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Relationships Between Adverse Childhood Experiences, Inflammation and Pain in Youth and Emerging Adults with Sickle Cell Disease

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Relationships Between Adverse Childhood Experiences, Inflammation and Pain in Youth and Emerging Adults with Sickle Cell Disease

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by
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Abstract

Sickle cell disease (SCD) is a prevalent genetic disorder involving red blood cells. SCD is a multisystem disease and is connected to various severe medical complications, including debilitating pain. Though pain and inflammation have been connected to adverse childhood experiences (ACEs) in other populations, no prior work has investigated ACEs within a SCD population. The current study examined the prevalence of ACEs as well as the association of ACEs, inflammation, and pain in a sample of youth and young adults with SCD. Utilizing the biopsychosocial model of pain, I examined individual and cumulative ACEs as possible factors relating to inflammation, pain severity and pain frequency. Self-report measures of ACEs, pain severity and pain frequency were completed by a sample of adolescents and young adults with SCD (*N*= 21; mean age = 17.57 years). Further, within the overall sample, 14 participants reported pain and 7 participants had C-reactive protein (CRP) reports. CRP, an inflammatory biomarker was collected via blood samples drawn from routine clinic visits. Approximately half of the current sample reported exposure to at least one ACE, suggesting a high prevalence of ACE exposure within a youth SCD population. Cumulative ACEs did not relate to inflammation or pain. However, our findings do suggest that inflammation and pain outcomes are associated with individual ACE types, specifically financial hardship, racial discrimination, and divorce, though not always in the direction hypothesized. The study findings support the importance of taking into consideration the differential impact of different individual ACEs and their relationships to inflammation and pain within a SCD population.

Introduction

Sickle cell disease (SCD) is a prevalent genetic disorder involving red blood cells that is a multisystem disease and is connected progressive organ damage (Rees, Williams, & Gladwin, 2010). SCD is particularly prevalent in people of African descent, with one in 400 babies in the United States being born with the disease (Lorey, Arnopp, & Cunningham, 1996). Globally, around 275,000 newborns are born every year with SCD, with around 85% of births occurring in Africa (Aygun & Odame, 2012). An individual diagnosed with sickle cell may experience several complications, including but not limited to, acute pain, chronic pain, infection, neurological complications, acute chest syndrome, pulmonary hypertension, and heart disease (Rees et al., 2010). Complications associated with SCD have significant negative impacts on the lives of youth and young adults with the disease. Research has shown that individuals with SCD are at high risk for poor health outcomes, poor quality of life, and early mortality (Toledo, Guedes, Alpoim, Rios, & Pinheiro, 2019).

A common complication in youth and adults with SCD is the experience of pain. Pain has been primarily linked to vaso-occlusive crisis (VOC). A VOC involves sickled cells promoting micro-and macro-vascular occlusions (e.g., blockages of blood vessel) (Schiavenato & Alvarez, 2013). These blockages cause tissue damage and irritation, which is then associated with severe, acute pain episodes. Around 95% of hospital admissions for individuals with SCD are due to complications involving acute pain episodes (Ballas, Gupta, & Adams-Graves, 2012).

The biopsychosocial model of pain proposes that pain experiences are based on the interplay of biological factors (e.g., neuroendocrine factors, genetics, inflammation), psychological factors (e.g., positive and negative affect, pain catastrophizing) and social factors (e.g., family and peer environment) (Schlenz, Schatz, & Roberts, 2016; Taylor, Stotts,

Humphreys, Treadwell, & Miaskowski, 2013). The model proposes that to understand pain comprehensively, one must take into account the individual and interactive ways these factors may impact how pain is experienced (Gatchel, Peng, Peters, Fuchs, & Turk, 2007). The biopsychosocial model has been applied to understanding pain in youth and young adults with SCD (Crosby, Quinn, & Kalinyak, 2015; Schatz et al., 2015; Schlenz et al., 2016; Taylor et al., 2013), with findings linking a range of biological (e.g., SCD genotype) and psychosocial (e.g., negative and positive affect, stress) factors to the pain experiences of individuals with SCD. In other populations, there is preliminary evidence linking adverse childhood experiences (ACEs) to pain experiences (Drevin et al., 2015; E. S. Nelson, Simons, & Logan, 2018; Sachs-Ericsson, Sheffler, Stanley, Piazza, & Preacher, 2017; Stensland, Dyb, Thoresen, Wentzel-Larsen, & Zwart, 2013; You, Albu, Lisenbardt, & Meagher, 2019). However, there is currently no research exploring ACES in individuals with SCD or the relationship ACEs and pain experiences in individuals within the population. In addition, ACE exposure has been linked to elevated inflammation in other populations, (A. Danese et al., 2009; Gouin, Caldwell, Woods, & Malarkey, 2017). Inflammation has been associated with worse SCD pain. However, no prior research has examined ACEs association with inflammation in individuals with SCD.

The purpose of the current study is to examine the prevalence of ACEs exposure in adolescents and young adults with SCD, and the relationships between ACEs, pain, and inflammation in this population. The following sections review the literature on ACEs, and the possible link between ACEs and SCD pain. Then followed by a section on the discussion of inflammation and its association with ACE exposure.

Adverse Childhood Experiences

ACEs are a collection of traumatic events that occur in childhood (ages 0 to 17 years) that have been connected to various poor outcomes, such as the development or exacerbation of chronic health conditions and overall low quality of life (Felitti et al., 1998). They include experiences such as abuse, neglect, or household dysfunction. The original ACE questionnaire contained seven types of childhood experiences consisting of three categories of childhood abuse (psychological abuse, physical abuse, sexual abuse), and four categories of household dysfunction (exposure to substance abuse, mental illness, violent treatment of mother, and criminal behavior). Since then, the list of ACEs has expanded to include various other factors, such as neighborhood violence, homelessness, and bullying (C. D. Bethell et al., 2017; Finkelhor, Shattuck, Turner, & Hamby, 2013). For example, a task force that consisted of health care providers, researchers, funders, and organizations in Philadelphia proposed that ACEs assessment should be expanded to include community-based stressors (e.g., witnessing violence, experiencing discrimination/racism, and experiencing bullying) that significantly contribute to poorer outcomes (Pachter, Lieberman, Bloom, & Fein, 2017). The first assessment of ACEs was the CDC-Kaiser Permanente Study, which collected data from around 10,000 adults and included adversities only relating to household dysfunction. The results revealed that over half the respondents (52%) experienced at least one ACE and 6.2% experienced four or more ACES (Felitti et al., 1998). Since the time of that study, a plethora of research has been done linking ACEs to poor health outcomes using adult retrospective reports (Hughes et al., 2017; Kalmakis & Chandler, 2015).

Studies also have assessed ACEs in pediatric populations, and findings have linked exposure to ACES reported during childhood to children's poor health and academic outcomes

(C. Bethell, Davis, MB, Gombojav, N, Stumbo, S Poweers, K., 2017; Burke, Hellman, Scott, Weems, & Carrion, 2011; Jimenez, Wade, Lin, Morrow, & Reichman, 2016; Liming & Grube, 2018). For example, the National Survey of Children's Health (NSCH) started collecting data on ACES for children aged 0 to 17 years around the United States using the nine category NSCH-ACE scale in its 2011/2012 survey (C. D. Bethell et al., 2017). Data collection for this study is completed via surveys administered via mail and internet, and all years where data has been collected represent a randomly selected nationwide sample. Data from the 2012 survey indicated that ACE exposure reported during childhood is negatively related to children's development as well as their physical and mental health (C. Bethell, Newacheck, Hawes, & Halfon, 2014). For example, children who were exposed to at least one ACE had lower rates of school engagement and higher rates of chronic disease. The nationwide survey was again completed in 2016, and results indicated that in the subgroup of children aged 3 to 5 years, three in four children who were exposed to at least one ACE had been expelled from school (C. Bethell, Davis, MB, Gombojav, N, Stumbo, S Poweers, K., 2017). Further, children exposed to two or more ACEs were over four times more likely to exhibit social and emotional problems compared to those who were not exposed to ACEs.

These findings are consistent with a review focused on exploring exposure to ACEs during early childhood (i.e., prior to the age of 6 years) and subsequent biopsychosocial outcomes (Liming & Grube, 2018). The review found a total of five studies that examined early childhood exposure to ACEs. Results revealed that in four of the five studies, there was significant evidence of a dose-response in relation to cumulative ACE exposure, behavioral issues, and physical health outcomes (i.e., more ACES leading to worse behavioral and physical outcomes). Interestingly, the authors indicated they chose a specific developmental period of

early childhood (ages 0 through 6) because it represents a time of increased vulnerability to the influence of external factors on development. The authors were interested in how exposure to adverse experiences during early childhood would affect brain structure and functioning as well as the overall development of health throughout the lifespan. This review highlighted the importance of taking into account developmental periods when examining the effects of exposure of ACEs on health.

ACEs are proposed to be linked to poor health outcomes through their disruption of the development of a broad range of biological systems, including the central nervous, endocrine, and immune systems (Berens, Jensen, & Nelson, 2017). For example, the brain continues to undergo structural development through childhood into early adulthood (Mills et al., 2016). Normative neurodevelopment allows for the growth of complex systems linked to advanced thought processes and the ability to adapt to environmental changes (e.g., new experiences and situations; (Berens et al., 2017)). There has been extensive literature that has linked early life adversity with variation in brain structure and functioning, such as negative effects on memory, learning, and emotional regulation. For the neuroendocrine system, early adversity has been linked to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis develops from the neonatal period up through adolescence (Kate Ryan Kuhlman, Chiang, Horn, & Bower, 2017). It is responsible for maintaining homeostasis (i.e., internal stability and balance) and supports adaption to environmental stressors. Dysregulation of this system predicts the development of chronic illnesses, such as cardiovascular, psychiatric and metabolic related diseases (Berens et al., 2017). Additionally, early adversity has been linked to chronic inflammation and overall immune dysregulation into adulthood (Fagundes, Glaser, & Kiecolt-Glaser, 2013). Dysregulation of the immune system and chronic inflammation has been linked to

a variety of poor health outcomes, such as cancer (Michael et al., 2006), age-related diseases (A. Danese et al., 2009), neurodevelopmental changes (Nusslock & Miller, 2016), and pain (Fabien, Mauro, & Stephen, 2005).

