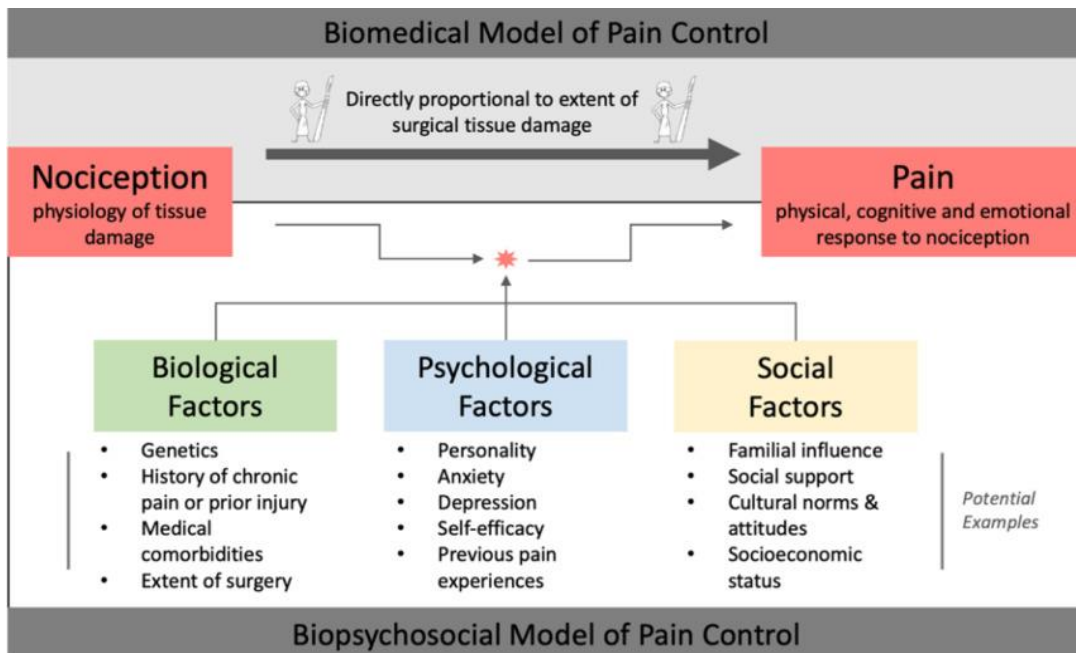


Figure 2. Interactions Between the Biomedical Model of Pain Control & Biopsychosocial Model of Pain Control (Gornitzky et al., 2021).

These two models of pain control examine the complex interplay of various biological, psychological, social, and cultural factors on pain control.

Adolescents with chronic pain are at higher risk for several long-term adverse effects including educational, social, vocational challenges, as well as increased co-morbidity and health risks (Murray et al., 2021). Understanding the multitude of factors that contribute to one's pain experience is most effectively achieved through the biopsychosocial model of pain (BPSm). This model posits that biological, psychological, social, and cultural factors are intricately intertwined and collectively shape one's pain perception and experience (Gornitzky et al., 2021).

Biological factors within the model account for genetics, physical injury, tissue damage, surgery, various other medical comorbidities, and chronic pain history. Psychological factors encompass personality, stress, anxiety, depression, pain catastrophizing, fear of pain, and previous pain experiences. Social factors include family and social environment, societal and cultural influences, and socioeconomic status. This model shown in Figure 2, takes into consideration the process in which the body responds to pain and where the factors from the biopsychosocial model can significantly interact within the biomedical model, demonstrating the complex interplay between the mind, body, and environment connection.

The BPSm promotes a holistic approach on pain medicine, allowing clinicians the ability to address pain through non-pharmacological interventions

that target psychosocial contributors (Roth et al., 2011). Following this model, a multimodal approach to pediatric pain care can be formulated to unveil the underlying causes, contributors, and consequences of pain (Lioffi et al., 2016).

Salivary Biomarkers Associated with Chronic Pain

C-Reactive Protein

Inflammation is closely associated with pain, whether acute or chronic. Inflammation can contribute to nociceptor sensitization, thereby promoting the development and exacerbation of pain symptoms. (Fang et al., 2023). The complex relationship between inflammation and chronic pain can provide insights into the maladaptive processes driven by neuroinflammation. C-reactive protein (CRP) is an acute inflammatory protein biomarker produced by the liver, commonly used as a clinical marker due to its tendency to rise in response to inflammation (Nehring et al., 2023). During inflammatory processes, CRP binds to the damaged cell membranes, marking it for elimination. Subsequently, CRP activates the complement pathway system responsible for opsonization—the process in which the immune system recognizes and eliminates foreign pathogens and damaged cells (Sproston et al., 2018; Mold et al., 1999; Thau et al., 2023). Following the resolution of the acute inflammation, the CRP levels will gradually decline.

Inflammation is also strongly linked to chronic pain. Among individuals with chronic pain, recently published literature demonstrated elevated CRP levels associated with intensified chronic pain in comparison to those with lower CRP levels (Huang et al., 2025). Additionally, CRP has also been attributed to increased functional disabilities in adolescent chronic pain groups (Hainsworth et al., 2021).

While research examining the correlation between CRP and DHEA, a study done on pancreatic cancer development, found DHEA to be inversely involved in inflammation, while CRP had a direct association. This study concluded there was an inverse relationship between CRP and DHEA, with DHEA having a potentially inhibitory role on CRP levels (Fazli et al., 2024).

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a steroid hormone which serves as a precursor for sex hormones testosterone and estradiol. It is produced from the cortex of the adrenal gland and its production is regulated by the adrenocorticotrophic hormone (ACTH) (Sato et al., 2018). ACTH is released in response to stress (Dutheil et al., 2021). The hypothalamic-pituitary axis (HPA) axis—a feedback system responsible for adaptive responses to stress—primarily controls ACTH (Smith et al., 2006; Dutheil et al., 2021).

DHEA often is regarded as a hormone modulating the stress response, functioning in contrast to stress cortisol—the known stress hormone. DHEA may help manage the stress response, and its relevance to chronic pain lies within it potentially modulating the pain perception and reducing pain severity (Joksimovic et al., 2018). However, chronic stress—whether psychosocial or oxidative stress—can result in dysregulation of the HPA axis, thereby altering both the levels of DHEA and cortisol, impairing the body's ability to manage pain-related outcomes (Basson et al., 2019). Although neuroendocrine mechanisms underlying chronic pain in adolescents remain insufficiently explored, reduced levels of the sulfated form of DHEA were observed among adult women with chronic pain (Li et al., 2021).

These two salivary stress biomarkers, CRP and DHEA, are shown among the most prominent indicators of the body's response to pain. While CRP's role in inflammatory processes is well understood from a biological perspective, it is essential to investigate whether CRP and DHEA levels are influenced by psychosocial stress thereby adding complexities to one's pain experience.

Psychosocial Factors Linked to Chronic Pain in Youth

Stress

Psychological stress significantly and negatively impacts an individual's quality of life, leading to various physical and mental health concerns. Extensive literature has been done examining the correlation between stress and chronic pain. Children exposed to psychological stress earlier in life are predisposed to various health disorders, particularly chronic pain conditions (Burke et al., 2017). Stressful experiences can also contribute to worsened psychosocial skills, anxiety, depression, and difficult peer relationships, as well as impair immune functioning and exacerbate somatic symptoms (Nelson et al., 2021). Individuals with chronic pain are even more susceptible to heightened stress due to the physical and emotional burdens associated with their pain.

