CHILDHOOD AND ADOLESCENT ADVERSITY AND CHRONIC PAIN

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Abstract

This dissertation used systematic review methods to examine the relationship between early life adversities and chronic pain later in life, with a focus on the temporal nature of the relationship and proposed moderating factors, such as the type, timing, and intensity of the adverse experience, whether or not it resulted in physical harm, and the presence or absence of subsequent posttraumatic stress disorder (PTSD) and related states. The first review paper aimed to examine the prospective relationship between child maltreatment and chronic pain, and the second review paper aimed to examine the prospective relationship between bullying victimization and chronic pain. Electronic searches of Medline, EMBASE, PsycINFO, and CINAHL were conducted. Standard methodological procedures consistent with Cochrane reviews of prognosis studies were used. The child maltreatment review included nine studies (17,340 participants). Findings revealed low to very low quality conflicting evidence across maltreatment types (sexual, physical and verbal/emotional abuse, neglect, and exposure to domestic partner violence), with the higher quality studies pointing to the absence of a direct (non-moderated and non-mediated) association between maltreatment and pain. PTSD was identified as a potential moderator and/or mediator. There was no available evidence regarding other proposed moderators. The bullying victimization review included four studies (6,275 participants). Findings revealed very low quality evidence of increased risk of pain among victimized compared to non-victimized youth, but the effect size was small and not clinically important. Only one study examined the inverse association (i.e., from pain to victimization), and there was not enough evidence to conduct a meaningful analysis of the proposed moderators. Overall, study findings were limited by the dearth of evidence on the prospective relationship between early life adversities and pain. Across the two reviews, only 13 prospective studies met

the inclusion criteria, of which only four studies measured and reported chronic pain as a primary outcome. High quality studies that measure and report key features of child maltreatment and bullying victimization, moderating factors, such as the presence or absence of PTSD and bodily injury, and chronic pain outcomes, such as pain severity and pain interference, are needed to advance the literature on the relationship between child and adolescent adversities and the emergence of chronic pain.

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Chapter 1: General Introduction

Chronic pain is pain that persists or recurs for more than three months (Treede et al., 2019). The average duration of pain in chronic pain patients is seven years (Breivik et al., 2006). Chronic pain affects between 20% and 25% of Canadians (Boulanger et al., 2007; Hogan et al., 2016; Schopflocher et al., 2011), creating an enormous burden on individuals (Hogan et al., 2017), their families and society at large. According to a 2011 survey conducted by the Canadian Pain Society, nearly one-third of all Canadians report pain-related disruptions in the workplace including reduced productivity and responsibility and loss of income. Another study estimated that the annual cost of chronic pain to Canadian taxpayers is $60 billion (Wilson et al., 2015). Despite this, we still know relatively little about risk factors for chronic pain (Katz, 2012), and effective treatments have not been identified (e.g., treatments for low back pain; Chou et al., 2009; Keller et al., 2007). Therefore, it is important to identify specific risk factors for the development of chronic pain, with the long-term goal of identifying targets for preventive intervention.

One factor that has been linked to the onset and chronicity of pain is exposure to early life adversity. This dissertation focuses on two broad categories of childhood adversity that may be particularly relevant to the development of chronic pain; namely, child maltreatment and bullying victimization. By examining the relationship between these early life exposures and pain experienced in childhood, adolescence, and adulthood, a developmental approach to the study of chronic pain is taken. This approach is important for a number of reasons. First, evidence indicates that chronic pain is a common experience throughout childhood and adolescence, with up to 40% of youth reporting persistent or recurrent pain (King et al., 2011). Not only does pediatric pain cause discomfort, impairment, and diminished health-related quality

of life (Hogan et al., 2017), but it leads to increased health care utilization, including physician visits and hospitalizations, thereby contributing substantially to the healthcare costs of pain in Canada (Hogan et al., 2016). Second, adolescence may be a critical window during which pediatric chronic pain emerges, especially in females, with prevalence rates of 11-38% (King et al., 2011; von Baeyer, 2011); therefore, it is important to capture risk factors occurring within this critical window. Third, evidence shows that pain symptoms track across childhood and adolescence (Mulvaney et al., 2006; Stanford et al., 2008), and up to 60% of youth with chronic pain continue to suffer from chronic pain as adults (Walker et al., 2012). Therefore, pain experiences among young people could have implications for chronic pain for years or even decades thereafter. Finally, early life adversity is also predictive of pain in adulthood, pointing to the role of early life biological programing in pain that is experienced many years later (Burke et al., 2017).

In this general introduction, I provide the background for two systematic reviews presented later in the dissertation. I begin by the presenting the literature linking early life adversity to mental and physical health in childhood and adulthood with an emphasis on potential pathways from adversity to chronic pain, including the roles of chronic stress, physical and social injury, and posttraumatic stress disorder (PTSD) and related states. I then discuss what is known about the relationships between both child maltreatment and bullying victimization and chronic pain, with a focus on methodological challenges of this research and limitations of previous work in this field. Next I provide a rationale for examining these relationships further using systematic review methods. In Chapter 2, following the general introduction, I report on the results of a systematic review of the relationship between child maltreatment and chronic pain. In Chapter 3, I transition away from the topic of child

maltreatment to a focus on bullying victimization, and in Chapter 4, I report on a second systematic review and meta-analysis, this one with a focus on bullying victimization and chronic pain. In both reviews, I aimed to (1) delineate the temporal nature of the relationship between early life adversity and chronic pain and (2) examine a set of pre-specified moderating factors (e.g., whether the exposure was chronic versus time-limited; the presence or absence of physical injury) that were expected to influence the magnitude of the relationship between early adversity and pain. Finally, I conclude the dissertation with Chapter 5 in which I present a general discussion of study findings and future directions.

Background

Definitions of Stress, Adversity, and Trauma

Psychological stress occurs when environmental demands exceed an individual's adaptive capacity or ability to cope (Cohen et al., 1997). Some conceptions of stress focus on the environmental event, whereas others emphasize the individual's perception and evaluation of the potential harm posed by the environment (i.e., threat appraisals) (Lazarus & Folkman, 1984). The environmental event may also be referred to as a stressor or adverse event, and in some cases, a traumatic event. Indeed, adverse events may or may not meet criteria for a traumatic event according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013), which in turn, may or may not be considered traumatic by the individual.

In this dissertation, the focus is on adverse experiences occurring at any time in childhood or adolescence (i.e., age 18 years or younger). I refer to this period of childhood and adolescence as "early life," and specify stages within this period as needed (i.e., early childhood, middle childhood, and adolescence). Although adversity is often discussed in terms of an adverse

event or experience, suggesting that it is an isolated experience with a definitive onset and offset (e.g., a physical assault), some adversity is characterized by repeated or chronic exposures. Moreover, adverse experiences may occur in the context of chronically stressful situations, such as "risky family environments," characterized by high levels of conflict, aggression, and neglectful relationships (Repetti et al., 2002), low socioeconomic status, and/or violence within the community. Although most measures of childhood adversity do not capture these background factors, in this dissertation, I attempt to distinguish between exposures that are time-limited versus those that are frequent or chronic in nature (i.e., occurring for six months or longer) (Hammen & Rudolph, 1999).

Childhood Adversity and Health

Early-life adversity increases vulnerability to poor health across the life span (Miller et al., 2011). For example, The Adverse Childhood Experiences (ACE) Study, a large-scale project of more than 17,000 adults, measured exposure to various kinds of maltreatment and household dysfunction before the age of 18 years (e.g., abuse, neglect, parental conflict, substance abuse, or mental illness). Findings indicated a 1.5-2.0-fold greater incidence of cardiovascular disease, autoimmune disorders, and premature mortality among those with versus those without ACEs (Anda et al., 2009; Dong et al., 2004; Dube et al., 2009). Moreover, a similar pattern of findings has been replicated across various samples and populations (Norman et al., 2012; Wegman & Stetler, 2009).

Although there is also a great deal of evidence linking early life adversity to chronic pain and pain-related outcomes in adulthood (Afari et al., 2014; Häuser et al., 2011; Paras et al., 2009), the published literature is limited by methodological challenges in the field (Raphael et al., 2004). In particular, given that pain is a personal, subjective experience (Raja et al., 2020), it

is best captured via self-report measures of pain severity, interference, and quality (Cleeland, 1989; Cleeland & Ryan, 1994; Melzack, 1987). However, there is a concern that people's reports of their symptoms may be influenced by individual differences in symptom perception, labeling, and reporting (Feldman et al., 1999), and therefore, may be less likely to capture underlying disease processes (Miller et al., 2011). In contrast, other health outcomes, such as stroke, myocardial infarction, and mortality, can be measured using more "objective" methodologies, and therefore the evidence linking early adversity to these outcomes is more easily interpreted (Miller et al., 2011; Wegman & Stetler, 2009).

This problem is exacerbated by the retrospective nature of much of this research. In other words, the use of retrospective self-reports of childhood adversity in combination with self-reported chronic pain raises concerns about alternative explanations (e.g., reporting biases, psychological distress) for any associations shown, and as a result, this field has received a great deal of scrutiny (Davis et al., 2005; Raphael et al., 2004). Therefore, in the study of early life adversity and chronic pain, there is a particular emphasis on using evidence from large prospective research designs with long follow-up periods with the goal of measuring adversity well before the onset of chronic pain.

Some of the most convincing findings on the relationship between early life adversity and pain come from the 1958 British Birth Cohort Study, a large, ongoing, prospective cohort study of all children born in England, Scotland, and Wales in one week in March 1958 (Power & Elliott, 2006). The sample includes 17,638 participants who were recruited at birth, supplemented by 920 early migrants, all born in the same week. When the children were 7 years of age, parents reported on a variety of adverse childhood events (e.g., hospitalization following a motor vehicle accident; surgery) and poor social and psychological environment (e.g., death of

a parent, periods in local authority care). Multiple follow ups have since been conducted, including measures of physical health. Jones and colleagues (2009) analysed these data to examine the relationship between childhood adverse events and reported chronic widespread pain at 45 years of age. Results indicated that a number of early life events were associated with increased risk of chronic widespread pain at follow up, including hospitalization following a road traffic accident, time spent in institutional care, maternal death, and familial financial hardship, independent of adult psychological distress or social class. These findings provide compelling evidence of a relationship between early life factors and chronic pain many years later.

Other studies assessing the prospective relationship between adversity and pain have examined the role of negative events in shaping pain trajectories over time. For example, Young Casey and colleagues (2008) examined the relationship between lifetime exposure to trauma and the transition from acute to chronic low back pain in middle-aged adults. Findings showed that cumulative trauma predicted increased severity of subsequent pain three months later (Young Casey et al., 2008), independent of baseline pain and depressive symptoms. Moreover, similar methods have been employed in the study of pediatric pain. For example, Mulvaney and colleagues (2006) asked caregivers of children with "functional abdominal pain" (i.e., abdominal pain without identifiable organic disease) to indicate the number of events their child had experienced that "caused him/her a great amount of worry or unhappiness" over the past year. The inventory included adverse events such as death of a parent, divorce, mental health disorder, or alcoholism in the family. Results showed that an increased number of negative life events at baseline was associated with long-term risk characterized by high levels of somatic symptoms and impairment that did not improve over five years.

Finally, there is growing interest in examining the transition from acute to chronic pain following an acute event, such as a surgery or an accident (Katz & Seltzer, 2009; Salberg et al., 2020). These studies highlight that acute pain following tissue damage usually serves an adaptive role (Raja et al., 2020), and it is the transition to chronic pain that is considered maladaptive and dysfunctional. Therefore, one question is whether early life adversity increases vulnerability to these problematic pain trajectories. Although post-surgical pain models have been used to identify a number of psychosocial risk factors for the emergence of chronic pain in adult samples (Katz & Seltzer, 2009), studies examining the role of early-life adversity are only just emerging, particularly in the field of pediatric pain (Salberg et al., 2020).

Taken together, the findings reviewed above show that childhood adversity is a risk factor for poor health later in life, including emerging evidence for chronic pain, both in adult and pediatric samples. However, there is also the question of whether early life exposures cause poorer health outcomes many years later, and if so, what the causal mechanisms might be. In the paragraphs below I review the evidence on life course pathways from childhood adversity to poor health later in life, and how they can be used to inform our understanding of early-life adversity as a risk factor for chronic pain.

Life Course Models of Adversity and Health

Just as chronic pain emerges over time, childhood adversity cannot be captured by a snapshot approach. Although the current dissertation focuses on adversity in early life, much can be gained from a life-course perspective. Life course models propose various pathways through which adversity at different life stages can influence health (Lynch & Smith, 2005). Three life course models that are relevant to this dissertation include critical period, current adversity, and cumulative adversity. Critical period and current adversity models emphasize the timing of the

exposure, whereas a cumulative adversity model emphasizes dynamic aspects of adverse experiences over time (Lynch & Smith, 2005).

Critical period models. According to critical period models, there is a window of time during which adversity exerts its most profound effects. Therefore, exposure to adversity, even if it is short-lived, may have long-term effects if it occurs within a critical developmental window. One example of a critical period is thought to be early childhood, when important developmental changes are occurring. The early life environment may program a pattern of biological and behavioral responses that have a long-term impact (Barker, 1992; Hertzman, 1999). Evidence from the mental health literature provides support for a pathway from early childhood adversity to psychopathology. For example, Kaplow and Widom (2007) showed that earlier onset child maltreatment (i.e., early [ages 0-5 years] versus later [ages 6-11 years]) predicted more symptoms of anxiety and depression in adulthood. Similarly, evidence indicates that the developmental timing of first exposure to maltreatment influences risk for depression and suicidal ideation in young adulthood, with exposure during early childhood (0-5 years) being more detrimental than if it occurred in adolescence (Dunn et al., 2013). First exposure to child maltreatment during early childhood (ages 0-5 years) has also been linked to elevated risk for PTSD relative to first exposure during middle childhood or adolescence (Dunn et al., 2017).