Of note, many biological systems, such as the HPA axis and central nervous system, are undergoing critical advancements during adolescence and early adulthood (Kate Ryan Kuhlman et al., 2017; Mills et al., 2016). Thus, these developmental periods may act as critical periods for exploring the link between ACES and health outcomes. Exposure to ACEs prior to or during adolescence and young adulthood can promote functional impairments that evolve throughout the lifespan. This is especially concerning, as research indicates that by the time a child reaches adolescence, a majority of children will have been exposed to at least one adverse experience. This is supported by findings from a study of 6,483 adolescent-parent pairs that found 61.8% of their sample of adolescents had experienced at least one ACE (McLaughlin et al., 2013). Also, the impact of ACEs may be particularly salient during adolescence and emerging adulthood as exposure to the ACE is proximal in occurrence.

In conclusion, childhood adversity is connected to poor health outcomes and behaviors and affects normative physiological development across various systems (Berens et al., 2017; Kate Ryan Kuhlman et al., 2017). The disruption and dysregulation of the central nervous, endocrine, and the immune systems stemming from early adversity are likely biomechanisms that link ACEs to poor health outcomes seen in in the literature. Further, the disruption of these systems and associated poor outcomes are particularly crucial to examine during critical developmental periods, such as adolescence and emerging adulthood.

The following section will explore how ACEs are currently being measured, with a particular focus on ACE assessment during childhood.

Assessing ACEs. Many studies focus on measuring ACEs in adult populations (Burke et al., 2011). For adult questionnaires, the format is generally to ask participants to answer whether they have been exposed to each type of trauma listed during their first 18 years of life. Each yes is equivalent to one ACE. For pediatric populations, there is currently a wide range of surveys being used in ACE screenings. A literature review (C. D. Bethell et al., 2017) assembled current pediatric ACE surveys used in the literature, with an objective of comparing each one to a newly created measure, the NSCH-ACE. The review identified ten child-focused ACE measures, with the NSCH-ACE included. Each measure had variability in the number of ACEs assessed with a range between 6 and 20 items. Additionally, there were only four types of ACEs being evaluated that were common across all measures: parental incarceration, domestic violence, household alcohol or substance abuse, and household mental illness/suicide. There were no community focused ACEs that were included among all assembled measures. All ten measures were available in parental report, but only three (i.e., the Center for Youth Wellness, Yale-Vermont Adversity Childhood Scale and Children's Hospital of Philadelphia's Childhood Adversity Questionnaire) had a complementary child report included. Age eight was the youngest age assessed in these youth-based measures, with a general age range of 8 to 19 years. All measures were found to be adapted from the original CDC/Kaiser ACE study and used a cumulative risk scoring methodology.

The NSCH-ACE was the first pediatric ACEs measure used on a nationally representative sample of US children (C. D. Bethell et al., 2017). In addition, the measure has been shown to have strong internal validity and reliability, and high acceptability. Internal validity was evaluated using confirmatory factor analysis (CFA), which indicated a single item factor solution was appropriate. Reliability was evidenced by high item-total correlations.

Acceptability was evidenced by calculating the percentage of unknown and missing values for each ACE item. The NSCH is a parent report measure for households that include children aged 0 to 17 years and it contains a total of nine categories based on the original CDC/Kaiser ACES study augmented by additional familial and community level ACEs (i.e., parental death, treated unfairly because of race/ethnicity, witnessing neighborhood violence). A benefit of the measure is the inclusion of community-based factors (i.e. witnessing neighbor violence, treated unfairly because of race/ethnicity) which are critical in understanding trauma that a child encounters not only at the household level, but also within their community (Pachter et al., 2017).

There are limitations with the NSCH-ACE measure, many of which are consistent with the majority of pediatric ACE measures. One limitation is that there is only a parent report and not a complementary child report. Parental reports may be inconsistent with what their child would report. For example, false negatives and underreporting could result because a parent is unwilling or unable to disclose abuse or maltreatment (Cprek, Williamson, Brase, & Williams, 2020). Additionally, reporting on some ACEs may promote feelings of intrusiveness and discomfort for parents and their children (Finkelhor, 2018). To address this issue, the NSCH-ACE measure excludes items related to abuse (i.e., sexual, emotional, and physical abuse). These ACEs are deemed particularly sensitive due to the extreme severity of the associated trauma to these ACEs and how they involve mandatory reporting to law enforcement (Herzog & Schmahl, 2018). This exclusion, however, limits the association between ACES and outcomes, as physical, emotional and sexual abuse have been significantly connected to a variety of poor mental and physical health outcomes (Leserman, 2005; Norman et al., 2012; Springer, Sheridan, Kuo, & Carnes, 2007). Notably, even with these items excluded, the NSCH-ACE measure has been

associated with poor health outcomes in literature (C. Bethell, Davis, MB, Gombojav, N, Stumbo, S Poweers, K., 2017; C. D. Bethell et al., 2017).

In conclusion, exposure to ACEs have been connected to poor outcomes across various domains and throughout the lifespan (C. Bethell, Davis, MB, Gombojav, N, Stumbo, S Poweers, K., 2017; Burke et al., 2011; Felitti et al., 1998; Hughes et al., 2017; Jimenez et al., 2016; Kalmakis & Chandler, 2015). Adolescence and emerging adults are pivotal developmental stages for addressing the impact of ACEs to mitigate the consequences as people age. Upon reviewing literature, the high prevalence of ACEs and the numerous associated health outcomes raises concern. With exposure to adversity disrupting physiological development, it is critical to understand the possible influence of ACEs on disease symptoms for youth and young adults with chronic illnesses, such as pain. The following sections present information on pain in youth and young adults with, and then discuss the existing literature on ACEs, inflammation, and SCD pain.

Youth and Young Adult SCD Pain

Pain experienced by youth and young adults with SCD is a significant complication (Sil (S. Sil, L. L. Cohen, & C. Dampier, 2016; Smith et al., 2008; William et al., 2013). As mentioned previously, youth and young adults with SCD often experience acute severe pain episodes (Schiavenato & Alvarez, 2013; Smith et al., 2008). These episodes can vary in location, intensity, and duration. One study asked 46 youth and young adults aged 8 to 21 years with SCD and their parents how many pain episodes the individual with SCD had experienced in the past 12 months (Schatz et al., 2015). Parents reported their children had an average of 4.3 episodes that resulted in an inpatient and/or ER visit and 14.5 episodes managed at home over a 12-month period. Youth and young adults reported an average of 4.6 episodes that required an inpatient

and/or ER visit, and 23.2 episodes managed at home over a 12-month period. Pain variability is additionally illustrated in a self-report diary-based study that assessed pain characteristics in a sample of 24 children with SCD aged 8 to 12 years over a period of eight weeks (Valrie, Gil, Redding-Lallinger, & Daeschner, 2007). The results showed children reported experiencing pain an average of 21.31% of the total diary days and an average pain severity rating on pain days of 49.83 (on a 0 to 100 mm VAS scale). Another study of 25 youth with SCD aged 7 to 12 years and their caregivers reported on pain sites using the Varni/Thompson Pediatric Pain Questionnaire (Graumlich et al., 2001). The number of pain sites self-reported by children ranged from 1 to 6, while parents reported a range of 1 to 7. The most common site reported by parents and children was the leg, with other pain sites including the arm, knee, stomach, and back. To conclude, pain can be frequent, severe, and highly variable for SCD patients.

Youth and young adult SCD pain has been connected to various poor outcomes. For example, one home-based daily diary study of 19 youth with SCD, aged 8 to 17 years, investigated the relation between pain and school performance across a total of 4,756 days (Shapiro et al., 1995). Youth were absent on 21% of the 3,186 school days, with half of the total absent days being as a result of severe pain. The study concluded that severe pain is linked to lower school attendance, which likely leads to poorer school performance. Another, daily diary-based study of 37 youth with SCD aged 13 to 17 years investigated the relation between pain intensity and a range of outcomes (Gil et al., 2003). The study found that higher ratings of SCD pain were significantly associated with same day activity (e.g., more school absences, reduced extracurricular activities, less household chores) and health care use (e.g. more ER visits). Results also indicated that high pain intensity was associated with high same day stress and negative mood, and low pain intensity was associated with high same day positive mood. Youth

SCD pain is also the most common reason for frequent hospital trips in the population (Benton, Boyd, Ifeagwu, Feldtmose, & Smith-Whitley, 2011). Lastly, a study of 40 individuals with SCD aged 12 through 19 found that during pain crises, all domains of health-related quality of life were reported as being diminished. With pain being the hallmark feature of SCD disease (Benton et al., 2011), these findings illustrate the importance of fully understanding the factors and mechanisms associated with the experience of pediatric SCD pain.

From a developmental perspective, the pain experience changes across the lifespan for individuals with SCD. A relationship between pain frequency and age has been established, with a multisite, longitudinal study finding a gradual increase of pain frequency until the age of 30 (Platt et al., 1991). Further, findings from this study showed that pain rates for individuals with SCD aged 20 to 29 years were significantly higher than for individuals aged 0 to 9 years. For individuals under the age of 20, pain rates were significantly higher in those aged 10 to 19 years compared to those aged 0 to 9 years. Collectively, these results indicate that during the developmental periods of adolescence (i.e., 12 to 18 years) into emerging adulthood (i.e., 18 to 25 years), individuals experience increasingly more frequent pain. These findings are further illustrated in another study that investigated rates of acute care utilization and re-hospitalizations for 21,112 patients aged 1 to 65 years and older with SCD using Healthcare Cost and Utilization Project State Inpatient Databases and State Emergency Department Databases (Brousseau, Owens, Mosso, Panepinto, & Steiner, 2010). They found that young adults aged 18 to 30 years had increased emergency department usage due to pain crises and the highest rate of re-hospitalizations compared to other sickle cell age groups. The authors suggested that this may be because of the disease worsening as the patient ages and the transition from pediatric to adult care.

To conclude, pain is highly variable in SCD patients. Each individual with SCD will display different pain features in regard to intensity, frequency, location and duration (N. Y. C. Dampier et al., 2004; Graumlich et al., 2001; Schatz et al., 2015). The mechanisms behind this pain variability are highly complex (C. Dampier et al., 2017; Field et al., 2019). According to the biopsychosocial model, factors that influence pain may include psychological and social factors, such as ACES (Ballas et al., 2012). The following section will discuss how ACEs may be related to pain experienced by youth and young adults with SCD.

ACEs and SCD Pain

There are no current studies assessing ACEs in relation to pain for individuals with SCD. In addition, there is limited research examining ACEs in other pain populations; however, preliminary studies suggest a link between ACEs and pain experiences. Results from a cross-sectional study of 232 pregnant women aged of 30 to 31 years indicated that more ACEs was associated with a high number of pain sites and high pain intensities for women later in pregnancies (Drevin et al., 2015). Another 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 first 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%).