The stress experience itself is highly variable and subjective, adding further complexity to the chronic pain model. Nevertheless, it is well established that there is a strong bidirectional relationship between stress and chronic pain, with those experiencing pain chronicity being at a higher risk for developing stress-related conditions such as depression and anxiety, which makes leaving this population particularly vulnerable to the cascading effects of stress on their daily functioning and pain experience.

Stress is a natural humanistic response defined as being in a state of worry where psychological, biological, and emotional tension can occur (WHO, 2023). Measures of stress can be seen all throughout the human body, from changes in blood pressure and heart rate to its effect on sleep, appetite, mood, and even salivary biomarker levels. Prolonged stress can result in maladaptive changes due to increased alostatic load—often referred to as “wear and tear” on the body (Nelson et al., 2021). Stress has been correlated to having implications on the HPA axis, a system which plays a critical role in pain chronicity and stress regulation (Nees et al., 2019; Nelson et al., 2021). This relationship gives rise to the question of how toxic stress amongst adolescents with chronic pain may be linked to DHEA levels, given the HPA axis’s role in pain management and stress response. Furthermore, it remains vital to examine how stress could impact CRP levels and sleep disturbances within this population, as these factors could provide more context in the variables shaping the chronic pain experience.

Pain Catastrophizing

Pain catastrophizing is a concept first introduced by Albert Ellis and later adapted by Aaron Beck, describing the rumination and fearful anticipation of painful stimulation that negatively affects the cognitive and emotional state (Quartana et al., 2009; Sullivan et al., 2024). This concept helps to better understand maladaptive cognition changes that influence pain modulation through the

biopsychosocial perspective. Therefore, it paves the way direction for implementation of evidence-based interventions known as cognitive behavioral therapy (CBT). CBT is designed to support mental health by promoting more adaptive interpretations of their circumstances (Curtiss et al., 2021). These interventions can assist pediatric patients in managing pain symptoms through a psychosocial standpoint (Petrini et al., 2020).

To further understand the connection and impact of psychosocial factors such as pain catastrophizing, stress biomarkers, and sleep disturbances on the pediatric pain population, it is necessary to investigate how these factors all interact in influencing the overall pain experience. By examining the role of pain catastrophizing, the findings can provide a better understanding of how the rumination of pain is linked to other factors involved in the pain experience. This will offer valuable insights, allowing perspectives to be gained on how maladaptive thought patterns amplify stress and contribute to pain perception.

Role of Sleep Disturbances in Adolescents with Chronic Pain

Previous research has shown that sleep deprivation is linked to a wide range of co-morbidities including a decline in mental health, cancer, obesity, heart disease, and various other health conditions (Whale et al., 2022). Among adolescents with chronic pain, sleep disturbances are a prevalent and significant issue. Across adolescents of all ages between 11-17 years old, sleep disorders

account for a prevalence of 3.7%, yet nearly half of those affected are adolescents living with chronic pain conditions (Oh et al., 2023). Adolescents with chronic pain often experience poor sleep quality, and without adequate rest, both the body and mind are unable to heal, which intensifies the physical and emotional burden of their pain. This striking overrepresentation of adolescents with chronic pain experiencing sleep disturbances, along with the impact of poor sleep quality on their condition, highlights the importance of addressing sleep issues as a critical aspect of pediatric pain management.

The regulation of sleep plays a crucial role in pediatric pain care, as without good sleep hygiene, it can significantly interfere with coping strategies which were designed for alleviation of pain symptoms (Lewis et al., 1999). Dysregulation of the sleep cycle not only alters one's perception of pain but can further amplify the overall pain experience (Oh et al., 2023). Slow-wave sleep, also known as deep restorative sleep, typically allows the body essential time to heal. However, extensive sleep disturbances have been associated with heightened pain responses, suggesting that disrupted sleep could compromise the body's natural mechanisms for pain modulation and recovery (Smith et al., 2004).

Disruption of sleep is a result of the dysregulation of inflammatory pathways and neurotransmitters existing in the hypothalamic-pituitary-adrenal (HPA) axis (Seiger et al., 2024). Without restful sleep, the body's ability to regulate

inflammation and pain processing is disrupted, exacerbating pain sensitivity and stress levels. Complaints of insomnia have been adversely linked with an increased risk for inflammatory diseases (Irwin et al., 2016). Having poor sleep quality can This complex relationship between sleep and chronic pain has far-reaching implications, including heightened pain experiences, decreased cognitive functioning, increased stress, and intensified inflammation (Whibley et al., 2019).

These findings prompt the critical question of how sleep disturbances might manifest itself through salivary stress biomarkers amongst youth—which is an area of exploration currently lacking well-established literature. This understanding could potentially reveal how sleep disturbances not only further compound the burden of stress, but also increase the release of these salivary stress biomarkers, offering a comprehensive view of the complex relationship between stress, pain, and sleep. Ultimately, exploring these connections can inform more effective strategies of managing the pain experience and improving the well-being of the entire mind-body.

This investigation seeks to illuminate the complex interplay between biological and psychosocial factors which shape an individual's pain experience by uncovering key findings related to sleep disturbances, C-reactive protein, DHEA, stress, and pain catastrophizing.

METHODS

Study Design, Participants, & Procedures

Data for this study were collected from the Boston Children's Hospital's (BCH) Pain Treatment Service under a protocol approved by the hospital's Institutional Review Board (IRB) in May 2018. Clinical information and salivary samples were from participants receiving treatment at the tertiary pain clinic within the Department of Anesthesiology, Critical Care, and Pain Medicine. The patient population included new patients presenting to the clinic for an evaluation of a chronic pain condition. Patients with chronic secondary pain stemming from a disease-based process, such as sickle cell disease or arthritis, or those unable to complete required questionnaires due to an English language barrier or cognitive impairment, were excluded. All clinical information collected from participants was securely stored on the Research Electronic Data Capture (REDCap) secure platform.

This study included 62 adolescent participants, aged 10 to 17 years ($M = 14.51$, $SD = 1.97$), all of whom have presented with current or past chronic pain symptoms. Among the 61 adolescent participants, 6 individuals identified as male (9.68%), 55 identified as female (88%), and 1 identified as other (1.61%).

Patient Assessment Tools

Participants are instructed to collect one saliva sample at home prior to their treatment service visit using a passive drool technique, where they allowed saliva to accumulate at the base of their mouth before letting it slowly flow into the collection container. This saliva collection occurred on the morning of their appointment, immediately after waking, and before consuming any food or drinks. The collected saliva sample was analyzed for C-reactive protein and DHEA. Following, the saliva sample collection, participants were provided a tablet computer to access REDCap, where they completed questionnaires regarding sleep disturbances, psychological stress, pain catastrophizing, and pain intensity.

Patient-Reported Outcomes Measurement Information System (PROMIS)

The Patient-Reported Outcomes Measurement Information System (PROMIS) was designed by the National Health Institute (NIH) Roadmap initiative as a psychometric measurement tool to measure patient-reported outcomes. For this study, the PROMIS Pediatric Short Forms were utilized to assess Sleep Disturbances and Psychological Stress.

PROMIS Sleep Disturbances

The PROMIS Pediatric Sleep Disturbance – Short Form 8 Child-Report scale is a self-reported measurement of sleep quality in the pediatric population (Yu

et al., 2011). Its primary goal is to assess sleep functioning, specifically the presence and frequency of sleep disturbances. The questionnaire is a short form comprised of 8 items related to sleep disturbances within the last 7 days. A 5-point scale system was used ranging from 1 to 5, with 1 = never and 5 = always. Questions covered topics surrounding insomnia and quality of sleep such as trouble sleeping, sleep quality throughout the night, difficulty falling asleep, the time it took to fall asleep, sleep-related worries, and disturbances during sleep (Brossoit et al., 2023). T-scores were calculated and interpreted to determine the severity of the child's sleep disturbance over time, where higher scores indicated greater sleep disturbances (PROMIS Health Organization, 2013).