The adolescent years may represent another critical window due to heightened social vulnerability because of the importance of peer connections at this stage (Connell & Dishion, 2006; Laursen & Collins, 1994), as well as increased biological responses to stress related to pubertal maturation (Bingham et al., 2011; Sumter et al., 2010). Indeed, adversity may interact with developmental factors such as puberty to influence pain trajectories during adolescence (Patton & Viner, 2007). There is growing evidence that adolescence is a time of increased

susceptibility to the development of chronic pain, but in regard to the role of adverse experiences, it's unclear whether early childhood exposures or adolescent exposures (or a combination of the two) contribute to this risk.

Cumulative adversity models. Models of cumulative risk focus on the additive effects of adverse experiences. Thus, individuals who are exposed to adversity for longer durations or who experience more frequent adverse events are thought to be at greater risk (Lynch & Smith, 2005). These models are consistent with the concept of allostatic load (McEwen, 1998), which describes the wear and tear on bodily systems as a result of frequent activation of the biological stress response (i.e., activation of the sympathetic nervous system and hypothalamic pituitary adrenocortical axis). Studies of ACEs provide overwhelming evidence in support of a cumulative risk model. For example, a recent systematic review and meta-analysis revealed that exposure to multiple types of ACEs is a major risk factor across health conditions (Hughes et al., 2017). In particular, individuals with at least four ACEs were at increased risk for cancer, heart disease, respiratory disease, psychopathology, and problematic drug and alcohol use compared to individuals with no ACEs. Cross-sectional data from studies of ACEs also point to a dose-response relationship between number of ACEs and pain outcomes in adults (Scott et al., 2011; Stickley et al., 2015; Von Korff et al., 2009).

Current adversity models. Although this dissertation focuses on the relationship between early life adversity (adversity in childhood or adolescence) and later chronic pain, current exposure to adversity and its potential impact on pain must be acknowledged. According to a model of current adversity, a person's current circumstances influence concurrent health status. This model is particularly relevant to the study of child maltreatment and pain outcomes given the high likelihood of re-traumatization (Scott-Storey, 2011) and the potential for current

injuries and psychological distress to impact current pain reports. Therefore, for purposes of this dissertation, current adversity is considered to be a potential confounding factor.

Summary. Taken together, the current evidence shows that early life adversity is an important risk factor across mental and physical health outcomes, including chronic pain, and that these effects are particularly profound in the case of cumulative adverse experiences (i.e., when there are multiple ACEs present). It is expected that there are general psychological, biological, and behavioral pathways from adversity to later health that are relevant across health conditions. For example, allostatic load is a general biological pathway linking stress to disease (McEwen, 1998), and health behaviors associated with early adversity, such as severe obesity, infrequent exercise, alcohol dependence, and illicit drug use, could have a similarly broad impact (Felitti et al., 1998). However, as I discuss in the paragraphs below, there are likely to be additional features of early life adversity that are specific to vulnerability to chronic pain, including the presence of physical injury and social injury, and the development of PTSD.

Specific Features of Childhood Adversity and Chronic Pain

The role of physical harm. Childhood adversity that involves physical harm or injury may be more likely to increase risk for later chronic pain compared to childhood adversity that does not have a physical component. It should first be acknowledged that all youth experience pain and that most recover quickly (Salberg et al., 2020). Indeed, one study linking everyday injuries (such as sports-related injuries or falls) to pain trajectories showed that these youth generally had a good prognosis in regard to pain outcomes (El-Metwally et al., 2005). Another study showed that injuries at age 10-11 years appeared to be protective in regard to trajectories of recurrent stomachaches (Stanford et al., 2008). The authors suggested that anxious children may avoid danger and therefore be less likely to sustain injuries, and that it is these children who are

more likely to show increasing pain symptoms over time. Therefore, injury and recovery appear to be a normal part of development. In contrast, injury and pain that occurs in very early childhood or in context of chronic stress or trauma may be associated with long-term consequences for pain.

Evidence indicates that pain and injury in infancy can cause lasting changes to developing somatosensory and pain systems, influencing pain reactivity in later life (Schwaller & Fitzgerald, 2014). Much of this evidence comes from research on pre-term infants who are exposed to clinically necessary skin-breaking procedures (e.g., injections, heel lances, blood draws). However, this phenomenon has also been shown for major surgery within the first three months of life, as well as moderate or severe burns in infancy. These findings suggest that early life adversity involving physical harm, such as in the case of child maltreatment, could have enduring effects on pain systems that set the stage for chronic pain later in life (Taddio & Katz, 2005). In addition, evidence from studies of rats and mice have shown that the combination of early life stress (i.e., maternal separation and social isolation) and peripheral nerve injury results in enhanced pain-related behavior (Burke et al., 2013; Nishinaka et al., 2015). Although it is unclear whether these findings translate to chronic pain disorders in humans, they suggest that when children suffer physical injuries in the context of chronically stressful environments, they may be more likely to experience prolonged pain and impaired recovery.

Finally, if physical injury occurs in the context of a traumatic event, such as a motor vehicle accident or physical assault, this situation could also contribute directly to physical pain (Katz et al., 2014). Indeed, the Jones et al. (2009) findings discussed above are consistent with this picture, as they showed that hospitalization following a car accident before the age of seven years was significantly associated with chronic widespread pain at 45 years of age. In contrast,

the experience of surgery in childhood, which also involves tissue damage, was not associated with pain in adulthood. In explanation of these findings, Jones and colleagues (2009) posit that the psychological consequences of motor vehicle accidents in combination with physical injury may play a role in the development of chronic pain.

The role of PTSD and related states. Among children and adolescents who experience adversity, their psychological and emotional responses to that adversity, including the emergence of PTSD or partial PTSD, may have consequences for chronic pain (Katz et al., 2014). The DSM-5 (American Psychiatric Association, 2013) characterizes PTSD as a maladaptive reaction to traumatic exposure characterized by four persistent symptom clusters, including re-experiencing the traumatic event (e.g., recurrent distressing dreams of the event), persistent avoidance (e.g., of stimuli associated with the traumatic event), hyperarousal (e.g., difficulty falling asleep or staying asleep), and negative alterations in cognitions and mood (e.g., diminished interest in life, self-blame, feeling detached from others). DSM-5 diagnosis of PTSD requires exposure to a Criterion A trauma (i.e., exposure to death or threat of death; actual, or threat of, serious injury; or actual, or threat of, sexual violence). However, many studies measure posttraumatic stress symptoms (PTSS) using self-report questionnaires, such as the PTSD Checklist (Blanchard et al., 1996), which capture clinically relevant symptoms that may or may not meet criteria for PTSD.

A growing body of evidence shows an important overlap between symptoms of PTSD and chronic pain. For example, the 12-month prevalence rate of PTSD in patients with back and neck pain is 7.3% (compared to a 12-month prevalence of 3.5% in the general population) (Katz et al., 2014). A similar pattern of findings has been observed in youth, such that youth with chronic pain have greater elevations in PTSD symptoms compared to youth without chronic pain

(Noel et al., 2016). Indeed, it has been argued that the symptoms of these two conditions are mutually maintaining, such that the physiological, affective, and behavioural symptoms of PTSD maintain and/or exacerbate the experience of pain, and vice versa (Asmundson et al., 2002; Katz et al., 2014; Sharp & Harvey, 2001). For example, according to the mutual maintenance model (Sharp & Harvey, 2001), pain sensations experienced by a person with chronic musculoskeletal pain elicit reminders of the traumatic event that precipitated the pain, and physiological arousal in response to recollection of the traumatic event contribute to avoidance of activities that may cause pain (Asmundson et al., 2002). The cycle becomes such that the symptoms of PTSD and chronic musculoskeletal pain interact to produce self-perpetuating distress and functional disability.

However, there is still the question of whether pain precedes PTSD or PTSD precedes pain (Katz et al., 2014). Empirical findings support both directions of effect. On the one hand, Jenewein and colleagues (2009) showed that PTSD is associated with increased risk for the transition from acute to chronic pain following severe accidental injury. Moreover, Raphael and Widom (2011), who examined the relationship between childhood victimization (verified by criminal court records) and pain 30 years later, found that individuals with both childhood abuse and a history of PTSD were at significantly increased risk of pain complaints in adulthood. On the other hand, traumatic injury is a leading cause of PTSD, with pain severity playing an important role (Katz et al., 2014). Indeed, one study showed that higher levels of pain within 48 hours of injury is associated with more severe symptoms of PTSD 8 months after injury (Norman et al., 2008). Evidence shows that, for vulnerable individuals, the experience of pain can be traumatic in itself (Katz et al., 2017; Kleiman et al., 2011), a finding that further exemplifies the complexities of the interrelationships between trauma, PTSD, and pain.

The role of social injury. Another factor related to childhood adversity that may influence pain outcomes is whether the adverse experience has an element of social threat (i.e., characterized by social rejection, exclusion or loss). Adverse experiences characterized by social rejection may be particularly impactful because they threaten a person's sense of belonging and acceptance. The need to belong is considered to be a fundamental human motivation evolved from our ancestors' dependence on group membership for survival and reproduction (Baumeister & Leary, 1995). Specifically, in the environment of evolutionary adaptation, the motive to create and maintain social bonds would have increased the chances of group membership and decreased the chances of social isolation. Groups offer a number of benefits including the opportunity to share food and resources, help care for offspring, and the ability to maintain defensive vigilance against predators. Therefore, a great deal of human thought, emotion, and behavior is likely to have evolved to serve this fundamental interpersonal motive.

Based on this premise, Eisenberger and colleagues (Eisenberger et al., 2003; Eisenberger, 2012) have hypothesized that "socially painful" situations rely on some of the same neurobiological substrates that underlie experiences of physical pain. According to this hypothesis, factors that increase or decrease social pain should have a similar effect on physical pain, and vice versa. Indeed, research evidence indicates that experiences of both failure and social exclusion are related to increased physical pain sensitivity (Levine et al., 1993; van den Hout et al., 2000).

Childhood Maltreatment and Bullying Victimization

Based on the factors described above, there are two types of childhood adversities that may be particularly relevant to the development of chronic pain; namely, child maltreatment (including childhood abuse and neglect) and bullying victimization by peers. This possibility is

supported by several lines of evidence. First, many youths experience these adversities chronically and across critical developmental windows, such as very early childhood and adolescence (Margolin & Gordis, 2000; McDougall & Vaillancourt, 2015; Scott-Storey, 2011). Second, these adversities are characterized by a profound psychological component, that in some instances, is accompanied by injury to the body. Indeed, child abuse and neglect are associated with physical injury, including skull vault fractures and burns (World Health Organization, 2006), with very young children at the highest risk of serious injury and death (Margolin & Gordis, 2000). As well, there is evidence to suggest that victims of bullying are at increased risk of suffering from accidental and perpetrated injuries compared to non-victims (Dukes et al., 2010; Srabstein & Piazza, 2008). Third, child abuse and bullying victimization are characterized by interpersonal rejection and loss and are therefore likely to activate concerns about belonging and related social pain/injury (Eisenberger, 2012). Finally, in the case of child maltreatment, there is risk for the development of PTSD or symptoms of PTSD (Kisely et al., 2020), which in turn elevate risk for chronic pain.

The current literature. Primary research and systematic reviews on child maltreatment and pain outcomes (Afari et al., 2014; Burke et al., 2017; Davis et al., 2005; Häuser et al., 2011; Paras et al., 2009) and bullying victimization and pain outcomes (Gini & Pozzoli, 2013; Gini et al., 2014) point to associations between these early life adversities and chronic pain, yet the evidence is by no means unequivocal (Raphael et al., 2004). First, there is a question of whether key features of adversity have been measured and accounted for in the extant literature. This includes more general factors, such as the developmental timing and intensity of maltreatment and peer victimization, as well as factors that are particularly relevant to pain outcomes, such as the presence or absence of physical injury and symptoms of PTSD. Moreover, even among

studies and review articles that have revealed a positive relationship, there is often uncertainty about interpretation due to methodological challenges and limitations within the field. I summarize these concerns in the paragraphs below.

Methodological challenges and limitations. The first methodological concern regarding the current literature is that most studies rely on cross-sectional study designs and retrospective reports of childhood adversity (Raphael et al., 1991; Widom et al., 2004). Thus, a positive association between child maltreatment or bullying victimization and pain may indicate a causal relationship, but it is equally plausible that a third variable such as reporting bias is driving the effect (Davis et al., 2005; Raphael et al., 2004). The concern here is not only that people with adult health problems may overreport adversity, but that individuals who are free of pain tend to underreport these events (McBeth et al., 2001), thereby creating a spurious association between adversity and chronic pain (Burke et al., 2017).

The second methodological concern relates to other potential confounding factors that could be driving the association between adverse childhood experiences and chronic pain, including psychological distress (Lunde & Sieberg, 2020; Meints & Edwards, 2018), socioeconomic status (Grol-Prokopczyk, 2017), and current adversity (Scott-Storey, 2011). Although socioeconomic status is often measured and accounted for in the maltreatment literature (Jaffee, 2017), the roles of current adversity and current psychological distress are most often ignored. This means that for observed associations between childhood adversities and pain, it is unclear whether early life adversity is driving the association or whether it is better explained by a person's current life circumstances or current level of psychological distress. This is not to say that these are unimportant pathways from early adversity to pain. Indeed, if a person's current psychological distress is associated with early life adversity and is, in turn,

shaping pain outcomes, this pathway is important and should be examined through tests of mediation.

Finally, the third methodological concern relates to the choice of outcome measures. Indeed, concerning the relationship between both child maltreatment and bullying victimization and pain there appears to be an emphasis on outcomes, such as "psychosomatic complaints" (Gini & Pozzoli, 2013) and "functional somatic syndromes" (Afari et al., 2014). Not only do these measures combine symptoms of pain with other somatic symptoms, such as dizziness and fatigue, thereby creating problems with interpretation of the findings, they imply that the outcomes are mediated by purely psychological and more specifically psychopathological processes. The consequence of measuring such outcomes rather than pain is that the symptoms, and the people reporting them, may be discounted and the link between early life adversity and subsequent somatic concerns chalked up to "psychogenicity."