Research on the role of ACEs in youth pain populations is also limited. A conceptual review that examined the relationship between ACEs and chronic pain in youth populations reported that there is currently little known in regard to this relationship and much more research is needed (E. S. Nelson et al., 2018; M. S. Nelson, Cunningham, & Kashikar-Zuck, 2017). The authors identified studies that had compelling preliminary evidence in beginning to establish the relationship between ACEs and chronic pain in youth. Specifically, the authors found three studies with findings that indicate children and adolescents (up the age of 20) with particular chronic pain conditions (e.g., abdominal pain, recurrent headache, fibromyalgia) generally report a higher number of ACEs in comparison to healthy cohorts. The first study explored patterns of physical comorbidity in 1,672 female youth aged 0 to 17 with PTSD (Seng, Graham-Bermann, Clark, McCarthy, & Ronis, 2005). Results found PTSD was associated with increased odds of adverse health conditions, such as pelvic pain and fibromyalgia. The second 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. The third study assessed the relationship between stressful life events and somatic complaints in 172 adolescents aged 11 to 19 (Greene, Walker, Hickson, & Thompson, 1985). Results indicated that patients with recurrent pain for which there was no identifiable organic cause reported significantly higher life stress in comparison to patients that were being seen for a routine checkup, had an acute minor illness, or a stable chronic illness or pain with an identifiable organic cause.

A few recently published studies have also supplied preliminary evidence for the relationship between ACEs and pain in youth and young adults (E. S. Nelson et al., 2018; You et

al., 2019). One investigated the relationship between ACEs and several chronic illnesses, including chronic pain conditions, in a sample of 141 individuals aged 9 to 19 years (E. S. 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 investigated whether more adverse events would be a risk factor for common chronic pain conditions in a sample of 3,073 undergraduates, with a mean age of 18.8 years (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).

Overall, preliminary research suggests a link between ACEs and pain in youth and young adults; however, more research is needed to validate this relationship. Additionally, to further understand this relationship, it would be insightful to explore how the experience of childhood trauma relates to biopsychosocial mechanisms linked to pain in youth and young adults. Although mechanistic research is limited linking ACEs to pain, potential pathways have been proposed, such as inflammation. Investigating associations between ACE exposure and inflammation would provide the grounding for future mechanistic work. The next sections will discuss inflammation in more detail as well as exploring its relation to SCD pain and ACEs.

Inflammation

Inflammation is the immune's system response to harmful stimuli, such as damaged cells, toxic compounds and pathogens (L. Chen et al., 2018). During this response, there are complex cellular and molecular interactions and events that occur internally in an attempt to remove harmful stimuli and initiate a healing process (Medzhitov, 2010). At a cellular level, the inflammatory response is made of a coordinated network of many cell types. Examples include lymphocytes (e.g., a type of white blood cell), monocytes, neutrophils, and many others (L. Chen

et al., 2018). This response contributes to restorative tissue homeostasis and resolution of acute inflammation. However, when the acute inflammatory response is unable to be resolved and the heighted inflammatory state remains, chronic inflammation and tissue damage may result.

Chronic inflammation acts as pathophysiological mechanism that underlies a variety of diseases, such as bowel and cardiovascular diseases, diabetes, cancer and arthritis (Libby, 2007). An outcome from acute inflammatory mechanisms failing to eliminate tissue injury leads to chronic inflammation, which promotes further tissue damage (L. Chen et al., 2018). Tissue damage stems from a coordination of inflammatory and vascular cell responses to the injury. Inflammation at a tissue level is characterized by redness, swelling, heat, pain, and loss of tissue function. The potential adverse effects of chronic inflammation depend on the initial stimulus (e.g., toxic compound, damaged cells) and the location within the body.

Cytokines (i.e., chemical messengers that are crucial for intracellular reactions within the body) are used to assess inflammation and are crucial in inflammatory research. They act as reliable biomarkers (i.e., measurable substances in an organism) due to how circulating levels of cytokines are produced by activated immune cells, which subsequently leads to activation of other cells that results in the further synthesis of more cytokines associated with inflammation (Hänsel, Hong, Cámara, & Von Känel, 2010). Commonly used inflammatory biomarkers include interleukins (IL), interferons (IFN), and tumor necrosis factor (TNF). In addition to cytokines, an acute phase protein called C-reactive protein (CRP) is another well-established inflammatory biomarker.

The biomarkers discussed above all play their own unique role in promoting inflammation in SCD as well as coordinating with one another. An example of this coordination is seen for cytokines IL-4 and IL-10. Both are released when the inflammatory state is high and

subsequently promote the release of other pro-inflammatory cytokines, such as IFN-γ and TNF-α (Hänsel et al., 2010). In addition, TNF-α acts as the main mediator of acute inflammatory responses. When plasma levels of TNF-α are high, the production of IL-6 increases, which then promotes the release of acute phase proteins involved in inflammation (Bandeira et al., 2014). Thus, it is important to measure levels of multiple biomarkers to fully understand the current inflammatory state. Notably, CRP, TNF-α, and IL-6 have been studied in relation to inflammatory levels and pain in patients with sickle cell (Francis & Haywood, 1992; Krishnan et al., 2010; Qari, Dier, & Mousa, 2012; Sarray et al., 2015). Additionally, those three biomarkers have been used in studies assessing inflammatory levels in relation to individuals who have experienced ACEs (A. Danese et al., 2009; Gouin et al., 2017; Kate Ryan Kuhlman et al., 2017). Thus, CRP, TNF-α, and IL-6 are some examples that can serve as biomarkers that can comprehensively examine inflammatory levels in both a physiological context (i.e., sickle cell and pain) and psychosocial context (i.e., ACEs).

Overall, inflammation is a complex physiological response that begins as beneficial, but if unresolved, then negative consequences such as tissue damage may result. Inflammation is particularly important for understanding sickle cell pain, as inflammatory processes have been found to be key components of many SCD complications (Conran & Belcher, 2018). The following section will discuss these key components of inflammation in SCD, specifically in relation to pain.

SCD Pain and Inflammation.

Inflammation plays crucial roles in the pathophysiology of SCD (Hoppe, 2014). Specifically, pro-inflammatory conditions contribute to the occurrence of VOCs and subsequent tissue damage (Lidiane et al., 2016). The tissue damage as a result of VOCs then proceeds to

promote the release of inflammatory mediators that are responsible for initiating the transmission of pain sensations and enhancing the perception of pain (Qari et al., 2012). This illustrates a continuous inflammatory cycle where inflammation promotes VOCs and VOCs then promote inflammation. Additionally, a common complication for individuals with SCD is leukocytosis (Abramson & Melton, 2000). When leukocytosis occurs, there is an elevation in inflammatory cytokines, which may lead to higher levels of inflammatory cytokines and subsequently promote VOCs, tissue damage, and SCD pain (Hoppe, 2014).

Inflammation has been found to be elevated in patients with SCD (Francis & Haywood, 1992; Hibbert et al., 2005; Lanaro et al., 2009; Zhang, Xu, Manwani, & Frenette, 2016). For instance, a study of individuals aged 4 to 65 investigated the effect of hydroxyurea therapy (HU) on the release of inflammatory mediators (i.e., TNF-α, IL-8) across three groups: a healthy control group with 33 participants, a group of 50 steady-state SCD patients, and another steady-state group of 26 SCD patients on HU (Lanaro et al., 2009). Participants were characterized as steady state if they were not in a crisis and had not received a blood transfusion in the previous three months. Results indicated that both SCD steady-state groups showed heightened TNF-α and IL-8 levels in comparison to healthy controls, concluding that inflammatory levels are elevated in individuals with SCD whether they are on HU or not. Additionally, participants on HU exhibited lower TNF-α levels, though not IL-8 levels, in comparison to the steady-state with no HU. A second study showed similar findings in 34 adults aged 19 to 37 with SCD when examining levels of TNF-α and IL-1(Francis & Haywood, 1992). Inflammatory markers were considered elevated by using the TNF standard (i.e., >60 pg/mL) and the IL-1 standard (i.e. > 75 pg/mL). Results revealed elevated levels of TNF-α in at least one occasion (i.e., steady state or painful crisis) in 27 of the 34 participants. Additionally, results indicated elevated levels of IL-1

in at least one occasion in 6 of the 34 participants with SCD. Lastly, another study investigated differences in CRP between 12 children with SCD and 9 healthy controls (Hibbert et al., 2005). Results indicated that CRP was significantly elevated in children with SCD compared to the healthy controls. Taken together, the findings from these three studies demonstrate an overall elevation in inflammatory biomarkers among individuals with SCD.

To conclude, findings indicate that inflammatory biomarkers are elevated in individuals with SCD in comparison to healthy controls. Inflammation has also been linked to VOCs, subsequent tissue damage, and a heightened perception of pain. Taken together, the consequences of inflammation and its role in pain support the need to understand what factors may contribute to elevated inflammation, such as ACEs. The following section will explore the relationship between ACEs and inflammation.

ACEs and Inflammation

The experience of ACEs is associated with toxic stress, which is then connected to subsequent physiological consequences. These consequences are particularly illustrated in the immune system (Lagraauw, Kuiper, & Bot, 2015), where exposure from toxic stress alters immune systems responses such as inflammation. Early life adversity has diverse effects across neural, endocrine, metabolic, immune (e.g. inflammation) and gut microbial axes (Berens et al., 2017; S. Nelson, Bento, & Enlow, 2021). Additionally, there is extensive literature on the relationship between adversity exposure and poor health outcomes, as discussed in the ACEs section. However, there is a gap of knowledge in the consideration of how early life adversity contributes to the risk of specific health outcomes. One pathway that has been suggested from a biological viewpoint as the potential biological factor relating ACEs to poor health outcomes is inflammation. There are various studies that have found overall elevated inflammatory

biomarker levels in adult participants who were exposed to ACEs (M. Chen & Lacey, 2018; Andrea Danese & McEwen, 2012; A. Danese et al., 2009; Andrea Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Gouin et al., 2017; Tietjen, Khubchandani, Herial, & Shah, 2012). This elevation provides preliminary support that inflammation may serve as a pathway linking ACEs to poor health outcomes. Notably, ACEs have not been assessed in patients with sickle cell; thus, literature cited in this section will focus on the general population.

Studies have found a correlation between exposure to ACEs and higher inflammatory levels (M. Chen & Lacey, 2018; Andrea Danese & McEwen, 2012; Andrea Danese et al., 2007; Tietjen et al., 2012). For instance, a longitudinal study of 972 participants followed from birth to the age of 32 found that participants who were exposed to childhood maltreatment and very high social isolation had a significant risk of elevated CRP levels (A. Danese et al., 2009). Another study of 174 adult participants found that exposure to multiple ACEs was associated with elevations in IL-6, but not CRP levels (Gouin et al., 2017). These studies exhibit an association between exposure to ACEs and elevations of inflammatory biomarkers in adult populations.