PROMIS Stress

The PROMIS Pediatric Item Bank v1.0–Psychological Stress Experiences–Short Form 8a was utilized to assess the participants' thoughts and feelings surrounding the personal and environmental challenges faced (Bevans et al., 2018). The form evaluated stress reactions from participants over the past 7 days, focusing on feelings of being overwhelmed, lack of control of their problems or life, and perceived disruptions in their life (PROMIS, 2021). Similarly to the PROMIS Sleep Disturbances form, raw scores of this short form were converted to T-scores to quantify the intensity of stress experiences.

Pain Catastrophizing Scale (PCS)

The Pediatric Psychology Pain Catastrophizing Scale (PCS) is a 13-item questionnaire was adapted from the original PCS scale developed by Sullivan & Bishop and later modified by Crombez et al. for children aged 8 to 17 years old (Crombez et al., 2003). This scale conceptualizes and measures individuals' thoughts surrounding helplessness, ruminating, and difficulty with effective management of pain symptoms (Sullivan et al., 1995). Responses are rated on a 5-point scale ranging from 0 = “not at all true” to 4 = “very true,” with a total score ranging between 0 to 52 and higher total sum scores demonstrating greater catastrophic thinking regarding the individual’s pain (Pielech et al., 2014).

Numeric Rating Scale (NRS) Pain Intensity – Child Report

The Numeric Rating Scale (NRS) Pain Intensity goes off a 10-point numeric rating system to examine pain levels, with 0 = “no pain at all” and 10 = “the worst pain possible (Nugent et al., 2021).” Participants responded to four questions about their pain intensity, including their typical pain level, best pain level, and worst pain level within the past week.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Version 29 software following data collection. Bivariate correlations were performed to examine the

relationships between the independent variables (C-reactive protein and dehydroepiandrosterone) and the dependent variables (sleep disturbances, psychological stress, pain catastrophizing, and pain intensity). Descriptive statistics, including frequencies, means, and standard deviations, were calculated for the study variables and demographic characteristics. CRP levels were categorized into tertiary and quaternary levels, while stress, sleep disturbances, and pain catastrophizing variables were coded using the final T-scores of participants.

Pearson correlations (parametric) and Spearman's rho (non-parametric) tests were used to evaluate associations between salivary biomarkers (CRP & DHEA) to dependent variables (sleep disturbances, stress, pain catastrophizing, pain intensity). Statistically significant relationships were identified at a threshold of $p < 0.05$.

Following the initial correlation analyses, one-way analysis of variance (ANOVA) tests were conducted to compare the dependent variables' T-scores. A univariate analysis of variance with Post Hoc tests using the Bonferroni method was performed to determine the significance of associations between salivary stress biomarkers (CRP and DHEA) and the dependent variables (stress, pain catastrophizing, and sleep disturbances). Estimated marginal means with bar graphs were generated to visually represent the relationships between CRP and DHEA and the dependent variables of psychosocial outcomes.

RESULTS

Descriptive Statistics

Table 1 demonstrates the demographic characteristics of all participants involved in the study ($N = 62$). The majority of participants identified as White/Caucasian ($N = 55; f = 88.71\%$) and female ($N = 55; f = 88.71\%$), while the remaining participants identified as male ($N = 6; f = 9.68\%$), with one participant identifying as other ($N = 1; f = 1.61\%$).

Participants ranged in age from 10 to 17 years ($M = 14.51$), with the largest proportion of participants falling within the 13-15 age range ($f = 43.55\%$). One participant did not report their age. Most adolescents were in middle school, primarily between 6th and 8th grade ($N = 22; f = 35.48\%$).

Table 1: Demographic Characteristics of Participants

Gender	<i>N</i>	<i>Frequency</i>
Male	6	9.68%
Female	55	88.71%
Other	1	1.61%
Total	62	100%
Age		
10-12	12	19.35%

13-15	27	43.55%
16-17	22	35.48%
Missing	1	1.61%
<hr/>		
Grade Level		
<hr/>		
Elementary School (4th-5th)	2	3.22%
Middle School/Junior High (6th-8th)	22	35.48%
Lower Classmen High School 9-10	19	30.65%
Upper Classmen High School 11-12	19	30.65%
<hr/>		
Race/Ethnicity		
<hr/>		
White	55	88.71%
Black or African American	3	4.84%
Asian	1	1.61%
Native America/Alaskan Native	1	1.61%
Hispanic	1	1.61%
Other	2	3.22%

Descriptive statistics were conducted to evaluate the range and central tendencies of the study variables, illustrated in Table 2 below. The mean scores provided insight into the average levels of salivary stress biomarkers and psychosocial outcomes, as well as pain intensity.

The mean level of C-reactive protein was $M = 340.56$ ($SD = 533.20$, $N = 54$), while the mean level of dehydroepiandrosterone was $M = 322.63$ ($SD = 226.69$, $N = 60$). Among the psychosocial outcomes, the average t-score for PROMIS Sleep Disturbances was $M = 60.14$ ($SD = 7.46$, $N = 54$), and for PROMIS Stress, it was $M = 57.09$ ($SD = 9.26$, $N = 62$). The mean score for Child Pain Catastrophizing Scale was $M = 24.93$ ($SD = 14.17$, $N = 30$). Regarding pain intensity, the average numeric rating scale (NRS) scores were as follows: usual pain intensity ($M = 6.46$, $SD = 1.85$), best pain intensity ($M = 4.66$, $SD = 2.53$), and worst pain intensity ($M = 8.07$, $SD = 1.48$).

Notably, using the PROMIS T-score Cut Points, the mean t-scores for sleep disturbances and stress indicated mild-to-moderate/average-to-high health level (Health Measures, 2025). Additionally, the average pain intensity ratings consistently exceeded 5 on a 0-10 scale, regardless of whether participants reported usual, best, or worst pain levels.

Table 2: Descriptive Statistics of Salivary Stress Biomarkers, Psychosocial Outcomes, & Pain Intensity in Participants

	Salivary Stress Biomarkers				
	<i>N</i>	<i>Minimum</i>	<i>Maximum</i>	<i>Mean</i>	<i>Std. Deviation</i>
C-Reactive Protein	54	2.51	2355.66	340.56	533.20
DHEA	60	18.62	824.41	322.63	226.69

Psychosocial Stress Variables					
	<i>N</i>	<i>Minimum</i>	<i>Maximum</i>	<i>Mean</i>	<i>Std. Deviation</i>
PROMIS Sleep Disturbances	54	46.80	78.50	60.14	7.46
PROMIS Stress	62	37	81.80	57.09	9.26
Pain Catastrophizing (PCS)	30	4	44	24.93	14.17

Pain Intensity					
	<i>N</i>	<i>Minimum</i>	<i>Maximum</i>	<i>Mean</i>	<i>Std. Deviation</i>
Usual Level of Pain	62	0	10	6.46	1.85
Best Level of Pain	62	0	10	4.66	2.53
Worst Level of Pain	62	4	10	8.07	1.48

Inferential Analyses

Bivariate Correlations

Inferential analysis was conducted to examine the relationships between salivary stress biomarkers (CRP and DHEA) and psychosocial outcomes (sleep disturbances, pain catastrophizing, stress) as well as pain intensity measures (usual, best, and worst pain levels). Bivariate correlations were performed and are presented in Table 3.

Pearson correlation analyses revealed a statistically significant negative linear relationship between DHEA and the best level of pain, indicating that higher levels of DHEA were associated with lower reports of best pain intensity. No significant correlations were identified between sleep disturbances and either CRP or DHEA, although both demonstrated negative linear relationships.

