Examining allostatic load as a biological mechanism linking childhood adversity and pediatric pain

A dissertation defense submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

by

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Table of Contents

List of Tables

List of Figures

Abstract

EXAMINING ALLOSTATIC LOAD AS A BIOLOGICAL MECHANISIM LINKING CHILDHOOD ADVERSITY AND PEDIATRIC PAIN

By: Angela Pascale, M.S.

A dissertation defense submitted in fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

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Despite a strong literature base relating childhood adversity to pain, the biological mechanisms underlying these associations remain unclear. Theoretical and preliminary empirical evidence supports allostatic load as a potential biological mechanism, though prior studies investigating associations between childhood adversity and elevated allostatic load and/or between elevated allostatic load and poorer pain outcomes have primarily focused on adult populations and individual allostatic load indicators rather than a comprehensive index. Thus, the current study built upon prior literature by testing longitudinal relationships between childhood adversity and multiple biological indicators spanning across physiological systems (i.e., comprehensive allostatic load index) and pediatric pain outcomes (i.e., pain intensity and pain-related disability) within the nationally representative sample of early adolescents from the ABCD study. Allostatic load index was hypothesized as a mediator explaining the relationship between childhood adversity and poor pediatric pain outcomes (i.e., pain intensity and pain-related disability). The current study found childhood adversity in year 1 was significantly related to increased pain intensity and pain related disability in year 2, but not in year 3. Allostatic load did not significantly mediate the relationship between childhood adversity and pediatric pain outcomes. Future research should explore other biological mechanisms (e.g., epigenetic mechanisms) that may link childhood adversity to pediatric pain-related outcomes.

Future research investigating allostatic load within a pediatric population should also consider the influence of key developmental stages (e.g., middle childhood, adolescence) to inform the selection of biological indicators as well as consider the type, duration and timing of adversity.

Introduction

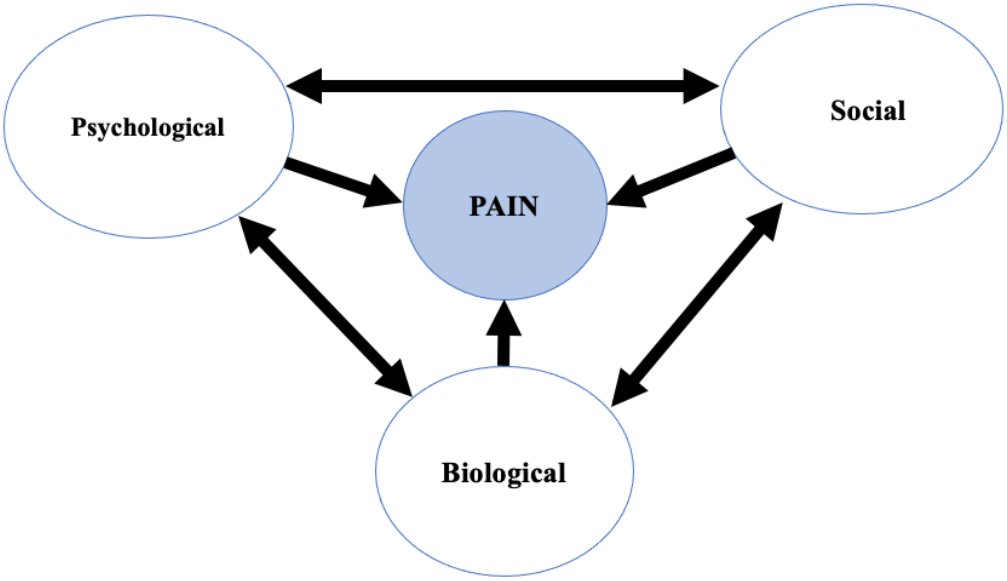
Pediatric pain is a severe public health problem resulting in high levels of disability and health care utilization. Responses from the 2019 National Survey of Children's Health (NSCH) indicated that 7.8% of youth aged 0 to 17 years experienced repeated or chronic physical pain during the past 12 months. This 7.8% national estimate is equivalent to 5,694,000 children across the total population of children in the United States ("U.S. Census Bureau Releases ", 2019). Youth reporting repeated or chronic physical pain are significantly more likely to use mental health, emergency, and other specialty care services (Groenewald et al., 2014; Groenewald et al., 2015). The cost of health care provided to children aged 10 to 17 years with moderate to severe pain in the United States is estimated to total about $19.5 billion annually (Groenewald et al., 2015). Experiencing chronic pain places youth at risk for a lifelong pattern of chronic pain and disability, resulting in profound negative impacts on physical, psychological, and social functioning, as well as high health care costs during adulthood (Gold et al., 2009; Murray et al., 2020; Soltani et al., 2019). Given the formidable individual and public health burdens associated with pediatric pain, it is critical to establish targeted prevention and intervention strategies to reduce pediatric pain risk and improve pain outcomes.

Pain in childhood may be acute, recurrent, chronic, or a combination of acute and chronic (Manworren & Stinson, 2016). Acute pain often resembles a warning of disease or threat to the body and is frequently related to medical procedures (e.g., surgery), injury (e.g., broken bones), an acute illness (e.g., strep throat), or exacerbation of a disease (e.g., juvenile idiopathic arthritis). However, when acute pain is unrelieved, there are a host of physical and psychological consequences, including potential chronic pain development (Manworren & Stinson, 2016). Chronic pain in childhood is described as pain lasting longer than 3 months or recurring pain that

occurs at least three times throughout a period of three months (Nicholas et al., 2019). Historically, acute and chronic pain experiences have been framed exclusively as a biomedical problem. However, decades of pain research demonstrate a complex multifactorial phenomenon underlying the creation and maintenance of pain and pain-related disability that stems from the interaction of various factors, including biological, cognitive, emotional, and psychosocial (Bettini & Steinhorn, 2018; Friedrichsdorf et al., 2016; Riddell et al., 2014).

An overarching framework describing the multifactorial nature of pain and pain-related disability is the Biopsychosocial model, which is extensively used throughout literature and applied in pain research (Bettini & Steinhorn, 2018; Collins, 2019; Matthews et al., 2021; Nelson et al., 2019; Torbey & Ribeiro, 2021). This model has two core concepts: (1) it proposes that biological, psychological, and social factors exert salient influences on pain and (2) that these different sets of factors interact with one another to create and influence the experience of pain and pain-related disability (Fillingim, 2017; Nelson et al., 2017; Truchon, 2001; Turk & Monarch, 2002; Turk et al., 2011). Identifying and ultimately understanding these interactions is critical in elucidating mechanisms driving pain development and maintenance. Thus, defining pain mechanisms entails disentangling the complex interactions among biological, psychological, and social factors as depicted in Figure 1.

Figure 1. Biopsychosocial Model of Pain



Empirical studies applying the biopsychosocial model to understand pediatric pain and pain impact have found associations with a host of psychosocial factors, such as family and parental support, emotional distress, and self-efficacy (Carter & Threlkeld, 2012; Donnelly et al., 2020; Edwards et al., 2016; Lewandowski et al., 2010; Liossi & Howard, 2016; Murphy et al., 2021; Pagé et al., 2013; Simons & Basch, 2016; Sinclair et al., 2016). For example, a systematic review investigated psychosocial factors associated with pain and pain impact in youth aged 19 years and younger diagnosed with pediatric inflammatory bowel disease (Murphy et al., 2021). Results provided consistent evidence of associations of high levels of child depression symptoms and child pain catastrophizing to high pain intensity and pain impact. A systematic review of the relationships among family functioning, pain, and pain-related disability in youth with chronic pain aged between 6 to 20 years (Lewandowski et al., 2010) found that worse family functioning was related to increased pain-related disability. Another systematic review investigated the current literature on personal and contextual factors affecting the functioning and disability of youth with chronic pain (Sinclair et al., 2016). In total, 33 studies were identified, and findings

indicated several personal factors (depression, anxiety, pain catastrophizing) and contextual/environmental factors (parenting characteristics) were associated with higher levels of functional disability. Collectively, these studies supply robust empirical evidence that a host of psychosocial factors are linked to pain-related outcomes in pediatric populations.

Of note, the influence of childhood adversity on pediatric pain is becoming increasingly recognized as a salient psychosocial risk factor related to pain, with several empirical studies finding associations between childhood adversity and worse pain-related outcomes (e.g., increased chronic pain risk, pain-related disability) in both pediatric and adult populations (Burke et al., 2017; Edwards et al., 2016; Nelson et al., 2017; Nelson, Borsook, et al., 2021; Nelson et al., 2020a). There is robust evidence of childhood adversity exposure altering biological processes, producing lasting changes in the functioning of biological systems, and resulting in consequences for development, behavior, and health across the lifespan (i.e., biological embedding) (Aristizabal et al., 2020; Bucci et al., 2016; Nelson, Borsook, et al., 2021). However, knowledge about the specific biological mechanisms underlying the association between childhood adversity exposure and pediatric pain is not clearly mapped and would allow for more precise targeting of biological systems as part of pediatric pain prevention and intervention efforts in the presence of childhood adversity (Bush et al., 2016; Kao et al., 2018; Nelson, Borsook, et al., 2021; Nelson et al., 2020a).

Thus, the current study focused on investigating a potential biological mechanism for the link between childhood adversity and pediatric pain, defined as a mechanistic linkage between adverse childhood experiences and pediatric pain or pain-related disability. The mechanism that was investigated is allostatic load, which represents a key biological mechanism that is under-examined and likely to explain in part the association between childhood adversity exposure and

pediatric pain outcomes (e.g., elevated pain intensity and pain related disability). The following sections will review the literature on childhood adversity and its relationship with pediatric pain and pain-related outcomes. This will be followed by a review of the current evidence for potential biomechanisms linking childhood adversity to pediatric pain, and then a section exploring allostatic load as a specific biological mechanism. Finally, results of the current study will be presented.

Childhood Adversity

Childhood adversity encompasses traumatic experiences and stressful life events prior to the age of 18 years (Bucci et al., 2016). Childhood adversity, early life stress, stressful life events (SLEs), and adverse childhood experiences (ACEs) are all related terms in pediatric stress research referring to a wide range of experiences and contexts that are non-optimal for human development (Gunnar, 2020). They encompass experiences such as physical, sexual, or psychological abuse, neglect, or exposure to violence in the home or community. These experiences may consist of ongoing exposure (e.g., parental neglect), as well as acute time-limited exposures (e.g., witnessing a violent crime; (Cohen et al., 2019).

Exposure to early life adversity may elicit strong, frequent, or prolonged activation of the body's stress response systems and subsequently disrupt normative development among youth, resulting in enduring structural changes and/or physiological dysregulations that lead to physical and mental health consequences across the lifespan (Shonkoff et al., 2021). This is of particular concern given the alarmingly high prevalence of childhood adversity exposure, with national estimates finding under half (46%) of children in the U.S. experience at least one adverse event prior to the age of 18 and one in ten reporting three or more ACEs (Sacks et al., 2014) (Child Trends). Moreover, the effects of childhood adversity not only pose a risk for poor physical

health in childhood but also across the lifespan (Petruccelli et al., 2019). A systematic review found childhood adversity linked to a range of poor health outcomes in adult populations, including physical health consequences (e.g., pain, diabetes, cardiovascular diseases) and mental health consequences (e.g., depressive and anxiety symptoms) (Guidi et al., 2021).

Research has also documented child adversity and subsequent poor health outcomes during childhood (i.e., aged 17 years and below; (Bright & Thompson, 2018; Flaherty et al., 2013; Flaherty et al., 2006; Flaherty et al., 2009)). A study of 96,677 youth aged 0 to 17 years using the National Survey of Children's Health examined the comorbidity between ACEs and physical (e.g., asthma, diabetes), mental (e.g., behavioral or conduct disorder, depression), and developmental conditions (e.g., learning disability, speech, or other language problems) (Bright et al., 2016). Results indicated across all three domains, children who experienced at least one ACE were significantly more likely than children who experienced zero ACEs to have at least one condition. Moreover, there was evidence of a graded relationship, with more ACEs exposure being related to an increased likelihood of having at least one condition in each domain across multiple domains. A systematic review examined prior literature exploring childhood adversity and pediatric health outcomes (Oh et al., 2018). The review identified 35 total studies with participants under the age of 20, with results indicating significant associations between exposure to childhood adversity and delays in cognitive development, asthma, infection, somatic complaints, and sleep disruption.

There is empirical evidence indicating the link between childhood adversity and poor health outcomes manifests as early as in early childhood (aged 2 to 5 years; (Bright & Thompson, 2018). A study of 19,957 children aged 2 to 5 from the National Survey of Children's Health investigated the co-morbidity of ACEs to physical (e.g., asthma, bone, joint, or muscle

problems), mental (e.g., anxiety problems, depression), and developmental problems (e.g., learning disability, ADD or ADHD) (Bright & Thompson, 2018). Results indicated experiencing three or more ACES before the age of 5 years was associated with an increased likelihood of co-occurring conditions across the 3 domains of health (i.e., physical, mental, and developmental).

Biological mechanisms linking childhood adversity to health. The observed health consequences of childhood adversity during the pediatric years indicate detectible physiological manifestations in childhood as a result of toxic or traumatic stress (i.e., prolonged, severe, or repetitive adversity promoting a maladaptive physiological stress response; (Franke, 2014). This is likely due to a hallmark feature of early life – the brain and other biological systems (e.g., neuroendocrine, immune) continuously undergoing critical advancements and having tremendous plasticity (i.e., the ability to adapt to meet environmental demands) (Kuhlman et al., 2017; Mills et al., 2016). This enhanced plasticity marks a period in which experiences are inordinately influential to synaptic growth, neurogenesis, and the organization of neural circuits (Knudsen, 2004). Brain development and other biological systems in childhood are shaped by interactions among social and physical environments, personal experiences, behavior, and biology, which in turn serve as the biological foundation for the transition to adulthood. Thus, childhood adversity exposure has the capability to result in measurable structural and functional changes in stress-sensitive areas within the body and subsequently modify the neurobiological landscape in enduring ways (Cross et al., 2017; Knudsen, 2004). That also makes childhood an optimal time for exploring and uncovering biological pathways linking childhood adversity to short and long-term poor health outcomes (Cross et al., 2017; Kuhlman et al., 2017).

Posited biological mechanisms and biological systems by which early adversity becomes "biologically embedded" in altered physiology span across neural, endocrine, immune, and

metabolic systems (Berens et al., 2017; Kuhlman et al., 2017). For example, prior literature has linked early life adversity to quantifiable variation in brain structure and function (Bick & Nelson, 2016; Hart & Rubia, 2012; McEwen & Gianaros, 2011). Specifically, alterations have been found in the "stress-sensitive" areas of the brain, such as limbic structures (e.g., hippocampus and amygdala), essential for memory, learning, and emotional regulation; and the prefrontal cortex, essential for the development of basic sensory and motor capacities, executive function, and higher cognition (Berens et al., 2017). Thus, it has been proposed that these neurodevelopmental changes act as a pathway in which early life adversity influences a host of health outcomes.

Another posited biological system part of the endocrine system is the hypothalamic-pituitary-adrenal (HPA) axis, defined as a major stress response system that regulates circulating levels of glucocorticoid hormones (Danese & McEwen, 2012; Guilliams & Edwards, 2010; Miller et al., 2007; Wesarg et al., 2020). Early life adversity and subsequent toxic stress elicit chronic activation of the HPA axis, which in turn has been implicated in the development of chronic illnesses, such as cardiovascular, psychiatric, and metabolic-related diseases (Berens et al., 2017; Danese & McEwen, 2012). The immune system is another posited biological system in which early life adversity and subsequent toxic stress lead to elevated inflammation (Kuhlman et al., 2017; Kuhlman et al., 2019). In turn, elevated inflammation has been connected to a host of poor health outcomes, such as cancer (Michael et al., 2006), age-related diseases (Danese et al., 2009), neurodevelopmental changes (Nusslock & Miller, 2016), and pain (Fabien et al., 2005; Kuhlman et al., 2019; Zhang & An, 2007).