For youth populations, the relationship between ACEs and inflammation is not as solidified. Kuhlman and colleagues (2019) completed a systematic review and meta-analysis gathering studies that assessed the relationship between ACEs and inflammatory levels in pediatric populations. Findings from the review indicated that only 27 studies had been published assessing this relationship, with CRP (9 total studies) and IL-6 (7 total studies) being the only biomarkers measured consistently in five or more studies. Results indicated significant associations between early life adversity and high CRP levels, although IL-6 was not consistently related to early life adversity. Additionally, they found that the use of saliva in measuring IL-6 and CRP was not as validated as using blood-based markers. Also, the relationship between early

life adversity and CRP was stronger in studies of infants and adolescents than studies of children during middle childhood. ACEs was assessed in a variety of ways with 37% child report, 40.7% caregiver report, 18.5% third party report, and 3.7% using a combination of reports. The sample characteristics varied significantly across studies, with small samples of 27 to large samples of 2,232 being assessed as well as with age ranges from birth through 19. The review findings highlighted the crucial need of more research being done in this field and the importance in understanding inflammation in youth populations who have been exposed to ACEs (Kate R. Kuhlman, Horn, Chiang, & Bower, 2019)

To summarize, it is well understood that early adversity negatively impacts various physiological systems, including the immune system and its responses (i.e., inflammation) (Berens et al., 2017). Researchers have found a relationship between exposure to ACEs and elevated inflammatory biomarkers in adult populations. The relationship between ACEs and inflammation in youth populations is preliminarily established. However, given that inflammation has been connected with both ACEs and pain, research is needed to explore the associations among ACEs, inflammation and SCD pain to inform future work.

The Current Study

The current study examined the prevalence of ACEs exposure in adolescents and young adults with SCD, and investigated the relationships between ACEs, pain, and inflammation in the sample. Given the current research showing negative outcomes associated with inflammation and pain experienced in adolescents and young adults with SCD (Benton et al., 2011; Gil et al., 2003; Shapiro et al., 1995), this study explored cumulative and individual ACEs as potential factors relating to SCD pain and inflammation. Understanding how ACEs is associated with inflammation and SCD pain will allow providers to better understand which adolescents and

young adult patients are more at risk for experiencing worse pain and other SCD outcomes, and to establish more individualized intervention plans to improve their quality of life.

Aims and Hypotheses

The current study had three primary aims:

Aim 1

To assess ACEs in adolescents and young adults with SCD. This includes describing the prevalence of cumulative ACEs as well as frequencies of specific ACE items.

Aim 2

To examine associations between cumulative ACEs, an inflammatory biomarker (CRP), and pain in adolescents and young adults with SCD.

Hypothesis 2a: I hypothesized cumulative ACEs will be positively associated with levels of CRP.

Hypothesis 2b: I hypothesized cumulative ACEs will be associated with worse pain outcomes (i.e., more severe pain and high pain frequency).

Aim 3

To assess the relationships between individual ACEs and pain in adolescents and young adults with SCD.

Hypothesis 3a: I hypothesized exposure to individual ACEs will be positively associated with levels of CRP.

Hypothesis 3b: I hypothesized exposure to individual ACEs will be associated with worse pain outcomes (i.e., more severe pain and high pain frequency).

Method

Participants

Adolescents and young adults with SCD and the youth's accompanying guardians were recruited from both the pediatric SCD clinic in the Children's Hospital of Richmond and the adult SCD clinic at Virginia Commonwealth University (VCU). Inclusion criteria included being aged 12 to 25 years, having a diagnosis of SCD, and speaking fluent English. Exclusion criteria included the inability to complete surveys as decided by health care provider, having a comorbid pain condition (e.g., arthritis), experiencing an active pain crisis at the time of study recruitment, or receiving chronic blood transfusions.

Procedure

After the Institutional Review Board approved the study, potential participants and their guardians were approached during their regular outpatient visit at the Children's Hospital of Richmond and the adult SCD clinics at VCU. Potential youth and young adult participants and the accompanying guardians of the youth were informed of the study and its procedure. If they were interested, young adults with SCD and guardians of youth with SCD completed informed consent forms, and youth completed assent forms. Consent included HIPAA authorization to review youth and young adult participants' medical records and access participants' bloodwork. The young adult participants and guardians of youth participants reported young adults' and youth's demographic and disease information. Youth and young adults reported their pain severity and frequency as well as their exposure to ACEs. Youth and young adults also had their blood drawn by a health care provider as part of their regularly scheduled visit.

Measures

Demographics and Disease Information. Youth and young adult's age in years, SCD genotype and sex (coded as 1=female and 0=male) were collected through guardian and young adult interview and confirmed using the participant with SCD's medical electronic record. SCD genotype was coded as 1=severe genotypes (e.g., HbSS and HbS/β^0), and 0=moderate genotypes (e.g. HbSC and HbSβ+, or other).

Adverse Childhood Experiences (ACEs) Questionnaire. The NSCH-ACE measure (C. D. Bethell et al., 2017) were used to assess ACEs with a total of nine items (see appendix) and were completed by youth and young adults. In the original NSCH ACE scale, there was one item involving discrimination due to race. This item was replaced with two items examining discrimination due to race in and outside of healthcare settings. Also, two items were added focused on discrimination due to SCD inside and outside of health care. For the purposes of creating the cumulative measure of ACEs, the two items on discrimination due to race were collapsed into one item where a participant who responded yes to any of the two race discrimination questions was considered one ACE. The items referring to SCD were excluded from the calculation of the cumulative ACEs score but examined when looking at individual ACE items. Thus, the cumulative ACE score was consistent with the original NSCH ACE scale from 0 to 9. This was done to remain consistent with the NSCH-ACE measure, while also exploring new ACE items that may be particularly salient among youth and young adults with SCD. Further, consistent with NSCH-ACE scoring, for the SES related item responses of either "somewhat often" or "very often" were counted as one ACE. The original measure was parental report and thus, for youth and young adults, the wording of the directions was modified. The

NSCH-ACE measure has been shown to have efficiency, strong internal validity and high acceptability (C. D. Bethell et al., 2017).

Inflammatory Biomarker - CRP. CRP was collected via blood samples drawn by nurses from routine clinic visits and were processed by VCU Pathology. The residual material from the routine blood draw were used for the study and measured with the Immunochemiluminometric assay (ICMA) (Shiesh, Chou, Lin, & Kao, 2006). The "normal" range for CRP is less than 10 mg/L (Windgassen, Funtowicz, Lunsford, Harris, & Mulvagh, 2011).

Pain Severity and Frequency. The Structured Pain Interview (Gil et al., 2001) was completed by youth and young adults to assess their pain severity and pain frequency. Pain frequency was measured via the report of the number of pain episodes youth and young adults experienced in the past 6 months. Pain severity was measured using the question, "on average how would you rate the severity of your painful episodes during the past 6 months" and having them respond on a scale of 0 through 10 (i.e., 0 being no pain and 10 being severe pain). Reliability and validity of the Structured Pain Interview has been exhibited in other studies with youth with SCD (Gil et al., 1993; Gil, Williams, Thompson, & Kinney, 1991).

Data Analysis Plan

Post-Hoc Analysis

Due to the low sample size, which was originally not anticipated, a post hoc power analysis was conducted using G*Power software to determine the current power with a sample size of 21(Faul, Erdfelder, Buchner, & Lang, 2009). The current power for correlation analyses with a power ≥ 0.8 and alpha ≤ 0.05 was 0.40.

Given how the p-value is dependent on sample size, the current study also focused on interpretations using Cohens' effect size estimates (2013), as they are independent of sample size and thus will allow for more reliable estimates of the study's results. Cohens' d is a quantitative measure of the magnitude of the relationship between two variables, hence the larger the effect size, the stronger the relationship it is. The cutoffs for Cohen's d used for interpreting comparison between two group on a continuous outcome are the following: *a*: 0.2 to 0.5 small effect size; *b:* 0.5 to 0.8 medium effect size; and *c*: > 0.8 large effect size. The cutoffs for Cohen's interpretation of correlations (i.e., assessing the magnitude of the association between two continuous variables), are the following: *a*: 0.1 to 0.3 small association; *b*: 0.3 to 0.5 medium association; and *c*: > 0.5 large association.

Descriptive Statistics and Preliminary Analyses Plan

The R software program was used for analyses. Descriptive statistics in the overall sample were reported for study variables and sample characteristics. Specifically, cumulative ACEs, CRP, pain severity, pain frequency, and age were described with means, standard deviations, and ranges. Additionally, individual ACEs, sex, and genotype severity were described with frequencies. Further, descriptive statistics were calculated for the subsample of participants with CRP reports. Prior to all analysis, data distributions were examined for normality and outliers for cumulative ACEs, CRP, pain severity and pain frequency.

Primary Analysis Plan

Study Aim 1 analyses included descriptive statistics for cumulative ACEs (i.e., ranges, mean, SDs). Further, percentages of each ACE using frequency tables were calculated to determine distribution of ACE types reported.

Study Aim 2 analyses included calculating correlations between cumulative ACEs, CRP, and pain outcomes (i.e., pain severity and frequency). If cumulative ACEs were statistically associated with outcome variables (e.g., CRP, pain severity, pain frequency), regression models were calculated with cumulative ACEs as the predictor and CRP, pain severity, and/or pain frequency as outcomes. Control variables included age, sex and SCD genotype severity. These covariates were selected in view of prior evidence finding higher age, being female and having a severe SCD genotype may put individuals with SCD at an increased risk for poor pain outcomes (Masese et al., 2021; Platt et al., 1991).

Study Aim 3 analyses included independent sample t-tests and calculation of Cohen's *d* for the relationship between each individual ACE and study outcomes (i.e., CRP, pain severity and frequency). Regression models would be run if more than one individual ACE was significant in t-test results to examine their unique relationship with inflammation and pain outcomes over and above the other ACEs. Control variables would include age, sex and SCD genotype severity.