Stress exhibited a negative correlation with CRP and a positive correlation with DHEA, but neither relationship reached statistical significance. Similarly, usual pain levels showed a negative linear correlation with both CRP and DHEA, without significance. Best pain level showed a positive correlation with CRP but was not statistically significant. Lastly, worst pain level demonstrated a negative correlation with both CRP and DHEA, also without statistical significance.

Table 3: Bivariate Correlation Between Independent Variables (Salivary Stress Biomarkers-CRP & DHEA) to Dependent Variables (Sleep, PCS, Stress, Pain Intensity)

		CRP	DHEA
Best Pain	<i>Pearson Correlation</i>	0.081	-0.340**
	<i>Sig. (2-tailed)</i>	0.559	0.008
	<i>N</i>	54	60
PROMIS Sleep	<i>Pearson Correlation</i>	-0.020	-0.063
	<i>Sig. (2-tailed)</i>	0.891	0.656
	<i>N</i>	51	53

PROMIS Stress	<i>Pearson Correlation</i>	-0.014	0.046
	<i>Sig. (2-tailed)</i>	0.920	0.728
	<i>N</i>	54	60
PCS	<i>Pearson Correlation</i>	0.090	0.185
	<i>Sig. (2-tailed)</i>	0.641	0.338
	<i>N</i>	29	29
Usual Pain	<i>Pearson Correlation</i>	-0.030	-0.160
	<i>Sig. (2-tailed)</i>	0.830	0.223
	<i>N</i>	54	60
Worst Pain	<i>Pearson Correlation</i>	-0.094	-0.105
	<i>Sig. (2-tailed)</i>	0.498	0.426
	<i>N</i>	54	60

** *Correlation is significant at the 0.01 level (2-tailed)*

* *Correlation is significant at the 0.005 level (2-tailed)*

Further bivariate correlation analyses were conducted to examine relationships among psychosocial outcomes (sleep disturbances, stress, pain catastrophizing) and their associations with each other and pain intensity measures. The results are summarized in Table 4.

Pearson correlations revealed a statistically significant positive correlation between sleep disturbances and stress, indicating that higher levels of stress were directly associated with increased sleep disturbances. Additionally, pain catastrophizing demonstrated a statistically significant positive correlation with

stress, suggesting that individuals with higher stress levels were more likely to exhibit pain catastrophizing tendencies. Usual pain level was also positively correlated with pain catastrophizing, demonstrating statistical significance and suggesting that greater usual pain intensity was associated with increased catastrophizing thoughts.

Although sleep disturbances and pain catastrophizing showed a positive correlation, this relationship did not reach statistical significance. Similarly, usual pain levels compared to stress and sleep disturbances revealed a negative correlation with stress and a positive correlation with sleep disturbances, but neither relationship was statistically significant. Lastly, best pain levels showed a negative correlation with stress and positive correlations with both sleep disturbances and pain catastrophizing, yet none of these correlations were statistically significant.

Table 4: Bivariate Correlations Amongst Dependent Variables of Psychosocial Outcomes & Pain Intensity

		PROMIS Stress	PROMIS Sleep	PCS
PROMIS Sleep	<i>Pearson Correlation</i>	0.530**	–	–
	<i>Sig. (2-tailed)</i>	< 0.001	–	–
	<i>N</i>	54	–	–
PCS	<i>Pearson Correlation</i>	0.411*	0.111	–

	<i>Sig. (2-tailed)</i>	0.024	0.560	–
	<i>N</i>	30	30	–
Usual Pain	<i>Pearson Correlation</i>	-0.030	0.132	0.447*
	<i>Sig. (2-tailed)</i>	0.820	0.341	0.013
	<i>N</i>	62	54	30
Best Pain	<i>Pearson Correlation</i>	-0.110	0.109	0.166
	<i>Sig. (2-tailed)</i>	0.393	0.431	0.381
	<i>N</i>	62	54	30
Worst Pain	<i>Pearson Correlation</i>	0.113	0.076	0.356
	<i>Sig. (2-tailed)</i>	0.383	0.587	0.053
	<i>N</i>	62	54	30

** *Correlation is significant at the 0.01 level (2-tailed)*

* *Correlation is significant at the 0.005 level (2-tailed)*

Analysis of Variance Tests

Following the correlation analyses, one-way analysis of variance (ANOVA) Post Hoc Tests were conducted to further examine the relationships between CRP tertiles and psychosocial outcomes. As shown in Table 5, ANOVA tests were performed between CRP tertiles 0-1 and 1-2 with the dependent variables of sleep disturbances, stress, and child pain catastrophizing.

The analysis revealed statistical significance between CRP tertiles 0-1 and stress, indicating a potential association between the lower levels of C-reactive

protein and heightened stress levels. This finding suggests that lower inflammatory marker levels may be linked to heightened psychological stress in this study population.

However, the ANOVA results did not demonstrate statistical significance between CRP tertiles and the variables of sleep disturbances and pain catastrophizing. These findings suggest that while stress may have a potential association with lower CRP levels, sleep disturbances and pain catastrophizing do not appear to significantly differ across CRP tertile groups amongst this sample.

Table 5: ANOVA Post Hoc Test Between CRP Tertiles & Examined Psychosocial Stressor Variables

PROMIS Sleep Disturbances					
CRP Tertiles	<i>Mean Difference</i>	<i>Std. Error</i>	<i>Sig.</i>	<i>Lower</i>	<i>Upper</i>
0.00-1.00	4.31	2.61	0.32	-2.17	10.80
1.00-2.00	-1.61	2.53	1.00	-7.90	4.68
<i>Based on observed means. The error term is Mean Square (Error) = 56.26</i>					
PROMIS Stress					
CRP Tertiles	<i>Mean Difference</i>	<i>Std. Error</i>	<i>Sig.</i>	<i>Lower</i>	<i>Upper</i>
0.00-1.00	7.46*	2.99	0.047	0.06	14.86
1.00-2.00	-2.52	2.99	1.00	-9.91	4.87
<i>Based on observed means. The error term is Mean Square (Error) = 80.35</i>					

Child Pain Catastrophizing Scale					
CRP Tertiles	<i>Mean Difference</i>	<i>Std. Error</i>	<i>Sig.</i>	<i>Lower</i>	<i>Upper</i>
0.00-1.00	9.33	6.47	0.482	-7.21	25.88
1.00-2.00	-9.83	6.47	0.421	-26.38	6.71