Summary of the Literature

There is evidence of a link between both child maltreatment and bullying victimization and pain outcomes, yet methodological limitations impede the interpretation of study findings. Based on the broader literature on early life adversity and mental and physical health outcomes, it is highly likely that early life adversity can have a cumulative impact on health, and there might be critical developmental windows during which the impact of adverse experiences is particularly profound. Based on findings from the pain literature, it is likely that there are additional features of adversity that are particularly relevant to the emergence of chronic pain, including physical injury, social injury, and the presence of PTSD. However, these features of adversity have not been considered in previous systematic reviews. Therefore, the current dissertation aimed to organize and assess the current literature on child maltreatment and

bullying victimization according to factors that are relevant to pain outcomes, with a particular focus on methodological issues that can be problematic in observational studies. Systematic review methods were utilized for both papers. The advantages of employing systematic review methods include (1) the potential to increase statistical power through the use of meta-analysis, (2) increased generalizability of the evidence by combining across studies and samples, and (3) the use of rigorous methods to assess the quality of the literature and identify priorities for future work in the field (Hayden et al., 2013; Higgins et al., 2019).

The Current Review Papers

The goal of this dissertation is to identify the features of childhood adversity that contribute to the emergence of chronic pain in youth and adult populations. The first review presented in Chapter 2 evaluates the literature on child maltreatment and chronic pain. The second review presented in Chapter 4 evaluates the literature on bullying victimization and chronic pain. In regard to the measurement of chronic pain as an outcome, many studies fail to specify the duration, thus it is unclear whether the study is actually measuring *chronic* pain. Although our objective was to review the evidence on early life adversity and chronic pain, we included studies regardless of the duration of pain. There were two main objectives across the two review papers. The first was to examine the temporal nature of the relationship between childhood adversity and chronic pain. The second was to examine whether various features of early life adversity shape the way in which adversity relates to chronic pain outcomes. In this regard, I aimed to examine the following factors as potential moderators of the adversity-pain relationship: (1) the particular type of adversity (e.g., physical abuse versus verbal abuse), (2) whether it incurred physical harm, (3) its frequency and chronicity, (4) the developmental timing,

and (5) for the review on child maltreatment, the presence or absence of subsequent PTSD or PTSS.

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Chapter 2: A Systematic Review of the Prospective Relationship Between Child Maltreatment and Chronic Pain

Child maltreatment is common, with at least one in seven children having experienced abuse and/or neglect in the past year (Centers for Disease Control and Prevention, 2020). These experiences are traumatic to the individual and have serious life-long consequences, including depression, anxiety, PTSD, and suicide (Breslau et al., 2014; Brown et al., 1999; Jaffee, 2017; Li et al., 2016; Thornberry et al., 2010). In addition to the psychological and emotional toll, research evidence shows that child maltreatment is associated with impaired physical health (Wegman & Stetler, 2009), including increased risk of chronic pain (Paras et al., 2009). This is important because chronic pain is often longstanding, with an average duration of seven years (Breivik et al., 2006), resulting in a tremendous burden on individuals, their families and society at large (Dueñas et al., 2016).

However, not all studies have found links between child maltreatment and pain (Raphael et al., 2004), and even for those that have, there is uncertainty about interpretation. Specifically, most studies have relied on retrospective designs, thus a positive association between maltreatment and pain may indicate a causal relationship, but it is also plausible that a third variable, such as a reporting bias, is driving the effect. The concern here is not only that people with adult health problems may overreport childhood adversity, but that individuals who are free of pain tend to underreport these events (McBeth et al., 2001) thereby creating a spurious association between maltreatment and pain (Burke et al., 2017). We must therefore rely on studies that examine the *prospective* relationship between maltreatment and pain, including the use of substantiated measures of child maltreatment, to delineate the nature of this association (Davis et al., 2005; Raphael et al., 2004).

In addition to these methodological issues, growing evidence suggests that the relationship between maltreatment and pain may depend on key moderating factors which could explain variability in findings across studies. These factors include (1) the presence of posttraumatic stress disorder (PTSD) or symptoms of PTSD, (2) the particular type of maltreatment and whether it involved physical harm, (3) its frequency and chronicity over time, (4) and whether it occurred within a critical development window. The following sections present evidence for each of these potential moderators.

PTSD

Among children and adolescents who are exposed to maltreatment, their psychological response to maltreatment, including the emergence of PTSD or symptoms of PTSD, may have consequences for chronic pain. Indeed, individuals with PTSD are at increased risk of chronic pain (Sareen et al., 2007), and it has been argued that the symptoms of these two conditions are mutually maintaining, such that the physiological, affective, and behavioural symptoms of PTSD maintain and/or exacerbate the experience of pain, and vice versa (Asmundson et al., 2002; Katz et al., 2014; Sharp & Harvey, 2001). This relationship has also been shown in younger populations, such that youth with chronic pain have greater elevations in PTSD symptoms compared to youth without chronic pain (Noel et al., 2016). Accordingly, if a child or adolescent exposed to child maltreatment develops PTSD or partial PTSD, they may be more likely to develop chronic pain. Raphael and Widom (2011) examined the relationships between childhood maltreatment (verified by criminal court records), PTSD, and pain 30 years later. They found that individuals with both childhood abuse and a history of PTSD were at significantly increased risk of pain complaints in adulthood. Clearly, an in-depth look at the role of PTSD across studies will clarify our understanding of the trauma-pain relationship.

Type of Child Maltreatment

Another feature of child maltreatment that may impact its association with chronic pain is the particular type of abuse, including physical abuse, sexual abuse, emotional abuse, neglect, and exposure to intimate partner violence. Although evidence from the mental health literature points to equivalence across abuse types (Norman et al., 2012; Vachon et al., 2015), less is known about the role of abuse type in the relationship between child maltreatment and chronic pain. Results from cross-sectional studies are mixed. For example, Scott and colleagues (2011) showed equivalence across abuse types in relation to pain outcomes, while Stickley and colleagues (2015) showed some evidence of specificity in a study of adult-onset chronic pain conducted in Japan. In particular, physical and sexual abuse were associated with chronic pain outcomes, whereas family violence and neglect failed to show independent effects.

In addition to accounting for the specific type of abuse, we propose that even greater specificity is needed at the level of physical harm or injury. Indeed, cases of physical and sexual abuse have a physical component in addition to a psychological component, which means that they may have a direct link to pain (Burke et al., 2017; Katz et al., 2014). Moreover, traumatic events involving physical injury are more likely to lead to PTSD compared to events without a physical component (Koren et al., 2006), and PTSD is highly co-morbid with chronic pain (Sareen et al., 2007). Therefore, we expect that child maltreatment resulting in physical harm or injury will be associated with increased risk for chronic pain. Although the role of physical harm resulting from violence has received little attention in the child maltreatment literature, studies of sexual abuse and rape provide indirect evidence that physical harm may be an important factor. For example, a meta-analysis by Paras et al. (2009) showed an association between sexual abuse and somatic symptoms, including fibromyalgia and pelvic pain, but only when sexual abuse was

defined as rape. However, it is unclear whether this effect is driven by the physical harm associated with rape or if it is mediated by psychological factors. Indeed, research evidence shows that sexual abuse including rape is more predictive of PTSD compared to sexual abuse without rape (Chen et al., 2010). Clearly, it is very challenging (and perhaps impossible) to disentangle the psychological and physical components of sexual abuse and rape. However, this work demonstrates the importance of specifying the nature of the maltreatment and considering the role of physical violence and resulting injury in the maltreatment-pain relationship.

Even if physical harm plays a role in the relationship between maltreatment and chronic pain, it is clear that other factors are involved. For example, there is evidence showing that some people develop chronic pain following non-injurious (to the child) forms of trauma, such as children's exposure to domestic partner violence (Lamers-Winkelman et al., 2012), and studies of traumatic injury show only a weak link between injury severity and chronic pain (Rosenbloom et al., 2013), highlighting the importance of emotional and psychological variables. Moreover, this literature is complicated by the high level of co-occurrence between different types of maltreatment (Gilbert et al., 2009), making it difficult to differentiate the impact of maltreatment types on pain outcomes or to parse out the independent effects of physical versus emotional injury (Burke et al., 2017). Finally, studies of child maltreatment and later health often fail to account for the role of non-inflicted injury and intentional self-injury, both of which occur more frequently among maltreated children (Lamers-Winkelman et al., 2012; Lang & Sharma-Patel, 2011; Ruiz-Casares et al., 2012). Indeed, there are likely to be multiple pathways from child maltreatment to the development and persistence of pain, some of which are specific to the type of maltreatment and others which apply across maltreatment types.

Frequency and Chronicity of Child Maltreatment

Another feature of child maltreatment that may impact its association with chronic pain is its intensity, captured by (1) the frequency of discrete episodes of abuse and (2) its chronicity over time. Much of what is known about the frequency of early life exposures and health outcomes comes from studies of adverse childhood experiences (ACEs), which include child physical and sexual abuse and neglect among other types of adversity, such as parental psychopathology and early parental loss. This work points to a graded relationship between the number of adversities and physical and mental health outcomes in adulthood (Björkenstam et al., 2013; Felitti et al., 1998; Hughes et al., 2017), and mounting evidence from cross-sectional studies suggests a similar pattern of findings for pain outcomes (Anda et al., 2006; Scott et al., 2011; Stickley et al., 2015; Von Korff et al., 2009). Indeed, a recent study showed that the number of childhood adverse events was a better predictor than the specific type of trauma in the prediction of chronic back pain, chronic headache, and dysmenorrhea (You et al., 2019). Although less is known about whether repeated incidents of maltreatment have a cumulative impact on chronic pain development, results from one prospective study showed that a higher number of documented maltreatment incidents predicted more severe health and behavioral outcomes (e.g., substance use and mental health treatment) among children and adults (Jonson-Reid et al., 2012), thereby mirroring the findings from the ACEs studies. We therefore expect to find a similar pattern in regard to chronic pain outcomes, with more frequent maltreatment episodes incurring greater risk.

That said, a singular focus on the frequency of maltreatment episodes may leave out important information about its overall intensity (which is captured by the combination of frequency and chronicity/duration). As articulated by Gilbert and colleagues (2009), for some

children, maltreatment is more accurately conceptualized as a chronic condition, rather than as an event (or a series of events that cannot be counted). In this regard, it is also important to capture the chronicity of maltreatment over time, although to our knowledge there is very little evidence examining the health consequences of chronic versus shorter-term maltreatment. However, we propose that this dimension may be especially relevant in the case of childhood neglect. Child neglect is characterized by lack of parental care and nurturance, and as such, often involves chronic situations that are not as easily identified as specific incidents, such as in the case of sexual or physical abuse (Hildyard & Wolfe, 2002). The health consequences of these chronic family situations have been captured by research on risky families (2002). Risky family environments, defined in terms of high conflict, deficient nurturing, and neglect, are associated with increased risk for mental health disorders, chronic diseases, and early mortality across the lifespan. Therefore, we would expect the chronicity of neglect and other forms of maltreatment to be an important factor in the development of chronic pain.

Developmental Stage of Maltreatment

In addition to the frequency and stability of maltreatment, the developmental stage during which it occurs may have implications for later chronic pain. Developmental timing is related to chronicity, as maltreatment that occurs across a longer timespan will inevitably cross more developmental stages. However, exposure to maltreatment, even when it's short-lived, may have long-term effects if it occurs within a critical developmental window. In this regard, early life models have received the most attention. For example, Kaplow and Widom (2007) showed that earlier onset maltreatment (i.e., early [ages 0-5 years] versus later [ages 6-11 years]) predicted more symptoms of anxiety and depression in adulthood. Similarly, research evidence indicates that the developmental timing of first exposure to maltreatment influences risk for depression

and suicidal ideation, with exposure during early childhood (0-5 years) being more detrimental than if it occurred in adolescence (Dunn et al., 2013). First exposure to child maltreatment during early childhood (ages 0-5 years) has also been linked to elevated risk for PTSD relative to first exposure during middle childhood or adolescence (Dunn et al., 2017), a finding which may have implications for chronic pain (Noel et al., 2016; Sareen et al., 2007). Taken together, the developmental timing of maltreatment is likely to play an important role in shaping chronic pain outcomes among maltreated children.

The Current Study

We conducted a systematic review of the prospective relationship between child maltreatment and chronic pain, with a focus on factors that are likely to shape this relationship. We aimed to answer the following five research questions:

1. Is there evidence of a temporal relationship between child maltreatment and chronic pain?
2. Do individuals who are exposed to child maltreatment and develop PTSD or partial PTSD differ in chronic pain outcomes from those who are exposed but do not develop these symptoms?
3. Does the particular type of maltreatment influence pain outcomes? To answer this question, we examined the differential association of physical abuse, sexual abuse, emotional abuse, and neglect. In the case of physical and sexual abuse, we also examined whether the presence of abuse-related physical harm influenced the relationship between abuse and chronic pain.
4. Does the intensity of maltreatment predict chronic pain? To answer this question, we examined the relationships between the frequency (i.e., has it occurred 10 times or more?)

and chronicity (i.e., has it been persisting for at least six months?) of maltreatment and subsequent chronic pain.

5. Does the developmental stage (early childhood, middle childhood, or adolescence) during which maltreatment occurred predict chronic pain outcomes?

Method

Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019142169 (Marin & Katz, 2019).

Inclusion Criteria

We included studies that investigated the relationship between maltreatment occurring in childhood and/or adolescence (i.e., 18 years or younger) and later pain. We included two types of study designs: (1) Prospective cohort studies with a clearly defined measure of child maltreatment (retrospective self-report or verified maltreatment) and a measure of pain obtained at least three months later (whether that was in childhood, adolescence or adulthood); and (2) cross-sectional studies with retrospective verified reports of child maltreatment (e.g., court documentation) and a measure of pain occurring at least three months later. We included only peer-reviewed articles.