Results

Descriptive Statistics

Descriptive information for study variables is presented in Table 1. There were 21 participants in the total sample, and 7 participants in the subsample had CRP reports. The average age of participants was 17.57 years, and the majority of the participants were female (71%) and diagnosed with a severe SCD genotype (67%). Fourteen of the participants (67%) reported experiencing a SCD pain episode in the last year. The average cumulative ACEs reported in the sample was 2.05 (Range = 0 to 6). Approximately 19% of the sample reported no ACE exposure, 9% of the sample reported one ACE, 43% reported two ACEs, and 29% reported

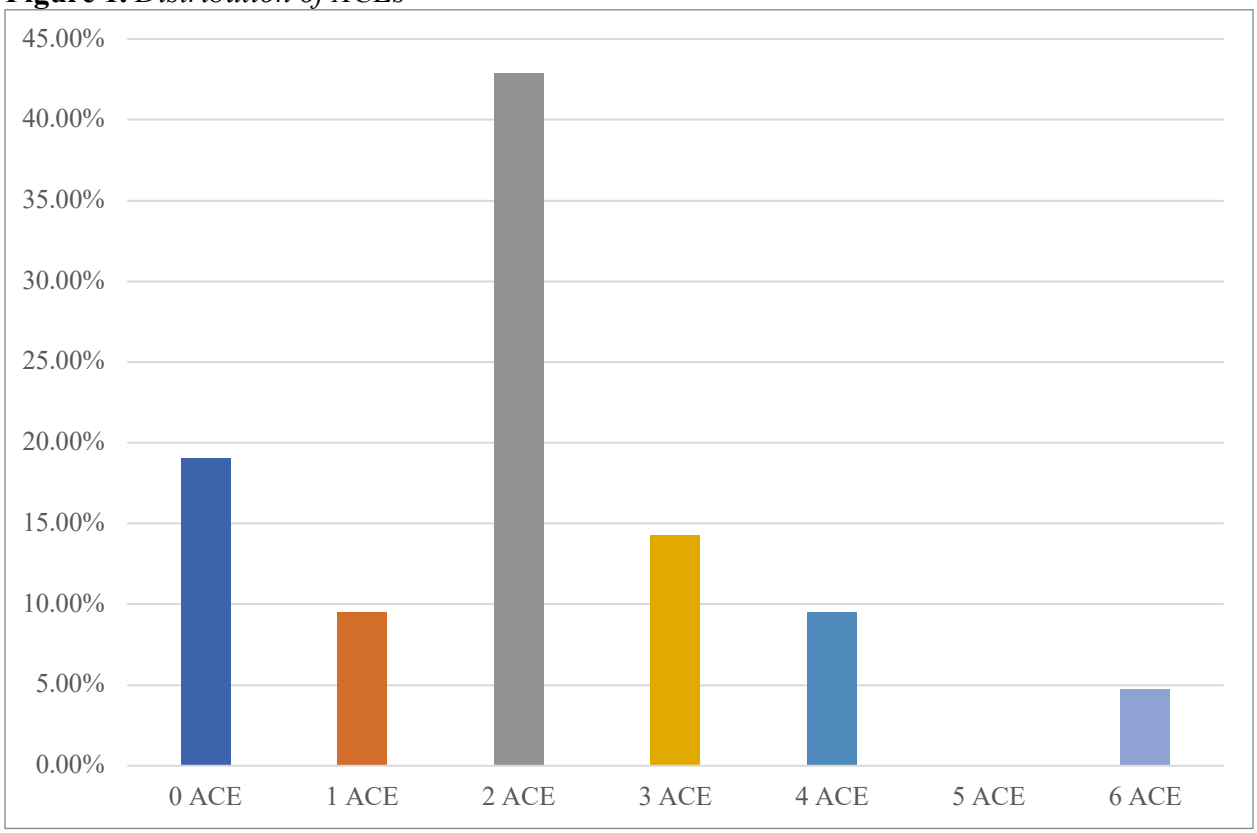
three or more ACEs (see Figure 1). In relation to pain, the average for pain severity was 8.07 on a 10-point scale (Range= 4 to 10) and for pain frequency was 78.86 episodes per year (Range = 1 to 35). The average CRP level was 6.61 mg/L (0.4 to 30.7 mg/L). In total, there were seven reports of CRP, with only one participant having a CRP level above normal range (i.e., greater than 10 mg/L).

Table 1. *Sample characteristics*

Continuous Descriptives	*M*	*SD*	*Range*	*n*
Age	17.57	4.43	12 to 25	21
Cumulative ACEs	2.05	1.50	0 to 6	21
Pain Severity[a]	8.07	1.90	4 to 10	14
Pain Frequency[a]	8.86	11.2	1 to 35	14
CRP	6.61	10.87	0.4 to 30.7	7
Categorical Descriptives	*n*	*%*	*N*	
Pain	14	67%	21	
Sex				
Female	15	71%	21	
Male	6	29%	21	
Genotype Severity				
Severe	14	67%	21	
Non-severe	7	33%	21	

Note. [a]Subsample of participants who reported pain. ACEs= Adverse Childhood Experiences; CRP = C-reactive protein.

Figure 1. *Distribution of ACEs*



Note. ACEs= Adverse Childhood Experiences

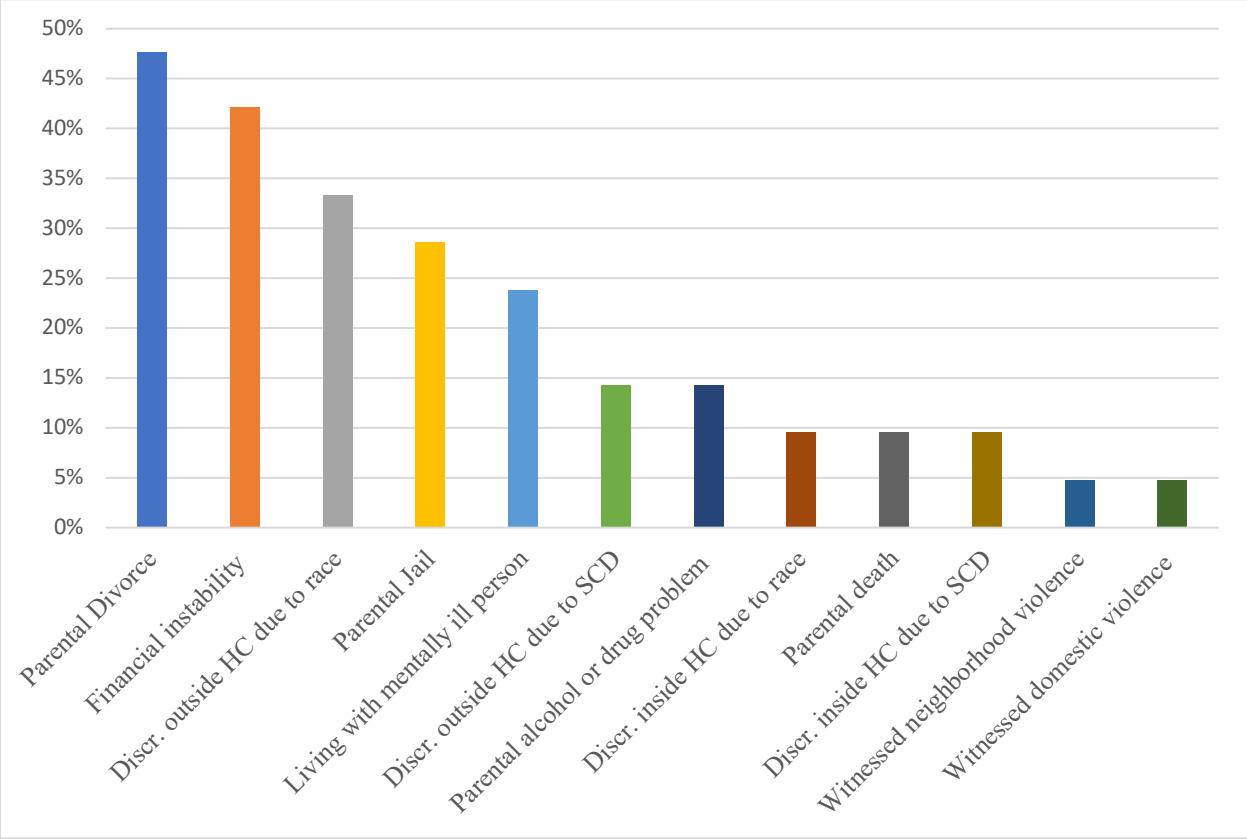
Cumulative ACEs, CRP, pain frequency and pain severity were assessed for normality through examining skewness and kurtosis statistics. All study variables were considered normal as absolute values for skewness and kurtosis in each variable fell within the range of +1 to -1.

Primary Analyses

Prevalence and Distribution of Individual ACEs. Aim 1 assessed the prevalence of ACEs using ranges, mean and SD for cumulative ACEs and frequencies for individual ACEs. The average cumulative ACEs reported in the sample was 2.05 (*SD* = 1.5; Range = 0 to 6). For ACE prevalence, approximately 48% percent of the sample reported exposure to divorce (*n*=10), followed by 42% percent to financial instability (n=8), 33% to discrimination outside healthcare settings due to race (n=7), 28% to parent going to jail (n=6), and 24% living with an individual

with a mental illness (n=5). (See Figure 2 for full distribution of ACEs.) Conversely, there was low prevalence of exposure to parental death, witnessing both domestic and neighborhood violence, parental drug use/abuse, and discrimination due to SCD. Notably, for the individual discrimination items, experiencing discrimination outside of healthcare due to race (n=7) was more prevalent then reports of experiencing discrimination inside healthcare due to race (n=2) as well as discrimination due to SCD both inside (n=2) and outside healthcare (n=3).

Figure 2. Rates of individual reported ACEs



Notes. Discr. = Discrimination; HC= Healthcare

ACEs and Pain

Cumulative ACEs and pain. Aim 2 examined associations between cumulative ACEs and pain outcomes using Pearson correlations, including both interpretations of effect sizes and *p*-values. Due to the small sample size and lack of statistical power for running regression models, no controls were included in the analyses. According to Cohen (2013), correlations between 0.1 to 0.3 indicate a small association, between 0.3 to 0.5 indicate a moderate association, and 0.5 or higher indicates a large association. None of the correlational analyses between ACEs and pain were statistically significant. However, using Cohen's interpretation of effect sizes, there was a small negative association between cumulative ACEs and pain frequency (r = -0.28, p = 0.32) (see Table 2).