Based on observed means. The error term is Mean Square (Error) = 198.02

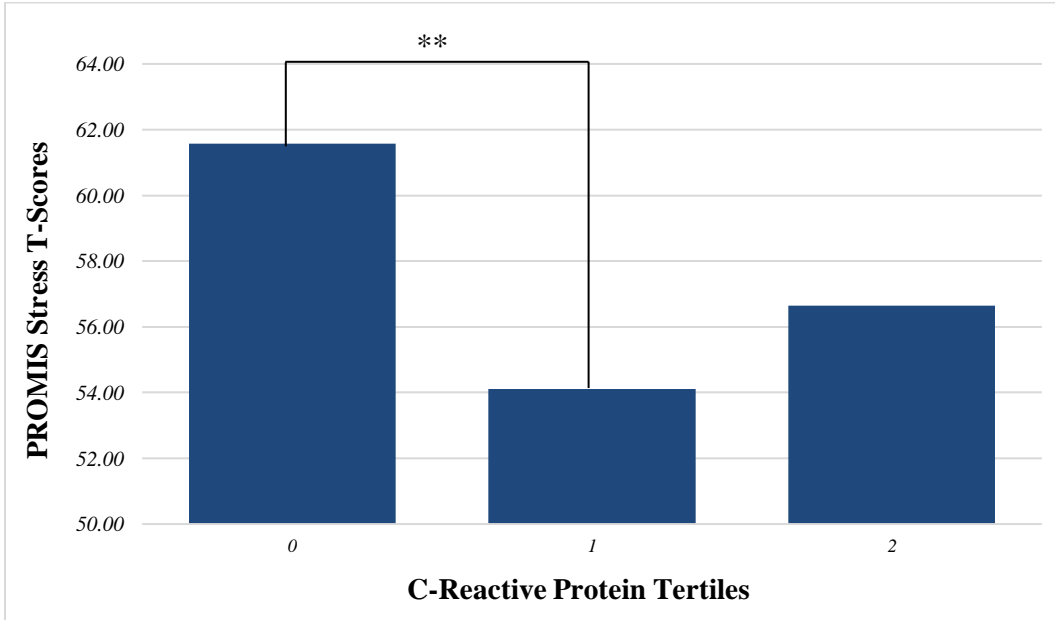
**The mean difference is significant at the 0.05 level.*

Figures 1 through 3 below present bar graphs depicting the estimated marginal means of the ANOVA results, illustrating the relationship between CRP tertiles and the variables of sleep disturbances, stress, and pain catastrophizing.

Stress and sleep disturbances were analyzed against CRP tertiles based on their respective t-scores, while pain catastrophizing was assessed using the total raw score. The bar graphs visually demonstrate the differences across CRP tertiles for each variable.

Among these comparisons, Figure 1 illustrates the statistically significant difference previously observed between CRP tertiles 0 and 1 in relation to stress, indicating that stress levels differ notably between these tertile groups.

Figure 1: Estimated Marginal Means Graph of CRP Tertiles & Stress



*** Statistical significance was observed at the 0.05 level.*

Figure 2: Estimated Marginal Means Graph of CRP Tertiles & Sleep Disturbances

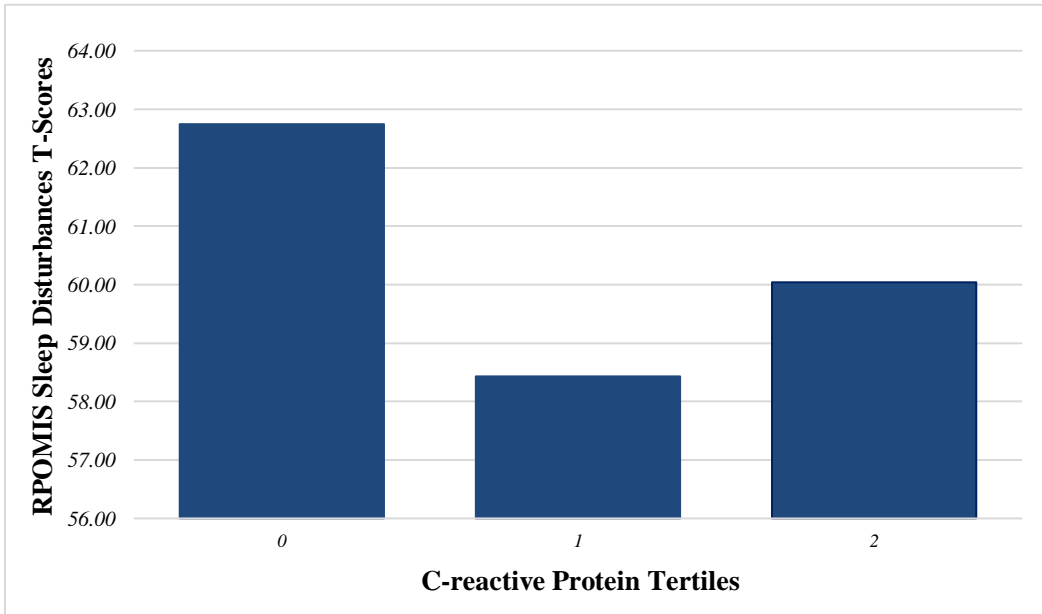


Figure 3: Estimated Marginal Means Graph of CRP Tertiles & Pain Catastrophizing

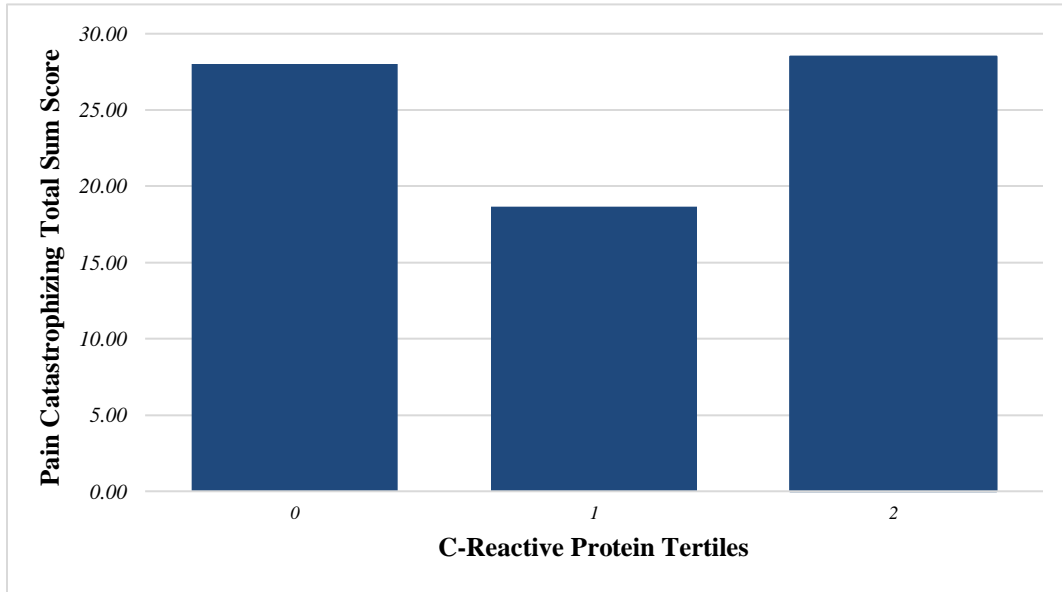


Table 6 demonstrates the results of one-way ANOVA tests conducted to examine potential associations between DHEA levels and the psychosocial variables of sleep disturbances, stress, and pain catastrophizing. To enhance accuracy, the logarithm of DHEA levels was calculated and categorized into two groups (0 and 1).

The findings revealed no statistically significant associations between DHEA and sleep disturbances, stress, or pain catastrophizing.

Table 6: One-Way T-Test Between DHEA & Examined Psychosocial Stressor Variables

PROMIS Sleep Disturbances					
DHEA	<i>Mean Difference</i>	<i>Std. Error</i>	<i>Sig.</i>	<i>Lower</i>	<i>Upper</i>
0.00	3.14	1.17	0.259	58.32	63.06
1.00		1.91		53.15	61.97
PROMIS Stress					
DHEA	<i>Mean Difference</i>	<i>Std. Error</i>	<i>Sig.</i>	<i>Lower</i>	<i>Upper</i>
0.00	1.29	1.34	0.694	54.51	59.93
1.00		2.78		49.63	62.23
Child Pain Catastrophizing Scale					
DHEA	<i>Mean Difference</i>	<i>Std. Error</i>	<i>Sig.</i>	<i>Lower</i>	<i>Upper</i>
0.00	-9.54	2.81	0.276	18.67	30.36
1.00		5.77		9.16	58.84

Figures 4 through 6 present bar graphs depicting the results of the one-way t-tests analyzing the relationship between DHEA levels and the psychosocial variables of sleep disturbances, stress, and pain catastrophizing. These graphical representations illustrate the differences between DHEA and each dependent variable, providing better understanding of the data.

