INVESTIGATING THE RELATIONSHIP BETWEEN ADVERSE CHILDHOOD EVENTS AND CHRONIC PAIN IN PEDIATRIC AND ADULT POPULATIONS

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ABSTRACT

Chronic pain is a highly prevalent condition in pediatric and adult populations, with epidemiological rates increasing over time. Literature has highlighted a correlation between adverse childhood experiences (ACEs) and chronic pain conditions, with a great focus on adult populations. This paper explored this existing research, while diving deeper into studies pertaining to children and adolescents with chronic pain. This review also examined proposed models that can explain this correlation to explore conceptual understandings, alongside the underlying biological mechanisms that facilitate this relationship to investigate physical processes. Adverse childhood events, and trauma is correlated with chronic pain and other pain conditions in both child, adolescent and adult populations, with differences in prevalence and intensity present depending on the adverse experience, and the number of experiences. A need for further research in pediatric populations is highlighted.

OBJECTIVE

Chronic pain is a severe public health concern with high prevalence rates in child, youth and adult populations [1-3]. This paper seeks to provide a comprehensive overview on: 1) How does the presence of childhood experiences and psychological trauma correlate with the development of childhood and youth chronic pain and other pain disorders; 2) How do these experiences reflect in adult chronic pain models; and 3) What are the underlying mechanisms and proposed models that facilitate this relationship? The purpose of this literature review is to investigate the existing literature on children and adolescents with regards to chronic pain and its connection to psychological distress and examine the ways in which adulthood chronic pain is connected to these adverse childhood experiences. Given the plasticity of the brain in youth and their higher activity levels than adults, the underlying processes in the emergence of pain may differ from the observations in adults, thus a comprehensive investigation into both populations would be beneficial. Further research in this field may elucidate treatment targets that could enhance existing psychological interventions earlier than adulthood for those who may experience or be predisposed to experiencing chronic pain.

BACKGROUND

Chronic pain is longstanding pain that persists typically defined as lasting longer than 3 months [1] involving an interaction of physiological and psychological variables, affecting daily functioning [4]. Chronic pain is a major public health concern with prevalence rates between 11-38% in children, with similar estimates found in adult populations [5] There is increasing evidence to support a significant association between early-life adversity and the incidence of chronic pain both in childhood, adolescence and later in life [5]. Despite high prevalence rates of chronic pain conditions in child and adolescent populations, the relationship between adverse childhood experiences (ACE) and chronic pain conditions is less researched as majority of research has investigated this matter in the context of adult populations [6].

A review of epidemiological rates found that chronic and recurrent pain is prevalent in child and adolescent populations, with girls generally experiencing more pain than boys, and that prevalence rates increase with age [1]. Further research suggests that the prevalence of childhood pain increased over the last few decades [5], and supports the idea that clinicians and researchers should be aware of this problem and the long-term consequences. Chronic pain is also highly prevalent in adult populations [6] with approximately 20% of adults worldwide experiencing chronic pain [7], making it a significant public health concern.

Considering the connection between ACE and pain, traumatic experiences are quite common in childhood [8]. The results of a large epidemiologic study found that approximately 30% of youth experienced one or more traumatic events by age 16, with 13% of those youth endorsing symptoms of post-traumatic stress [8]. In pain literature, the relationship between Adverse Childhood Events (ACEs) and increased risk for pain outcomes have been investigated, however, this research is largely conducted in adult populations and in the context of retrospective accounts. In addition, it is often limited to abuse and trauma alone [6]. The lack of empirical research in this subject matter is concerning, as chronic pain conditions are highly prevalent in youth and can be disabling [1, 2].

RESULTS

The Correlation Between Childhood Adverse Events and Pediatric Pain

The relationship between psychological trauma and pain in adolescence has not been investigated thoroughly, however, of the research that has been conducted, pediatric populations with chronic pain conditions such as juvenile onset fibromyalgia and migraine have a higher likelihood of reporting an ACE [9]. The 1998 Adverse Child Event study investigating the relationship between childhood abuse and household dysfunction to death, demonstrated that the association between ACEs and chronic conditions was frequency dependent [10]. This finding is further substantiated by evidence from a 2020 study that described a dose-dependent relationship between ACEs and chronic pain during childhood and adolescence [11]. In contrast, some research has found that average pain intensity does not significantly differ across the number of ACEs reported [12]. Nonetheless, after controlling for demographic and clinical factors in the United States, a study found that exposure to one or more ACE was associated with a 60-170% increased likelihood of experiencing chronic pain [11]. Furthermore, in a retrospective study, the highest proportion of participants who reported greater than or equal to 3 ACEs had a primary pain diagnosis of widespread musculoskeletal pain [12]. Interestingly, among youth with traumatic brain injuries, PTSD symptoms predict pain symptoms [13] further demonstrating that the effects of trauma can increase pain. Interestingly, the relationship is not the same for all kinds of pain. For instance, research has shown that adolescents with widespread pain are more likely to report frequent abuse or trauma than those with chronic migraines [11].