Table 2. *Pearson Correlations Between Study Variables*

	1.	2.	3.	4.
1.Cumulative ACE	_			
2. Pain Severity	0.04 (0.88)	_		
3. Pain Frequency	- 0.28 [a] (0.32)	- 0.24 (0.41)	_	
4. CRP	- 0.02 (0.96)	- 0.75 [c] (0.46)	- 0.08 (0.95)	_

Note. Parentheses indicate *p*-value; Cohen Effect Size: *a*: 0.1 to 0.3 small association; *b*: 0.3 to 0.5 medium association; *c*: > 0.5 large association

Individual ACEs and Pain. Aim 3 assessed the relationships between individual ACEs and pain outcomes using independent sample t-tests. T-tests were run to determine if there were differences in pain severity and pain frequency based on exposure to an individual ACE. Since there were low frequency of several ACE items, I chose to analyze the top three most frequently reported ACEs as described in Aim 1 (i.e., financial instability, discrimination outside of healthcare due to race, and divorce). There were significant differences in pain severity based on financial instability (t (12) = -2.50, $p < 0.05$) and on divorce (t (12) 2.58, $p < 0.05$) (see Table 3).

Table 3. *Independent sample t-tests for differences in pain outcomes*

ACE Type	Yes *M*	No *M*	t	p	Cohen *d*
Pain Severity					
Financial Instability	9.14	7.00	-2.50	0.02*	-1.34[c]
Divorce	7.13	9.33	2.58	0.02*	1.39[c]
Discrimination outside HC due to RACE	6.80	8.78	2.10	0.06	1.17[c]
Pain Frequency					
Financial Instability	9.29	8.44	-0.14	0.89	-0.07
Divorce	7.75	10.33	0.41	0.69	0.22[a]
Discrimination outside HC due to RACE	9.40	8.55	-0.13	0.90	-0.07

Note. * = $p < .05$; Cohen *d* Effect Size: *a:* 0.2 to 0.5 small effect size; *b:* 0.5 to 0.8 medium effect size; *c*: > 0.8 large effect size

Acording to Cohen's *d*, there was a large negative relationship between financial instability and pain severity (*d* = -1.34). Specifically, participants with no exposure to financial instability had lower pain severity (M = 7.00) compared to those with financial instability exposure (M = 9.14). For divorce and pain severity, there was a large positive relationship between divorce and pain severity (*d* = 1.39). Specifically, participants with no exposure to divorce had higher pain severity (M = 9.33) compared to those with divorce exposure (M= 7.13). For divorce and pain frequency, there was a small positive relationship between divorce and pain frequency (*d* = 0.22). Specifically, participants with no exposure to divorce reported more pain frequency (M = 10.33) compared to those reporting divorce exposure (M =7.75). For discrimination due to race outside healthcare and pain severity, there was a large positive relationship (*d* = 1.17). Participants with no exposure to discrimination reported more pain severity (M = 8.78),

compared to those reporting discrimination exposure (M =6.80). For discrimination due to race outside healthcare and pain frequency, there was no relationship (d = -0.07).

ACEs and Inflammation

Cumulative ACEs and Inflammation. Aim 2 examined the association between cumulative ACEs and inflammation using a Pearson correlation, including both the interpretation of the effect sizes and p-value. Due to the small sample size and lack of statistical power for running regression models, no controls were included in the analyses. The correlational analysis between cumulative ACEs and inflammation had no relation and was not statistically significant (see Table 2).

Individual ACEs and Inflammation. The descriptives for the subsample of the seven participants with CRP reports are the following: average age of 17.29 years (Range 13 to 24), pain frequency of 7.67 (Range 1 to 20), pain severity of 8.33 (Range 6 to 10), and cumulative ACEs of 1.71 (Range 0 to 4). Based on t-tests, there were no significant differences in age, pain outcomes, or cumulative ACEs between the CRP subsample and the overall sample. Further, approximately 86% of the CRP subsample was female and had a severe SCD genotype. Based on chi-square tests, there were no significant sex or SCD genotype differences between the CRP subsample and the overall sample.

Aim 3 assessed the relationships between individual ACEs and CRP using independent sample t-tests. T-tests were run to determine if there were differences in CRP based on exposure to an individual ACE (i.e., financial instability, divorce, discrimination outside healthcare due to race). There were no statistically significant differences in CRP levels based on exposure to financial instability, divorce, or discrimination outside healthcare due to race (Table 4).

Table 4. *Independent sample t-tests for differences in CRP*

ACE Type	Yes *M*	No *M*	t	p	Cohen *d*
Financial Instability					
	1.92	13.31	0.84	0.45	0.72[b]
Divorce					
	1.59	13.31	1.58	0.18	1.20[c]
Discrimination outside HC due to race					
	11.62	2.86	-1.07	0.33	-0.82[c]

Note. Cohen d Effect Size: *a:* 0.2 to 0.5 small effect size; *b:* 0.5 to 0.8 medium effect size; *c*: > 0.8 large effect size

However, according to Cohen's *d* (i.e., 0.2 to 0.5 small; *b*: 0.5 to 0.8 moderate; *c*: > 0.8 large), there was a moderate positive relationship between financial instability and CRP (*d* = 0.72). Specifically, participants with no exposure to financial instability had higher CRP levels (M = 13.31) compared to those reporting financial instability exposure (*M*= 1.92). For divorce, there was however a large positive relationship between divorce and CRP (*d* = 1.20). Specifically, participants with no exposure to divorce had higher CRP levels (M = 13.31) compared to those with divorce exposure (M= 1.59). For discrimination outside healthcare due to race there was large negative relationship between discrimination outside healthcare due to race and CRP (*d* = 0.82). Specifically, participants with no exposure to discrimination outside healthcare due to race had lower CRP levels (M= 2.86), compared to those with discrimination exposure (M = 11.62).

Discussion

Previous research has indicated ACEs are related to worse pain in pediatric populations (Groenewald, Murray, & Palermo, 2020). Prior studies have also found a relationship between

ACE exposure and elevated inflammation in adult populations (Berens et al., 2017; Andrea Danese & McEwen, 2012), with preliminary support in pediatric populations as well (Kate R. Kuhlman et al., 2019). However, no prior research has been done to assess the relations of ACEs to pain and inflammation within a SCD population. This is of particular concern as pain in SCD is a significant complication connected to a host of poor health outcomes and poor quality of life (L. S. Sil, L. L. Cohen, & L. C. Dampier, 2016; Smith et al., 2008). Moreover, inflammation plays a critical role in the pathophysiology of SCD and is linked to a host of clinical complications, including pain (Hoppe, 2014). Thus, the overall goals of the current study were to describe the prevalence of ACES in adolescents and young adults with SCD, and to examine the relationships between ACEs, inflammation, and pain in this population.

ACEs Prevalence and Distribution

Cumulative ACEs were assessed using the NSCH-ACE measure original score of 0 to 9. Of note, the discrimination due to SCD both inside and outside of healthcare items were not included in the cumulative ACE measure and the and the discrimination due to race inside and outside of healthcare items were collapsed to maintain consistent scoring of the original NSCH-ACE measure. The majority of participants in the current sample reported exposure to at least one ACEs (80%). This prevalence contrasts with data from the National Survey of Children's Health (NSCH) using the NSCH-ACE measure, which found approximately 49.8% of children reporting at least one ACE (Groenewald et al., 2020), and a study of college students that found 51.7% of the sample reported at least one ACE (Grigsby et al., 2020). The most frequently reported ACEs in the sample were divorce (48%), racial discrimination outside healthcare settings (33%) and financial instability (42%). These patterns are consistent with a study examining ACE type prevalence using the NSCH data (Crouch, Probst, Radcliff, Bennett, &

McKinney, 2019), with the most frequently reported being economic hardship (22.5%) and parental divorce (21.9%). Conversely, only 3.3% of this national representative sample reported being treated unfairly due to race. Of note, in the 2018-2019 NSCH data, the prevalence of the discrimination due to race item among Black youth was 10.6% (Child Adolescent Health Measurement Initiative, 2021). This in contrast to prevalence estimates of 1.3% reported by White youth, 5.5% reported by Hispanic youth and 8.0% reported by Other. Thus, given how SCD impacts primarily Black individuals, this high prevalence of racial discrimination within the NSCH Black sample of youth, is consistent with the high prevalence found in the current sample. Of note, 33% of the current sample reporting exposure to discrimination due to race outside of healthcare is substantially higher than the 10.6% found in the NSCH Black sample, suggesting an increased risk of exposure to racial discrimination within pediatric sickle cell populations. Although the current sample size is small, this provides preliminary support that individuals with SCD may experience more ACEs than the general population as well as the general Black population. A potential explanation for elevated ACEs in a SCD population, may involve racial inequities, as SCD impacts primarily Black individuals. A national population study found higher ACE exposures reported by participants who identified as Black, Hispanic, or multiracial compared to White participants (Merrick, Ford, Ports, & Guinn, 2018). These findings are consistent with previous research indicating individuals with SCD are more likely to experience socioeconomic hardship and face stigma associated with their diagnosis of SCD (Lee, Smith-Whitley, Banks, & Puckrein, 2019).

The high parental divorce rate in the current sample is also consistent with Crouch (2019) findings of Non-Hispanic Black children were more likely to be exposed to parental divorce than their counterparts – 34.7% among Black children, 26% among Latinx children, and 22% among

White children (Maguire-Jack, Lanier, & Lombardi, 2020). Further, given these study findings and how approximately half of the study sample reported exposure to parental divorce, individuals with SCD may experience higher exposure rates than the general Black population as well. Lastly, an additional reason for such high parental divorce rates may involve the management of sickle cell and its impact on family functioning. Parents often assume the primary responsibility of managing their child's disease management. This often results in considerable stress and thus may negatively impact the parents' relationships (Sil, Woodward, Johnson, Dampier, & Cohen, 2021).

The second most frequently reported ACE type was discrimination outside healthcare settings due to race. This is consistent with numerous studies finding Black youth face racial discrimination more frequently than the general population (Cheng, Cohen, & Goodman, 2015; Umaña-Taylor, 2016). For example, one study found approximately 90% of Black youth reporting they had experienced at least one discriminatory experience in the past year (Seaton, Caldwell, Sellers, & Jackson, 2008). Further, parents of Black youth were more likely to endorse the NSCH ACE item "treated unfairly due to race or ethnicity" compared to parents of White, Hispanic, and Other youth in the NSCH data (Child Adolescent Health Measurement Initiative, 2021). Moreover, a systematic review found evidence that individuals with SCD face are at high risk of experiencing racial discrimination (Bulgin, Tanabe, & Jenerette, 2018). Lastly, individuals with SCD and their families often face financial hardship and lack of resources, which may contribute to the 33% of the current participants reporting financial hardship (Barbarin, Whitten, Bond, & Conner-Warren, 1999a).

Taken together, our results suggest that cumulative ACE exposure may be higher within a SCD population compared to the general population as well as the general Black population.