Despite examining potential associations, no statistically significant relationships were identified between DHEA and any of the psychosocial

variables—sleep disturbances, stress, or pain catastrophizing—within this study sample.

Figure 4: Estimated Marginal Means Graph of DHEA & Sleep Disturbances

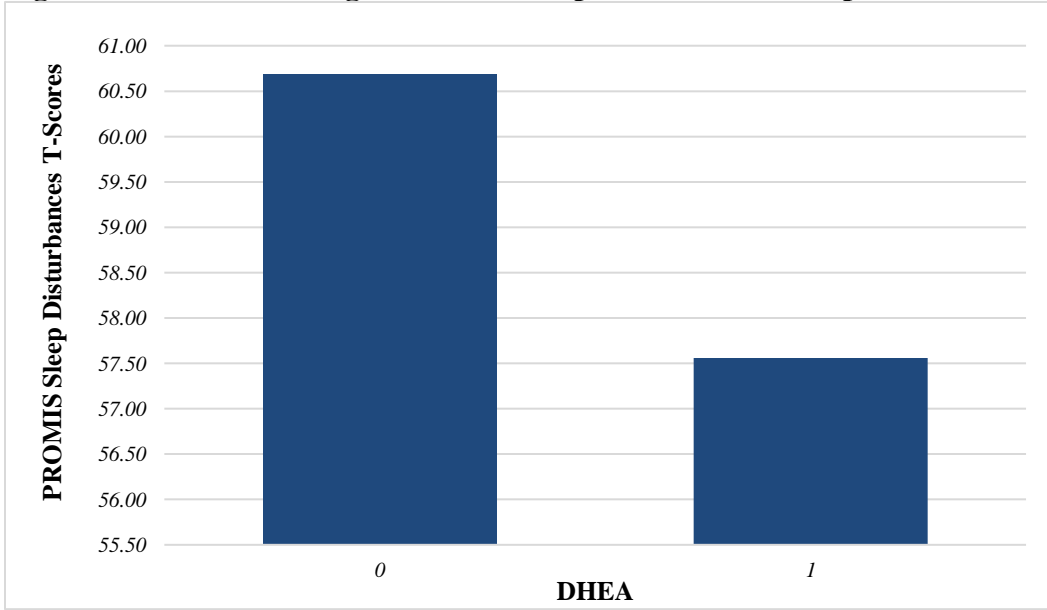


Figure 5: Estimated Marginal Means Graph of DHEA & Stress

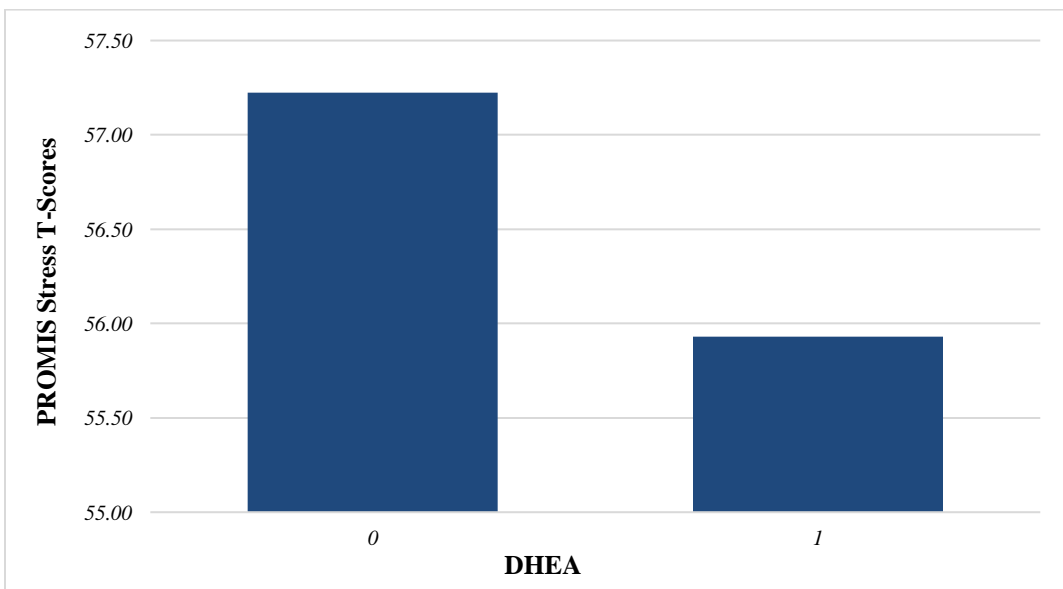
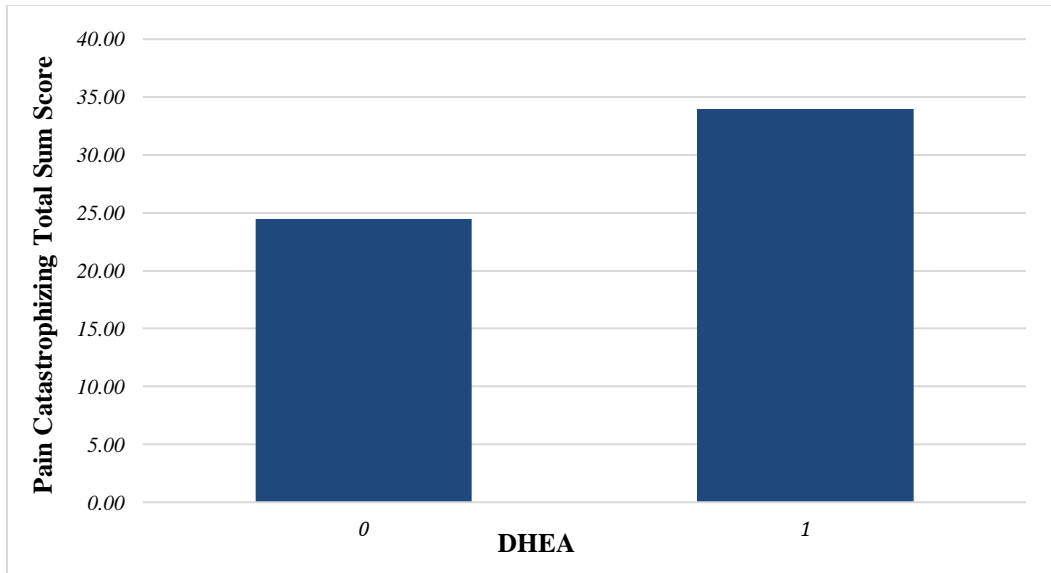


Figure 6: Estimated Marginal Means Graph of DHEA & Pain Catastrophizing



DISCUSSION

The intersectionality influence of biological, psychological, and social factors tunes the experience of pain in ways that we are still striving to understand. Their cumulative influence augments the experience of pain during stressed states, a phenomenon defined as allostatic load in the field of neuropsychology. Allostatic load leads to the from the dysregulation of the nervous system due to extensive and prolonged stress (McEwen, 2000; Nelson et al., 2021). Psychosocial factors have been previously found to contribute to allostatic load, with stress, anxiety, trauma, and depression influencing the body's physiological response to psychological stressors (Nelson et al., 2021). As maladaptive changes accumulate, individuals face a heightened risk of developing other co-morbidities, potentially leading to greater health disparities such as access to care and treatment (Rodriguez et al., 2019). Although various mechanisms are involved in the chronic pain experience, the multifaceted influence of allostatic load may help explain the underlying pathophysiology of the body's response to pain. The role of allostatic load in pain can be seen through numerous components, including the HPA-axis with DHEA, inflammation biomarkers like CRP, and the intersection of sleep and mental health disorders (Nelson et al., 2021; Chen et al., 2014; Borsook et al., 2012).