Exclusion Criteria

We excluded (1) studies of pain induced in the laboratory, (2) intervention studies, (3) case studies, review articles, dissertations, letters, editorials, book chapters, qualitative studies and conference abstracts, and (4) non-English articles.

Defining Child Maltreatment

Child maltreatment and neglect include acts of commission or omission by a parent or other caregiver resulting in harm, potential for harm, or threat of harm to the child's health, survival, development, or dignity. The five primary forms of maltreatment are physical abuse, sexual abuse, neglect, emotional maltreatment and exposure to domestic violence (Canadian Child Welfare Research Portal, 2020; Radford et al., 2011). We included studies that measured child maltreatment using self-report questionnaires and interviews, reports by parents and other caregivers, and information extracted from official documents, such as court documentation of child maltreatment and medical documentation of abuse-related physical trauma.

Coding specific features of child maltreatment. Where available, we coded for the following aspects of child maltreatment:

Type of maltreatment. We coded for the type of child maltreatment, specifically physical abuse, sexual abuse, neglect, emotional maltreatment, and exposure to domestic violence. For sexual abuse we coded for the presence of penetration (vaginal, anal, or oral) with a body part or foreign object. We also coded for the presence of physical violence (yes/no). We considered physical violence to be present in cases of physical abuse, rape, and other violent sexual acts. When different types of maltreatment were combined in a single measure, we coded the type of maltreatment as unspecified. Given that different types of abuse often co-occur (Gilbert et al., 2009), we noted whether or not this was accounted for in the measurement of maltreatment and/or using statistical controls.

Bodily harm. We coded for bodily harm resulting from physical and sexual abuse (yes/no). We also recorded information pertaining to the specific type of harm or injury (e.g., laceration, burn, fracture). Finally, we recorded any additional information about the occurrence of other types of childhood injuries (e.g., accidental injury and intentional self-injury) because of

their associations with child maltreatment (Lamers-Winkelman et al., 2012; Lang & Sharma-Patel, 2011; Ruiz-Casares et al., 2012).

Frequency of maltreatment. We coded for whether or not the maltreatment occurred frequently. Frequent maltreatment was defined as maltreatment that occurred more than 10 times or was rated as occurring "often" or "frequently." This definition is based on frequency data reported by Anderson and colleagues (1993) indicating that among women who had been sexually abused, 58% of were abused once, 28% were abused 2-10 times, and 14% were abused more than 10 times. Therefore, our definition captures the higher intensity of maltreatment experienced by a portion of survivors.

Chronicity of child maltreatment. We coded for whether exposure to maltreatment was chronic or not. Chronic child maltreatment was defined as maltreatment that persisted for at least six months or was reported to be present at two measurement points spaced at least six months apart. This definition is consistent with definitions of chronic stress, where the stressor needs to be present for at least six months (Hammen & Rudolph, 1999).

Developmental timing of maltreatment. We coded the stage of childhood during which participants had been exposed to maltreatment. Consistent with previous research examining the impact of developmental timing of trauma exposure on health, we defined early childhood as age 0-5 years, middle childhood as age 6 to 10 years, and adolescence as 11 to 18 years (Dunn et al., 2013; Dunn et al., 2017; Kaplow & Widom, 2007).

Defining PTSD

To examine the moderating role of PTSD, we included studies that report diagnosed PTSD, as assessed by clinical interviews such as the National Institutes of Mental Health Diagnostic Interview Schedule (Robins et al., 1989b), as well as subsyndromal PTSD (i.e.,

symptoms typically measured via self-report questionnaires such as the PTSD Checklist (Blanchard et al., 1996)).

Defining Pain Outcomes

Our primary outcome was chronic pain, defined as pain lasting longer than 3 months (Treede et al., 2019). In addition to including studies that captured pain intensity or frequency, we included studies that reported the outcome as presence of a chronic pain condition (e.g., migraine, chronic musculoskeletal or abdominal pain). We included studies that measured pain via self-report (e.g., visual analogue scale, numeric rating scale, McGill Pain Questionnaire (Melzack, 1975)), parental report or clinician examination or interview.

We included studies that measured pain more than three months after the trauma. This was to avoid capturing pain that may have been present as a direct result of maltreatment (i.e., acute pain). That said, many studies that report pain outcomes fail to specify the duration, thus it is unclear whether the study is actually measuring chronic pain. We therefore made an a priori decision to include studies regardless of duration, and if possible, account for any such measurement issues in our analysis.

In regard to secondary outcomes, we included studies that reported pain-related outcomes, such as pain-related interference or disability. Where possible, we also coded for information regarding pain medication use.

Search and Screening Strategy

Electronic searches of Medline, EMBASE, PsycINFO, and CINAHL were conducted by an experienced librarian (QM). The search strategy was adapted from a previous systematic review examining risk factors for chronic pain (Higgins et al., 2015). Search terms initially covered three broad categories: (1) Exposure: trauma, (2) Outcome: chronic pain, and (3) Study

design: captured by terms such as “risk” and “association” (see search terms for Medline presented in Appendix 1). The searches were customized for each database, using a combination of index and free text terms. To identify studies for inclusion, we screened the references from these searches for relevance through title/abstract and full-text review. Following the full-text review, a decision was made to conduct a more focused review on child maltreatment and chronic pain. The literature search was then revised to reflect this new focus, and this more specific search strategy was used to update the search prior to finalizing the manuscript.

Recognizing potential limitations of electronic search strategies (Hayden et al., 2014), we also searched references of previously published reviews of child maltreatment and pain (Afari et al., 2014; Burke et al., 2017; Davis et al., 2005; Häuser et al., 2011; Paras et al., 2009; Raphael et al., 2004) and conducted a review of references for all included studies and citation searches of key articles in the field (Gilbert et al., 2009; Sachs-Ericsson et al., 2005; Scott et al., 2011; Stickley et al., 2015).

Data Extraction

Two independent reviewers (TM and RL) extracted data and reached consensus using electronic extraction forms. A consensus method was used and a third reviewer (JK) consulted in the case of disagreements. See Table 2.1 for a list of variables extracted.

Assessing Risk of Bias

We assessed each study’s risk of bias using an approach based on the Quality in Prognosis Studies (QUIPS) tool (Hayden et al., 2013) for studies examining risk factors. This involved consideration of six important domains: study participation, study attrition, measurement of the risk factor of interest, outcome measurement, confounding, and analysis/reporting. For each of the six domains, responses to the prompting items were taken

together to inform the risk of bias judgment. To judge risk of bias for the confounding domain, we considered whether statistical analyses were unadjusted, minimally adjusted (i.e., controlled for participant age and sex) or adequately adjusted (i.e., controlled for age, sex, baseline pain, a measure of social status, such as family income or parental education, a measure of negative affect, such as neuroticism or symptoms of anxiety or depression, and the presence of adult abuse or current abusive relationship). For analyses examining the association of a specific type of abuse on pain outcomes, we considered the model to be adequately adjusted if it also controlled for other types of abuse. Unadjusted studies were rated as having high risk of bias, minimally adjusted studies were rated as having moderate risk of bias, and adequately adjusted studies were rated as having low risk of bias. Finally, we judged overall study validity by defining studies with a low risk of bias as those in which at least half of bias domains were rated to be low risk and there were no serious sources of potential bias across the domains. This assessment was conducted in duplicate by TM and JK, and any disagreements were resolved through discussion.

Measures of Association Extracted

Using methods described by Hayden and colleagues (2019) (Borenstein et al., 2009; Peterson & Brown, 2005), we extracted unadjusted and adjusted measures of the association between child maltreatment and pain and used odds ratios (ORs) in the natural log scale as the common measure of the relationship. We converted effect sizes to the natural log scale and calculated standard errors (SEs) by log-transforming confidence intervals and then converting using an appropriate formula. We converted standardized regression coefficients for continuous outcomes to natural log ORs (Borenstein et al., 2009; Peterson & Brown, 2005).

Data Synthesis

We conducted a meta-analysis when three or more sufficiently homogenous studies assessed the relationship between child maltreatment or a proposed moderator variable and chronic pain. Data were analyzed using Review Manager software (RevMan version 5.3, the Cochrane Collaboration) with a random-effects generic inverse variance meta-analysis model, which accounts for between-study heterogeneity in the exposure effect. The meta-analysis was summarized by the pooled estimate (the average exposure effect) and its 95% CI. We conducted these analyses separately using both unadjusted statistics and values adjusted for potential confounders.

To further test the proposed moderation models, we used subgroup analysis to explore between-study differences in the presence of PTSD or symptoms of PTSD, the specific nature of maltreatment, including type of child maltreatment, presence of bodily injury, and the frequency, chronicity and developmental timing of exposure. We also planned to use subgroup analysis to explore the impact of differences in the timing of outcome measurement, specifically whether the assessment was conducted in childhood (18 years or younger) or adulthood (>18 years).

We planned to use sensitivity analysis to explore the association of other study factors on the relationship between maltreatment and chronic pain. In particular, we planned to examine the measurement of chronic pain, RoB, and adjustment for confounders by limiting our analyses to studies that (1) clearly captured chronic pain, (2) were assessed as having low RoB, and (3) adequately adjusted for confounders.

Interpretation of Results

The strength of observed associations was defined, for binary factors, based on effect size as small (OR < 1.5), moderate (1.5 ≥ OR ≤ 2), or large (OR > 2) (Hartvigsen et al., 2004; Hayden

et al., 2019). We considered moderate or large effect sizes (OR ≥ 1.5) to be clinically important. Statistical heterogeneity between studies was assessed using the I^2 test; heterogeneity was considered important if I^2 was greater than 50%. In cases where it was not appropriate to combine results using meta-analysis due to the small number (fewer than 3) of sufficiently homogeneous studies with available data, the results were presented qualitatively as follows:

(1) Strong evidence of effect: Consistent findings (defined as greater than 75% of studies showing the same direction of effect) in multiple low risk of bias studies

(2) Moderate evidence of effect: Consistent findings in multiple high risk of bias and/or one study with low risk of bias

(3) Limited evidence of effect: One study

(4) Conflicting evidence: Inconsistent findings across studies

(5) No evidence: No association between child maltreatment variable and the outcome of interest.

We used an approach modified from the GRADE framework (Guyatt et al., 2011; Hayden et al., 2019) to assess overall quality of evidence on the relationship between child maltreatment and pain. We rated the overall strength of evidence as high, moderate, low or very low considering internal validity, size and precision of effect, heterogeneity, generalizability, and potential reporting bias.

Results

Description of Studies

Results of the search. Our extensive literature search identified 18,730 unique references citations for appraisal against our inclusion and exclusion criteria. After reviewing the titles and abstracts, we retrieved 476 full-text articles (456 from general trauma search, 17 from

focused search update, and 3 articles identified through other sources) for further assessment and study selection. Ultimately, nine studies met our inclusion criteria for the current review. The search was last updated on July 28, 2019. See Figure 2.1 for the study flow diagram and Table 2.2 for the characteristics of included studies.

Included studies. This review is comprised of nine studies (17,340 participants) that examined the relationship between child maltreatment and pain (Beal et al., 2020; Biskin et al., 2014; Brown et al., 2005; Kopec & Sayre, 2005; Lamers-Winkelman et al., 2012; Linton, 2002; Raphael & Widom, 2011; Rimsza & Niggemann, 1982; Sachs-Ericsson et al., 2017). Six studies were conducted in the United States of America (Beal et al., 2020; Biskin et al., 2014; Brown et al., 2005; Raphael & Widom, 2011; Rimsza & Niggemann, 1982; Sachs-Ericsson et al., 2017), two studies were conducted in Europe (Lamers-Winkelman et al., 2012; Linton, 2002) and one was conducted in Canada (Kopec and Sayre, 2005). Four studies were cohort studies with retrospective self-reports of maltreatment (Biskin et al., 2014; Kopec & Sayre, 2005; Linton, 2002; Sachs-Ericsson et al., 2017), three studies followed specialized cohorts (i.e., individuals with a history of child maltreatment) and matched cohorts (Beal et al., 2020; Raphael & Widom, 2011; Rimsza et al., 1988), and two were cross-sectional with retrospective verified reports of maltreatment (Brown et al., 2005; Lamers-Winkelman et al., 2012). One study followed participants with a diagnosis of borderline personality disorder (Biskin et al., 2014), and two followed participants who were free of pain at baseline (Kopec & Sayre, 2005; Linton, 2002). Follow up periods for the longitudinal studies ranged from one year to 16 years. Some studies used data from official reports made well before the study baseline, so the time between exposure and the final pain measure is much longer (see data for recency of maltreatment exposure and study follow-up periods reported in Table 2.2).

The age of participants at baseline ranged from two years to more than 65 years. Three studies included all females (Beal et al., 2020; Linton, 2002; Rimsza et al., 1988), and the remaining six studies included mixed samples of male and female participants (% female ranged from 47 to 77). Two studies examined the relationship between child maltreatment and childhood pain (Lamers-Winkelman et al., 2012; Rimsza et al., 1988), while the other studies examined the relationship between child maltreatment and pain in adulthood.

Excluded studies. We excluded 466 articles after full-text screening. The most common reasons for exclusion were: (1) child maltreatment and pain measured cross-sectionally, (2) no measure of child maltreatment, and (3) no measure of pain or pain was not included as an outcome in the maltreatment analyses.

The measurement of child maltreatment. Studies in this review identified child maltreatment using various methods. Four studies relied on either self-report questionnaires (Kopec & Sayre, 2005; Linton, 2002) or interviews (Biskin et al., 2014; Sachs-Ericsson et al., 2017). Three studies abstracted information from official reports (Beal et al., 2020; Brown et al., 2005; Raphael & Widom, 2011). One study recruited a sample of children referred for intervention due to exposure to intimate partner violence and then used parent reports and official reports to ascertain the presence of additional exposures to abuse (Lamers-Winkelman et al., 2012). Finally, Rimsza and colleagues (1988) recruited children who had been identified as victims of sexual abuse following evaluation by a sexual abuse team at a medical centre in Phoenix, Arizona. The prevalence of maltreatment in each study is reported in Table 2.2.