Furthermore, our results indicate that divorce, discrimination due to race, and financial hardship may be particularly prevalent experiences for youth and young adults with SCD. Future research is needed using a larger sample of individuals with SCD to validate these findings.

Relation between ACEs and Pain

Cumulative ACEs. The associations between cumulative ACEs and pain indicators were not statistically significant. However, there was a small negative association between cumulative ACEs and pain frequency – more ACEs was associated with fewer pain episodes per year. These findings were inconsistent with the hypothesis that more ACEs would be related to more frequent pain. It may be that examining ACEs as cumulative is not a good strategy for understanding the relationship between ACEs and SCD pain. It may be that individual ACEs differentially relate to pain, rather than cumulative ACEs. This is supported by a study of 48,567 youth aged 6 to 17 that found certain ACEs were more robustly associated with risk for chronic pain compared to other ACE types (Groenewald et al., 2020). Specifically, children who were exposed to living with a mentally ill person or those exposed to financial instability were more likely to have chronic pain compared to children exposed to parental divorce or parental death. As discussed more in detail in the next section, these findings suggest ACE types may have distinctive relations with pain presentation. Given that a cumulative ACE measure does not account for the strength of each adverse experience (e.g., taking into consideration duration of adversity) (Dennis, Clohessy, Stone, Darnall, & Wilson, 2019) on pain, future work should attempt to replicate these findings within a larger sample size. By understanding the relation of cumulative ACEs to pain, health care providers may be able to establish more effective targeted interventions (Groenewald et al., 2020).

Individual ACEs. Although there were few statistically significant differences in pain outcomes based on financial hardship, divorce and racial discrimination, effect sizes indicated small to large associations between specific ACEs and pain. Consistent with our hypotheses, participants who reported exposure to financial instability had higher pain severity compared to those with no exposure. These findings are also consistent with a study that found increased chronic pain risk for children who report exposure to financial instability compared to other ACE types, such as divorce or parental death (Groenewald et al., 2020). In children with SCD, financial instability has also been associated with parental anxiety (Barbarin, Whitten, Bond, & Conner-Warren, 1999b) and a lack of medical care (Barbarin et al., 1999a). Notably, parental anxiety and fear have been related to an increase of functional disability risk and overall poorer functioning for children with SCD (Sil et al., 2021). Factors related to exposure of financial hardship in SCD (e.g., lack of medical care, parental functioning) may further explain the current study findings of strong associations between financial hardship and higher pain severity in youth with SCD as well as inform future interventions. For example, augmenting child focused interventions with parent focused interventions may buffer the relation of financial stability on higher pain severity. Parent focused interventions may include parent support groups, parent mindfulness training or parental problem-solving skills (Sil et al., 2021).

Inconsistent with the hypotheses, participants who reported exposure to divorce had low pain severity and low pain frequency compared to those with no exposure. It may be that divorce is not an inherently negative experience for all children and may instead have positive effects for some and their families (Braver, Hipke, Ellman, & Sandler, 2004; Hetherington & Kelly, 2003). For example, numerous studies have found positive effects as a result of parental divorce, such as happier parents, less parental conflict (Halligan, Chang, & Knox, 2014), increased closeness

with siblings (Abbey & Dallos, 2004), and personal growth as a result of witnessing their parents' emotions in a new way (Smart, 2006). In addition, exposure to divorce has differential impacts on children based on age exposed to divorce, with research indicating younger children are more negatively affected compared to older children and young adults (Kalter & Rembar, 1981; Leon, 2003). As the current study sample consists of adolescents and young adults, this may have contributed to relations found between parental divorce and pain outcomes. Additional research is needed to examine relationships between parental divorce and pain outcomes for youth with SCD, with consideration of differential associations based on age of exposure to divorce.

Inconsistent with our hypothesis, participants who reported exposure to racial discrimination had less pain severity compared to those with no exposure. Further, there was no relationship between racial discrimination and pain frequency. This in contrast to a study of 1,908 individuals aged 30 to 84 that found psychological distress due to perceived discrimination related to chronic pain development (Brown et al., 2018). Another study in a nationally representative sample of children that found a strong association of exposure to racial discrimination and chronic pain risk (Groenewald et al., 2020). More research investigating the association between racial discrimination and pain is limited, particularly in pediatric populations. Additional research is needed to examine these inconsistent findings and investigate relationships between racial discrimination and pain outcomes for youth with SCD with a larger sample.

Collectively**,** the results found differential relations of pain outcomes based on ACE type. These findings underscore the need for future studies with larger sample sizes focused on

investigating the differential relationships between distinct ACEs and SCD pain outcomes in pediatric populations.

Relations between ACEs and Inflammation

Cumulative ACEs. Contrary to our hypotheses, in the subsample of 7 participants with CRP reports, cumulative ACEs was not associated with inflammation. Of note, the small sample size and the average CRP within the current study being the normal clinical range (< 10mg/L) may have impacted findings. Previous research findings have indicated that elevated CRP levels are related to pain outcomes (Krishnan et al., 2010; Mohammed, Mahdi, Sater, Al-Ola, & Almawi, 2010). Also, only one inflammatory biomarker, CRP, was collected, which limits our findings. Cumulative ACEs have been related to other inflammatory biomarkers, such as TNF-a and IL-1b, in other youth populations (Condon, 2018). It may be that cumulative ACEs within a SCD population are associated with inflammatory biomarkers beyond CRP. More research is needed to assess a range of inflammatory biomarkers and their relation to ACE exposure within a SCD population.

Individual ACEs. Three specific ACEs – racial discrimination outside of healthcare, financial instability, and divorce – were examined in relation to inflammation. Although there were not statistically significant differences in inflammation based on exposure to the three specific ACEs examined, effect sizes indicated small to large associations between specific ACEs and inflammation. Consistent with our hypotheses, participants who reported exposure to racial discrimination outside of healthcare had higher CRP levels compared to those with no exposure. This is consistent with a systematic review suggesting a relationship between exposure racial discrimination in childhood, and systemic inflammation later in life (Cuevas et al., 2020). Of note, there are few studies examining the relation between exposure to discrimination and

inflammatory outcomes during childhood. The few studies however have found evidence of racial discrimination as associated with elevated CRP levels among Black youth (Brody, Yu, Miller, & Chen, 2015; Goosby, Malone, Richardson, Cheadle, & Williams, 2015). Given the current study findings of racial discrimination and SCD, future research should explore the relationships between various form of racial discrimination, including interpersonal or structural forms of racial discrimination (Simons et al., 2018), and inflammatory biomarkers in adolescent and young adult populations. Future studies may also want to investigate the extent to which interventions can reduce the association between inflammation and racial discrimination.

Inconsistent with our hypothesis, participants who reported no exposure to financial instability had higher inflammation compared to those with exposure. This is in contrast with findings from other studies indicating financial hardship, instability, and low socioeconomic status are connected to immune system activation and subsequent elevated inflammation (Carmeli et al., 2020; Jensen, Berens, & Nelson, 2017). However, few studies have examined disadvantaged socioeconomic conditions in relation to inflammatory levels in youth populations (Carmeli et al., 2020). Also inconsistent with our hypothesis, participants who reported no exposure to divorce had higher CRP levels compared to those with exposure. There is limited literature investigating the individual effects of divorce on inflammation. However, the few studies in adult populations suggest parental divorce and separation are related to elevations of inflammation (Lacey, Kumari, & McMunn, 2013; Lacey, Pinto Pereira, Li, & Danese, 2020). Future research should investigate both financial hardship and divorce's relation on inflammation within larger sample sizes of youth with SCD as well as incorporate a wider range of inflammatory biomarkers. As financial hardship and divorce differ in duration of exposure and divorce may have mixed effects (i.e., divorce may be perceived as positive when it reduces

parental conflict), it is possible inflammatory biomarkers are related to distinct ACE types based on those underlining features, such as timing, duration, and consequences (Lacey et al., 2020). Establishing specific adverse childhood experiences relation on inflammatory outcomes may allow future research to develop targeted interventions by identifying at risk youth with SCD to ultimately mitigate inflammatory sequelae throughout the lifespan.

Overall, these findings suggest specific ACEs have differential relationships with inflammatory outcomes among youth with SCD. More research is needed to validate these findings concerning the relationships between specific ACEs and inflammation in youth with SCD.

Additional Findings

Inconsistent with prior investigations, there was a large negative association between inflammation and pain severity, such that low CRP was associated with more severe SCD pain. These findings are inconsistent with several studies finding elevated inflammation resulting in vaso-occlusive crises (i.e., acute pain crises) (Ballas et al., 2012; Conran & Belcher, 2018; Darbari, Sheehan, & Ballas, 2020; Hebbel, Osarogiagbon, & Kaul, 2004). The average CRP in the sample fell within normal (i.e., not clinical) range, which may explain these inconsistent findings as elevated CRP has been connected to acute pain crises. In addition, other inflammatory biomarkers including interleukins (e.g., IL-6) have been implicated in SCD pain severity (Qari et al., 2012). Thus, future research should examine these findings within a larger sample size as well as a incorporate a range of inflammatory biomarkers based on respective inflammatory pathways.

Limitations

Beyond the limitations mentioned above, it is important that the results of the study are viewed in the context of other limitations. Due to the small sample size, possible confounding factors – age, SCD genotype, and hydroxyurea use – were not included in the analyses. Given that pain increases as one ages (Platt et al., 1991), and pain tends to decrease when taking hydroxyurea (Wong, Brandow, Lim, & Lottenberg, 2014), it is imperative to understand the association of ACEs and SCD pain in the context of these possible confounding factors. Further, the majority of the sample was female, which may have impacted the study's findings. This is consistent with other pediatric SCD samples in other studies, which have tended to have a higher percentage of female compared to male participants (Fisher et al., 2018; Graves & Jacob, 2014; Schatz et al., 2015; Sehlo & Kamfar, 2015; Sil et al., 2021; Valrie et al., 2019). This may suggest gender differences in recruitment and completion rates among youth with SCD. Given how prior investigations have found significant sex differences in both pain outcomes (Ilesanmi, 2013) and inflammation (Casimir, Mulier, Hanssens, Zylberberg, & Duchateau, 2010), future work should implement recruitment strategies targeted towards Black male youth for a more equal distribution of female and male participants.

Further, the study used a cross-sectional design, making it correlational and unable to identify causal relationships. Thus, the results could not indicate whether ACE exposure caused worse inflammation and pain for adolescents and young adults with SCD. Future research should implement longitudinal designs examining the temporal relationship between ACEs, inflammation, and pain outcomes within a SCD population. Identifying a temporal relationship between ACEs, inflammation, and pain, would highlight the enduring effects of toxic stress and support the importance of prevention efforts to combat the impact of ACEs in reducing inflammation and pain risk across.