However, despite these posited relationships and preliminary evidence, biological pathways through which childhood adversity is linked to physical and mental health

consequences remain unclear. The vast majority of research in this area has been published in theoretical reviews, with limited empirical investigations (Kuhlman et al., 2017; Nelson, Borsook, et al., 2021; Nelson et al., 2020a). Moreover, the limited empirical studies investigating biological mechanisms have primarily been in adult populations with small sample sizes. The robust evidence of co-morbidity between childhood adversity and child health outcomes underscores the need to address these limitations in research in efforts to prevent long-term health consequences. Among these expansive poor health outcomes, pain-related outcomes are becoming increasingly recognized. The following section will review the literature investigating the relationship between childhood adversity and pediatric pain.

Childhood Adversity and Pediatric Pain

A growing body of literature has found associations between childhood adversity exposure and worse pain-related outcomes, including increased risk of chronic pain development, elevated pain intensity, and functional disability due to pain (Groenewald et al., 2020; Nelson, Borsook, et al., 2021; Pieritz et al., 2015; You et al., 2019; You & Meagher, 2016). However, the majority of empirical investigations have been in adults or in late adolescent to adult samples, with fewer samples exclusively in childhood. A study of 5,001 participants aged 15 to 55 years examined the association between reports of ACEs and painful medical conditions (Sachs-Ericsson et al., 2017). The study used ten-year longitudinal data that was obtained from the National Comorbidity Surveys. The baseline survey obtained reports of ACEs and a 10-year follow-up survey assessed for painful medical conditions, such as chronic back and neck problems, severe headaches, arthritis, and other chronic pain. Results indicated that certain ACEs, such as verbal and sexual abuse and parental loss, were associated with a higher likelihood of reporting painful medical conditions. The most common painful medical

condition reported was back and neck problems (25.9%), followed by arthritis or rheumatism (23%). Another study of 3,073 undergraduates, with a mean age of 18.8 years investigated whether more childhood adverse events would be a risk factor for common chronic pain conditions (You et al., 2019). Results indicated that more adverse events were significantly associated with a 1.2 to a 1.3-fold increase in odds of having any chronic pain disorder (e.g., chronic back pain, headache, dysmenorrhea). Collectively, research from adult population studies suggests a significant association between childhood adversity and pain-related outcomes.

Similar patterns of associations have been found in exclusively pediatric studies. A study of 10,464 adolescents aged 12 to 20 years (Stensland et al., 2013) found significant associations between exposure to traumatic interpersonal events and recurrent headaches. Further, they found a dose-response relationship, where an increase in exposure to traumatic events was associated with a higher prevalence of recurrent headaches. A study of 141 youth aged 9 to 19 years investigated the relationship between ACEs and several chronic illnesses, including chronic pain conditions (Nelson et al., 2018). Researchers reported that over 80% of the sample with chronic pain reported at least one ACE in their lifetime. Another study of 48,567 children aged 6 to 17 years using the National Survey of Children's Health (NSCH) explored the association between ACEs and chronic pain risk (Groenewald et al., 2020). Results indicated children with ACEs had increased odds for chronic pain. Further, results indicated a graded relationship, where increased reports of ACEs were associated with an increased likelihood of reporting chronic pain. Another study of 4,738 children aged 10 investigated the relationship between ACEs and pain-related outcomes (Abrahamyan et al., 2022). Results indicated a dose-response association between the

cumulative number of ACEs and increased multisite pain and high-intensity pain compared to children with no ACEs.

Despite the documented relationship between childhood adversity and pain-related outcomes, there is a critical gap in studies investigating biological mechanisms and pathways linking these variables (Nelson, Borsook, et al., 2021; Nelson et al., 2020a). The following section will describe potential biological mechanisms linking childhood adversity to pain-related outcomes.

Biological mechanisms linking childhood adversity to pain. Biological pain mechanisms are defined as mechanistic linkages and interactions among adverse psychosocial experiences and physiological changes that converge in generating pain (Berens et al., 2017). To date, the majority of research in this area has been in theoretical and conceptual reviews, with limited empirical investigations. Mechanisms posited for the link between childhood adversity and pediatric pain have centered on the overlapping neurobiological pathways (e.g., HPA axis) implicated in the physiological stress response as a result of exposure to adversity (McInnis et al., 2020; Nelson et al., 2017; Timmers et al., 2019). However, there are limited comprehensive empirical investigations of the physiological stress response (e.g., neuroendocrine response) as well as limited research considering individual differences (e.g., genetics) that shape a child's pain experience (Nelson, Borsook, et al., 2021; Nelson et al., 2020a).

Conceptual and theoretical reviews have utilized the biopsychosocial framework to posit potential mechanisms linking childhood adversity to pain outcomes in adulthood, with fewer reviews discussing mechanisms during childhood (Burke et al., 2017; Nelson, Borsook, et al., 2021). In a recently published review, a comprehensive theoretical model was proposed that encompasses neuroendocrine and neurobiological based pathways relating to both childhood

adversity, subsequent stress response, and pediatric pain (Nelson et al., 2020a). In this review, childhood adversity was defined as adverse childhood experiences (ACEs) involving psychological trauma (e.g., abuse, parental divorce, conflictual community environments). The authors posited several potential biological processes that may link childhood adversity and pediatric pain development and maintenance.

The condensed proposed theoretical model (Nelson et al., 2020a), adapted from the foundational work of McEwen (1998), centers on the neurobiological connection between adverse experiences, stress response, and subsequent pain. Specifically, this model posits the experience of chronic or repeated stress exposure (e.g., childhood adversity exposure) initiates a host of biological processes and neuroendocrine/immunological changes, including the HPA-axis and autonomic nervous system activation. In turn, prolonged activation of these systems has been linked to allostatic load, defined as physiological wear and tear of multiple physiological regulatory systems in response to repeated stress (Juster et al., 2010; McEwen et al., 2015). Allostatic load subsequently impairs normative negative feedback processes as part of the physiological stress response and thus, disrupts homeostatic functioning. This cyclical process of childhood adversity and subsequent stress response, disruptions in biological processes, development of allostatic load, and in turn impaired negative feedback, has been implicated in pain development and maintenance (Nelson et al., 2017; Nelson et al., 2020).

Of the research that has been performed investigating pathways linking childhood adversity and pain-related outcomes, the majority has focused on associated biological processes (e.g., HPA axis, inflammation, brain regions) as part of the overarching concept of allostatic load (Nelson et al., 2020; Nelson et al., 2021). For example, the authors of the review posited the HPA Axis, regulated by the autonomic nervous system, as a relevant physiological system

connecting childhood adversity and pain as exposure to psychological stress may elicit hyperarousal of the HPA-axis. In addition, immunological-related processes, such as inflammation, were posited as psychological stress increases the production of inflammatory cytokines, such as c-reactive protein, which in turn has been implicated in influencing pain-related outcomes. Neuroendocrine-related processes were posited as well, specifically glucocorticoids, such as dehydroepiandrosterone (DHEA) and cortisol. Both of these hormones are responsible for regulating HPA axis activity and in response to psychological stress become dysregulated. Collectively, alterations in these biological processes encompass allostatic load, which in turn has been implicated in worse pain-related outcomes (Burke et al., 2017; McInnis et al., 2020; Nelson et al., 2017; Timmers et al., 2019).

To summarize, the current study focused on allostatic load as a novel biological mechanism between childhood adversity and pediatric pain-related outcomes (i.e., pain intensity, pain related disability). Allostatic load offers a comprehensive biological mechanism for measuring dysregulation across biological systems rather than exploring and measuring dysregulation in one system, thus, allowing for a broader understanding of the biological embedding of childhood adversity and how it relates to pain-related outcomes (Nelson et al., 2021). The following sections will explore the empirical literature of allostatic load as a biological mechanism and its potential role in linking childhood adversity to pediatric pain-related outcomes. First, the research on allostatic load, including its measurement and current literature linking it to pediatrics, will be reviewed.

Allostatic load

Allostatic load is a core concept in the field of psychobiology and encompasses dysregulation across biological processes implicated in the physiological stress response

(McEwen, 1998; McEwen, 2000; McEwen & Wingfield, 2003). First posited by McEwen et al., 1998, allostatic load describes the biological embedding of early life stress in which significant biological changes occur and in turn, modify the maturation and functioning of physiological regulatory systems (Danese & McEwen, 2012; McEwen & Wingfield, 2003). In research, it serves as a multisystem construct that measures and quantifies stress-induced biological risk across physiological systems (e.g., immune, cardiovascular, endocrine, and nervous systems).

The process of allostatic load, described in Figure 2, first begins when the body faces a stressor where the brain initiates behavioral and physiological adaptations, referred to as allostasis (Juster et al., 2010). As part of allostasis, the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis are activated. This activation then releases primary mediators (e.g., catecholamines, cytokines, glucocorticoids), defined as chemical messengers released as part of allostasis that interact with one another as part of a complex and nonlinear biological network (McEwen, 2000; McEwen & Wingfield, 2003; Juster et al., 2010). Primary mediators both increase and decrease in response to stress and compensate to regain homeostasis and maintain normal physiological system functioning. Thus, short-term allostasis is adaptative and represents a period of the body returning to baseline and regaining normal physiological system functioning (McEwen, 1998; McEwen, 2000; McEwen & Wingfield, 2003). However, when a toxic stress response occurs as a result of chronic and/or severe stress exposure (i.e., childhood adversity), allostatic load ensues.

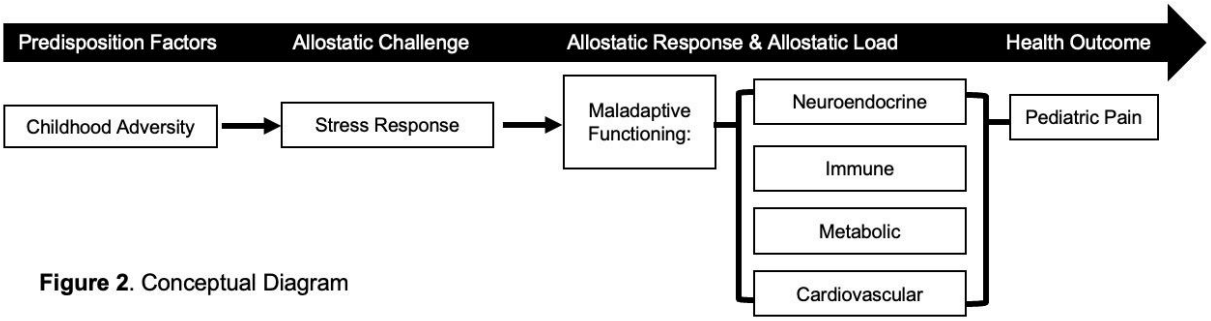


Figure 2. Conceptual Diagram

Allostatic load is characterized by a prolonged release of primary mediators, hindering the development and function of neuroendocrine, immune, metabolic, cardiovascular, and respiratory systems as well as disrupting brain circuitry (McEwen, 2007). Disruptions of physiological development are referred to as secondary outcomes of the stress response. Moreover, given the high integration of physiological systems, the activation and alteration of one system commonly result in alterations in response to other systems and consequently affect physiological functioning across multiple systems (Danese & McEwen, 2012). Thus, secondary outcomes as a result of elevated allostatic load are seen across physiological systems. Examples include high blood pressure, elevated body mass index, and elevated cholesterol levels (Beckie, 2012; Danese & McEwen, 2012; Juster et al., 2010; Mauss et al., 2015; Whelan et al., 2021).

The disruption of brain circuitry and normative functioning across biological systems as part of allostatic load exerts long-term effects on health (Guidi et al., 2021; McEwen, 2012; McEwen & Wingfield, 2003; Misiak et al., 2022). A systematic review examined the relationship between allostatic load and physical and mental health consequences in adult populations (Guidi et al., 2021). This review identified 267 studies and found elevated allostatic load was significantly related to numerous physical health (e.g., increased risk for cardiovascular diseases, cancer, diabetes) and mental health (e.g., mood and anxiety disorders) consequences. Further, in pediatric populations, allostatic load has been connected to physical and mental health consequences as well (Berger et al., 2019; Nelson, Borsook, et al., 2021; Rogosch et al., 2011; Whelan et al., 2021). A systematic review consolidated literature that examined various adverse childhood experiences and biological health outcomes occurring prior to the age of 20 (Oh et al., 2018). Results identified 35 studies and found significant evidence of detectable physiological

manifestations as a result of trauma exposure in youth populations, including delays in cognitive development, asthma, infection, somatic complaints, and sleep disruption.

Measuring allostatic load. Currently, there is no gold standard or consensus on which individual biological indicators are necessary to remain consistent with the theoretical premise of allostatic load in both pediatric and adult populations (King et al., 2019; Whelan et al., 2021). The most common approach for measuring allostatic load is a summative count method, where scores for each indicator are divided into risk quantiles based on the psychometrics established in the foundational study testing allostatic load within an adult population, the MacArthur Studies of Successful Aging (Seeman et al., 2010; Seeman et al., 1997). The MacArthur Studies originally proposed an index of allostatic load comprised of 10 biological indicators, representing systemic dysregulation across the neuroendocrine, cardiovascular, metabolic, and immune systems. This index, however, was not proposed as the gold standard, but rather was the first attempt in operationalizing the latent construct of allostatic load in a population of older adults. Since the time of the MacArthur studies, researchers have extended and revised the selection of biological indicators as part of allostatic load, promoting significant variability in the operationalization of allostatic load in current research (Guidi et al., 2021; King et al., 2019; McLoughlin et al., 2020; Whelan et al., 2021). Thus, there is no consensus on which measurement approach best aligns with the theoretical evidence of allostatic load (King et al., 2019).

A systematic review identified variations in measures across allostatic load studies in adolescent populations (aged 10 to 24) (Whelan et al., 2021). A total of 25 studies were included in the final synthesis, with total biomarkers (i.e., biological indicators) ranging from 1 to 14, and sample sizes ranging from 107 to 2,400. The most common biomarkers measured were cortisol,

epinephrine, norepinephrine, systolic blood pressure, diastolic blood pressure, and body mass index (Whelan et al., 2021). Only 20% of studies (n=5) incorporated biomarkers encompassing neuroendocrine, cardiovascular, metabolic, and immune systems. Instead, most studies (n=17), included indicators of the cardiovascular, metabolic, and neuroendocrine systems, excluding an indicator of immune function. Given the robust research that has linked chronic stress to the dysregulation of the immune system (e.g., elevated inflammation), the authors underscored that importance to include biological indicators reflective of immune system functioning as part of the allostatic load index. Outside of the most common indicators in adolescent populations (i.e., cortisol, epinephrine, norepinephrine, systolic blood pressure, diastolic blood pressure and body mass index), other biological indicators investigated among adolescent populations included dehydroepiandrosterone-sulfate (DHEA-S) (Bahreinian et al., 2013; Nelson, Borsook, et al., 2021; Rogosch et al., 2011), cholesterol (Bahreinian et al., 2013; Sun et al., 2020; Theall et al., 2012), high-density lipoprotein (HDL) (Bahreinian et al., 2013; Sun et al., 2020; Theall et al., 2012), and glycosylated hemoglobin (HBA1c) (Sun et al., 2020; Theall et al., 2012).

Thus, the findings of this systematic review highlighted substantial variation and inconsistency in indicators used to measure allostatic load as well as limited studies incorporating biological indicators across the physiological systems underlying allostatic load (i.e., immune, neuroendocrine, metabolic, cardiovascular) in pediatric populations (Whelan et al., 2021; King et al., 2019). The authors stressed the importance of additional research needed in measuring allostatic load in pediatric populations to increase our understanding of the utility of allostatic load in predictive and explanatory models of psychobiological health in children. Additionally, the authors noted the limited consensus on statistical approaches used in literature

to calculate allostatic load indices and suggested the potential utility of a structured equation modeling (SEM) approach in calculating an allostatic load index.

SEM is an advanced statistical framework that allows for the evaluation of how well a set of observed variables (i.e., indicators) are represented by a latent variable by calculating a factor analysis and quantifying which indicators have the highest factor loading (King et al., 2019). A factor analysis is a method of measurement that identifies underlying latent factors (e.g., unobserved constructs, such as allostatic load) describing the relationship between observed items (e.g., measurable biological indicators, such as blood pressure) (Schreiber et al., 2006). A factor loading is calculated per item which represents the strength of its association with the underlying latent factor (e.g., allostatic load). Thus, a high factor loading indicates that the item (i.e., biological indicator) strongly represents the latent construct (allostatic load) (Brown, 2015). Therefore, indicators with stronger factor loadings explain more of the variance in the respective latent variable being measured (e.g., allostatic load).