Type of child maltreatment. Studies in this review measured a range of abuse types, including sexual abuse, physical abuse, verbal/emotional abuse, neglect, and exposure to intimate partner violence. Eight studies measured sexual abuse (Beal et al., 2020; Biskin et al.,

2014; Brown et al., 2005; Lamers-Winkelman et al., 2012; Linton, 2002; Raphael & Widom, 2011; Rimsza et al., 1988; Sachs-Ericsson et al., 2017), although only five of these provided usable information regarding the relationship between sexual abuse and pain (Biskin et al., 2014; Linton, 2002; Raphael & Widom, 2011; Rimsza et al., 1988; Sachs-Ericsson et al., 2017). Three studies included substantiated cases of sexual abuse (Beal et al., 2020; Brown et al., 2005; Raphael & Widom, 2011), with Raphael et al. (2011) providing the most detail regarding the nature of the charges made, stating that they "ranged from relatively non-specific charges of 'assault and battery with intent to gratify sexual desires' to more specific charges of 'fondling or touching in an obscene manner,' rape, sodomy, incest, etc." (p. 164). For the studies that used questionnaires and interviews, Lamers-Winkelman et al. (2012) and Sachs-Ericsson et al. (2017) specified "contact sexual abuse" in their definition (i.e., rape or molestation), and Rimsza et al. (1988) included "any forced sexual activity or sexual activity between an adult and a child/adolescent." In contrast, Linton et al. (2002) captured a range of sexual acts, from non-contact acts (e.g., someone exposing their sex organs) to contact acts (e.g., molestation and rape) (Linton, 2002). Biskin et al. (2014) did not provide a definition of sexual abuse. Only one study specified the presence of intercourse (Rimsza et al., 1988), with 73.6% of participants reporting vaginal or anal penetration; however, no usable information was provided regarding the relationship between the presence of intercourse and the relationship between sexual abuse and pain.

Six studies captured exposure to childhood physical abuse (Beal et al., 2020; Brown et al., 2005; Kopec & Sayre, 2005; Lamers-Winkelman et al., 2012; Raphael & Widom, 2011; Sachs-Ericsson et al., 2017), although only four studies provided usable information about the relationship between physical abuse and pain (Brown et al., 2005; Kopec & Sayre, 2005;

Raphael & Widom, 2011; Sachs-Ericsson et al., 2017). Of the studies that relied on substantiated reports, Raphael and Widom (2011) provided the most detailed qualitative information, describing evidence of physical injury resulting from the abuse (see section below on Presence of Physical Harm). While Lamers-Winkelman et al. (2012) and Sachs-Ericsson et al. (2017) used in-depth interviews to measure physical abuse, Kopec and Sayre (2005) relied on a single question (i.e., "Were you ever physically abused by someone close to you?").

Two studies in the review measured verbal and/or emotional abuse (Lamers-Winkelman et al., 2012; Sachs-Ericsson et al., 2017). Lamers-Winkelman and colleagues (2012) defined emotional abuse as "recurrent humiliation," and Sachs-Ericsson and colleagues (2017) defined verbal abuse as behaviours by a parent or stepparent, including being insulted, sworn at, or threatened to be hit.

Four studies measured neglect (Beal et al., 2020; Biskin et al., 2014; Brown et al., 2005; Raphael & Widom, 2011), three of which were based on official reports. In the Raphael and Widom (2011) study, "neglect cases reflected a judgment that parents' deficiencies in childcare were beyond those found acceptable by community and professional standards at the time. These cases represented extreme failure to provide adequate food, clothing, shelter, and medical attention to children." (p. 164). The interview used by Biskin and colleagues (2014) captured different types of neglect, including physical neglect, emotional withdrawal, and inconsistent treatment (Zanarini et al., 1997).

Two studies measured exposure to domestic partner violence (Beal et al., 2020; Lamers-Winkelman et al., 2012). The Lamers-Winkelman study (2012) recruited primary caregivers of children who had witnessed violence and provided evidence about the relationship between exposure to additional types of maltreatment and pain among the child witnesses (described

below). Beal and colleagues (2020) captured childhood exposure to domestic violence using the Comprehensive Trauma Interview, however this measure also captured other forms of maltreatment, so there was no usable information about the relationship between exposure to domestic violence and pain at follow-up specifically.

One study combined verbal and physical abuse into a single measure (Biskin et al., 2014), and in two studies, a composite variable was created to capture any type of abuse (Beal et al., 2020; Raphael & Widom, 2011).

Two studies described the co-occurrence of abuse types. In particular, Lamers-Winkelman (2012) created a category to capture sexual abuse, emotional abuse and/or neglect among child witnesses to intimate partner violence. They found that 71% of children in this group had experienced more than one form of abuse or neglect in addition to witnessing intimate partner violence. In a similar regard, Brown et al. (2005) also reported substantial overlap between abuse types, with neglect being present in 6 of 14 cases of physical abuse.

Presence of physical harm. None of the included studies measured physical harm as an outcome variable or as a potential moderator of the maltreatment-pain association. However, we were able to garner some information about physical harm based on the descriptions of the different types of abuse exposures. By definition, we expect most instances of physical abuse to be accompanied by at least some degree of physical harm. Although six studies in this review measured childhood physical abuse, only the study by Raphael and Widom (2011) explicitly stated that cases of physical abuse included physical injuries, such as "bruises, welts, burns, abrasions, lacerations, wounds, cuts, bone and skull fractures and other evidence of physical injury" (p. 164). However, no additional information regarding the occurrence of specific injuries or the severity of physical harm was provided.

In studies of sexual abuse, the presence of physical harm depends on the specific nature of the sexual abuse. For example, the sexual abuse measure used by Linton (2002) captured a range of sexual acts, some of which involved no physical contact, such as being exposed to someone's sex organs or someone threatening to have sex with you. However, sexual abuse also includes violent acts, such as rape and sodomy (Raphael & Widom, 2011; Rimsza et al., 1988), as well as "assault and battery with intent to gratify sexual desires" (Raphael & Widom, 2011). Thus, it may cause genital-anal injury or general body injury. However, only the study by Rimsza and colleagues (1988) provided descriptive information about the frequencies of vaginal penetration (61%) and anal penetration (12.5%) in their sample. Given the above, we coded physical harm as present in six studies that captured physical abuse and one study that captured sexual abuse (Rimsza et al., 1988).

Although physical harm resulting from non-inflicted injury or self-harm may also be more likely in the context of child maltreatment, none of the included studies measured non-inflicted injury. Only one study measured self-harm (Lamers-Winkelman et al., 2012) but did not report associations between self-harm and pain outcomes.

Frequency of maltreatment. Only two studies measured "frequent maltreatment," defined in our protocol as maltreatment that occurred more than 10 times or was rated as occurring "often" or "frequently" (Linton, 2002; Sachs-Ericsson et al., 2017). Specifically, Sachs-Ericsson and colleagues (2017) coded both physical abuse and verbal abuse on a scale ranging from "never" to "often." Their findings showed that 2.6% of their sample reported "frequent" physical abuse and 9.3% of their sample reported "frequent" verbal abuse. However, no usable information was provided regarding the relationships between "frequent" abuse and pain. Linton and colleagues (2002) also captured "frequent" abuse by measuring sexual abuse on a similar

scale. However, they then dichotomized the data, counting any positive response as abuse and losing the information about frequency.

Other studies in the review either captured multiple exposures and then dichotomized the data (Lamers-Winkelman et al., 2012) or measured abuse on a dichotomous scale (Beal et al., 2020; Brown et al., 2005; Kopec & Sayre, 2005; Raphael & Widom, 2011; Rimsza et al., 1988), or there was a lack of clarity about how the maltreatment was operationalized (Biskin et al., 2014).

Dichotomous scores were more often used for measures of sexual abuse as compared to other types of abuse, meaning that the presence of any sexual abuse meant classification into the exposed group. For example, Linton and colleagues (2002) used the same rating scale in their measures of sexual abuse and physical abuse, with response options ranging from "no/never" to "yes/often." For sexual abuse, any positive response was counted as abuse, while for physical abuse, a person was classified as being abused if she reported being "hit, kicked or beaten occasionally or often" (Linton, 2002). Similarly, Biskin et al. (2014) used dichotomous scores to denote the presence/absence of sexual abuse, while their measure of verbal and physical abuse and neglect captured the severity/intensity of abuse. Finally, although Sacs-Ericsson and colleagues (2017) reported frequency data for physical and verbal abuse, for sexual abuse, they only differentiated between "never," "once," and "more than once."

Chronicity of maltreatment. Only one study in the review measured and reported the timespan over which child maltreatment occurred. In particular, Rimsza and colleagues (1988) reported that among the 72 victims of sexual abuse in their sample, 31 had been exposed for less than six months and 41 had been exposed for greater than six months. In our protocol we defined "chronic" maltreatment as maltreatment that persisted for at least six months or was

reported to be present at two measurement points spaced at least six months apart. According to this definition, 57% of the Rimsza et al. (1988) sample experienced "chronic" maltreatment. In addition, the interview used by Biskin and colleagues (2014) captured "chronic" verbal abuse, physical abuse, and neglect, as the measure tapped "disturbed behavior chronically engaged in by full-time caregivers." Therefore, although the timespan over which abuse occurred was not reported, we considered abuse captured in this study to reflect a "chronic" exposure.

Timing of child maltreatment. The included studies measured child maltreatment that occurred across a range of ages from 0 to 18 years. Three of the studies narrowed their focus to abuse that occurred earlier in childhood (i.e., at 14 years or younger) (Lamers-Winkelman et al., 2012; Linton, 2002; Raphael & Widom, 2011)). In four of the studies the timing of the exposures was reported more specifically. Two studies captured exposures that occurred in early childhood (Raphael & Widom, 2011; Rimsza et al., 1988), three captured exposures that occurred in middle childhood (Lamers-Winkelman et al., 2012; Raphael & Widom, 2011; Rimsza et al., 1988), and two studies captured exposures that occurred in adolescence (Beal et al., 2020; Rimsza et al., 1988).

The measurement of PTSD and posttraumatic stress symptoms (PTSS). Three studies measured the presence of PTSD using structured clinical interviews (Biskin et al., 2014; Raphael & Widom, 2011), such as the National Institutes of Mental Health Diagnostic Interview Schedule Version III-R (Robins et al., 1989b), The Structured Clinical Interview for DSM-III-R Axis I Disorders (SCID-I) (Spitzer et al., 1992), and the Composite International Diagnostic Interview (World Health Organization, 1990). Sachs-Ericsson and colleagues (2017) reported that 7.3% of their sample met criteria for lifetime PTSD measured at baseline, and Raphael and Widom (2011) reported that 28.7% of their sample (cases plus matched controls) met criteria for

lifetime PTSD (as assessed in young adulthood, approximately 20 years after documented maltreatment). Biskin and colleagues (2014) failed to report descriptive statistics on this variable. In addition, Beal and colleagues (2020) measured baseline PTSS using the Comprehensive Trauma Interview (Barnes et al., 2009).

In regard to associations between maltreatment and PTSD/PTSS and PTSD/PTSS and pain, Beal and colleagues (2020) reported that women with confirmed maltreatment had significantly higher PTSS across the symptom domains of re-experiencing, arousal, and avoidance compared to matched controls. Moreover, the studies by Beal et al. (2020), Raphael and Widom (2011), and Sachs-Ericsson et al. (2017) reported statistically significant associations between PTSD/PTSS and pain in the expected direction (all p values < 0.05). In contrast, Biskin and colleague (2014) reported no association between PTSD at baseline and pain at follow-up (n.s.). Only the Raphael and Widom study (2011) provided usable information about PTSD as a moderator of the maltreatment-pain relationship.

The measurement of pain. Seven studies measured pain in adulthood as the primary outcome (Beal et al., 2020; Biskin et al., 2014; Brown et al., 2005; Kopec & Sayre, 2005; Linton, 2002; Raphael & Widom, 2011; Sachs-Ericsson et al., 2017), and two studies measured pain in childhood as the primary outcome (Lamers-Winkelman et al., 2012; Rimsza et al., 1988). Moreover, two studies focused on change in pain or pain status over time (Kopec & Sayre, 2005; Linton, 2002).

Four studies measured site-specific pain, such as headache (Lamers-Winkelman et al., 2012; Rimsza et al., 1988) stomachache/abdominal pain (Lamers-Winkelman et al., 2012; Rimsza et al., 1988), back and neck pain (Kopec & Sayre, 2005; Linton, 2002; Rimsza et al., 1988), chest pain (Rimsza et al., 1988), vaginal pain (Rimsza et al., 1988). Five studies

measured pain in various body locations (Beal et al., 2020; Biskin et al., 2014; Brown et al., 2005; Lamers-Winkelman et al., 2012; Raphael & Widom, 2011). Finally, Sachs-Ericsson et al. (2017) captured pain by measuring the number of painful medical disorders, including arthritis or rheumatism, chronic back or neck problems, frequent or severe headache, or other chronic pain. In regard to secondary outcomes, four studies captured pain interference (Biskin et al., 2014; Brown et al., 2005; Linton, 2002; Raphael & Widom, 2011). None of the studies reported pain medication use.

Four studies measured pain using validated measures (Beal et al., 2020; Biskin et al., 2014; Lamers-Winkelman et al., 2012; Raphael & Widom, 2011), such as the Brief Pain Inventory (Cleeland, 1989), the Somatic Complaints Scale within the Child Behaviour Checklist (Achenbach & Rescorla, 2001), the Diagnostic Interview Schedule III-R (Robins et al., 1989a), whereas other studies used questions about pain that appeared to have been developed for the study (Brown et al., 2005; Kopec & Sayre, 2005; Linton, 2002; Rimsza et al., 1988). Finally, Sachs-Ericsson et al. (2017) asked participants whether they experienced any one or more of four painful medical disorders since the baseline assessment and used the number of medical conditions as the dependent variable in their analyses. As the authors note, the dependent variable is not a measure of pain experience or intensity and instead simply represents the number of painful disorders reported.