Empirical evidence also suggested a strong correlation between exposure to potentially traumatic interpersonal events (PTIE) and consequent psychological distress with recurrent headaches in adolescents [14]. Increased exposure to PTIEs was associated with a higher prevalence of recurrent headache disorders, possibly indicating a dose-response relationship [14].

Interestingly, in this study, generally, twice as many girls as boys reported recurrent headache, and prevalence increased with age in girls but not boys [14], indicating some sex differences in this relationship.

Investigating younger populations, a cross sectional study in Portugal found a dose response association between the number of ACE's and reported pain outcomes in children aged 10, suggesting that the pain effects of ACE's start earlier in childhood than previously reported and investigated [15]. There is some preliminary and limited research in pediatric complex regional pain syndrome (CRPS). For instance, an article by Wager et al highlights that there is limited understanding of the relationship between psychological factors and complex regional pain syndrome (CRPS) in children, particularly regarding which factors trigger CRPS and which arise as a consequence of the chronic pain [16] However, they have found that these children experienced a larger number of stressful life events than controls [16]. This research highlights that prospective long-term studies are needed to further explore this correlation. Interestingly, a recent prospective study found that boys with recurrent abdominal or pelvic pain at age 7 were more likely to report headaches, abdominal/pelvic and musculoskeletal pain at age 13 [17], demonstrating that early childhood pain associated with psychological distress can predict pain in adolescence as well. A systematic review supports this finding, discussing that some types of pain may become chronic in childhood and be predictive of long-term pain related disabilities [1].

A comprehensive meta-analysis by Davis and colleagues revealed that adults who have endured childhood abuse and neglect exhibit heightened pain symptoms compared to those who were not exposed to trauma [18]. This finding is aligned with the growing body of evidence that illuminates an important correlation between early life adversity and a greater incidence of chronic pain in adulthood [19]. Moreover, research highlights that individuals who have reported stressful events in childhood were more likely to develop back pain and chronic low back pain (CLBP) compared to individuals who did not undergo such adversities [20, 21]. Similarly, Creed et al. observed this association with adverse events like interpersonal difficulties and abdominal pain [22]. Notably, while severe childhood abuse did not directly impact chronic pain, physical abuse emerged as a significant factor [21]. Furthermore, women with Chronic Pelvic Pain (CPP) showed a significantly higher incidence of severe childhood sexual abuse than patients with headaches or no pain [21, 23]. These findings collectively suggest a distinct correlation between sexual abuse and CPP and a general association with physical abuse and chronic pain.

Pain is frequently reported among individuals with PTSD [24]. Researchers have proposed that traumatic events and their subsequent PTSD symptoms can increase the risk for development or worsening of chronic pain, and that these factors are mutually maintained [25]. Individuals who reported trauma exposure were found to be 2.7 times more likely to manifest a functional somatic syndrome [26]. A systematic review found that people with psychological trauma face a 3.3 times heightened risk of developing generalized pain disorder, and temporomandibular pain, 2.2 times more susceptible to OBS, and 2.5 times more likely to develop fibromyalgia [27]. Notably, the age of trauma has no influence on these results, rather, the most robust association was observed with high levels of emotional stress, surpassing that of physical abuse [26]. In a separate investigation with 62 females from a community-based sample, emotionally abused individuals had reduced heat pain tolerance [19]. Furthermore, Scott et al. identified a correlation between neglect, family violence, abuse, or family criminal behavior and symptomatic pain conditions [28]. Collectively these findings substantiate that there is a complex interplay between trauma and chronic pain.

The first MRI study on patients with Irritable Bowel Syndrome (IBS), a chronic condition in which individuals report visceral pain [29], found an increased perception of pain in patients with a history of abuse had a stronger activation of the left, middle, and posterior cingulate cortex compared to controls. These brain regions are related to attention regulation, which has been interpreted by authors as an indication of pain amplification [30]. Furthermore, the authors found less activity in the left supragenual anterior cingulate cortex which is involved in pain inhibition and emotional arousal. It was similarly found that sexually abused individuals showed changes in neuronal processing with higher activation in the lateral and medial superior frontal gyrus and lower hippocampus activations than controls [31]. Moreover, patients with a history of physical and sexual trauma exhibited a greater temporal summation which indicates increased pain to repetitive painful stimuli, a larger number of pain sites, and more pain related disabilities compared to patients without trauma [32]. This suggests altered neuronal processing of perceived pain in patients with a trauma background.