Prior studies utilizing an SEM framework have found promising results, with evidence suggesting it as an efficient avenue for operationalizing allostatic load in line with its theoretical premise (Booth et al., 2015; King et al., 2019; Seeman et al., 2010). There are several potential advantages to an SEM approach for allostatic load measurement (Brown, 2015; King et al., 2019). One advantage is how SEM allows for allostatic load to be treated as a continuous variable, rather than the common approach of dichotomizing individual indicators at a high-risk cut-off level and thus, potentially leading to a loss of information on the indicators. Second, a factor analysis allows researchers to explore proposed factor structures for conceptualizing allostatic load and identify the relative weights of the indicators to the allostatic load latent variables. This allows for drawing conclusions of which biological indicators best represent

allostatic load. Lastly, an SEM framework may reduce the measurement error of allostatic load by reflecting only the common variance shared among each indicator variable, thus creating a more reliable and valid measure.

There is a limited number of pediatric studies that have utilized SEM to measure allostatic load, with only one study to date applying this approach. A study of 1,900 adolescents aged 12 to 18 years measured allostatic load as a latent variable using factor analyses and utilized findings from adult population studies as a guide (King et al., 2019). A total of 14 biological indicators were measured as part of allostatic load. In total, the authors explored five allostatic load factor structures, with Figure 3 illustrating one, a unidimensional factor structure, out of the tested five-factor structures.

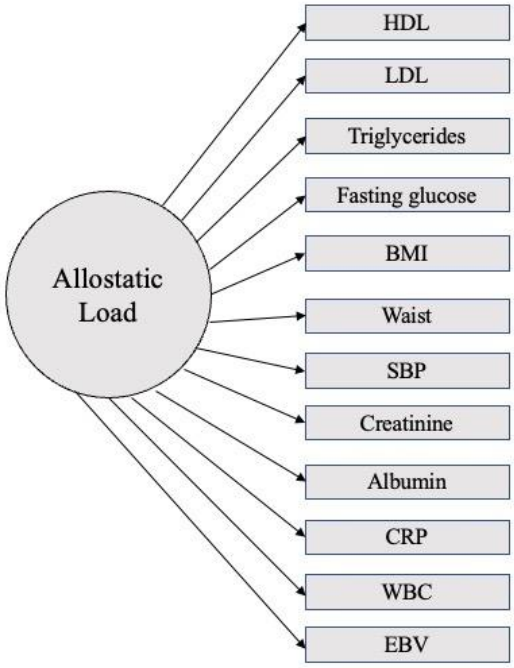


Figure 3. Unidimensional Factor Structure (King et al., 2019)
Notes. SBP = Systolic blood pressure; BMI = Body mass index; HA1C = glycated hemoglobin; HDL and LDL = High-density and Low-density lipoprotein; CRP = C-reactive protein; WBC = White blood cell count; EBV = Epstein-Barr viral index

Results indicated a unidimensional allostatic load structure was the best measurement approach. This is interpreted as all 14 indicators signified dysregulation of various body systems and shared common variance representing the construct of allostatic load. This contrasts with literature on adult populations, primarily supporting second order-factor structures (Booth et al., 2013; Johnston, 2004; Seeman et al., 2010). This may potentially illustrate the salience of age and corresponding differences in how stress manifests itself physiologically over time, underscoring the need for future research for measuring allostatic load utilizing an SEM framework among pediatric populations. Moreover, the authors found the biomarkers associated with dysregulation of the metabolic system (e.g., BMI, waist circumference) were the best indicators of allostatic load (i.e., had the highest factor loadings). Consistent with the prior adolescent study utilizing an SEM approach to measure allostatic load, the current study utilized a unidimensional factor structure underlying allostatic load.

Given how stress may manifest physiologically differently over time, the following sub-section will review the implications of allostatic load and health during childhood.

Childhood adversity, Allostatic Load, and Health

Despite evidence of detectable physiological manifestations as part of allostatic load in pediatric populations (Dahmen et al., 2018; Evans, 2003; Evans et al., 2007; Oh et al., 2018; Thomason et al., 2015; Tyborowska et al., 2018), the majority of prior research investigating associations among childhood adversity, allostatic load and health have been in adult populations. Moreover, empirical evidence of this relationship mainly consists of studies measuring an individual biological indicator from a single physiological system as part of allostatic load, rather than multiple biological indicators spanning across physiological systems (Nelson et al., 2021). Nevertheless, there is evidence of elevated individual biological indicators

in response to adversity exposure within adult populations, suggesting the utility of a more comprehensive measure of biological indicators spanning across multiple systems (i.e., allostatic load) (Mauss et al., 2015; Guidi et al., 2021; Whelan et al., 2021). A scoping review consolidated prior studies that investigated the relationship between adverse childhood experiences (ACEs) and elevated biological indicators in adults (Deighton et al., 2018). The authors found significant evidence of a link between ACEs and elevated biological risk markers (e.g., inflammatory markers, cardio-metabolic risk markers). Another systematic review consolidated prior studies that used a composite allostatic load index in adult populations to explore relationships between childhood adversity with allostatic load (Misiak et al., 2022). Results also indicated ACEs were associated with an elevated allostatic load index in adults. Thus, collectively, findings from adult population studies suggest the utility of allostatic load as a construct examining and quantifying the biological embedding of childhood adversity (Deighton et al., 2018; Misiak et al., 2022).

Although studies of childhood adversity and allostatic load have largely focused on adult populations (Whelan et al., 2021; Nelson et al., 2021), there is preliminary support highlighting the applicability of allostatic load in understanding pediatric health outcomes (Nelson, Borsook, et al., 2021; Soares et al., 2021). A systematic review summarized evidence on epigenetic and/or neuro-immuno-endocrine embedding of adverse childhood events in pediatric populations under the age of 18 (Soares et al., 2021). Adverse events in this review included individual ACE types (e.g., physical abuse) as well as a cumulative measure of ACEs. The most common adverse event was sexual abuse, followed by a cumulative life stressor assessment, and physical neglect. The biological indicators were divided by biological processes: immune system, structural and functional brain changes, and genetic and epigenetic. Populations consisted of any individual

under the age of 18. The most common age range was during childhood with a total of 34 studies identified (seven from 3 to 12 years, five from 3 to 5 years, and 21 from 6 to 12 years), followed by 15 during adolescence (12 studies from 13 to 18 years, one from 13 to 15 years, and two from 15 to 18 years) and seven studies including all youth under 18 years of age.

Twenty-seven studies were identified in the systematic review that addressed the biological consequences of ACEs on the immune system, with seventeen studies finding a positive association between ACE exposure and biological indicators of the immune system (Soares et al., 2021). Thirteen studies addressed structural and functional brain changes, with findings from ten studies indicating a strong association between ACE exposure and structural brain changes (e.g., hippocampal volume, amygdala functional connectivity, BDNF). Further, twenty studies examined genetic and epigenetic factors (i.e., DNA methylation), with findings from eighteen studies indicating higher methylation in participants exposed to ACEs.

Consistent with adult population literature, the authors noted the limited research investigating associations between childhood adversity and a comprehensive allostatic load index in pediatric populations (Soares et al., 2021). To date, only a few studies have examined associations between childhood adversity and elevated allostatic load index in a pediatric sample. For example, a study of 247 children in low-income families aged 8 to 10 years investigated associations between child maltreatment and indicators of allostatic load in relation to health problems (e.g., physical health status, utilization of health services) and psychological symptomatology (e.g., depression) (Rogosch et al., 2011). Childhood adversity was measured using the maltreatment classification system (MCS), assessing subtypes of maltreatment (i.e., neglect, emotional maltreatment, physical abuse, and sexual abuse). The allostatic load index consisted of body mass index, waste-hip ratio, blood pressure, cortisol, and DHEA. Results

indicated childhood adversity did not independently predict differences in allostatic load. However, the authors noted their sample consisted of children from low-income families and thus, were presumed to experience high levels of stress, given the neighborhoods they were living in and low socioeconomic status. In turn, this may have confounded their results given a high-stress sample and explain the elevated allostatic load in the overall sample (only 26.9% of the sample had zero risk factors). Collectively, a significant limitation of studies investigating associations between adversity and elevated allostatic load index in pediatric populations, is the selection of study samples (i.e., youth in low-income families or rural elementary schools), affecting the potential generalizability of findings (Evans, 2003; Rogosch et al., 2011). Thus, a national representative sample would be of particular importance in exploring and drawing conclusions on the associations between childhood adversity, allostatic load, and health.

Overall, the findings from this systematic review provide strong evidence of observed relations between childhood adversity and individual biological risk indicators in childhood (i.e., risk defined as measured increases or decreases depending on the nature and type of biological indicator). Given the evidence of the association between individual biological indicators and childhood adversity, the authors suggested utilizing allostatic load as a comprehensive measure of biological risk and exploring its utility as a pathway linking early life adversity to physical health consequences (Soares et al., 2021). As reviewed previously, physical health consequences as a result of allostatic load are expansive and include pain-related outcomes (e.g., pain intensity, pain-related disability). The following section will review evidence of pain as a specific physical health consequence as a result of allostatic load as well as review allostatic load as a potential mechanism in the childhood adversity-pain relationship.

Childhood Adversity, Allostatic load, and Pain

Allostatic load has been implicated in pain-related outcomes, including chronic pain risk, intensity, and disability (Nelson et al., 2017; Nelson, Borsook, et al., 2021; Timmers et al., 2019). The associations between allostatic load and pain are explained by complex overlapping physiological pathways (Nelson et al., 2020a; Woda et al., 2016). Specifically, disruptions in biological processes as part of allostatic load (e.g., HPA-axis and autonomic nervous system (ANS)) are implicated in pain chronicity and intensity (Nelson et al., 2020). For example, the reactivity of the sympathetic and parasympathetic nervous systems as part of the ANS has been implicated in affecting pain processing via heightened central sensitization (def; abnormal state of responsiveness of the nociceptive system resulting in pain hypersensitivity; (Latremoliere & Woolf, 2009; Nelson et al., 2017). This is supported by a study that found childhood adversity was associated with increased activation of the ANS (measured via electrodermal activity and heart rate) in youth with chronic pain compared to healthy controls (McInnis et al., 2020). Another example of a shared physiological pathway between allostatic load and pain is through HPA axis activation, a hallmark feature of allostatic load (Woda et al., 2016). Specifically, increases and decreases in basal cortisol levels as well as overall alterations in cortisol reactivity, a primary stress hormone and regulator of HPA axis functioning, have been implicated in chronic pain risk (Woda et al., 2016). Notably, HPA axis hyperactivation and associated physiological consequences have been directly implicated in increasing risk for the development and or/maintenance of chronic pain regardless of adversity exposure (Gatchel et al., 2007; Grunau & Tu, 2007; McEwen & Kalia, 2010). Overall, there is robust evidence of associations between allostatic load and associated biological processes (e.g., hyperactivation of ANS, HPA) and pain-related outcomes (e.g., chronic pain risk, pain intensity) (Borsook et al., 2012; Chapman et al., 2008; Woda et al., 2016).

Despite associations found between allostatic load and associated biological processes with childhood adversity and pain-related outcomes, there remains limited empirical evidence investigating allostatic load as a mechanism mediating the relationship between childhood adversity and pain-related outcomes. Theoretical and conceptual reviews, however, have posited several potential biological mechanisms and processes linking childhood adversity and pain (Burke et al., 2017; Bush et al., 2016; Nelson, Borsook, et al., 2021; Nelson et al., 2020a). Posited biological mechanisms center on the overlap between the neurobiology implicated in childhood adversity (i.e., subsequent biological stress response) and processes involved in altered pain processing (Nelson et al., 2020, Nelson et al., 2021). Theoretical models conceptualizing possible mechanisms linking childhood adversity to pain-related outcomes are primarily in adult populations, with less focus on exploring these mechanisms while individuals are still in childhood (Nelson et al., 2021, Burke et al., 2017). However, conceptual reviews with a focus on pediatric populations suggest the potential utility of allostatic load in elucidating the childhood adversity- pediatric pain relationship (Nelson et al., 2017; Nelson et al., 2020). Notably, a review posited a theoretical model describing allostatic load and associated biological processes as it relates to childhood adversity and pediatric chronic pain risk (Nelson et al., 2017).

Specifically, the authors suggested allostatic load and associated biological processes (e.g., HPA axis) are likely to mediate the physiological effect of prolonged stress as a result of childhood adversity exposure on chronic pain risk (Nelson et al., 2017). An example is the hyperactivation of the HPA axis, the primary stress response system comprised of the hypothalamus, pituitary gland, and adrenal cortex, which acts as a primary moderator of the neuroendocrine and neurobiological stress response (de Kloet et al., 2005; Frodl & O'Keane, 2013). Common biological indicators reflecting HPA axis functioning include levels of

glucocorticoids (e.g., cortisol) and hormones (e.g., dehydroepiandrosterone (DHEA)) (Taylor-Cavelier et al., 2021). Prolonged glucocorticoid release can have severe consequences on physiological functioning and has been implicated in pain-related outcomes. For example, it may affect structural brain development, where several studies have found prolonged glucocorticoid release in response to toxic stress exposure resulting in a decrease in hippocampal volume (Carrion et al., 2007; Frodl & O'Keane, 2013; McEwen, 2001). Moreover, the amygdala, prefrontal cortex, and locus coeruleus are additional brain regions impacted by prolonged activation of the HPA axis. These major brain areas are implicated both in the stress response and pain processing, suggesting a shared underlying neurobiological mechanism (de Kloet et al., 2005; Nelson et al., 2020a). In sum, there is a strong theoretical basis of shared neurobiological mechanisms uncovering the stress-pain relationship (Nelson et al., 2020, Nelson et al., 2021). Given how childhood adversity elicits a toxic stress response, allostatic load may serve as a potential mechanism explaining the association between childhood adversity and pain-related outcomes.

To date, only one study has empirically tested associations of childhood adversity, allostatic load, and pediatric pain, with no prior studies testing the mediating effect of allostatic load (Nelson, Bento, et al., 2021). In a study of 61 children and adolescents with chronic pain aged 10 to 17, the authors examined relations between childhood adversity, pain intensity, fear of pain, functional disability, and allostatic load. Childhood adversity was defined as adverse childhood experiences (ACEs) using the parental report of the Childhood Trust Events Survey (Pearl, 2000). The allostatic load index was comprised of cortisol, DHEA, c-reactive protein, blood pressure, waist-hip ratio, and BMI. Analyses included calculating a cumulative allostatic load index (a scale of 0 to 6 consisting of individual allostatic risk factors) and dividing the

sample into a high risk (i.e., two or more risk factors), and a low-risk group. Descriptive statistics revealed 70.5% of their sample reported at least one ACE and almost half of the sample (45.9%) reported two or more ACEs. Most participants (80.3%) had at least one risk factor for allostatic load, followed by 57.4% of participants with two or more risk factors. Results indicated ACEs and cumulative allostatic load risk score were not related and the only individual allostatic load factors related to ACEs was the waist to hip ratio indicator. However, the authors suggested these nonsignificant results may stem from the study methods that can be improved in future investigations, including the inclusion of a control group, a longitudinal design, and a larger sample size. The authors called for future research to assess allostatic load and pain-related outcomes in a nationally representative sample to broaden the understanding of the associations between ACEs, allostatic load, and pediatric pain.

Relatedly, another study in a pediatric population explored associations of childhood adversity, single biological indicators, and pain (McInnis et al., 2020). The study consisted of 35 youth aged 9 to 17 with chronic pain and two control groups of 35 youth that examined differences in relationships among adverse life events, and biological markers (heart rate, heart rate variability, c-reactive protein (CRP)) between children with chronic pain and control groups (McInnis et al., 2020). Results showed youth with chronic pain had increased reports of adverse life events as well as elevated heart rate, heart rate variability, and CRP compared to controls. Although the directionality of these associations was not investigated apart of the study, findings suggest youth with chronic pain report more adverse life events and have elevated biological markers compared to age- and sex-matched healthy controls. This supports the potential utility of allostatic load as a comprehensive mechanism linking childhood adversity and pain among youth.