Previous literature has established the association of salivary stress biomarkers—CRP and DHEA—with mechanisms of chronic pain. As a biomarker

of systemic inflammation, CRP has a well-defined relationship with chronic pain, where individuals with higher CRP levels are more likely to experience chronic pain (Farrell et al., 2023). DHEA, a neuroendocrine hormone integral to the stress experience and HPA axis regulation, has also been linked to chronic pain, with lower levels observed in affected individuals (Grimby-Ekman et al., 2017).

Upon examining the psychosocial component of the pain experience reveals findings that highlight the significant impact of psychosocial stress on chronic pain perception. Stress contributes to various pain-related outcomes, including emotional distress (such as pain catastrophizing), functional disabilities, and heightened pain perception (Meints et al., 2018). Beyond mental health impacts, stress also disrupts sleep, creating a bidirectional relationship that emphasizes the critical role of sleep regulation in maintaining homeostasis and promoting healing. However, chronic stress can disturb this cycle by activating the HPA system (Han et al., 2012). Given DHEA's involvement in HPA system regulation, chronic stress's activation of the system, stress-induced sleep disturbances disrupting HPA regulation, and the understanding inflammation through CRP is a large contributor to all these mechanisms, an underlying connection remains unanswered.

Although the roles of salivary stress biomarkers, sleep disturbances, and psychosocial outcomes in pediatric pain patients have been individually studied, little research has examined the interactions among these factors. This gap in

knowledge motivated the current investigation, which aimed to explore the interplay between sleep disturbances, salivary stress biomarkers, psychosocial and pain-related outcomes in the adolescent chronic pain population.

Summary of Study Results

The cohort for this investigative study primarily consisted of White females, consistent with current literature indicating that chronic pain disproportionately affects White individuals more than people belonging to other racial/ethnic groups and females more than males (Bartley et al., 2013). The highest percentage of participants were high school students (9th to 12th grade), aged 13 to 17 years, with a mean age of 14.51.

Results of bivariate correlations revealed that high stress levels were significantly associated with elevated sleep disturbances, while high stress levels were also linked to increased pain catastrophizing. Notably, the lowest tertile of CRP levels was associated with heightened stress levels. This finding is significant as it

Additionally, in line with prior literature (Quartana et al., 2009), pain catastrophizing was correlated with higher pain levels. These findings suggest that stress interactions are interwoven throughout the pain experience, indicating a

potential link between lower CRP levels to more sleep disturbances, both of which were shown to have significant associations with sleep.

Sleep Quality & Stress in Chronic Pain

Proper sleep is crucial for maintaining homeostasis and regulating the immune system. Dysregulation of the sleep cycle can have major implications, such as activating inflammatory and stress mechanisms that amplify pain sensitivity and perception (Irwin et al., 2023; Haack et al., 2019). This change in the pain experience can lead to a heightened risk of poor pain outcomes and compromised mental health. The role of stressors in sleep disturbances is depicted in Figure 7, where moderators such as chronic pain, stress burden, and other cognitive-emotional factors contribute to sleep cycle dysregulation (Kalmbach et al., 2018).

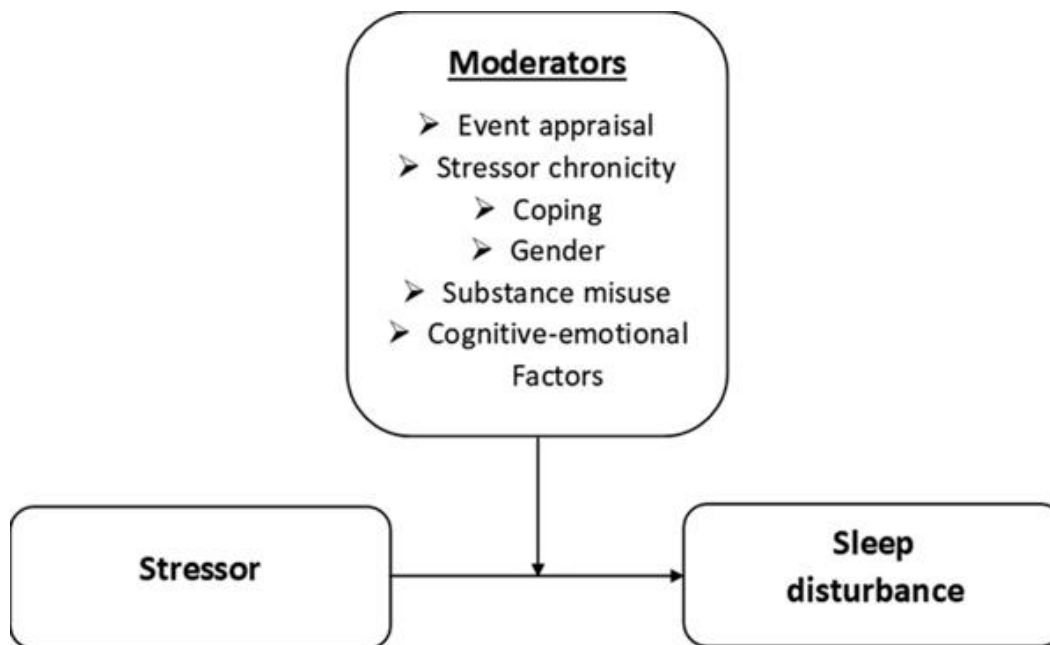


Figure 7: Diagram of Chronic Stressors Resulting in Increase Risk of Sleep Disturbance (Kalmbach et al., 2018).

Meanwhile, current mechanisms underlying sleep disturbances in pain remain poorly understood, studies on rheumatoid arthritis have found that sleep disturbances exacerbate inflammation and increase pain sensitivity (Wilcox et al., 2023). This feedback cycle is further supported by research demonstrating how inflammation contributes to sleep disturbances and stress. Previous studies have shown that CRP levels are elevated in individuals with chronic pain, independently of other psychosocial factors (Farrell et al., 2024). Additional findings indicate that CRP levels are higher in individuals with stress-related disorders, suggesting that stress may be associated with increased CRP levels (Kennedy et al., 2022). Figure

8 illustrates this interconnected feedback loop, particularly among rheumatoid arthritis patients, where various predisposing factors—including psychosocial stress—contribute to circadian rhythm dysregulation, elevating inflammatory responses and heightening pain sensitivity.

This study contributes new insights by highlighting a unique finding in pediatric pain patients: lower CRP levels were associated with psychological stress, which in turn, was associated with increased sleep disturbance and pain catastrophizing. Specifically, CRP was linked with covariates of stress, and sleep disturbances were also associated with stress. It is possible that, although not directly related to specific pain outcomes like sleep or pain catastrophizing, CRP indirectly contributes to poorer function, with a maladaptive cascading effect of multiple other areas.

This noteworthy discovery raises intriguing questions about how stress interplays with sleep disturbances and inflammatory biomarker CRP. One previous study in this area investigated the regulation of CRP and cortisol in patients with severe mental health disorders. This group found that participants with schizophrenia had lower cortisol and CRP ratios which was associated with poor cognitive functioning (Inova et al., 2025). This evidence may help explain the findings in our adolescent pain cohort, where lower CRP levels were associated with stress. This relationship could stem from dysregulation within the HPA axis

and immune system, which play a key role in mediating inflammatory responses. The observed linkage between stress and other covariates within this chronic pain cohort underscores the complex bidirectional interaction they have on pain chronicity.