Proposed Mechanisms and Models Facilitating the Relationship Between Childhood Adversity and Pain

The Stress Allostatic Load Model of Chronic Pain:
Evidence supports the role of the Hypothalamic-pituitary-adrenal (HPA) axis, the immune system, the opioid and endocannabinoid system as well as epigenetic mechanisms on the connection between early life adversity and chronic pain.

The stress allostatic load model of chronic pain posits that persistent pain can develop from a sustained endocrine response, such as consistently high levels of cortisol in the brain, predisposing individuals to sensitization - remaining in a state of arousal, alongside a reduced hippocampal volume. With repeated trauma and exposure to ACEs, the sympathetic and parasympathetic responses become dysregulated and allostatic load in addition to the dysregulation of the HPA axis may occur [6]. Interestingly, while acute stress can elicit analgesia in humans, early life and chronic stress acts more pronociceptive, increasing cold allodynia and heat hyperalgesia and increasing sensitivity to noxious inflammatory stimuli [33, 34]. Thus, the modulations of the HPA axis associated with early life stress can dysregulate corticosterone signaling and contribute to heightened pain responses. According to a study on cortisol secretions in fibromyalgia (FM) and rheumatoid arthritis (RA) patients compared to healthy controls, saliva samples for cortisol analysis, over two days showed that HPA axis dysfunction both with increased and decreased cortisol levels has been reported in these chronic pain patients [35]. FM and RA patients had higher average cortisol levels than healthy controls, but there were no differences in cortisol diurnal patterns or reactivity to psychological stress. Despite reporting lower stress levels, the patient groups differed from controls on stress measures. Adjusting for psychosocial and lifestyle factors did not alter these cortisol findings. These findings provide additional evidence of hypothalamic–pituitary–adrenal axis disturbance [35].

The Cognitive Appraisal Model of Chronic Pain:
Furthermore, a prolonged or exaggerated stress response associated with psychological trauma can perpetuate cortisol dysfunction with exaggerated physiological responses. For example, catastrophizing can lead to altered cognitive appraisals of stimuli as being threatening, creating sensations of pain [36]. Along a similar model, Nelson et al. has proposed that youth with a history of chronic stress or ACEs engage in cognitive distortions that surround perceived stress like pain, which influence coping styles, length of pain, and impairment overall [36]. Thus, the neuronal remodeling that follows chronic stressors can exacerbate pain perception due to the loss of anti-nociceptive signaling in the central pain matrix.

Pro-inflammatory Signaling in Trauma and Pain Perception:
Pro-inflammatory signaling is directly associated with chronic pain [36]. As childhood is a sensitive period, when combined with acute and even toxic levels of stress, evidence suggests that it is predictive of increased inflammation in preadolescent and adolescent years [37], demonstrating a physiological response to psychological distress. Slopen et al. particularly found that adverse events in middle childhood (ages 6-8) and

cumulative adversity from birth to the age of 8 was associated with elevated levels of CRP and IL-6 by age 10 and 15, respectively [37]. Interestingly, adverse events experienced earlier in childhood (aged 1.5 to 6 years) were not associated with the same level of inflammation. The brain increases production of cytokines such as tumor necrosis factor-alpha (TNF-a), interleukin-6 (Il-6) and C-reactive protein (CRP) in response to acute and prolonged stress in child populations [38, 39]. In a study of 92 individuals, levels of CRP were directly associated with somatic pain complaints [40]. Family violence, assessed with regards to inter-parental conflict and aggression, has also been correlated with biomarkers of increased cortisol signaling in children and adolescents. In addition, caregiver depression is a predictor of inflammation in early adolescence.

Furthermore, epigenetic and inflammatory models describe how stress has been linked to alterations in DNA which feeds into pro-inflammatory signaling. Particularly, DNA methylation and histone acetylation patterns in the brain increases the expression of pro-nociceptive neurotransmitters [41]. This DNA methylation can diminish glucocorticoid receptor sensitivity leading to resistance [42]. As glucocorticoids are anti-inflammatory agents, desensitization to this system increases inflammatory signaling and consequently pain [43]. Interestingly, another epigenetic mechanism has been posited to be involved in the pain trauma pathway. Childhood trauma has been found to induce demethylation of the gene FKBP5 which alters the expression of the FKBP51 protein; a critical mediator of chronic pain [44]. From these mechanisms, it is apparent that inflammatory signaling acts as a mediator of the relationship between psychological trauma and chronic pain, modulated by epigenetic changes.

The Role of Endogenous Opioid and Cannabinoid Systems in Pain Signaling:

The endogenous opioid and endocannabinoid systems play a role in the underlying enhanced nociceptive behavior, possibly explaining pain hypersensitivity in individuals exposed to childhood adversity. Rat studies have shown that Maternal deprivation (MD) reduced overall brain opioid receptor binding with altered expression of endogenous opioids in key brain areas involved in the modulation of nociceptive processes [45]. Early life stress has been shown to alter the endocannabinoid system in both the short and long term. For instance, MD results in decreases in cannabinoid receptor type 1 (CB1) receptor expression with increases in CB2 expression [46]. Evidence shows that endocannabinoids regulate pain and are modulated by stress. Further, they are antinociceptive in inflammatory and neuropathic pain models [47], therefore, deficits have been proposed to underlie hyperalgesia. Sensitivity to pain is often present in chronic pain patients.