Conclusion

To summarize, there is significant evidence of childhood adversity resulting in toxic stress response and subsequent allostatic load. In turn, there is evidence supporting the relationship between allostatic load and pain-related outcomes. Despite the robust evidence of these direct effects (i.e., childhood adversity to allostatic load, allostatic load to pain), there remain limited empirical studies investigating the possible mediating effect of allostatic load on the childhood adversity-pediatric pain relationship.

The Current Study

Despite a strong literature base relating childhood adversity to pain, the biological mechanisms underlying these associations remain unclear (Nelson et al., 2021; Burke et al., 2017). Theoretical and preliminary empirical evidence supports allostatic load as a potential biological mechanism, though prior studies investigating associations between childhood adversity and elevated allostatic load and/or between elevated allostatic load and poorer pain outcomes have primarily focused on adult populations and individual allostatic load indicators rather than a comprehensive index (Soares et al., 2021, Nelson et al., 2021; Deighton et al., 2018; McInnis et al., 2020). Moreover, the few pediatric studies assessing allostatic load in relation to childhood adversity and/or pain have been in small samples drawn from specific populations (i.e., youth in low-income families or rural elementary schools) that have only tested associations of childhood adversity, allostatic load, and pediatric pain, with no prior studies testing the mediating effect of allostatic load (Evans, 2003; Rogosch et al., 2011; Nelson, Bento, et al., 2021).

Thus, the current study built upon prior literature by testing relationships between childhood adversity to multiple biological indicators spanning across physiological systems (i.e.,

comprehensive allostatic load index) and pediatric pain outcomes (i.e., pain intensity and pain-related disability) within a nationally representative sample of early adolescents. In addition, the current study expanded on limitations in the current literature by determining the directionality of associations among childhood adversity, allostatic load, and pediatric pain and testing the mediating effect of allostatic load index in the childhood adversity-pediatric pain relationship using a longitudinal design. Given how childhood adversity has been linked to allostatic load and has been implicated in the development and maintenance of pain (Nelson et al., 2021), a comprehensive allostatic load index was hypothesized as a mediator explaining the relationship between childhood adversity and poor pediatric pain outcomes (i.e., pain intensity and pain-related disability). Mechanistic studies are essential for establishing youth pain prevention and intervention strategies (Day et al., 2012; Flor, 2014; Jensen et al., 2014).

Aims and Hypotheses

The current study had two primary aims:

Aim 1. To validate the relationship between childhood adversity to allostatic load index and between childhood adversity to pediatric pain outcomes in a nationally representative sample of early adolescents.

> **Hypothesis 1a.** Childhood adversity will be associated with poor pediatric pain outcomes (i.e., higher pain intensity and pain-related disability).
>
> **Hypothesis 1b.** Childhood adversity will be associated with an elevated allostatic load index.

Aim 2. To test the mediating effect of an allostatic load index on the association between childhood adversity and pediatric pain outcomes using a longitudinal design within a SEM framework.

Hypothesis 2. Allostatic load will mediate the relationship between childhood adversity and pediatric pain, such that elevated allostatic load will explain childhood adversity's impact on poor pain outcomes (i.e., higher pain intensity and pain-related disability).

Method

Participants

The proposed study involved secondary quantitative data analysis from the Adolescent Brain Cognitive Development (ABCD) Study. The ABCD Study is a longitudinal U.S. population-based study of 11,875 youth, born between 2006 and 2008 (aged 9 to 10 at baseline), who will be followed for up to 10 years (Garavan et al., 2018). In the current study, the 4.0 data release was used, which include data from the overall sample at baseline (beginning in 2018), Year 1 (2019), Year 2 (2020), and Year 3 (up until 2021).

Procedure

Youth were recruited from public schools, including charter and private elementary schools. To achieve sociodemographic variation and demographic diversity of the U.S. population, a stratified probability sample of schools was selected for recruitment. However, some participants (<10%) were recruited from other avenues as well, such as community events, referral systems, and non-targeted schools. Further, recruitment was restricted to schools and other avenues within 50 miles of a research institution (i.e., study site) with research expertise and neuroimaging equipment required by the ABCD protocol. In total, there were 21 study sites as part of the ABCD study, distributed across the U.S. After identifying schools within 50 miles of each study site, a subset of schools was selected randomly, and then eligible children from each school were recruited. Recruitment materials were sent out to caregivers via delivery of

hard and electronic copies for initial recruitment. A total of 11,875 children and caregivers completed the baseline assessment. Once a year, all youth are asked to attend an in-person assessment session where self-report and guardian report, behavioral, and biospecimen collections take place. There are currently curated data available for baseline and Years 1 through 4 (up until 2021). The current study will use data collected at baseline, Year 1, Year 2, and Year 3. Specifically, Year 1 childhood adversity reports were selected to assess the longitudinal effects on Year 3 pain outcomes. Year 2 was selected for allostatic load variables given the availability of biomarkers collected during this survey year.

Measures

Covariates. The following covariates that were significantly associated with Year 3 pain outcomes were included in the primary analyses using correlations, one-way ANOVA, and t-tests ($p > 0.05$). Baseline caregivers' reports on the child's race/ethnicity (coded as White = 1, Black = 2, Native American = 3, Asian = 4, and Hispanic = 5,), and sex (male = 0, female = 1) were controlled for in the analyses. For analyses, a dummy code variable was created for race/ethnicity with White participants selected as the reference group as they are the largest racial/ethnic group in the sample. In addition, sex hormones (i.e., estradiol and testosterone) assessed via saliva (continuous measure in pg/mL), were controlled for in Year 1. In addition, pubertal development stage was controlled using the parent-report Pubertal Development Scale (PDS), a questionnaire assessing physical changes associated with puberty. Based on the questionnaire results according to parents, youth were then designated a Puberty Category Score with approximate pubertal stages (pre-, early, mid-, late, or post-pubertal) (Cheng et al., 2021). Child anxiety and depression-related symptoms were controlled for in Year 1 using the anxious/depressed syndrome scale from the Child Behavior Checklist (CBCL), a parent

questionnaire that assesses the behavioral and emotional problems of children (Achenbach, 2001). Year 1 was selected for sex hormones, PDS, and child anxiety and depression-related symptoms due to availability of these measures in that survey year as well as to examine potential confounding factors influencing the relationship between early adversity and later pain.

Allostatic Load. Allostatic load was calculated as a latent variable using data from Year 2 and was represented by several biological indicators that characterize stress-mediated systematic physiological dysregulation of the following systems: neuroendocrine, immune, cardiovascular, and metabolic. This approach allows indicator variables to be treated as continuous, rather than the common practice of dichotomizing values at a high-risk cut-off level and potentially leading to loss of information in the indicators. Biological indicators were selected based on availability in the ABCD data and prior allostatic load literature. Neuroendocrine: Dehydroepiandrosterone (DHEA), collected through saliva using the passive drool method. Immune: Immune cell indicators of white blood cell count (WBC) and red blood cell distribution width (RDW) collected through a blood draw. Cardiovascular: High-density lipoprotein cholesterol (HDL) measured via a blood draw; resting heart rate, and systolic and diastolic blood pressure measured using an instrument that provided three consecutive blood pressure and pulse measurements, with a 1-minute interval between each reading. Metabolic: Body mass index (BMI), waste-hip ratio.

Childhood adversity. Youth completed the Life Event Scale, a 25-item questionnaire administered annually beginning in Year 1 (Hoffman et al., 2019; Karcher & Barch, 2021). Youth are asked to report yes or no to experiencing a given event. Examples items include, “Someone in the family died?”, “Parents separated or divorced?” or “Saw or heard someone getting hit.” (for complete list of items see Appendix). A sum score was calculated, with each

"Yes" coded at 1, making a total range of 0 to 25. Measuring early-life adversity as a cumulative risk score is a well-validated approach, with several childhood adversity measures utilizing this summed score approach (Bethell et al., 2017; Burgermeister, 2007; Evans et al., 2013).

Pain Intensity and Pain-Related Functional Disability. Youth completed a pain questionnaire based on the Seattle Child and Adolescent Pain Questionnaire (CAPQ) beginning in Year 2 and repeated annually (ABCD). Youth are first asked if they have experienced pain within the past month. If they reported yes, they proceed to answer several items assessing aspects of pain. One item assessed pain intensity over the past month ranging from 1 = *not at all* and 11 = *the worst*. The numerical rating scale is a valid measure of pain intensity used throughout pain research (Miró et al., 2009; Rothaug et al., 2013; Thong et al., 2018; von Baeyer et al., 2009). Another item assessed pain-related functional disability asking: "how much did the pain stop you from doing your normal activities," with a 10-point scale option ranging from 1 = *not at all* to 11 = *stop me from doing anything*. If youth did not report pain the past month, they were coded as 0 on pain intensity and pain-related disability. The pain-related functional disability item is consistent with other well-validated questionnaires assessing limitations of normal activities due to pain on a numeric rating scale, such as the Pain Disability Index (Tait et al., 1990).

Data Analysis Plan

Descriptive Statistics and Preliminary Analyses

All analyses were done using R Core Team (2020). Descriptive statistics were calculated for study variables, including mean, standard deviation and range for continuous variables and frequencies and proportion for categorical variables. Pearson correlations were estimated to examine associations among child depression and anxiety symptoms, sex hormones (i.e.,

testosterone and estradiol), individual allostatic load indicators, and pain variables. And one-way ANOVAs and t-tests were calculated to examine for differences in pain outcomes by race/ethnicity, sex, and pubertal development stage. Significant covariates were controlled for in subsequent analyses. Missing data was handled using list-wise deletion.

Missing Data. Participants with reports of allostatic load indicators across the four key physiological systems were included in the current study analyses (i.e., metabolic, cardiovascular, neuroendocrine, and immune). Few studies in adolescent populations have incorporated biological indicators across metabolic, cardiovascular, neuroendocrine, and immune systems, where a systematic review found that out of 25 studies that assessed allostatic load within adolescent populations, only 20% (n = 5) incorporated biological indicators across the four physiological systems (Whelan et al., 2021). However, due to COVID-19, there were significant patterns of missing data in the ABCD data 4.0 release. Specifically, from early 2020 continuing into late 2021, blood and in-person laboratory tests (e.g., blood pressure) were not collected, and subsequently, this missingness significantly impacted the latter half of the Year 2 follow-up data and the first half of the Year 3 follow-up data. Thus, there is significant missing blood-based (i.e., immune system indicators) data in Year 2 with less than 500 reports (see Table 1).

Table 1 Sample Sizes of Study Variables of Overall Sample with Y3 Pain Reports and Sub-Sample with Blood-Based Data

	Overall Sample with Y3 Pain Reports (N = 6,220)	Yes Blood Sub-Sample with blood-based data (N = 429)	Survey Year
Main Study Variables	**N**	**N**	
Childhood Adversity	5,297	427	Y1
Pain Intensity	6,219	429	Y3
Pain Related Disability	6,219	429	Y3
HDL Cholesterol (mg/dL)	621	414	Y2
Systolic BP (mm Hg)	2,031	420	Y2
Diastolic BP (mm Hg)	2,031	420	Y2
BMI (kg/m2)	6,031	429	Y2
Waist (cm)	6,031	428	Y2
Pulse Rate (per minute)	5,276	386	Y2
DHEA (pg/mL)	3,982	173	Y2
WBC (K/uL)	429	429	Y2
RDW (fL)	429	429	Y2

Thus, the final sub-sample, referred to as the Yes Blood (YB) sub-sample, used for current study analyses consisted of 429 participants (i.e., participants with reports of all indicators including blood-based/immune system biological indicators) (See Figure 4 for schematic describing final sample selection). This 429 participant YB sub-sample allowed for examination of allostatic load across the four key physiological systems underlying allostatic load (i.e., metabolic, cardiovascular, neuroendocrine, and immune). This is of particular importance as the immune system is the least consistent physiological system included as part of the allostatic load index in adolescent populations where less than one third of studies (i.e., 8 studies out of 25 studies) incorporate indicators of immune function, despite its central role in the stress response and development of allostatic load (Whelan et al., 2021).

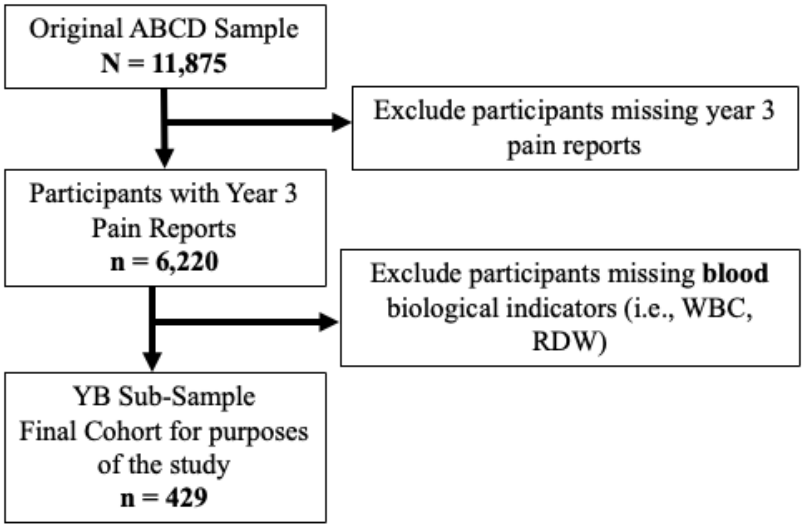


Figure 4. Schematic describing sub-sample and final sample selection.

Of note, due to patterns of missing data, additional analyses described more below were completed to examine differences in demographics and main study variables between the overall sample with Year 3 pain reports (N = 6,220) and the YB sub-sample with reports of blood-based biological indicators (N = 429). In turn, this will aid the interpretation of the research findings in the context of the missing data.

CFA of Allostatic Load. Confirmatory factor analysis (CFA) was conducted to examine the factor structure of the latent variable allostatic load. Due to the theoretical basis of allostatic load (i.e., a single indicator capturing dysregulation across the four key physiological systems), a unidimensional factor structure within the YB sub-sample was examined (in which all the indicators are explained by a single allostatic load factor; See Figure 5).

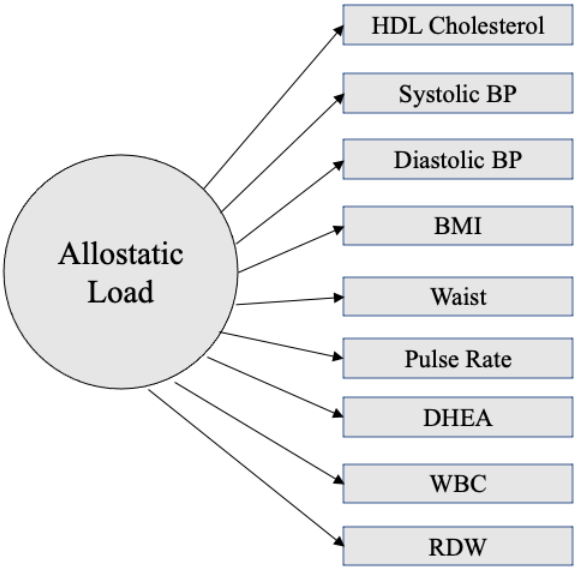


Figure 5. Proposed allostatic load factor structure. A unidimensional factor structure.