Seven studies measured pain using self-report (Beal et al., 2020; Biskin et al., 2014; Brown et al., 2005; Kopec & Sayre, 2005; Linton, 2002; Raphael & Widom, 2011; Sachs-Ericsson et al., 2017), one relied on parent reports (Lamers-Winkelman et al., 2012), and one used chart review with the addition of parent/caregiver reports for part of the sample (Rimsza et al., 1988).

Three studies used measures of pain or pain interference that captured the experience of chronic pain (for pain interference Brown et al., 2005; Kopec & Sayre, 2005; Lamers-Winkelman et al., 2012). Other studies captured pain occurring for the past week (Beal et al., 2020) or the past 24 hours (Biskin et al., 2014) or the duration of pain was unclear (frequent pain Brown et al., 2005; Linton, 2002; Raphael & Widom, 2011; Rimsza et al., 1988; Sachs-Ericsson et al., 2017).

The Risk of Bias in Included Studies

We judged six studies to have low risk of bias overall (Beal et al., 2020; Brown et al., 2005; Kopec & Sayre, 2005; Linton, 2002; Raphael & Widom, 2011; Sachs-Ericsson et al., 2017). The results of the "risk of bias" assessment are summarized in Figure 2.2. It is notable that although these studies were deemed to be higher quality than the other studies in the review, they each suffered from moderate risk of bias due to study confounding. Indeed, none of the studies in the review met our criteria for adequate adjustment (i.e., statistical control for age, sex, baseline pain, social status, negative affect, and adult or current abuse, and for analyses examining the relationship between specific abuse types and pain, other types of abuse). Basic demographic factors were generally well controlled for, whereas other key confounders, including baseline pain, current abuse, and other types of abuse (in analyses of specific abuse types) were largely ignored. When baseline pain is not accounted for, there is no way to discern whether maltreatment is a true "predictor" (i.e., pain developed after a pain-free interval) or if it was there to begin with. In this review two studies followed participants who were free of pain at baseline (Kopec & Sayre, 2005; Linton, 2002), and one study statistically controlled for baseline pain severity (Sachs-Ericsson et al., 2017). The remaining studies did not statistically

control for baseline pain, thereby limiting our ability to draw conclusions about the temporal nature of the relationship.

Two studies ensured that participants were no longer in abusive situations at the time of assessment (Beal et al., 2020; Lamers-Winkelman et al., 2012) and Biskin and colleagues (2014) statistically controlled for adult abuse. For the remaining studies, the presence of current physical abuse is an alternative explanation for any observed association between maltreatment and pain. Finally, in regard to statistical control for other types of maltreatment, two studies examined independent effects (Biskin et al., 2014; Sachs-Ericsson et al., 2017). None of the other studies accounted for the co-occurrence of maltreatment types. This means that for most of the studies in this review, we cannot be sure whether the relationship between a specific type of maltreatment and pain is driven by that particular type of maltreatment or if it is being driven by co-occurring maltreatment.

Risk of bias related to the measurement of child maltreatment was another common source of potential bias, with five studies being rated as having moderate risk of bias in this domain. Studies that captured child maltreatment via official reports (Beal et al., 2020; Brown et al., 2005; Raphael & Widom, 2011) or by a medical team (Rimsza et al., 1988) were considered to have lower risk of bias related to measurement of the exposure because reporting biases can be ruled out as a potential third variable. It should be noted that three studies that relied on self-reported maltreatment (Kopec & Sayre, 2005; Linton, 2002; Sachs-Ericsson et al., 2017) were considered to have an overall low risk of bias. One of the strengths of these studies is that they accounted for baseline pain, thereby controlling for individual differences in pain reports, and giving us more confidence that any associations between maltreatment and pain are not simply a function of reporting biases.

We judged three studies to have high risk of bias overall (Biskin et al., 2014; Lamers-Winkelman et al., 2012; Rimsza et al., 1988). These studies suffered from high risk of bias in one domain (Biskin et al., 2014), two domains (Lamers-Winkelman et al., 2012), or three domains (Rimsza et al., 1988). It should be noted that for each of these studies there were concerns about selective reporting, indicating that positive associations may be over-represented in the results.

Findings

Zero to five studies provided sufficiently similar data regarding each of our research questions, and zero to three studies were available for each of our planned meta-analyses. Given the small number of studies, we were unable to conduct the planned subgroup and sensitivity analyses. Overall, the level of evidence was assessed to be low to very low quality. See Table 2.3 for a summary of the evidence for each research question and the corresponding GRADE analysis.

Is exposure to any child maltreatment associated with pain at follow-up? Low quality evidence from three studies (1,421 participants) examined the relationship between any child maltreatment (i.e., two or more types of maltreatment measured and then combined in a single index) and pain at follow-up (Beal et al., 2020; Biskin et al., 2014; Raphael & Widom, 2011). In unadjusted analyses, Beal and colleagues (2020) found that women with a documented history of maltreatment were more likely to report experiencing pain at follow-up compared to women without a maltreatment history ($p<0.05$), and Biskin and colleagues (2014) showed that severity of any verbal or physical abuse was significantly and positively associated with pain at follow-up ($p = 0.001$). However, adjusted analyses yielded mixed findings. In the Beal et al. (2020) study, after adjusting for covariates, including PTSD, there was no direct association

between maltreatment status and pain (n.s.). Similarly, in adjusted analyses, Raphael and Widom (2011) found no difference in pain (n.s.) among participants with a documented history of any maltreatment compared to matched controls. In contrast, Biskin and colleagues (2014) showed that the severity of verbal and/or physical abuse was associated with pain after controlling for covariates, including other types of abuse ($p < 0.05$). See Table 2.3 for GRADE summary.

In regard to secondary outcomes, adjusted analyses reported by Raphael and Widom. (2011) revealed no difference in pain interference between participants with and without a history of any maltreatment (n.s.). Although Biskin and colleagues (2014) measured pain interference, the relationship between any maltreatment and interference was not reported.

Does the presence of PTSD or PTSS influence the maltreatment-pain relationship? Low quality evidence from one study (807 participants) tested moderation of the maltreatment-pain relationship by PTSD (Raphael & Widom, 2011). Adjusted analyses revealed a significant interaction between maltreatment status and PTSD, such that maltreatment history *plus* lifetime PTSD was associated with elevated pain in middle adulthood compared to no history of maltreatment ($p < 0.001$). The authors state that after accounting for this synergistic effect, neither the effect of child maltreatment alone nor PTSD alone approached statistical significance. However, the results of the statistical analysis for moderation are not fully reported, and there is no graph of the interaction effect, so there is no way to assess if the results of the data analysis are consistent with the authors' interpretation. See Table 2.3 for GRADE summary.

It should be noted this same research group had also measured pain 10 years prior (when the participants were in young adulthood) (Raphael et al., 2001). When they reanalyzed the data from the earlier study, they again reported to have found evidence for moderation of the

maltreatment-pain association by PTSD, such that the combination of PTSD and child maltreatment predicted pain in young adulthood (Raphael & Widom, 2011).

In regard to secondary outcomes, Raphael and Widom (2011) showed the same interaction effect in the prediction of pain interference ($p<0.001$).

Does the type of maltreatment influence the maltreatment-pain relationship? Each study in the review specified maltreatment type, including the studies by Raphael and Widom (2011) and Beal and colleagues (2020), which also reported the overall effects of any documented history of maltreatment (as summarized above). The Raphael and Widom (2011) findings for each maltreatment type (sexual abuse, physical abuse, and neglect) are described in the sections below. In contrast, Beal and colleagues (2020) did not report associations between each maltreatment type and pain. However, they reported results of unadjusted analyses showing that pain did *not* significantly differ among women who had experienced neglect only, sexual and/or physical abuse only, and both abuse and neglect. This finding suggests that the impact of maltreatment on pain is uniform across maltreatment types.

Sexual abuse. Very low quality evidence from five studies (6,203 participants) provided information about the longitudinal relationship between child sexual abuse and pain. Two studies with high risk of bias reported unadjusted results only (Biskin et al., 2014; Rimsza & Niggemann, 1982). These studies yielded mixed findings, with one study pointing to elevated pain at follow-up in survivors of sexual abuse compared to controls (p-value not reported) (Rimsza et al., 1988) and the other study showing no association (n.s.) (Biskin et al., 2014). It should be noted that the Rimsza et al. (1988) finding is for abdominal pain, whereas findings for other pain areas (i.e., headaches, chest pain, back pain, and vaginal pain) were not reported. In addition, findings from three low risk of bias studies that adjusted for potential confounders were

also mixed (Linton, 2002; Raphael & Widom, 2011; Sachs-Ericsson et al., 2009). In the Linton et al. (2002) study, history of childhood sexual abuse was unrelated to pain at follow-up, among both participants who were free of pain at baseline and those who reported pain at baseline (n.s.). Similarly, Raphael and Widom (2011) showed no differences in pain at follow-up in cases of documented sexual abuse compared to controls (n.s.) (Raphael & Widom, 2011). In contrast, Sachs-Ericsson et al. (2009) reported a statistically significant and positive association between sexual abuse and pain at follow-up ($p < 0.001$). See Table 2.3 for GRADE summary.

In regard to secondary outcomes, evidence from two studies (Linton, 2002; Raphael & Widom, 2011) showed no association between childhood sexual abuse and pain interference at follow-up (n.s.).

Physical abuse. There was low quality evidence from four studies (15,150 participants) with information about the longitudinal association between child physical abuse and pain (Brown et al., 2005; Kopec & Sayre, 2005; Raphael & Widom, 2011; Sachs-Ericsson et al., 2017). Each of these studies reported findings adjusted for potential confounders. None of the studies showed a significant association between physical abuse and pain, as shown in meta-analysis of three studies with usable data (OR [95% CI] = 1.04 [0.99-1.10], n = 3) (Brown et al., 2005; Kopec & Sayre, 2005; Sachs-Ericsson et al., 2017). See Figure 2.3 for forest plot and Table 2.3 for GRADE summary.

In regard to secondary outcomes, two studies provided evidence about the relationship between physical maltreatment and measures of pain interference (Brown et al., 2005; Raphael & Widom, 2011), both yielding null results (n.s.).

Verbal abuse. There was very low quality evidence from one study (5,001 participants) regarding the relationship between verbal abuse and pain at follow-up (Sachs-Ericsson et al.,

2017). Results adjusted for potential confounders showed a significant association between childhood verbal abuse and pain at follow-up, such that higher frequency verbal abuse was associated with increased risk for pain ($p < 0.001$). See Table 2.3 for GRADE summary.

This study provided no evidence regarding secondary outcomes.

Neglect. Very low quality evidence from three studies (1,538 participants) provided information about the relationship between child neglect and pain at follow-up (Biskin et al., 2014; Brown et al., 2005; Raphael & Widom, 2011). In unadjusted analyses, Biskin and colleagues (2014) reported a significant and positive association, such that more severe neglect was associated with higher pain at follow-up ($p < 0.01$). However, adjusted findings from three studies (Biskin et al., 2014; Brown et al., 2005; Raphael & Widom, 2011) showed no significant relationship between history of neglect and pain at follow-up (n.s.). See Table 2.3 for GRADE summary.

In regard to secondary outcomes, adjusted analyses showed no association between neglect and measures of pain interference (Brown et al., 2005; Raphael & Widom, 2011).

Exposure to domestic partner violence. There was no available evidence regarding the relationship between exposure to domestic partner violence and pain or pain interference.

Exposure to additional maltreatment among witnesses of domestic partner violence.

Lamers-Winkelman and colleagues (2012) examined whether reports of maltreatment (abuse and neglect) were associated with increased risk for subsequent pain among children who had witnessed domestic partner abuse. Findings revealed that compared to witnesses only, witnesses who had also experienced physical abuse were at increased risk for frequent stomachaches ($p < 0.05$) (but not headaches or aches and pains (n.s.)). When comparing witnesses only with witnesses who had also experienced any other form of abuse (sexual abuse,

emotional abuse, and/or neglect, with, or without physical abuse), there were no significant differences in pain outcomes (n.s.). There was no evidence regarding secondary outcomes. These findings should be interpreted with caution given that they are based on a single study rated as having high risk of bias.

Does the presence of physical harm influence the maltreatment-pain relationship? Physical harm was coded as present in seven studies, including one study that measured the presence of intercourse (Rimsza et al., 1988) and six studies that measured physical maltreatment (Beal et al., 2020; Brown et al., 2005; Kopec & Sayre, 2005; Lamers-Winkelman et al., 2012; Raphael & Widom, 2011; Sachs-Ericsson et al., 2017). However, given that there was no usable information reported by Rimsza et al. (1988) on the relationship between intercourse (yes/no) and pain, the remaining studies provided no evidence beyond what was discussed above regarding the association between physical maltreatment and pain. See Table 2.3 for GRADE summary.

Do the frequency and/or chronicity of maltreatment influence the maltreatment-pain relationship? There was not enough evidence available to conduct a meaningful synthesis of whether maltreatment frequency or chronicity was related to pain outcomes. None of the studies provided usable information about the relationship between "frequent" maltreatment and pain, and only one study provided usable information about the relationship between "chronic" maltreatment (i.e., chronic neglect and chronic verbal and/or physical abuse) and pain (Biskin et al., 2014). Therefore, there was not enough evidence to examine whether the maltreatment-pain relationship depended on the intensity of the maltreatment. See Table 2.3 for GRADE summary.