DISCUSSION

This review highlights the intricate relationship between adverse childhood experiences (ACEs) and chronic pain, with emphasis on pediatric and adult populations. While a correlation between ACEs and chronic pain is well-documented, nuances in this relationship warrant deeper exploration. This section will expand on key findings, examine mechanistic insights, and propose directions for future research.

Pediatric populations with chronic pain conditions have a higher likelihood of reporting an ACE in a dose dependent fashion [9-12]. More robust associations have been observed between high levels of emotional stress, surpassing that of physical abuse [19]. Interestingly, the relationship is not the same for all kinds of pain and trauma. For instance, sexual abuse in childhood can be considered a risk factor for the development of CPP [21,23] while physical abuse is more associated with CLBP [20]. Emotional stress, surpassing physical abuse, emerges as a robust predictor of heightened pain responses and pain-related disabilities. Additionally, findings suggest that the type of pain experienced, such as musculoskeletal pain versus migraines, may be influenced by the nature of the trauma. Furthermore, a recent cohort study found that the pain effects of ACE's start earlier in childhood than previously reported and investigated [15]. This finding indicates a need for further research and specificity.

Interestingly, studies have noted that traumatic events and their subsequent PTSD symptoms can increase the risk for development or worsening of chronic pain and that these factors are mutually maintained [24,25]. These findings highlight the reveals the bidirectional relationship between psychological distress and pain. Adults who have endured childhood abuse and neglect exhibit heightened pain symptoms than those who were not exposed to trauma [18,19]. Specific studies have noted this association with chronic lower back, pelvic, and abdominal pain as well as pain disorders such as fibromyalgia, IBS, and other generalized pain disorders in addition to altered pain perception with temporal summation [20-23,30]. Neuroimaging studies have shown alterations in brain regions such as the cingulate cortex and frontal gyrus as well as hippocampus, all associated with pain perception, and emotional arousal [29,31,32], highlighting structural changes in the brain as a mediator of chronic pain in patients with a trauma history.

Emerging evidence indicates that the timing of ACEs plays a critical role in determining their impact on chronic pain. For example, pain effects of ACEs appear to manifest earlier in childhood than previously recognized. Studies have demonstrated that pain symptoms, such as recurrent abdominal or pelvic pain at age seven, can predict the presence of chronic pain in

adolescence. This emphasizes the necessity of early intervention to disrupt the trajectory from childhood trauma to long-term pain disorders. The findings demonstrate that early childhood pain associated with psychological distress can predict pain in adolescence as well.

Mechanistic studies provide valuable insights into how ACEs contribute to chronic pain. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, pro-inflammatory signaling, and epigenetic modifications are key pathways implicated in this relationship. Researchers have posited that adverse childhood experiences have a physiological impact by altering cortisol signaling with marked changes in the HPA axis [6], and DNA, altering inflammatory pathways posited to cause peripheral sensitization [33,34] which can lead to hyperalgesia and chronic pain alongside other pain disorders [36]. Other models have proposed changes in cognitive appraisals of stimuli, creating sensations of pain; a phenomenon known as catastrophizing as a response to exaggerated stress responses associated with psychological trauma [6,36]. Endogenous signaling molecules are also implicated in this process, with evidence indicating that endocannabinoids and opioids are sensitive and responsive to early childhood stressful experiences.

In summary, this review underscores the multifaceted nature of the relationship between ACEs and chronic pain, emphasizing the need for a nuanced approach that considers trauma types, developmental timing, sex differences, and mechanistic pathways. These insights provide a foundation for advancing research and clinical care in this critical area.

FUTURE DIRECTIONS

Several limitations in existing research must be addressed to advance the field. Current studies focus mainly on physical and sexual abuse, neglecting other ACEs like household dysfunction or parental mental illness. Most research relies on cross-sectional designs, limiting causal inference. Prospective longitudinal studies are needed to explore the temporal relationship between ACEs and chronic pain, particularly in pediatric populations, where brain-based mechanisms of stress and pain remain poorly understood [6].

Future research should examine cumulative and dose-dependent effects of multiple ACEs on diverse pain conditions, while considering environmental and behavioral factors such as socioeconomic disparities and healthcare access. Addressing these gaps will improve prevention and intervention strategies for trauma-exposed populations.

Finally, existing models linking stress and pain in adults and youth often overlook the complex interplay of physiological, psychological, behavioral, and environmental factors.

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