The final CFA model used for primary analyses was based on multiple approximate fit indices, including the chi-square test statistic ($\chi 2$), root-mean-squared error of approximation (RMSEA), comparative fit index (CFI), and standardized root mean square residual (SRMR). A significant chi-square test statistic indicates that a significant amount of observed covariance between items remains unexplained by the model, while insignificance indicates a good fit to the data (Cole, 1987). However, given how the chi-square test statistic is heavily dependent on model sample size and complexity where a large sample size may have good fit results with a statistically significant $\chi 2$, values were reported for completeness (Marsh et al., 1988;

Schermelleh-Engel et al., 2003). RMSEA estimates the discrepancy per degree of freedom between the model implied covariance matrix and the population covariance matrix, with the cut-off values of < 0.08 indicating adequate fit and < 0.05 indicating good fit (Hu & Bentler, 1999). SRMR represents the mean absolute residual correlation, with < 0.08 indicating acceptable fit and < 0.06 indicating good fit (Hu & Bentler, 1999). CFI represents an improvement in fit when comparing the researcher's model to the baseline exact fit ($\chi 2$) model, with > 0.90 indicating acceptable fit and > 0.95 indicating good fit. The effect of missing data was addressed with full information maximum likelihood (FIML) to improve parameter recoverability and increase power.

Primary Analyses

In Study Aim #1, three path models were fitted to examine if childhood adversity predicted elevated allostatic load and worse pediatric pain outcomes. In the first model, childhood adversity was the predictor and the latent variable allostatic load was the outcome. In the second and third models, childhood adversity was entered as the predictor, and pain intensity and pain-related disability as outcomes. In all models, control variables included were based on preliminary analyses of significant covariates ($p < 0.05$) related to pain outcomes (i.e., pain intensity, and pain-related disability). Path models were calculated using R software with the package lavaan using the function{sem}(Rosseel, 2012).

In Study Aim #2, SEM was employed using R software with the package lavaan (Rosseel, 2012). In this step, the overall theoretical model was fitted, consisting of the measurement model (i.e., factor analysis completed for allostatic load), and structural model (i.e., path analysis that examined the direct and mediating effects of interest between latent and observed variables). Two theoretical models were fitted, one with pain intensity as an outcome and the other with a pain-related disability as an outcome. Figure 6 illustrates the overall theoretical model, consisting of an allostatic load latent variable, as well as directly observed variables (i.e., childhood adversity, pain outcomes, and covariates) that examines the mediating effect of allostatic load on the association between childhood adversity and pediatric pain outcomes (i.e., pain intensity, pain-related disability).

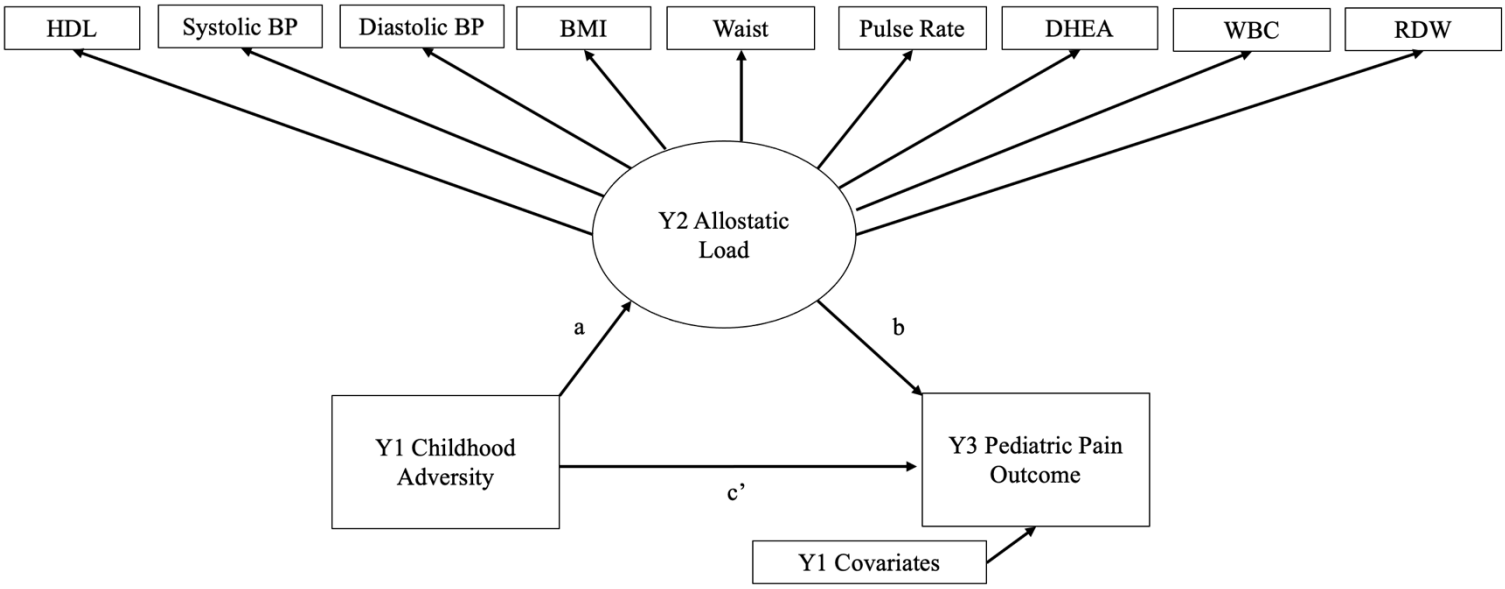


Figure 6. Theoretical Model

Path analyses consisted of calculating multiple pathways as illustrated in Figure 6, in which the letters denote partial regression coefficients that quantify the relation between two variables connected by the path. Pathway *a* represented the effect of childhood adversity on

allostatic load; pathway *b* represented the effect of allostatic load on pediatric pain outcomes, holding childhood adversity constant; and pathway *c'* represented the direct effect of childhood adversity on pain outcomes, holding allostatic load constant. Conceptually, a significant mediating effect of allostatic load results when childhood adversity affects pediatric pain outcomes through its effects on allostatic load. Thus, statistically, a significant mediating effect was indicated by the effect of childhood adversity on pediatric pain outcomes that was mediated by the allostatic load with controlling for the effects of covariates. Covariates included in the SEM models (i.e., race/ethnicity, sex, sex hormones, pubertal development stage, child depression, and anxiety symptoms) were based upon preliminary analyses of significant covariates ($p < 0.05$) related to pain outcomes (i.e., pain intensity and pain-related disability).

Model Fit for Path and SEM Models. Path models (Aim 1) and theoretical SEM models (Aim 2) were estimated using a robust Maximum Likelihood estimator (MLR) (Weston & Gore Jr, 2006). Missing data were handled via full information maximum likelihood estimation (FIML). The unstandardized (B) and standardized (β) coefficients were calculated to measure direct and indirect effects among variables of interest. For the estimated parameters of the direct and indirect effects, a p-value < 0.05 was considered statistically significant. Overall model fit was evaluated using the same fit indices and cut-offs described above for the CFA analysis of allostatic load: Chi-square ($\chi 2$), CFI (> 0.90), SRMR (< 0.08), and RMSEA (< 0.08). Although the $\chi 2$ is reported, it was not used as a fit criterion as it tends to reject models that are based on large sample sizes.

Results

Post-Hoc Power Analysis

Using the semPower package in R (Moshagen & Erdfelder, 2016), a post-hoc power analysis was conducted based on the YB sub-sample to confirm that the sample size for the SEM models were adequate. This analysis was based on a sample size of N = 427, df = 41, and an RMSEA of 0.05. Using an alpha of 0.05, results indicated the power to reject an incorrect model was 96.97. Thus, there was adequate power in the current study.

Differences between the Overall Pain Data Sample and YB Sub-Sample.

Chi-squares and t-tests were calculated to examine significant differences in demographic and main study variables between the overall sample, consisting of 6,220 participants with Year 3 pain data, and the YB sub-sample. For the YB sub-sample, significant differences in race/ethnicity were found between the overall sample and the YB sub-sample (χ^2 (4) = 16.70, p < 0.05). Specifically, there were significantly more White participants, Native participants, and fewer Hispanic participants in the YB sub-sample compared to the overall sample. No significant differences in sex, Year 1 childhood adversity, or Year 3 pain intensity were found between the overall sample and the YB sub-sample. There were significant differences in Year 3 pain-related disability between the overall sample and YB sub-sample (t (525) = -2.66, p < 0.05). Specifically, the YB sub-sample reported significantly less pain-related disability (M = 0.80) compared to the overall sample (M = 1.02).

CFA Results

The final unidimensional factor structure in the YB sub-sample had acceptable model fit in which all the biological indicators are explained by a single allostatic load factor: (χ2 (25) = 40.70, p = 0.03, CFI = .99, SRMR = 0.05, RMSEA = 0.04 (95% CI [0.01, 0.06]). Standardized and unstandardized factor loadings are shown in Table 2.

Table 2: Final Unidimensional Allostatic Load CFA Model (n = 429)

Biological Indicator	Factor Loadings (S.E)	Standardized Factor Loadings	*p*	R^2
BMI	4.43 (0.22)	0.95	<.001	0.91
Waist	4.37 (0.23)	0.91	<.001	0.82
WBC	0.59 (0.09)	0.34	<.001	0.11
HDL Cholesterol	-4.23 (0.52)	-0.38	<.001	0.15
RDW	0.28 (0.06)	0.29	<.001	0.09
Systolic BP	2.93 (0.62)	0.27	<.001	0.07
Diastolic BP	2.57 (0.46)	0.30	<.001	0.09
Pulse Rate	2.30 (0.42)	0.29	<.001	0.08
DHEA	15.32 (4.72)	0.23	<.001	0.05

Notes. BMI = body-mass-index; systolic BP = systolic blood pressure; diastolic BP = diastolic blood pressure; DHEA = Dehydroepiandrosterone; WBC = White blood cell count; RDW = Red blood cell distribution width.

Descriptive Statistics

Descriptive information for study variables is presented in Table 3. The study sample consisted of 429 youth from the YB sub-sample with stressful life event questionnaire reports from Year 1 (aged 10 to 11), allostatic load indicators from Year 2 (aged 11 to 12), and pain reports from Year 3 (aged 12 to 13 years). The majority of the study sample were male (n =236, 55%), and White (n = 269, 62.7%) followed by Hispanic (n=58, 13.5%%), Black (n =58, 13.5%), Asian (n = 19, 4.4%), and Native American (n=18, 4.2%). Average pain intensity (on a scale of 0 to 11, with higher scores indicating greater pain intensity) was 2.15 (*SD* = 3.47, Range: 0 to 11), and average pain-related disability (on a scale of 0 to 11, with higher scores indicating greater pain-related disability) was 0.80 (*SD* = 1.64, Range: 0 to 9).

Table 3 Descriptive Statistics

	Mean	SD	Range	N	Survey Year
Main Study Variables					
Childhood Adversity	4.95	3.14	0.00 to 16.00	427	Y1
Pain Intensity	2.15	3.47	0.00 to 11.00	429	Y3
Pain Related Disability	0.80	1.64	0.00 to 9.00	429	Y3
Allostatic Load Variables					
HDL Cholesterol (mg/dL)	55.30	11.05	31.00 to 93.00	414	Y2
Systolic BP (mm Hg)	103.10	10.77	71.33 to 142.33	420	Y2
Diastolic BP (mm Hg)	60.12	8.50	41.67 to 99.00	420	Y2
BMI (kg/m2)	20.53	4.65	13.02 to 34.61	429	Y2
Waist (cm)	28.47	4.82	20.40 to 43.67	428	Y2
Pulse Rate (per minute)	72.13	7.90	53.08 to 99.00	386	Y2
DHEA (pg/mL)	86.05	67.09	4.19 to 279.83	173	Y2
WBC (K/uL)	6.48	1.74	2.80 to 16.80	429	Y2
RDW (fL)	13.30	0.97	11.40 to 16.85	429	Y2
Continuous Covariates					
Estradiol	0.87	0.42	0.03 to 2.54	144	Y1
Testosterone	38.03	16.73	3.90 to 113.30	360	Y1
Anxiety/Depression	53.24	5.57	50.00 to 82.00	425	Y1
Categorical Covariates	**n**	**%**		**N**	**Survey Year**
Race/Ethnicity					Baseline
White	269	62.7%		429	
Black	58	13.5%		429	
Native	18	4.2%		429	
Asian	19	4.4%		429	
Hispanic	58	13.5%		429	
Sex					Baseline
Male	236	55%		429	
Female	193	45%		429	
Pubertal Development Stage					Y1
Pre-	52	24.6%		211	
Early	77	36.5%		211	
Mid-	70	33.2%		211	
Late	12	5.7%		211	

Prior to completing preliminary analyses, requirements for SEM were assessed. First, normal distribution (both univariate and multivariate distribution) of the data is required for SEM. To test this assumption the distribution of each observed variable was examined using skewness, and kurtosis statistics (univariate distribution) (Weston & Gore Jr, 2006). Variables

were considered normal if absolute values for skewness and kurtosis in each variable fell within the acceptable range (skew > 3 and kurtosis > 7) (Morrison et al., 2017; Weston & Gore Jr, 2006). All study variables were found to be normal and fell within the acceptable range. Multivariate distribution of the current data was also examined using Mardia (1970) test of multivariate skewness and kurtosis. Mardia's coefficient of skewness (= 972. 60, $p < 0.001$) and kurtosis (= 5.64, $p < 0.001$) indicated the assumption of multivariate normality was not met. To account for this, SEM models were estimated using the robust Maximum Likelihood estimator (MLR) (Weston & Gore Jr, 2006), which takes potential violations of the data distribution within the recommended range in skewness and kurtosis and corrects for non-normality-induced bias in the standard errors (Finney & DiStefano, 2006; Satorra & Bentler, 2010).

Second, a requirement of no multicollinearity among the observed variables was calculated. To examine this, bivariate correlations were computed, with Pearson's correlations < 0.85 indicating no potential multicollinearity problems (Kline, 2005). Pearson correlations between outcome variables (i.e., pain intensity and pain-related disability), predictor (i.e., childhood adversity), and mediating variables (i.e., individual allostatic load indicators) were < 0.85, suggesting no potential problems in multicollinearity in both SEM models (Table 4).

Table 4. Pearson Correlations among continuous Childhood Adversity, Individual AL Indicators and Pain Outcomes

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
1. Y1 Childhood Adversity	--											
2. Y3 Pain Intensity	0.10*	--										
3. Y3 Pain Related Disability	0.10*	0.82**	--									
4. Y2 HDL Cholesterol	-0.02	0.08	0.04	--								
5. Y2 Systolic BP	0.03	-0.05	-0.03	-0.19**	--							
6. Y2 Diastolic BP	0.01	-0.09	-0.07	-0.16**	0.59**	--						
7. Y2 BMI	0.06	-0.04	-0.01	-0.35**	0.25**	0.28**	--					
8. Y2 Waist	0.06	-0.04	-0.03	-0.37**	0.23**	0.25**	0.87**	--				
9. Y2 Pulse Rate	0.12*	-0.03	-0.06	-0.05	0.03	0.20**	0.27**	0.25**	--			
10. Y2 DHEA	-0.02	-0.07	-0.09	-0.14	0.25**	0.22**	0.22**	0.23**	-0.08	--		
11. Y2 WBC	-0.10*	0.03	0.04	-0.02**	0.11*	0.13**	0.33**	0.28**	0.19**	-0.01	--	
12. Y2 RDW	0.14**	0.00	0.02	-0.05	0.14**	0.14**	0.28**	0.26**	0.07	0.13	0.08	--

Notes. ** $p < 0.01$; * $p < 0.05$. BMI = body-mass-index; systolic BP = systolic blood pressure; diastolic BP = diastolic blood pressure; DHEA = Dehydroepiandrosterone; WBC = White blood cell count; RDW = Red blood cell distribution width.

Preliminary Analyses

Pearson correlations were calculated to examine associations among the main study variables (i.e., childhood adversity, individual allostatic load indicators, pain outcomes) (Table 4). Significant correlations included the following: a positive association between childhood adversity and increased pain intensity ($r = 0.10$) and between childhood adversity and increased pain-related disability ($r = 0.10$). There were no significant associations between pain intensity and pain-related disability with individual allostatic load indicators.