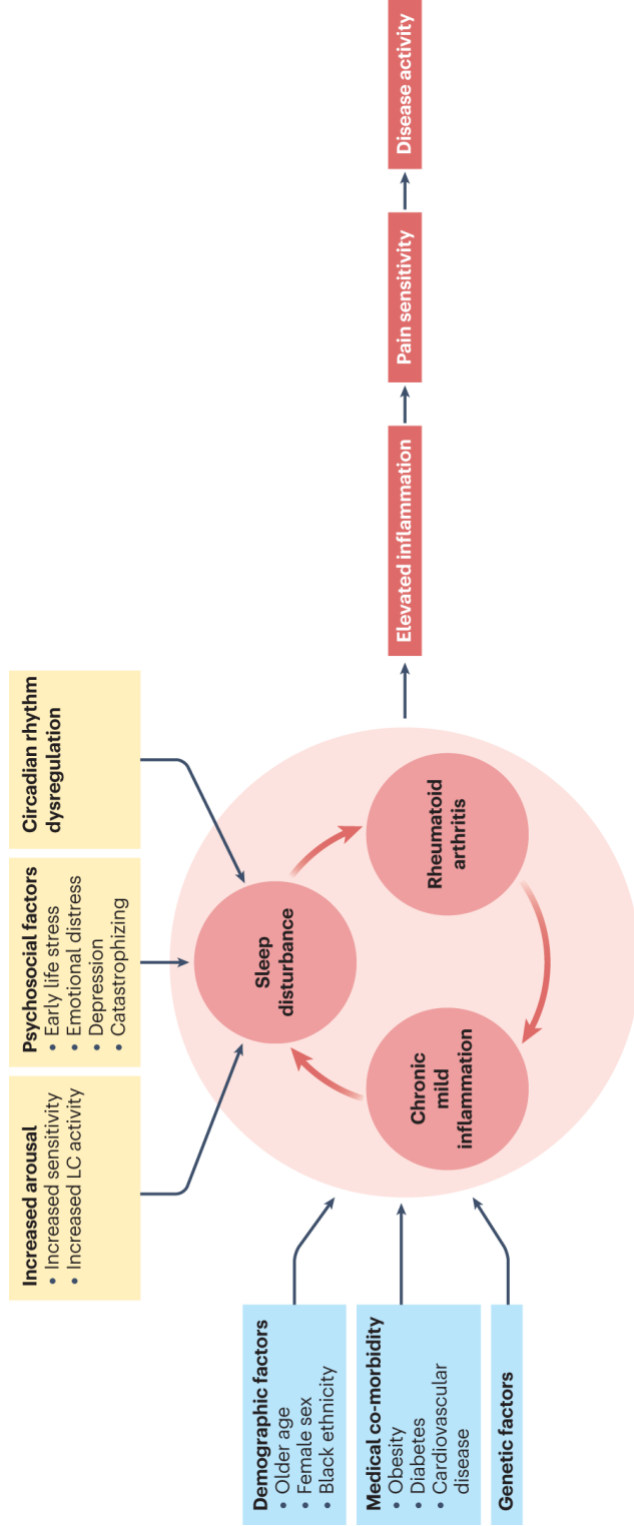


Figure 8: Conceptual Diagram Examining Interplay of Sleep Disturbances to Chronic Pain & Pain-Related Outcomes (Irwin et al., 2023)

DHEA, the other salivary biomarker we examined, plays a critical role in stress regulation via the HPA axis. Previous studies have linked DHEA to chronic pain disorders, with findings indicating that sex hormones like testosterone are associated with lower pain sensitivity, while estrogen shows significant associations with chronic pain (Erceg et al., 2025). Although research on DHEA's role in pediatric pain patients is limited, studies among older adults have found that lower DHEA levels correlate with reduced physical functioning (Rendina et al., 2016). However, within this study population, no significant associations were observed between DHEA, sleep disturbances, and psychosocial outcomes. It is important to acknowledge that the small sample size may limit the generalizability of these results, and future studies with larger cohorts may uncover potential associations between DHEA and these psychosocial outcomes. While the current findings do not establish definitive conclusions about DHEA's role in sleep disturbances, stress, pain catastrophizing, and pain intensity in pediatric pain patients, future research is warranted to further investigate these relationships. Understanding the relationship between DHEA and sleep disturbances, along with other psychosocial outcomes, will offer deeper insight into the role of the HPA axis in regulating the sleep cycle.

Strengths & Limitations

This study demonstrated several strengths, including a robust and representative sample of pediatric pain patients. The use of credible and validated self-report questionnaires, combined with saliva sample collection, offered both subjective and objective insights into the pain experience of this population. Additionally, the choice to utilize saliva collection methods for CRP and DHEA measurement was a less invasive alternative compared to blood serum assays, commonly used in similar studies. Due to the non-invasive nature of this method, the potential stress imposed on participants was minimized, potentially resulting in a more accurate representation of their daily pain experience.

However, several limitations must be acknowledged. The study sample exhibited limited racial and ethnic and gender diversity and was relatively small in size, which may impact the generalizability of the findings. Furthermore, as the study only examined two salivary stress biomarkers (CRP and DHEA), the understanding of biological perspectives on pain was inherently limited to these specific markers. Another limitation was the focus on a narrow set of pain-related outcomes and stressor variables—stress, pain catastrophizing, sleep disturbances, and pain intensity—providing only a small glimpse into the broader influences of psychosocial outcomes on sleep disturbances and salivary stress biomarkers.

Future Directions

Results from this study serve as a foundational step toward more comprehensive research in the field of chronic pain. One important area for future investigation is examining the observed association between lower CRP levels and stress, as well as exploring the potential relationship between CRP and sleep disturbances. Clarifying this connection will offer valuable insights into the bidirectional relationship between systemic inflammation and sleep regulation in pediatric pain patients. While this study did not find significant associations with DHEA, future research should consider a more thorough and diverse examination of the role of DHEA in relation to sleep disturbances and stress among adolescents with chronic pain.

Expanding the examination to include additional stress biomarkers—such as heart rate variability, epinephrine, norepinephrine, and cortisol—along with a wider range of psychosocial outcomes, including anxiety, depression, and trauma, could provide a more holistic understanding of the biopsychosocial relationship of pain. Further, investigating additional pain-related outcomes—such as pain sensitivity, quality of life, and functional disabilities—would deepen our insight into how these factors connect with sleep disturbances and inflammation. Gaining a clearer understanding of this relationship will enable the development of more targeted interventions to support pediatric patients in alleviating their pain

symptoms and leading healthier, more fulfilling lives, free from the persistent burden of pain.

CONCLUSION

Chronic pain affects many individuals with diverse physiological, psychological, and social profiles, creating unique pain experiences that profoundly impact daily life. The intersection of these components forms the foundation of one's pain perception and coping mechanisms. This study highlights the intricate interplay between chronic stress, sleep quality, and CRP, shedding light on a potential linkage between dysregulation in sleep, inflammation, and stress mechanisms that may disturb and exacerbate pain perception.

While this study serves as an initial contribution to the field of pediatric chronic pain, its statistical analyses and findings are not comprehensive or diverse enough to fully delineate the relationship between salivary stress biomarkers, sleep disturbances, and psychosocial outcomes. Nonetheless, the findings underscore the importance of approaching pediatric pain management through a multidimensional biopsychosocial perspective—one that acknowledges and addresses the complex interplay of factors shaping each patient's pain experience. By adopting this approach, healthcare providers can better support the body's regulation mechanisms and alleviate the burden of chronic pain.

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