Does the developmental stage of child maltreatment influence the maltreatment-pain relationship? None of the included studies examined the role of the developmental timing

of maltreatment in the relationship between maltreatment and pain. The included studies did however capture maltreatment at different stages of development, with two studies that focused on maltreatment that occurred in early and middle childhood (Lamers-Winkelman et al., 2012; Raphael & Widom, 2011) and one study that measured exposures that occurred in adolescence (Beal et al., 2020). However, because there were too few studies, we could not conduct a meaningful analysis of the relationship between developmental stage of the exposure (i.e., maltreatment occurring in childhood vs. adolescence) and later pain. See Table 2.3 for GRADE summary.

Discussion

The goal of this review was to provide evidence on the longitudinal relationship between child maltreatment and pain. We aimed to delineate the specific nature of the maltreatment-pain relationship by examining potential moderating factors, including PTSD or PTSS, type of maltreatment, bodily injury, intensity of maltreatment (chronicity and frequency), and the developmental stage during which maltreatment occurred. Although the review included nine studies with data from 17,340 participants, the available evidence was limited across our research questions. In general, we found conflicting evidence regarding the relationship between child maltreatment and pain at follow-up, with the higher quality, well-adjusted studies being more likely to reveal evidence of no association. However, evidence from studies that accounted for the role of PTSD or PTSS suggests that psychological and emotional factors are key aspects of this phenomenon and may be essential to clarifying the nature of the maltreatment-pain relationship.

Summary of the Main Results

We found low quality conflicting evidence regarding the association between any child maltreatment (i.e., two or more types of maltreatment measured and then combined in a single index) and pain at follow-up. Findings from unadjusted analyses suggested a positive and significant association between any maltreatment and pain, yet adjusted analyses revealed a more complicated picture. Specifically, findings from two low risk of bias studies pointed to a key role of PTSD/PTSS in the final statistical models, with Raphael and Widom (2011) reporting significant moderation by PTSD and Beal and colleagues (2020) reporting full mediation through PTSS (thereby explaining why their adjusted models, which included adjustment for PTSS, yielded null findings). Taken together, the results from these two studies suggest that a complete model of maltreatment and pain *must* account for PTSD/PTSS. Consistent with our hypothesis, the Raphael and Widom (2011) findings provided low quality evidence that the nature of the maltreatment-pain relationship depended on the presence or absence of PTSD. Specifically, it was the combination of a maltreatment history *and* PTSD that was associated with risk of pain in adulthood, whereas neither maltreatment nor PTSD alone showed a robust association with pain. Replication of this finding with additional high quality studies (i.e., studies with low risk of bias) is needed to increase our understanding of, and confidence, in this moderation effect. Given that we did not have any *a priori* hypotheses about mediator models, we discuss the evidence on mediation by PTSD/PTSS and in the Additional Findings section below.

In regard to the role of maltreatment type (sexual, physical, and emotion/verbal abuse and neglect, and exposure to domestic violence), there was low to very low quality evidence from zero to five studies on the relationship between each type of maltreatment and pain at follow up. The pattern of results across studies showed some differentiation across abuse types. In

particular, there was limited evidence (one study; very low quality) that verbal abuse was associated with pain at follow-up, independent of baseline pain, other types of abuse, and other covariates. In contrast, the findings for physical abuse and pain (four studies; low quality evidence) and neglect and pain (three studies; low quality evidence) consistently showed no associations in models adjusted for covariates. Regarding sexual abuse, the evidence was conflicting, with inconsistent results across five studies (very low quality evidence), regardless of whether or not the analyses were adjusted. Finally, there was no available evidence regarding the relationship between exposure to domestic partner violence and pain at follow up.

Despite some variation in the pattern of findings across abuse types, the most consistent (negative) findings are for physical abuse and neglect, in that they largely showed evidence of no association with pain at follow-up. Therefore, the findings on specific maltreatment types again point to a lack of a direct (non-moderated or non-mediated) association between maltreatment and pain, especially in adjusted models and when the exposure involves physical abuse or neglect. This begs the question of whether information on PTSD/PTSS is needed to delineate relationships of specific types of maltreatment to pain. Indeed, Raphael and Widom (2011) showed evidence of moderation by PTSD across maltreatment types. These results provide additional evidence for the key role of PTSD in the maltreatment-pain relation and point to a lack of specificity when comparing sexual abuse, physical abuse, and neglect (the three types of abuse captured in the Raphael and Widom study (2011)).

Unfortunately, we were not able to examine the roles of other proposed moderators (bodily injury, frequency of maltreatment, chronicity of maltreatment, and developmental stage) because there was no available evidence, evidence from only a single study, or not enough variability across studies to perform a between-study comparison.

Findings for secondary outcomes. In regard to secondary outcomes, four studies measured pain interference (Biskin et al., 2014; Brown et al., 2005; Linton, 2002; Raphael & Widom, 2011), and zero studies measured pain medication use. The findings for pain interference largely mirrored those of the primary results. Specifically, the evidence pointed to the absence of a direct association between maltreatment and pain interference, regardless of whether any maltreatment or a specific type of maltreatment (e.g., sexual abuse, physical abuse or neglect) was included in the model. Moreover, Raphael and Widom (2011) reported the same interaction effect for pain interference as reported for pain, specifically, that it was the combination of child maltreatment and PTSD that was associated with increased pain interference in adulthood. Again, this finding should be interpreted with caution given that it is based on a single study.

Additional Findings

Our review revealed some additional findings that, although pertinent to our research questions, provide only indirect evidence. First, the design of the Lamers-Winkelman et al. (2012) study was unique in that it recruited child witnesses of domestic partner violence and then looked at the association between additional abuse exposures and parent-reported pain. Therefore, their models tested both the specificity of abuse types (e.g., physical abuse), as well as the cumulative impact of exposure to multiple abuse types (i.e., witnessing violence plus experiencing physical abuse compared to witnessing violence alone). Results from this study generally showed no added risk of pain with the addition of physical abuse and other abuse types among child witnesses to domestic violence. Although this finding is based on a single study with high risk of bias, it provides some initial evidence that exposure to additional abuse types

does *not* have a cumulative influence on pain outcomes, a finding that is inconsistent with the cumulative effects shown across the ACEs literature (Stickley et al., 2015; You et al., 2019).

Second, given the reported findings on mediation by PTSS (Beal et al., 2020), and the fact that mediation models shed light on our research question about the prospective relationship been maltreatment and pain, we discuss these findings in the paragraphs below. However, because these results were based on *post hoc* tests and were not subject to our quality appraisal, they should be assumed to be based on very low quality evidence. As described above, Beal et al. (2020) showed that PTSS fully mediated the maltreatment-pain relationship, indicating that PTSS is more proximally related to pain. Evidence from other studies in the review also points to PTSD/PTSS as an important pathway. Specifically, Sachs-Ericsson and colleagues (2017) reported findings consistent with a mediation model, such that the reported associations between maltreatment indices (verbal abuse and sexual abuse) and pain at follow-up were no longer statistically significant when PTSD was added to the model. Finally, Kopec and Sayre (2005) also reported findings consistent with a mediation model. These authors reported a high degree of correlation between physical abuse and a measure capturing the experience of significant fear in childhood (i.e., "Did something happened that scared you so much you thought about it for years after?," p. 479) with 68% of respondents who reported physical abuse also reporting fear. In statistical models that included both childhood physical abuse and fear, only the latter remained significantly associated with pain. This finding provides further evidence that the emotional response to maltreatment may be at the core of the maltreatment-pain relationship. That said, not all studies that measured PTSD and related indices found evidence consistent mediation. Specifically, Raphael and Widom (2011) reported that there was no evidence of mediation by PTSD (although it should be noted that the results of the statistical analysis for

mediation were not fully reported in the published paper), and Biskin and colleagues (2014) reported no association between baseline PTSD and pain at follow-up, a finding that is also inconsistent with mediation by PTSD.

Strengths and Limitations of the Review

This review has a number of strengths. First, the methods were planned and registered with PROSPERO a priori. This included a pre-specified set of potential moderating variables related to the presence of PTSD or PTSS, the specific nature of child maltreatment (i.e., its type and intensity and whether it involved physical harm), as well as other factors potentially related to heterogeneity, such as whether pain was measured in childhood or adulthood. Similarly, we considered what it would mean for a model to be minimally versus adequately adjusted and then accounted for the level of control in the risk of bias assessment. Second, we conducted a comprehensive literature search, including an electronic search and a review of references of key articles in the field (e.g., previously published reviews) to identify included studies. Third, we judged the overall quality of the evidence, accounting for such factors as risk of bias, size and precision of effect, heterogeneity, generalizability, and potential reporting bias.

This review also has some limitations. The main limitation relates to the dearth of evidence in combination with between-study variability in the measurement of maltreatment and pain, which rendered cross-study comparisons largely inconclusive. For example, some studies specified contact sexual abuse (e.g., rape or molestation) in their definitions of sexual abuse (e.g.,Sachs-Ericsson et al., 2017), whereas Linton et al. (2002) included both contact abuse and non-contact abuse (someone exposing their sex organs), thereby capturing sexual abuse at lower thresholds. However, it's unclear whether inconsistent findings across studies (e.g., the significant association reported by Sachs-Ericsson and colleagues (2017) versus the absence of

an association reported by Linton and colleagues (2002)) can be attributed to these varying definitions of sexual abuse or if other factors are involved, such as specific covariates included in the statistical models or the way in which pain was operationalized and measured.

An additional limitation is that our review may not reflect the full body of work on this topic. Given that this is a prognostic factor review, we suspect the presence of reporting and publication biases due to difficulty publishing findings showing no connection between maltreatment and pain. Moreover, we excluded non-English studies, thereby limiting the pool of published studies for inclusion in the review. A final limitation is that we had concerns about the internal validity (risk of bias) of included studies. In particular, we cannot rule out the impact of potential confounding (baseline pain, current/adult abuse, and co-occurring abuse types) on the study results reported.

Overall Completeness and Applicability of the Evidence

This review provides evidence regarding the prospective relationship between child maltreatment and pain. However, the literature failed to cover all relevant types of participants, risk factors, and outcomes. The evidence represents community, medical, and psychiatric samples in the United States, Europe, and Canada, thus is unclear whether the findings generalize to people outside of these geographic areas, including in developing nations. In regard to the measurement of maltreatment, there are some concerns about the generalizability of findings based on official reports. Although these measures minimize the impact of reporting biases on study findings, evidence indicates that only a small portion of children who are maltreated receive official attention (Gilbert et al., 2009). This means that findings from this review may not represent unreported cases of maltreatment. In regard to our questions about the proposed moderators, the evidence was incomplete. As shown in the GRADE table (Table 2.3),

none of the included studies provided evidence about the moderating effects of physical harm, the frequency and/or chronicity of maltreatment, or the development stage during which it occurred, and there were too few studies to conduct between-study comparisons. Finally, only three of the nine included studies actually measured chronic pain, which was our primary outcome variable. The other studies either failed to specify the duration of pain or examined pain occurring for a shorter duration. Therefore, the applicability of our findings to chronic pain is unclear.

Agreements and Disagreement with Other Reviews

Compared to the findings presented in the current review, reviews on similar topics published over the last decade have generally pointed to a more consistent and robust relationship between child maltreatment and pain and pain-related outcomes across maltreatment types. Indeed, reviews by Afari et al. (2014), Häuser et al. (2011), and Paras et al. (2009), each reported large effect sizes, indicating increased risk of pain and somatic disorders among participants with a history of maltreatment. Although we can only speculate on the reasons for this discrepancy, it may be a reflection of the quality of evidence in our review versus the earlier reviews, with the latter suffering from higher risk of bias.

In an effort to delineate the temporal nature of the maltreatment-pain relationship and bolster the overall quality of the evidence reviewed, we limited our review to studies that included prospective measures of child maltreatment. In contrast, the aforementioned reviews cast a wider net by also including case-control studies, and as a result, the vast majority of evidence is from studies of this design. In particular, the Häuser et al. (2011) review of sexual abuse and fibromyalgia syndrome was based on 18 case-control studies, the Paras et al. (2009) review of sexual abuse and somatic disorders (including non-specific chronic pain and chronic

pelvic pain) was based on 19 case-control studies and 4 cohort studies, and the Afari et al. (2014) review of psychological trauma (including child maltreatment) and somatic syndromes (including fibromyalgia and chronic widespread pain) was based on 58 case-control studies and 13 cohort studies. Each of these reviews included meta-analyses and reported impressive effects, including the Paras et al. (2009) finding that individuals with a history of sexual abuse were 2.2 times more likely to have a diagnosis of non-specific chronic pain and the Afari et al. (2014) finding that individuals with a history of emotional abuse were 2.11 times more likely to have a somatic syndrome.

The problem is that case-control studies are subject to high risk of bias, including both participation/sampling and measurement bias, thereby lowering our confidence in the combined effects reported. Specifically, there is a concern that healthcare seeking individuals (who are often recruited into case-control studies) are more likely to disclose abuse histories compared to nonpatients. Indeed, Davis, Luecken, and Zautras (2005) showed that patients with chronic pain were more likely to report a history of abuse compared to nonpatients recruited from the community. Moreover, some evidence points to differences in reporting among people with and without pain, such that individuals with pain in adulthood may be more likely to overreport child adversity, while individuals who are free of pain may be more likely to underreport these events (McBeth et al., 2001). Indeed, systematic differences in reporting between patients and non-patients with chronic pain and between individuals with and without chronic pain could certainly contribute to inflated associations between maltreatment history and pain in the context of case-control designs.

The way in which maltreatment is measured may also influence its relationship with pain. Indeed, official reports of maltreatment (e.g., court-documented cases) are associated with the

lowest risk of bias because they eliminate the impact of reporting biases on study findings. However, for studies that relied on self-report methods, the validity of the particular measure may have influenced its relationship with pain outcomes. For example, the Afari et al. review (2014) showed that the magnitude of the association between trauma and somatic syndromes was larger in studies using non-validated questionnaires compared to those using validated questionnaires for trauma assessment, suggesting that inaccurate trauma history can influence the magnitude of associations found. Although potential bias cannot be eliminated completely, in the current review, we attempted to minimize its influence by only including studies that captured prospective associations between maltreatment and pain and weighing the lower risk of bias studies (e.g., those that used more valid measures of maltreatment and pain) more heavily in our overall conclusions, an approach that may account for differences in our findings compared to those of previously published reviews.