Table 5. Pearson Correlations among continuous pain outcomes and continuous covariates

	1.	**2.**	**3.**	**4.**	**5.**	**6.**
1. Y1 Childhood Adversity	--					
2. Y3 Pain Intensity	0.10*	--				
3. Y3 Pain Related Disability	0.10*	0.82**	--			
4. Y1 Estradiol	-0.06	-0.12	-0.08	--		
5. Y1 Testosterone	-0.03	-0.04	-0.04	0.45**	--	
6. Y1 Anxiety/Depression	0.04	0.05	0.05	0.16	-0.02	--

Notes. ** $p < 0.01$; * $p < 0.05$

Pearson correlations were calculated to examine associations between pain variables and continuous covariates (i.e., estradiol, testosterone, anxiety/depression). Findings indicated no significant correlations between pain variables and the continuous covariates (Table 5). Thus estradiol, testosterone, and anxiety/depression were not included as covariates in primary analyses. One-way ANOVAs were calculated to examine differences in pain variables based on race/ethnicity and pubertal development stage. The ANOVA results revealed no significant differences in pain intensity based on race/ethnicity (F (4, 417) = 1.29, $p = 0.27$) and in pain-related disability based on race/ethnicity (F (4, 417) = 1.00, $p = 0.41$). There were no significant differences in pain intensity (F (3, 207) = 0.62, $p = 0.60$) and in pain-related disability based on the pubertal developmental stage (F (3, 207) = 1.00, $p = 0.65$). An independent sample t-test was

calculated to examine differences in pain variables based on sex. There were no significant differences in pain intensity (t (427) = -1.42, p = 0.16) and in pain-related disability based on sex (t (427) = -0.69, p = 0.49). Thus, no covariates, including estradiol, testosterone, anxiety/depression, race/ethnicity, pubertal developmental stage, and sex were included in primary analyses.

Primary Analyses

Aim 1 Regression Models. Aim 1 examined relationships between childhood adversity and allostatic load as well as between childhood adversity and pain outcomes using path models. Results indicated childhood adversity was not significantly related to allostatic load, pain intensity, and pain-related disability (see Table 6). This contrasts with the significant Pearson correlations found between childhood adversity and pain related outcomes and may be a function of how missing data was handled when calculating the Pearson correlations (using list-wise) versus the path models (using FIML).

Table 6. Path Models

	Y2 Allostatic Load					Y3 Pain Intensity					Y3 Pain-Related Disability				
	B	**β**	**SE**	***p***	**R^2**	**B**	**β**	**SE**	***p***	**R^2**	**B**	**β**	**SE**	***p***	**R^2**
Y1 Childhood Adversity	0.02	0.06	0.02	0.27	0.004	0.12	0.10	0.06	0.07	0.011	0.05	0.10	0.03	0.09	0.010

Notes. *$p < 0.05$

Aim 2 SEM Mediation Models. Two SEM mediation models were fitted, one with pain intensity as the outcome and the other with pain-related disability as the outcome. Model 1 examined the mediating of allostatic load between childhood adversity and pediatric pain intensity. Model 1 showed an overall good fit with a chi-square of 67.08 (p = 0.01), a CFI of 0.98, an RMSEA of 0.04 (95% CI = 0.02, 0.05), and an SRMR of 0.05. The measurement component (i.e., factor loadings of observed biological indicators) of the model is detailed in Table 7. The path coefficients are shown in Table 8, with both standardized and unstandardized coefficients reported. Allostatic load did not significantly mediate the association of childhood adversity with pain intensity (β= -0.003, p = 0.35). Direct path coefficients between childhood adversity to allostatic load (β = 0.06, p = 0.27), allostatic load to pain intensity (β= -0.05, p = 0.31), and childhood adversity to pain intensity (β = 0.11, p = 0.11) were nonsignificant.

Model 2 examined the mediating of allostatic load between childhood adversity and pediatric pain-related disability. Model 2 showed an overall good fit with a chi-square of 67.19 (p = 0.01), a CFI of 0.98, an RMSEA of 0.04 (95% CI = 0.02, 0.05), and an SRMR of 0.05. The measurement component of the model is detailed in Table 7. The path coefficients are shown in Table 8, with both standardized and unstandardized coefficients reported. Allostatic load did not significantly mediate the association of childhood adversity with pain-related disability (β= -0.001, p = 0.35). Direct path coefficients between childhood adversity and allostatic load (β= 0.06, p = 0.27), allostatic load and pain intensity (β= -0.02, p = 0.66), and childhood adversity and pain intensity (β= 0.10, p = 0.08) were nonsignificant.

Table 7. Measurement Model Results

	Model 1: Y3 Pain Intensity (N = 427)				Model 2: Y3 Pain-Related Disability (N = 427)			
AL Indicators	**B**	**β**	**SE**	***p*-value**	**B**	**β**	**SE**	***p*-value**
BMI	4.43	0.95	0.22	0.00	4.43	0.95	0.22	0.00
Waist	4.37	0.91	0.23	0.00	4.37	0.91	0.23	0.00
WBC	0.59	0.34	0.09	0.00	0.59	0.34	0.09	0.00
HDL Cholesterol	-4.24	-0.38	0.52	0.00	-4.23	-0.38	0.52	0.00
RDW	0.28	0.29	0.06	0.00	0.28	0.29	0.06	0.00
Systolic BP	2.93	0.27	0.62	0.00	2.93	0.27	0.62	0.00
Diastolic BP	2.57	0.30	0.46	0.00	2.57	0.30	0.46	0.00
Resting HR	2.31	0.29	0.42	0.00	2.31	0.29	0.42	0.00
DHEA	15.32	0.23	4.71	0.00	15.32	0.23	4.72	0.00

Notes. *$p < 0.05$

Table 8. Direct and Indirect Effects

	Model 1: Y3 Pain Intensity (N = 427)				Model 2: Y3 Pain-Related Disability (N = 427)			
Structural Path Coefficients	**B**	**β**	**SE**	***p*-value**	**B**	**β**	**SE**	***p*-value**
Direct Effects								
Childhood adversity to Allostatic Load (a)	0.02	0.06	0.02	0.27	0.02	0.06	0.02	0.27
Allostatic load to Pain Outcome (b)	-0.18	-0.05	0.17	0.31	-0.04	-0.02	0.09	0.66
Childhood Adversity to Pain Outcome (c')	0.12	0.11	0.06	0.11	0.05	0.10	0.03	0.08
Indirect Effect								
Childhood Adversity via Allostatic Load (a*b)	-0.003	-0.003	0.004	0.35	-0.001	-0.001	0.002	0.64
Total Effect								
Total effect of Childhood Adversity on Pain Outcome (c' + (ab))	0.12	0.10	0.06	0.07	0.05	0.10	0.03	0.09

Notes. *$p < 0.05$

Post-Hoc Analyses with Year 2 Pain Outcomes

Preliminary Analyses. An additional series of post-hoc analyses were completed to examine relationships between Year 1 childhood adversity, Year 2 allostatic load, and Year 2 pain outcomes. This post-hoc analysis allowed for the examination of more proximal temporal effects of childhood adversity and allostatic load on pain outcomes. Examining proximal temporal effects would in turn further our understanding of how childhood adversity and pain related outcomes differ as a function of time and development. This analysis was further supported by significant correlations found between Year 1 childhood adversity and Year 2 increased pain intensity (r = 0.17) and between Year 1 Childhood Adversity and Year 2 increased pain-related disability (r = 0.13). Average Year 2 pain intensity was 2.60 (SD = 3.72; Range: 0 to 11) and average Year 2 pain-related disability was 1.05 (SD = 2.03, Range: 0 to 11).

As completed in the primary analyses above, both Aim 1 (regression path models) and Aim 2 (SEM Mediation Models) models were fitted using Year 2 pediatric pain intensity and pain-related disability as outcomes. Prior to completing analyses, covariate testing was done to examine associations among race/ethnicity, sex, Year 1 estrogen, Year 1 testosterone, Year 1 depression and anxiety, and Year 1 pubertal development stage with Year 2 pain outcomes. For continuous covariates (i.e., estradiol, testosterone, anxiety/depression), a significant negative correlation was found between testosterone and pain intensity (r = -0.12) and between testosterone and pain-related disability (r = -0.16). No significant correlations were found between Year 2 pain variables, estrogen, and anxiety/depression.

The ANOVA results revealed no significant differences in Year 2 pain intensity based on race/ethnicity (F (4, 417) = 0.56, p = 0.69) and in Year 2 pain-related disability based on race/ethnicity (F (4, 417) = 0.57, p = 0.68). There were no significant differences in Year 2 pain

intensity based on the pubertal developmental stage (F (3, 207) = 2.75, p = 0.05) and in Year 2 pain-related disability based on the pubertal developmental stage (F (3, 207) = 1.17, p = 0.33). There were no significant differences in Year 2 pain intensity based on sex (t (427) = 0.88, p = 0.38) and in Year 2 pain-related disability based on sex (t (427) = 0.14, p = 0.89). Thus, testosterone was the only covariate included in the post-hoc analyses with Year 2 pain outcomes.

Post-Hoc Year 2 Pain Path Models. Results indicated significant relationships between childhood adversity and pain intensity as well as between childhood adversity and pain-related disability (see Table 9).

Post-Hoc Year 2 Pain SEM Mediation Models. Two SEM mediation models were fitted, one with Year 2 pain intensity as the outcome and the other with Year 2 pain-related disability as the outcome. Model 1 examined the mediating role of allostatic load in the path between childhood adversity and Year 2 pediatric pain intensity. Model 1 showed an overall acceptable fit with a chi-square of 161.02 (p = 0.00), a CFI of 0.90, an RMSEA of 0.07 (95% CI = 0.06, 0.08), and an SRMR of 0.09. The measurement component (i.e., factor loadings of observed biological indicators) of the model is detailed in Table 10. The path coefficients are shown in Table 11, with both standardized and unstandardized coefficients reported. Allostatic load did not significantly mediate the association of childhood adversity with pain intensity (β= -0.004, p = 0.36). Direct path coefficients between childhood adversity to pain intensity were significant (β = 0. 17, p = 0.00). However, direct path coefficients between childhood adversity and allostatic load (β = 0.06, p = 0.28) and allostatic load and pain intensity (β= -0.06, p = 0.17) were nonsignificant. Lastly, the total effect of childhood adversity on pain intensity was significant (β = 0.17, p = 0.00).

Table 9. Post-Hoc Analysis Year 2 Path Models

	Y2 Allostatic Load					Y2 Pain Intensity					Y2 Pain-Related Disability				
	B	**β**	**SE**	***p***	**R^2**	**B**	**β**	**SE**	**p**	**R^2**	**B**	**β**	**SE**	***p***	**R^2**
Y1 Childhood Adversity	0.02	0.06	0.02	0.27	0.004	0.22	0.19	0.07	0.00*	0.050	0.11	0.17	0.04	0.01*	0.054
Y1 Testosterone	--	--	--	--	--	-0.03	-0.12	0.01	0.01*		-0.02	-0.15	0.01	0.00*	

Notes. *$p < 0.05$

Table 10. Post-Hoc Measurement Model Results

	Model 1: Y2 Pain Intensity (N = 427)				Model 2: Y2 Pain-Related Disability (N = 427)			
AL Indicators	**B**	**β**	**SE**	***p*-value**	**B**	**β**	**SE**	***p*-value**
BMI	4.43	0.96	0.22	0.00	4.42	0.95	0.22	0.00
Waist	4.35	0.91	0.23	0.00	4.36	0.91	0.23	0.00
WBC	0.58	0.34	0.09	0.00	0.58	0.34	0.09	0.00
HDL Cholesterol	-4.21	-0.38	0.52	0.00	-4.22	-0.38	0.52	0.00
RDW	0.28	0.29	0.06	0.00	0.28	0.29	0.06	0.00
Systolic BP	2.93	0.27	0.61	0.00	2.93	0.27	0.61	0.00
Diastolic BP	2.57	0.30	0.46	0.00	2.57	0.30	0.46	0.00
Resting HR	2.30	0.29	0.42	0.00	2.30	0.29	0.42	0.00
DHEA	15.24	0.23	4.71	0.00	15.30	0.23	4.71	0.00

Notes. *$p < 0.05$

Table 11. Post-Hoc Direct and Indirect Effects

	Model 1: Y2 Pain Intensity (N = 427)				Model 2: Y2 Pain-Related Disability (N = 427)			
Structural Path Coefficients	**B**	**β**	**SE**	***p*-value**	**B**	**β**	**SE**	***p*-value**
Direct Effects								
Childhood adversity to Allostatic Load (a)	0.02	0.06	0.02	0.28	0.02	0.06	0.02	0.28
Allostatic load to Pain Outcome (b)	-0.23	-0.06	0.17	0.17	0.01	0.00	0.09	0.96
Childhood Adversity to Pain Outcome (c')	0.20	0.17	0.06	0.00*	0.08	0.13	0.04	0.03*
Covariates								
Testosterone	-0.02	-0.11	0.01	0.03*	-0.02	-0.16	0.01	0.00*
Indirect Effect								
Childhood Adversity via Allostatic Load (a*b)	-0.004	-0.004	0.005	0.36	0.000	0.000	0.002	0.96
Total Effect								
Total effect of Childhood Adversity on Pain Outcome (c' + (ab))	0.20	0.17	0.06	0.00*	0.08	0.13	0.04	0.03*

Notes. *$p < 0.05$

Model 2 examined the mediating of allostatic load between childhood adversity and Year 2 pediatric pain-related disability. Model 2 showed an overall acceptable fit with a chi-square of 156.50 (p = 0.00), a CFI of 0.90, an RMSEA of 0.07 (95% CI = 0.06, 0.08), and an SRMR of 0.09. The measurement component of the model is detailed in Table 10. The path coefficients are shown in Table 11, with both standardized and unstandardized coefficients reported. Allostatic load did not significantly mediate the association of childhood adversity with pain-related disability (β= 0.000, p = 0.96). Direct path coefficients between childhood adversity and pain related disability were significant (β = 0.08, p = 0.03). However, direct path coefficients between childhood adversity and allostatic load (β = 0.06, p = 0.28) and allostatic load and pain-related disability (β= 0.00, p = 0.96) were nonsignificant. Lastly, the total effect of childhood adversity on pain-related disability was significant (β = 0.08, p = 0.03).

Discussion

The current study examined the relationship of childhood adversity to allostatic load index and pediatric pain outcomes (i.e., pain intensity and pain-related disability) in a nationally-representative sample of early adolescents (Aim 1). This study also examined the mediating effect of allostatic load on the association between childhood adversity and pediatric pain outcomes using a longitudinal design within a structural equation modeling framework (Aim 2). This is the first study to examine associations between childhood adversity, allostatic load, and pediatric pain in a nationally representative sample as well as the first study to examine the potential mediating effect of allostatic load. Moreover, only one study to date has examined allostatic load utilizing confirmatory factor analysis within a pediatric population and only a few studies to date have examined allostatic load within a pediatric population, with other studies having small sample sizes within specific populations (i.e., rural, low-income, chronic pain) (Rogosh, 2011; Nelson, Bento, et al., 2021, Evans, 2003), thus limiting the generalizability of study findings and our understanding of allostatic load within pediatric populations.

Prior to discussing the current study's findings, additional context of the study sub-sample from the overall ABCD sample is described. Though no significant differences were found between pain intensity of the current study sub-sample and the overall larger ABCD sample with year 3 pain reports, youth reported relatively lower mean pain intensity (Mean = 2.15; on an 11-point numeric rating scale) compared to other non-chronic pain adolescent populations. One study of 149 adolescents aged between 10 to 17 reported an average pain intensity of 5.97 on an 11-point numeric rating scale (Groenewald et al., 2014), and another study of 178 adolescents aged between 11 and 14 reported an average pain intensity of 3.14 on a 10-point numeric rating scale (Wilson et al., 2013). As found in the t-test, pain-related disability

(Mean =0.82; on an 11-point numeric rating scale) in the sub-sample was significantly less compared to the overall ABCD sample with year 3 pain reports (Mean =1.01). Thus, the sub-sample in the current study may have reported overall less severe pain outcomes compared to other non-chronic pain adolescent samples. This overall less severe pain outcomes reported in the study sample may be the result of the age in which pain was assessed (ages 12 to 13) and how prevalence of pain increases with age in pediatric populations (King et al., 2011; Swain et al., 2014). In addition, the majority of other studies utilizing nationally representative samples examine the risk of developing chronic pain risk (i.e., yes or no chronic pain) rather than pain-related outcomes (e.g., pain severity, pain related disability, pain duration) (Groenewald et al., 2020; M. Noel et al., 2016).