Lastly, due to the sample size, we were unable to investigate whether inflammation mediated the relationships between ACEs and pediatric SCD pain. Mechanisms underlying the relationship between ACEs and pain remain unclear. Although there was not a significant correlation between cumulative ACEs and inflammation, there was a strong association between inflammation and worse SCD pain severity. Further, there were strong associations between specific ACEs and pain outcomes. Thus, future work with a larger sample size is needed to establish whether associations exist between both cumulative ACEs and ACE types with inflammation within a SCD population. This would then suggest a potential mediating effect of inflammation between ACEs and pain in SCD.

Future Research Directions and Applied Implications

The high prevalence of ACEs in our sample of adolescents and young adults with SCD supports the importance of future work investigating ACES prevalence in a larger sample of individuals with SCD. No prior studies have examined the prevalence of ACEs in a SCD population. Moreover, ACE questionnaires often exclude discrimination as an ACE type (Cronholm et al., 2015). However, consistent with the traditional ACEs (e.g., parental divorce, financial hardship), exposure to discrimination by individuals with SCD and other populations has been widely associated with negative health consequences Given the negative impact on health and the high prevalence of racial discrimination found in the current sample, it is critical for future studies to include this as an ACE item, particularly for SCD populations.

Further, although there are studies investigating ACEs in other adolescent and young adult populations, this work may not be generalizable to a SCD population. In the United States, it is well-established that significant health disparities exist for those that are low-income, racial minorities, and publicly insured (Lee et al., 2019). Individuals with SCD and their families bear a

distinct and pronounced burden with these health disparities, as the majority of the patient population are Black, face financial hardship, and are publicly insured (DeBaun & Telfair, 2012). In combination with the severity of the disease itself, these disparities exacerbate stress, may reduce one's quality of life (Perry Caldwell & Killingsworth, 2021), and may leave a child with SCD at an increased risk of ACE exposure as well as an increased vulnerability to the effects of toxic stress as a result of adverse experiences. Thus, future work is critically needed to address ACEs within a SCD population and its impact on health and health-care outcomes.

Further, investigating strength-based approaches to managing the possible effects of ACES, such as resilience, is a promising avenue for future work. 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 individual ACEs on pain. Resilience is a particularly significant area for establishing interventions as its 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, Kalapurakkel, Cohen, & Simons, 2015). Some examples of components in a resilience intervention are emotional regulation training, cognitive behavioral approaches, physical health information on exercise, nutrition, and social support . (Southwick & Charney, 2012). Interventions such as this provide a promising avenue to mitigate the impact of ACEs. In addition, psychological and behavioral based interventions may also reduce inflammation and provide a promising avenue for future intervention work. For example, one study found resilience resources (e.g., awareness of self and others, physical health behaviors), attenuated the association between ACEs and inflammation in a sample of adults (Gouin et al., 2017).

Conclusion

This study lays the groundwork for future studies on ACEs in individuals with SCD, and relationships between ACEs, inflammation, and pain outcomes in adolescents and young adults with SCD. Approximately half of the current sample reported exposure to at least one ACE, suggesting a high prevalence of ACE exposure within a youth SCD population. Cumulative ACEs did not relate to inflammation or pain. However, our findings do suggest ACE types relate distinctively to inflammation and pain outcomes, specifically financial hardship, racial discrimination, and divorce. The study findings support the importance of taking into consideration the differential impact of different adverse experience experiences and their relationships to inflammation and pain within a SCD population. These results have implications for informing the potential salience of interventions aimed at mitigating the physiological consequences of ACEs and in turn, an improvement of inflammation and pain outcomes. Further, findings highlight the critical need for future work to investigate factors that may attenuate the long-term impact of ACEs (e.g., such as resilience).

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Appendix A
NSCH-ACE Youth and Young Adult Measure

1. SINCE YOU WERE BORN, how often has your family experienced a very hard time to get by on the family income- hard to cover the basics like food or housing?

☐ Never

☐ Rarely

☐ Somewhat often

☐ Very often

The next questions are about events that may have happened during your life. These things can happen in any family, but some people may feel uncomfortable with these questions. You may skip any questions you do not want to answer.

To the best of your knowledge, have you EVER experienced any of the following?

2. Parent or guardian divorced or separated ☐ yes ☐ no

3. Parent or guardian died ☐ yes ☐ no

4. Parent or guardian served time in jail ☐ yes ☐ no

5. Saw or heard parents or adults slap, hit, kick, punch one another in the home ☐ yes ☐ no

6. Was a victim of violence or witnessed violence in neighborhood ☐ yes ☐ no

7. Lived with anyone who was mentally ill, suicidal, or severely depressed. ☐ yes ☐ no

8. Lived with anyone who had a problem with alcohol or drugs ☐ yes ☐ no

9. Treated or judged unfairly because of his or her race or ethnic group

a. Inside of health care settings ☐ yes ☐ no

b. Outside of health care settings ☐ yes ☐ no

10. Treated or judged unfairly because of you have sickle cell disease

a. Inside of health care settings ☐ yes ☐ no

b. Outside of health care settings ☐ yes ☐ no

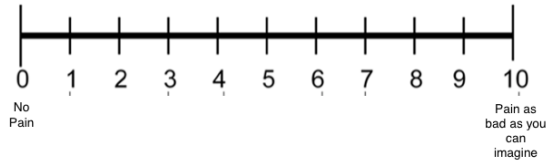
Appendix B
STRUCTURED PAIN INTERVIEW

I. Pain **"Painful episode"** = any episode of pain that you would attribute to SCD, lasting anywhere from 20 minutes to a period of days. Not limited to or exclusive of "crises".

A. Frequency:
How many painful episodes have you had in the past 6 months? _____

B. Duration:
How long do your painful episodes last in hours or days?
_____(Indicate hours or days)
(If you cannot give average, what is the length of short episode? _____ the length of a long episode?_____)

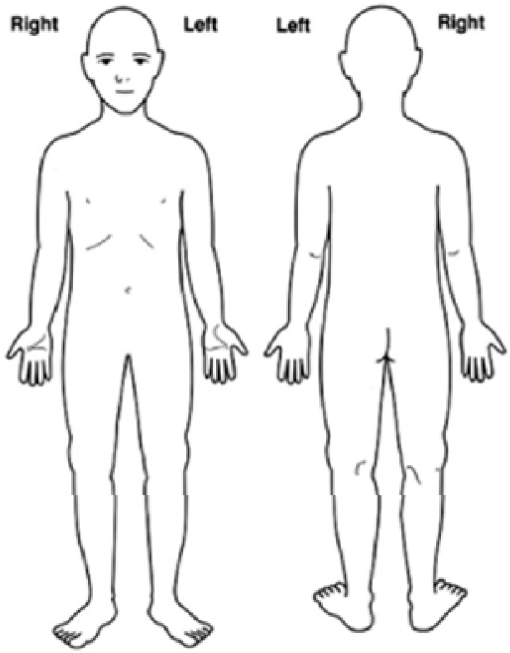
C. Severity:
Using the following 0-10 scale (0= no pain, 10 = pain as bad as you can imagine), on average, how would you rate the severity of your painful episodes, during the past 6 months? (Circle a number on the line)



D. Unpleasantness:
Using the following 0-10 scale (0 = not unpleasant, 10 = most unpleasant feeling possible), on average, how would you rate the unpleasantness of your painful episodes during the past 6 months? (Circle a number on the line).

E. Location:

Color in the areas on these drawings to show where you have pain. Make the marks as big or small as the place where the pain is.



F. In the past month:

How many pain days have you had in the **past month**? _____

Circle the number of days you had pain per week in the **past month**?

Everyday

- 5 to 6 days per week
- 3 to 4 days per week
- 1 to 2 days per week
- A few days per week
- None

How long have you experienced this current level of monthly pain frequency?_____ (Indicate in months or years)

G. Severity: (Past Month)

Using the following 0-10 scale (0= no pain, 10 = pain as bad as you can imagine), on average, how would you rate the severity of your painful episodes, during the past month? (Circle a number on the line)

H. Unpleasantness: (Past Month)

Using the following 0-10 scale (0 = not unpleasant, 10 = most unpleasant feeling possible), on average, how would you rate the unpleasantness of your painful episodes during the past month? (Circle a number on the line).

I. Additional Signs of Pain

When in pain, have you had any of these signs? (Check all that apply)

_____ Palpation (i.e., pushing on) the region of the pain produces pain or tenderness

_____ Movement of the region of pain produces pain

_____ Decreased range of motion or weakness in the region of pain

_____ Evidence of skin ulcer in the region of pain

_____ Your doctor(s) has indicated evidence of hepatobiliary or splenic imaging abnormalities (e.g., splenic infarct, chronic pancreatitis) consistent with the region of pain

_____ Your doctor(s) has indicated evidence of imaging abnormalities consistent with bone infarction or avascular necrosis in the region of pain

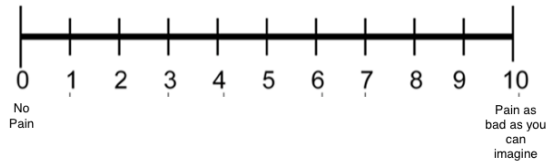
Is there another diagnosis that better explains the signs and symptoms of your pain?

(Check one) _____ No

_____Yes, What? _____

J. Severity: (Past Week)

Using the following 0-10 scale (0= no pain, 10 = pain as bad as you can imagine), on average, how would you rate the severity of your painful episodes, during the past <u>week</u>? (Circle a number on the line)



K. Unpleasantness: (Past Week)

Using the following 0-10 scale (0 = not unpleasant, 10 = most unpleasant feeling possible), on average, how would you rate the unpleasantness of your painful episodes during the past week? (Circle a number on the line).

II. <u>Health Care Utilization:</u>

A. Emergency Room Visits:

How many times have you gone to the emergency room because of your pain in the past 6 months? _____

B. Hospitalization:

How many times have you been hospitalized because of pain in the past 6 months?_____

How long has each stay lasted on average? _____

C. Doctor Visits or Calls:

How many times have you gone to see a doctor or other healthcare professional because of pain in the past 6 months? _____

L. Pain Medication:

What over the counter analgesic medications (e.g. Tylenol, aspirin, or Motrin) do you take for pain?

_____
_____
_____

What prescription narcotic analgesic medication (e.g. percodan, Demerol, Tylenol13 codeine) do you take for pain?

_____
_____
_____