For race/ethnicity, there were significantly more White participants (63%) compared to the overall ABCD sample with year 3 pain reports and compared to other nationally representative pediatric samples (e.g., 52% White participants in a study using the National Survey of Children's Health sample (Groenewald et al., 2020) and 51% White participants in A study using the national Add Health sample (Wickrama et al., 2016). Though childhood adversity in the current sub-sample did not significantly differ from the overall ABCD sample with year 3 pain reports, the average adverse events reported was higher (Mean = 4.95, Possible range: 0 to 25) relative to other nationally representative samples. A study of 11,271 youth aged between 12 and 19 using the national Add Health sample found that youth experienced an average of 1.81 adverse events (Possible range: 0 to 27) (Wickrama et al., 2016). Gender proportions in the current sub-sample (55% male and 45% female) were consistent with other pediatric nationally representative samples (e.g., 51% male and 49% female in the National Survey of Children's Health sample of 48,567 participants) (Groenewald et al., 2020). The age of

the current sample was restricted to individual survey years (e.g., adolescents were aged between 10 to 11 in the Year 1 survey). The majority of pediatric samples in pain research, however, have broader age range samples (Groenewald et al., 2020; Nelson et al., 2018; Nelson, Bento, et al., 2021). Collectively, the sub-sample had similar gender proportions, but relatively lower pain intensity/pain-related disability and a higher proportion of White participants and number of adverse events reported relative to other pediatric samples. These differences within the sub-sample may have resulted in nonsignificant associations found between childhood adversity and pain-related outcomes given the lower pain-related outcomes reported. Of note, White youth tend to report significantly lower levels of pain intensity and pain-related disability relative to other racial/ethnic groups (Evans et al., 2010).

Aim 1: Relationships between Childhood Adversity, Allostatic load, and Pain

Childhood Adversity and Pain. The first part of Aim 1 was to validate the relationship between childhood adversity and pediatric pain outcomes. It was hypothesized that childhood adversity would be associated with higher pain intensity and pain-related disability. Contrary to the hypothesis, Year 1 childhood adversity was not significantly associated with Year 3 pain outcomes. Interestingly, as part of post-hoc analyses with Year 2 pain outcomes, a direct effect was found between Year 1 childhood adversity and increased Year 2 pain intensity and Year 2 pain-related disability, suggesting differing temporal effects of childhood adversity on pediatric pain outcomes.

The significant finding of childhood adversity in Year 1 relating to increased pain intensity and pain-related disability in year 2 highlights the salient impact of childhood adversity on pain-related outcomes in a nationally representative sample. This finding is consistent with an another nationally representative sample of 48,567 youth aged 6 to 17, where researchers found

youth with adverse childhood experiences had an increased risk for chronic pain and this association increased in a dose-dependent fashion (Groenewald et al., 2020). Thus, future prospective research should focus on deepening knowledge of the underlying mechanisms that may explain the association between adversity and pain, with a focus on modifiable psychological and family-based targets to improve prevention and treatment approaches in pediatric populations.

Childhood adversity in Year 1 did not significantly relate to pain-related outcomes in Year 3. This is inconsistent with prior research that has found both short-term and long-term effects of childhood adversity exposure on physical, mental, and behavioral health outcomes, including pain-related, across the lifespan (Anda et al., 2006; Felitti & Anda, 2010; Felitti et al., 1998; Herzog & Schmahl, 2018; Marin et al., 2021). There is limited empirical evidence that has examined more proximal longitudinal associations during a narrow window of time (e.g., early adolescence) between childhood adversity and pediatric pain-related outcomes (e.g., intensity, related disability, duration) (Nelson et al., 2018; Nelson et al., 2017; Nelson et al., 2020a). Rather, empirical evidence thus far has been either cross-sectional across broad age ranges or has examined long-term longitudinal associations between childhood adversity and subsequent pain-related outcomes later in life or adulthood (Groenewald et al., 2020; Nelson et al., 2018; Nelson et al., 2020a).

The pattern of direct effects found may suggest that the association between adversity and pain changes as a function of the physiological stress response and subsequent dysregulation of biological processes that overlap with pain outcomes. In the context of the current study, youth in the sample may have experienced a more acute stress response after an adverse event (s), resulting in pain promoting processes (e.g., HPA axis activation) and subsequent increased

pain intensity and pain related disability reported in Year 2. Then in the presence of protective factors, such as supportive relationships and/or time limited challenges, the physiological stress response may have returned to baseline and homeostatic functioning resumed, resulting in the nonsignificant association found with Year 3 pain outcomes.

Of note, the ABCD measure included adverse events that occurred throughout childhood, rather than a narrow window of time. Thus, the timing of adversity and how it may relate to the current study's findings is unclear and this is a critical gap, as systems underlying the physiological stress response (e.g., HPA axis, immune system) undergo critical development through childhood and adolescence, underscoring the plausibility that the functioning of these systems and subsequent health outcomes vary according to the timing of adversity (Kuhlman et al., 2017; Kuhlman et al., 2019). For example, preliminary evidence suggests adversity during infancy is associated with HPA axis dysregulation and subsequent amplified cortisol early in life, which may then lead to glucocorticoid receptor insensitivity and contribute to persistently elevated cortisol into childhood (Kuhlman et al., 2017). Whereas exposure to adversity during adolescence represents a developmental period in which social environments become biologically embedded, and as such, preliminary evidence suggests exposure to adversity during adolescence is associated with distinctive physiological effects, such as lower cortisol and elevated inflammation (Kuhlman et al., 2017).

Studies, however, investigating effects of adversity and subsequent physiological consequences and poor health outcomes during relatively narrow windows of time (e.g., adolescence) are limited (Kuhlman et al., 2017; Kuhlman et al., 2019). Thus, the role of the timing of adversity is unclear as is whether the effects of adversity may be short-lived, where more proximal measures of adversity may be more predictive of the dysregulation of biological

processes and subsequent deleterious health outcomes. It is also possible that early life adversity (e.g., adversity in infancy) has long-term effects on biological processes, but the associated health consequence does not manifest until later in life (Kuhlman et al., 2019). Examining the longevity of observed physiological effects as a result of adversity exposure across developmental periods was not able to be examined due to the narrow age range of the current study sample (i.e., aged between 10 and 13). Given how the current study was an early adolescent sample, it is possible that adversity exposure assessed exclusively during adolescence may distinctively relate to physiological effects and subsequent poor pain outcomes.

Nevertheless, the multiple interpretations of the pattern of direct effects found and the current limited research underscore the importance of probing the role of timing in the biological effects of adversity and subsequent manifestation of physical health consequences (i.e., pain). Future research should examine differences in the associated health consequences of early life adversity (e.g., infancy) versus more proximal measures of adversity during distinctive developmental periods (e.g., middle childhood, adolescence) (Kuhlman et al., 2019; Nelson et al., 2018; Nelson et al., 2020b). In turn, this may provide new avenues for exploring the interaction between adversity and functioning of key physiological stress systems and subsequent health outcomes across developmental periods.

Childhood Adversity and Allostatic Load. The second part of Aim 1 was to validate the relationship between childhood adversity and allostatic load. It was hypothesized that childhood adversity would be associated with an elevated allostatic load index. Contrary to the hypothesis, childhood adversity in Year 1 did not significantly relate to allostatic load in Year 2. The finding however was consistent with another study of 247 children in low-income families aged 8 to 10 years that found childhood adversity did not independently predict differences in

allostatic load (Rogosch et al., 2011) and a study of 61 children with chronic pain aged 10 to 17 that found a nonsignificant association between childhood adversity and allostatic load (Nelson, Bento, et al., 2021).

A possible explanation for this finding may be attributed to differences in the development of the dysregulation in biological processes associated with allostatic load during childhood versus adulthood. The biological indicators underlying allostatic load may be different in pediatric populations versus adult populations. Preliminary empirical evidence utilizing CFA to measure allostatic load within an adolescent population found evidence of developmental differences (e.g., adults vs adolescents) in how stress manifests physiologically over time in response to adversity (King et al., 2019). Consistent with the current study, King (2019) and colleagues found a unidimensional factor structure underlying allostatic load (i.e., indicating that the allostatic load construct directly influences each biological indicator). This finding of a unidimensional factor structure contrasts with findings in adult populations where second-order factor structures were supported (i.e., indicating biological indicators are indirectly influenced through the cardiometabolic and immune systems) (Booth et al., 2013; Johnston, 2004; Seeman et al., 2010). The difference in the significance of biological systems in adolescents versus adult populations suggests that the physiological manifestations underlying allostatic load may differ as a function of one's development.

Future research should identify essential biological indicators to include in an allostatic load index for use in pediatric populations and implement a developmental perspective when creating an allostatic load index, such as modifying biological indicators as part of the allostatic load index according to one's development period. Selecting biological indicators that are more likely to become dysregulated earlier in life would allow for a more robust examination of

allostatic load and relevant health outcomes within a pediatric population. For example, neuroendocrine-related biological indicators are likely antecedent to biological indicators reflecting measurable systemic dysregulation in the cardiovascular, metabolic, and immune systems (King et al., 2019; Nelson, Borsook, et al., 2021; Nelson et al., 2020a). Thus, future research is warranted to examine what biological pathways may contribute to elevated allostatic load early in life explicitly, as well as validate a distinct allostatic load index for pediatric and adolescent populations.

Allostatic Load and Pain. In contrast to prior evidence in literature, allostatic load was not significantly related to pain related intensity and pain related severity (Nelson et al., 2017; Nelson, Borsook, et al., 2021; Timmers et al., 2019). Given how the majority of evidence investigating the relationship between allostatic load and pain-related outcomes have been in chronic pain populations, it is possible that there are overlapping physiological pathways (e.g., HPA axis) between allostatic load and pain occur in the context of chronic pain. This is supported by a study of children aged 9 to 17 years old that found both increased reactivity of the autonomic nervous system and activation of immune-inflammatory system, which has been implicated in pain sensitivity and severity, in children with chronic pain compared to healthy controls (i.e., non-chronic pain) (McInnis et al., 2020). Thus, it may be stress-system dysregulation and ensuing allostatic load development is more robust in children with chronic pain compared to children without chronic pain development. Future research examining the association between allostatic load and pain-related outcomes in a representative pediatric chronic pain sample is warranted.

Aim 2: Mediating Effect of Allostatic Load

The second aim of this study examined the mediating effect of allostatic load on the association between Year 1 childhood adversity and Year 3 pediatric pain. It was hypothesized that allostatic load would mediate the relationship between childhood adversity and pediatric pain, such that elevated allostatic load would explain childhood adversity's impact on poor pain outcomes (i.e., higher pain intensity and pain-related disability). Contrary to the hypothesis, allostatic load did not significantly mediate the relationship between childhood adversity and pain-related outcomes in Years 2 and 3. Beyond the consideration of key developmental differences of allostatic load in pediatric populations discussed above, other explanations may explain the nonsignificant mediating effect of allostatic load.

First, the current study used a nationally representative sample, rather than a chronic pain sample. However, the majority of research investigating allostatic load as it relates to childhood adversity and pain-related outcomes has been in chronic pain pediatric and adult populations (Berens et al., 2017; Nelson et al., 2017; Nelson, Bento, et al., 2021; Nelson, Borsook, et al., 2021; Nelson et al., 2020b). Youth with chronic pain are significantly more likely to be exposed to adverse experiences, such as psychological trauma, parental separation/divorce, or conflictual home or community environments (Nelson et al., 2018; Nelson et al., 2017). In addition, youth with chronic pain are significantly more likely to report symptoms of posttraumatic stress at a higher rate compared to youth with no chronic pain (Holley et al., 2016; Melanie Noel et al., 2016). Given how elevated allostatic load results from repeated or prolonged stress and is maintained through continued exposure to stress (McEwen & Wingfield, 2003), it may be that the current sample experienced overall lower levels of stress relative to a chronic pain sample, resulting in an absence of physiological manifestations as part of allostatic load. Thus, future

research should explore the mediating effect of allostatic load on the association between childhood adversity and pain-related outcomes in a chronic pain sample.

Second, assessing cumulative adversity rather than examining distinctive individual adverse events, or ACE types, may also explain the nonsignificant mediating effect of allostatic load on the association between childhood adversity and pain outcomes. Although considerable research has found that cumulative effects of ACE exposure are determinantal to health outcomes, including pain-related outcomes, prior research has also found that different adversities, such as ones that involve physical trauma, may have unique physiological consequences (Kuhlman et al., 2017; Kuhlman et al., 2019; Oh et al., 2018). Individual adverse experiences have been distinctively connected to an altered HPA-axis and inflammatory response as well as to the development of the central nervous system with implications for physiological adaptations involved in the stress response (Kuhlman et al., 2017; K. A. McLaughlin et al., 2014; Katie A. McLaughlin et al., 2014; Teicher et al., 2003). It may be that each element of an adverse experience (e.g., degree of physical threat, caregiving disruption, unpredictability) differs in biological salience and, in turn, affects biological systems differently (Kuhlman et al., 2017). Moreover, empirical evidence has found that different types or distinctive combinations of adverse experiences are associated with more deleterious outcomes compared to other adverse types or other combinations (Groenewald et al., 2020; Kuhlman et al., 2017; Lanier et al., 2018).

Thus, allostatic load may act as a mechanism linking the association between adverse experiences with distinctive physiological effects underlying allostatic load and subsequent poor pain-related outcomes. For example, there is a significant overlap between the physiological effect of physical trauma exposure and pain processing. Specifically, exposure to physical

trauma is associated with robust activation of the threat response system leading to an exaggerated HPA-axis response to acute stress and subsequent elevated inflammation (Kuhlman et al., 2017). In turn, elevated inflammation has been robustly linked to poor pain-related outcomes, such as increased pain intensity (Zhang & An, 2007). Future research should examine the biological salience of each adverse type as it relates to allostatic load within a pediatric population.

Exposure to distinctive types of adversity at various points in development may differentially affect the manifestation of allostatic load and ensuing health consequences. As such, individual adverse events and/or the developmental period (s) in which the event occurred may distinctively promote elevated allostatic load and subsequent deleterious pediatric pain outcomes. Future research examining allostatic load as a potential mechanism should ideally assess allostatic load indicators during distinctive developmental periods of childhood (e.g., middle childhood, adolescence), and multiple times in adulthood to elucidate long-term associations of how the timing and type of adversity may affect biological processes underlying allostatic load across the lifespan.

Third, allostatic load may not mediate the relationship between childhood adversity and pain-related outcomes. It is possible that the hyperactivation of the stress-response system and ensuing allostatic load as a result of adversity exposure is not directly connected to altering pain processing. Though childhood adversity is robustly connected to poor pain-related outcomes, it remains unclear the mechanisms that mediate this relationship. Allostatic load is a mechanism that focuses on the physical stress response. A significant challenge however is disaggregating the effects of physical versus psychological stress resulting from childhood adversity (Burke, 2017). This challenge is especially difficult given how stressful and traumatic events can

have profound psychological impacts as well as physiological impacts. It may be the mechanism underlying childhood adversity and pain related outcomes center more on the psychological impact rather than the physiological impact (i.e., allostatic load). Specifically, empirical studies measuring the psychological stress on pain responses may be more salient than the physical stress on pain responses. For example, emotional, cognitive, social, and behavioral factors that accompany traumatic experiences may mediate the relationship between childhood adversity and pain-related outcomes rather than a measure of the physiological stress response accompanying traumatic experiences.

Limitations

Beyond limitations described above, findings from the current study should be interpreted in the context of its limitations. First, the study findings were unable to be examined across different racial/ethnic groups due to proportions of racial/ethnic participants in the current sample (i.e., over half of the participants (62.7%) of the sample were White). Significant racial/ethnic differences have been found in both childhood adversity exposure and allostatic load index (Beckie, 2012; Slopen et al., 2016). For example, a study of 11,378 youth aged 8 to 17, found Mexican American and Black participants exhibited a higher allostatic load score compared to White participants (Park et al., 2022). Another study of 43,711 youth aged 0 to 17 found that White participants had lower exposure to specific ACEs, including neighborhood violence, parental incarceration, and racial discrimination, as well as the total number of ACEs compared to non-Latinx Black and Latinx children (Maguire-Jack et al., 2020). Therefore, the current study's findings may have significantly differed across racial/ethnic group.

Second, the ABCD pain measure consisted of individual items per aspects of pain (i.e., one item of pain intensity, one item of functional disability due to pain). However, more

comprehensive pain measures commonly used in pediatric pain research may be more impactful and relevant when examining the relationships among childhood adversity, allostatic load, and pediatric pain outcomes. For example, the Pediatric PROMIS (Patient-Reported Outcome Measurement Information System) measure, a frequently used and validated measure in pain research, consists of comprehensive domains of pain, includes pain interference, physical function/mobility and pain quality domains (Varni et al., 2014; Varni et al., 2010). The PROMIS pain interference domain evaluates the impact of pain on physical, psychological, and social functioning and the PROMIS physical function-mobility domain examines physical activity and mobility related to pain (DeWalt et al., 2015; Varni et al., 2010). The PROMIS pain quality domain examines the specific subjective sensations associated with pain (e.g., sharpness, pressure, temperature) and to the frequency, duration and intensity of pain (Jacobson et al., 2015). Comprehensive measures such as these may be informative in deepening our understanding of the association between childhood adversity, allostatic load, and pediatric pain. Lastly, the ABCD pain measure included pain experiences that occurred within the past month. However, chronic pain is defined as pain lasting longer than three months or recurring pain that occurs at least three times throughout a period of three months (Nicholas et al., 2019). Given how the majority of pediatric pain research have been in chronic pain populations and how youth with chronic pain are significantly more likely to be experience poor behavioral, mental and physical health outcomes (Nelson et al., 2018; Holley et al., 2016; Noel et al., 2016), research examining the associations between childhood adversity, allostatic load and pain-related outcomes within a chronic pain population is warranted.

Third, though the study utilized the nationally representative ABCD sample, multiple limitations arose in the current study using this existing dataset. Due to COVID-19 occurring

during year 2 data collection, there is a significant amount of missing data in the latter half of the 2-year follow-up data and the first half of the 3-year follow-up data. Given how the current study utilized biological indicators from year 2 and pain reports from year 3, this significantly impacted the sample size and all aspects of measurement. Subsequently, the current study could not examine possible confounding factors in pain-related outcomes including race/ethnic group and gender differences. Beyond the limitations described above of the pain measure used in the ABCD study, there were also limitations in the stressful life event questionnaire used as a measure of childhood adversity. Salient adverse experiences that are part of the original CDC Kaiser Permanente ACE scale (Felitti et al., 1998) (e.g., sexual abuse, physical neglect) were not included in the stressful life event questionnaire. In addition, the list of ACEs has expanded in research to include various other community-based stressors, such as neighborhood violence, bullying and exposure to discrimination and racism, where researchers have found these stressors distinctively contribute to poorer health outcomes (Bethell et al., 2017; Finkelhor et al., 2013; Pachter et al., 2017).

Another limitation of using the ABCD dataset was the restrictions of the age range as each survey year in the ABCD study focused on a narrow age range (e.g., 10 to 11) and consequently the analyses of the current study were limited to early adolescence (i.e., aged 10 to 13). There are distinctive social environment influences as well as neurophysiological and hormonal alterations that overlap with the neurobiological stress response (Dahl & Gunnar, 2009; Lo Iacono & Carola, 2018) and pain related outcomes (Eccleston et al., 2008; Stanford et al., 2008) across distinctive phases of development of adolescence (e.g., early adolescence versus late adolescence). Thus, the relationship and underlying biological mechanisms between childhood adversity and subsequent pain related outcomes may differ across adolescence.

Understanding developmentally relevant areas of childhood adversity and subsequent pain impact may inform optimal assessment and treatment approaches and the use of developmentally informed strategies to tailor pain interventions (Rosenbloom et al., 2017). Future research investigating childhood adversity, neurobiological stress response and subsequent pain-related outcomes should consider investigating these relationships in a broad age range of adolescents (i.e., age 10 to 18) with consideration of distinctive developmental phases of adolescence (i.e., early-, mid-, late-).

Fourth, the current study only investigated a biological-related pathway. However, research has found considerable evidence of three primary pathways that connect childhood adversity to poor physical health: biological, behavioral, and cognitive (Schnurr & Green, 2004; Schnurr et al., 2007; Sowder et al., 2018; Wade et al., 2022). Individuals exposed to adversity report higher rates of involvement in health risk behaviors, including drug use, risky sexual behaviors, physical inactivity, and unhealthy dietary practices (Benjet et al., 2013; Healy et al., 2021; Kovensky et al., 2020). Given how health risk behaviors increase the risk for a variety of health consequences, including pain (Kamper et al., 2019; McLaren et al., 2017; Mikkonen et al., 2016), behavioral related pathways may act as another or complementary mechanism (with biological related pathways) in mediating the relationship between childhood adversity and pediatric pain. One study in a sample of 8,116 participants aged 15 to 64 found that health risk behaviors (e.g., smoking, alcohol use, low exercise, obesity) mediated the relationship between childhood adversity and adult physical health outcomes, including pain interference (Chartier et al., 2009). Empirical evidence however examining behavioral related pathways have largely been in adult populations and have primarily focused on mental health rather than physical health related outcomes. A systematic review also summarized robust evidence of significant

associations found between health risk behaviors (e.g., overeating/obesity, alcohol, smoking, drug use, physical activity) and an elevated allostatic load index (Suvarna et al., 2020).

Similarly, cognitive related pathways may act as another or complementary mechanism (with biological related pathways) in mediating the relationship between childhood adversity and pediatric pain. Several studies have indicated individuals exposed to adversity report high pain catastrophizing, defined as the tendency to ruminate, magnify and feel helplessness in regards to the threat of pain (Craner et al., 2022; Simon et al., 2022; Zlotnick et al., 2022). In turn, pain catastrophizing facilitates an enhanced fear of pain that may contribute to avoidance behaviors, promoting depression and disability, and subsequent exacerbated pain experiences (e.g., increased sensitivity to pain) (Simons & Kaczynski, 2012; Vlaeyen et al., 2016). Thus, future research should examine behavioral pathways (e.g., health risk behaviors) and cognitive pathways (e.g., pain catastrophizing) both as unique and complementary mechanisms underlying the association between childhood adversity and pediatric pain.

Future Directions and Clinical Implications

The present study is the first to investigate the mediating effect of allostatic load on the association between childhood adversity and pediatric pain. This study is also one of the few that have examined longitudinal associations between childhood adversity and pain within a pediatric sample. The present study adds to the limited body of literature measuring allostatic load within a nationally representative pediatric population. Thus, findings from the present study supports future research and provides clinical implications.

The present study found evidence of childhood adversity in year 1 relating to increased pediatric pain intensity and pain-related disability in year 2. This relationship underscores the potential relevance of addressing childhood adversity as a target of tailored pain prevention and

intervention. A prevention effort, for example, may involve routine screening of adverse experiences among youth reporting pain and improving education and skills to screen for adversity among health care providers to identify youth who may be at risk for poor pain-related outcomes as well as improve appropriate referrals to psychological treatment (e.g., trauma focused cognitive behavioral therapy) (Groenewald et al., 2020). Intervention programs that promote resilience in children is another promising avenue to address childhood adversity and subsequent health impacts. Resilience is defined as the "capacity of a system to adapt successfully to challenges that threaten the function, survival or future development of the system" (Masten, 2011). Future work could investigate resilience as a factor mitigating the effects of childhood adversity on pain. Resilience is a particularly significant area for establishing interventions as it is a modifiable and a strength-based factor that entails practical and targeted interventions and has been applied toward improving pain related outcomes in other populations (Cousins et al., 2015). Resilience focused interventions may involve components such as emotional regulation training, cognitive behavioral approaches, physical health information on exercise, nutrition, and social support (Southwick & Charney, 2012).

Though the current study did not find support for allostatic load, investigating other potential biological mechanisms underlying the relationship between childhood adversity and pediatric pain remains a critical area for future research. For example, other factors or neurobiological mechanisms may mediate the association between the neurobiological stress response following adversity exposure and subsequent pediatric pain outcomes. The monoamine system and endogenous opioid system have a well-recognized role in the modulation of the stress response, and pain promoting processes (e.g., nociception) (Benarroch, 2012; Burke et al., 2017; Drolet et al., 2001; McEwen & Kalia, 2010). Genetic contributions underlying pain have also

been proposed as having a salient role in the relationship between childhood adversity, subsequent stress response, and pain-related outcomes (Burke et al., 2017; Fillingim, 2017). Genes associated with pain related phenotypes (e.g., chronic pain, pain severity) have been implicated in stress-response systems, highlighting a potential overlapping genetic component between the neurobiological stress response and pain phenotypes (Burke et al., 2017; Sibille et al., 2012). Genetic related pathways may include epigenetic mechanisms, which refers to molecular mechanisms that regulate gene expression without changing DNA sequences (e.g., DNA methylation, small RNA signaling) (Dupont et al., 2009; Hao et al., 2018). The majority of studies examining epigenetic mechanisms in the context of both childhood adversity and pain have focused on DNA methylation (Aroke et al., 2019).

DNA methylation has the potential to identify new etiology through which childhood adversity becomes biologically embedded and in turn promotes physical health consequences, such as pain (Burke et al., 2017; Hao et al., 2018). Considerable evidence has linked DNA methylation of genes implicated in pain promoting processes (e.g., risk of developing chronic pain) (Descalzi et al., 2015; Massart et al., 2016) and the functioning of the neurobiological stress response (e.g., HPA axis, immune system) associated with adversity exposure (Hao et al., 2018; Houtepen et al., 2018; Neves et al., 2019; Tang et al., 2020). It is plausible that DNA methylation modifications in genes related to stress-response systems (e.g., HPA axis, immune system) could mediate the effect of childhood adversity on pain outcomes. No studies to date have explored the potential role of DNA methylation or other epigenetic mechanisms in the childhood adversity-pain relationship. Future research should explore other neurobiological mechanisms and mediators, such as DNA methylation, linking childhood adversity to pediatric pain outcomes.

Investigating mediating biological mechanisms that overlap with the neurobiological stress response and that are amenable to intervention may inform targeted intervention strategies to improve pain-related outcomes. Prior evidence suggests interventions that downregulate the body's stress response system may promote healthy functioning of the stress system and in turn, serve as an important component of a multidisciplinary pain treatment program (McInnis et al., 2020). For example, the dysregulation HPA axis may be modified by improving the sensitivity and responsiveness of caregivers and increasing healthy and positive relationships. This effect is supported in studies that have shown family-based interventions resulting in measurable differences in cortisol levels and diurnal variation in cortisol levels (Fisher et al., 2007; Gonzalez, 2013; Saxbe et al., 2014).

Prior evidence has also found dysregulation of the autonomic nervous system measured by baroreceptor sensitivity, electrodermal activity and heart rate variability, may be modified by slow-breathing exercises and regular exercise (McInnis et al., 2020; Paccione & Jacobsen, 2019). Prior evidence has found dysregulation of the immune-inflammatory system, measured by inflammatory biomarkers such as c-reactive protein, may be modified by dietary related interventions (e.g., anti-inflammatory diet) (McInnis et al., 2020; Sears & Saha, 2021; Totsch et al., 2015). Given how dysregulation of these stress response systems (e.g., HPA axis, ANS, immune-inflammatory system) have been distinctively implicated in deleterious pain related outcomes (Cortelli et al., 2013; Knudsen et al., 2019; Nees et al., 2019; Nelson et al., 2017; Nelson et al., 2020a; Zhang & An, 2007), this information underscores the importance of future mechanistic studies identifying distinctive biological mechanisms linking childhood adversity to pain. It is widely accepted that adversity in childhood has effects on physical health, including pain, not only in childhood but across the lifespan (Craner et al., 2022; Hughes et al., 2017; Oh et

al., 2018; Shonkoff, 2012; Taylor et al., 2011; You et al., 2019). Thus, identifying distinctive biological mechanisms that inform targeted intervention strategies would promote an improvement of both short-term health in childhood and long-term health spanning into adulthood.

Future studies expanding on the limitations of the current study and investigating allostatic load as a potential mechanism should utilize a developmental perspective. Given how biological systems underlying allostatic load undergo critical and distinct advancements from the neonatal period through adolescence (Kuhlman et al., 2017), future research should investigate an allostatic load index that captures systemic dysregulation with consideration of the respective developmental period (e.g., early childhood, middle childhood, adolescence). This in-depth examination of allostatic load in the context of developmental stages would further our understanding of how stress manifests physiologically over time and in turn inform the potential clinical utility of allostatic load in improving pediatric health outcomes, including pain-related outcomes.

Lastly, though there are strengths of SEM, such as the ability to treat allostatic load as a continuous variable and the ability to identify relative weights of the indicators via factor loadings, the summative count method remains the most common statistical approach for calculating allostatic load (Whelan et al., 2021; King et al., 2019). The summative count method entails calculating scores for each allostatic load indicator by dividing them into risk quartiles based on the allostatic load psychometrics established in the MacArthur Studies of Successful aging. Then each biological indicator is dichotomized into normal versus abnormal values, and a summed total allostatic load score is created. The cumulative allostatic load score has been found to predict health outcomes (e.g., mortality, cardiovascular disease) (Beckie, 2012; Seeman

et al., 2010). Moreover, this approach has advantages over SEM, including determining participants with higher risk profiles and creating a clinically relevant summary score (i.e., high risk versus low-risk summary score), which may aid in the interpretation of findings and further the clinical relevancy of allostatic load to aid in relevant interventions to reduce allostatic load (Seeman et al., 2010). Though there are weaknesses in the summative count method, such as a potential loss of information of biological indicators due to dichotomizing individual indicators into normal versus abnormal values as well as not being able to identify the relative weights of which individual biological indicators best represent allostatic load. Thus, there are strengths and weaknesses to each approach. Future research should compare how well these differing methods relate to pediatric health outcomes and consider investigate the associations among childhood adversity, allostatic load and pain related outcomes using the summative count method for measuring allostatic load.

Conclusion

The current study found childhood adversity in year 1 was significantly predicted increased pain intensity and pain related disability in year 2, but not with year 3 pain outcomes in a nationally representative sample of adolescents. Allostatic load did not significantly mediate the relationship between childhood adversity and pediatric pain outcomes. Future research should explore other biological mechanisms (e.g., epigenetic mechanisms) that may link childhood adversity to pediatric pain related outcomes. Future research investigating allostatic load within a pediatric population should consider the influence of key developmental stages (e.g., middle childhood, adolescence) to inform the selection of biological indicators as well as consider the type, duration and timing of adversity. To date, knowledge about the specific mechanisms (biological, behavioral, and cognitive) underlying the association between

childhood adversity exposure and pediatric pain is not clearly mapped and would allow for more precise targeting of mechanisms as part of pediatric pain prevention and intervention efforts (Finlay et al., 2022; Nelson, Borsook, et al., 2021; Nelson et al., 2020a). Addressing childhood adversity and subsequent pain outcomes during childhood is critical as interventions during childhood could prevent deleterious health outcomes later in life into adulthood.

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Appendix: ABCD Stressful Life Event Questionnaire

*All items had the following response options: 1 = Yes; 0 = No

1. Someone in family died?
2. Family member was seriously injured?
3. Saw crime or accident?
4. Lost a close friend?
5. Close friend was seriously sick/injured?
6. Negative change in parent's financial situation?
7. Family member had drug and/or alcohol problem?
8. You got seriously sick?
9. You got seriously injured?
10. Parents argued more than previously?
11. Mother/father figure lost job?
12. One parent was away from home more often?
13. Someone in the family was arrested?
14. Close friend died?
15. Family member had mental/emotional problem?
16. Brother or sister left home?
17. Was a victim of crime/violence/assault?
18. Parents separated or divorced?
19. Parents/caregiver got into trouble with the law?
20. Attended a new school?
21. Family moved?
22. One of the parents/caregivers went to jail?
23. Got new stepmother or stepfather?
24. Parent/caregiver got a new job?
25. Got new brother or sister?