Early reviews on the topic of child maltreatment and chronic pain identified many of the same methodological concerns discussed above (Davis et al., 2005; Raphael et al., 2004). Fifteen years later, we found only nine studies examining the prospective relationship between child maltreatment and pain. Although we consider these nine studies to reflect the best available evidence on this topic, our GRADE analysis revealed designations of "low quality," "very low quality" and "no available evidence" across our research questions, reflecting the significant methodological challenges faced by the field. High quality studies continue to be published, as exemplified by the Beal et al. (2020) study included in the current review, albeit the progress is slow. In the meantime, creative solutions are needed to address key methodological concerns in a timelier way, a topic that we turn to in the paragraphs below.

Implications for Research

Findings from this review suggest that there is no direct association between maltreatment and pain, but that PTSD or symptoms of PTSD may play a role as a mediator and/or a moderator of this relationship. However, our findings are based on low to very low quality evidence, therefore additional high quality studies are needed to delineate the nature of this association. This is important because reviews of case-control studies point to a robust relationship between child maltreatment and pain (Häuser et al., 2011; Paras et al., 2009), and the literature on ACEs suggests that child maltreatment is one of a number of childhood adversities that has a dose-effect relationship with pain outcomes (Stickley et al., 2015; You et al., 2019). Therefore, if child maltreatment is on its own *not* a risk factor for later pain, this will have important implications for future research and prevention efforts. For example, the focus could be shifted away from episodes of maltreatment measured in isolation toward a more comprehensive study of contextual factors (e.g., risky families, social support) that accentuate versus buffer their impact on young people. On the other hand, if child maltreatment only acts in combination with PTSD, this is equally important for guiding future work. In this regard, the focus could be shifted away from child maltreatment per se and toward a study of personal vulnerabilities that increase risk for PTSD and pain in the aftermath of such an experience, including individual differences in psychological and physiological vulnerability factors, such as anxiety sensitivity, low threshold for alarm, and selective attention to threat. These factors have been identified as risk factors for the development of both chronic pain and PTSD following traumatic injury (Turk, 2002), as well as mechanisms through which PTSD exacerbates the experience of pain, and vice versa (Sharp & Harvey, 2001).

As mentioned above, the ideal situation would be to have data from large, well-controlled prospective cohort studies with long follow ups to examine the temporal relationship between child maltreatment and chronic pain, as well as formal tests of mediation and moderation by PTSD and other theoretically derived variables (such as the moderators proposed in this review). However, given the significant amount of time and additional resources needed to obtain such data, we suggest the use of alternative methods to accelerate research in this field. One possibility would be to employ models of the transition from acute to chronic pain. For example, Salberg et al. (2020) have proposed surgical procedures and traumatic brain injury (both of which increase risk for chronic pain) as models for investigating the transition from acute to chronic pain in adolescence. In this regard, child maltreatment could be examined as a risk factor for the emergence of chronic pain following these events. Another possibility would be to take a life course perspective by collecting detailed maltreatment histories (including early life, repeated, and/or current exposures) (Gilbert et al., 2009; Scott-Storey, 2011). Trajectories of maltreatment could then be examined in relation to the emergence of pain across critical stages, such over the course of adolescence (King et al., 2011).

Given that it is often necessary to measure maltreatment retrospectively, to reduce the impact of reporting biases and increase the validity of these measures, we recommend the use of standardized measures with multiple informants (self-, sibling-, and parent-reports) in combination with official records (e.g., court documentation) (Gilbert et al., 2009). The aim should be to capture specific types of maltreatment and co-occurring maltreatment types, including the frequency and chronicity of these exposures over time (Gilbert et al., 2009; Scott-Storey, 2011). We also recommend that future work incorporate formal tests of mediation and moderation by PTSD and symptoms of PTSD, including in-depth analysis of PTSD symptom

clusters of reexperiencing, avoidance, and arousal (e.g., McKernan et al., 2019; Ravn et al., 2018). In this regard, it will also be important to delineate the characteristics child maltreatment that increase the likelihood of the emergence of PTSD and chronic pain, such as the presence of rape in child sexual abuse (Chen et al., 2010; Paras et al., 2009), or more generally, the presence of physical injury (Koren et al., 2006).

In addition to in depth measurement of child maltreatment, we recommend comprehensive pain assessment, including the use of well-validated and reliable measures that provide information about pain severity and pain interference (e.g., Brief Pain Inventory-Short Form [BPI-SF] (Cleeland, 1989; Cleeland & Ryan, 1994), as well as pain quality (e.g., Short Form-McGill Pain Questionnaire [SF-MPQ] (Melzack, 1987)). These measures are typically used with adults, but they can also be used with children and adolescents (Turk & Melzack, 2011). Finally, we recommend repeated symptom measures to capture changes in pain outcomes over time, as well as dynamic associations between symptoms of pain and symptoms of PTSD across development (Noel et al., 2016; Ravn et al., 2018).

Table 2.1: *Variables extracted from articles included in the review.*

Variable information extracted
Patient characteristics
Sample size
Study setting
Follow-up period
Child maltreatment (yes/no)
Type of child maltreatment (physical abuse, emotional abuse, sexual abuse, neglect, and exposure to domestic violence)
Additional characteristics of child maltreatment, including the presence of physical violence (yes/no) and penetrative sexual assault (yes/no)
Co-occurrence of different types of child maltreatment
Frequency and chronicity of child maltreatment
Developmental stage during which maltreatment occurred
Presence and type of abuse-related physical harm
Presence of additional childhood physical harm, including non-inflicted injury and self-harm (yes/no)
Post-traumatic stress disorder (yes/no)
Post-traumatic stress symptoms
Presence of current abuse or adult abuse (yes/no)

Pain at baseline
Pain outcome measures used to determine pain intensity or incidence
Presence of a chronic pain condition

Table 2.2: *Characteristics of included studies.*

	Number of subjects with complete data	**Age at baseline (mean (SD) or range in years) plus baseline pain status**	**Child maltreatment measure plus prevalence data**	**Develop-mental timing of maltreatment**	**Recency of maltreatment exposure**	**Measurement, reporting, and analysis of proposed moderators**	**Measures of pain and pain interference, and whether chronic pain was captured**	**Pain measurement timepoint(s)[1]**
Beal 2020	383	Maltreated 15.2 (1.1) Comparison 15.3 (1.04) Caregiver reports of pain at baseline = 49% in the maltreatment and 59% in the comparison sample for past 2-year pain symptoms	Official reports + structured interview Comprehensive Trauma Interview for maltreatment experiences by type (Barnes et al., 2009). Of 273 cases, there were 31% allegations for physical abuse, 49% for sexual abuse, 15% for neglect, 5% for multiple types	Adolescence	Approximately 10 years	<u>Moderators measured</u> Abuse type (sexual abuse, physical abuse, neglect) PTSS (Comprehensive Trauma Interview (Barnes et al., 2009)) <u>Moderators reported</u>[2] Abuse type (abuse only, neglect only, both abuse and neglect) PTSS <u>Moderators analyzed</u>[3] None	Measure of pain = self-reported pain (yes/no) Measure of pain interference? No Brief Pain Inventory (Cleeland, 1989) Chronic pain captured? No	Baseline and 9-year follow-up
Biskin 2014	231	27.0 (6.3) Pain at baseline in BPD sample = unknown	Semi-Structured Interview Revised Childhood	Unknown (<18 years)	Unknown	<u>Moderators measured</u> Abuse type (sexual (yes/no), verbal and physical	Measure of pain = self-reported pain severity Measure of pain	16-year follow-up

	Number of subjects with complete data	Age at baseline (mean (SD) or range in years) plus baseline pain status	Child maltreatment measure plus prevalence data	Develop-mental timing of maltreatment	Recency of maltreatment exposure	Measurement, reporting, and analysis of proposed moderators	Measures of pain and pain interference, and whether chronic pain was captured	Pain measurement timepoint(s)[1]
			Experiences Questionnaire (CEQ-R) (Zanarini et al., 1997) No descriptive data provided regarding maltreatment exposures in BPD sample			combined, neglect) Chronic maltreatment PTSD The Structured Clinical Interview for DSM-III-R Axis I Disorders (SCID-I) (Spitzer et al., 1992) <u>Moderators reported</u> Abuse type (sexual (yes/no), verbal and physical combined, neglect) Chronic maltreatment PTSD <u>Moderators analyzed</u> None	interference? Yes The Brief Pain Inventory (Cleeland, 1989) Chronic pain captured? No	
Brown 2005	602	22	Official reports	Unspecific (<18 y.o.)	Unknown	<u>Moderators measured</u>	Measure of pain = self-reported	All data collected at

	Number of subjects with complete data	Age at baseline (mean (SD) or range in years) plus baseline pain status	Child maltreatment measure plus prevalence data	Develop-mental timing of maltreatment	Recency of maltreatment exposure	Measurement, reporting, and analysis of proposed moderators	Measures of pain and pain interference, and whether chronic pain was captured	Pain measurement timepoint(s)[1]
		Pain at baseline: 13.4% of sample reported frequent pain and 18.5% of sample reported chronic pain in past year that impaired functioning.	4.6% of sample had a documented history of physical abuse and/or neglect, including 14 cases of physical abuse, 16 cases of neglect (with no abuse), and 4 cases of sexual abuse.			Abuse type (sexual abuse, physical abuse, neglect) <u>Moderators reported</u> Abuse type (physical abuse, neglect) *Too few cases of sexual abuse to examine separately <u>Moderators analyzed</u> None	"frequent pain" Measure of pain interference? Yes Measured using a single question for each. Chronic pain captured? Yes, but for pain impairment only	single timepoint
Kopec 2005	9552	Age 18-24 11.8% Age 25-44 41% Age 45-64 26.8% Age 65+ 20.4% Pain at baseline: Participants were free of	Self-report questionnaire Single question developed by researchers at Statistics Canada based on unpublished analyses. 6.5% of sample reported any	Unspecified (<18 y.o.)	Unknown	<u>Moderators measured</u> Abuse type (physical) <u>Moderators reported</u> Abuse type (physical) <u>Moderators analyzed</u> None	Measure of pain = self-reported onset of back pain Measure of pain interference? No Interviewer-administered questionnaire (single	Baseline and 4-year follow-up

	Number of subjects with complete data	Age at baseline (mean (SD) or range in years) plus baseline pain status	Child maltreatment measure plus prevalence data	Develop-mental timing of maltreatment	Recency of maltreatment exposure	Measurement, reporting, and analysis of proposed moderators	Measures of pain and pain interference, and whether chronic pain was captured	Pain measurement timepoint(s)[1]
		back pain at baseline.	exposure to physical abuse				question). Chronic pain captured? Yes	
Lamers - Winkelman 2012	275	8.62 (1.7) Pain at baseline: 7.7% aches and pains, 9.9% headache, and 13.5% stomachache among children exposed to intimate partner violence	Maltreatment data collected from multiple informants Parent reports (Parent Report of Traumatic Impact (Friedrich, 1997) plus interviews) Official agency reports Prevalence of additional maltreatment among children exposed to intimate partner violence: 53% for physical abuse, 11% for sexual abuse, 36% for emotional	Middle childhood	Unknown	<u>Moderators measured</u> Abuse type (physical abuse, contact sexual abuse, emotional abuse (recurrent humiliation), neglect) <u>Moderators reported</u> Abuse type (physical abuse, contact sexual abuse, emotional abuse (recurrent humiliation), neglect) <u>Moderators analyzed</u> None	Measure of pain = parent reports of aches and pains, stomachache, headache Measure of pain interference? No Somatic Complaints Scale within the Child Behaviour Checklist (Achenbach & Rescorla, 2001) Chronic pain captured? Yes	All data collected at single timepoint

	Number of subjects with complete data	Age at baseline (mean (SD) or range in years) plus baseline pain status	Child maltreatment measure plus prevalence data	Develop-mental timing of maltreatment	Recency of maltreatment exposure	Measurement, reporting, and analysis of proposed moderators	Measures of pain and pain interference, and whether chronic pain was captured	Pain measurement timepoint(s)[1]
			abuse, and 36% for neglect					
Linton 2002	417	35 – 45 Pain at baseline: <u>No pain group</u> (46%): participants reported that they had not suffered any spinal pain in past year <u>Pain group</u> (54%) – any pain in the past year	Self-report questionnaire 5 questions from previous studies (Bradley & McKendree-Smith, 2001; Leserman et al., 1998) Prevalence data includes adult exposures – 23% reported some form of sexual abuse and 22% reported physical abuse	Unspecified (<14 y.o.)	>20 years	<u>Moderators measured</u> Abuse type (sexual) Frequent sexual abuse <u>Moderators reported</u> Abuse type (sexual) <u>Moderators analyzed</u> None	Measure of pain = self-reported spinal pain. Measure of pain interference? Yes Pain was measured using questions to assess back and neck pain, and if present, pain intensity. Physical function was measured using self-administered physical function tests (Hellsing et al., 1997). Chronic pain captured? Unclear for pain and no	Baseline and one-year follow-up

	Number of subjects with complete data	Age at baseline (mean (SD) or range in years) plus baseline pain status	Child maltreatment measure plus prevalence data	Develop-mental timing of maltreatment	Recency of maltreatment exposure	Measurement, reporting, and analysis of proposed moderators	Measures of pain and pain interference, and whether chronic pain was captured	Pain measurement timepoint(s)[1]
							for physical function.	
Raphael 2011 (and Raphael 2001)	807	29.1 years Pain at baseline: pain symptom counts for any maltreatment group was 2.51 (0.08) and for control group was 2.32 (0.09)	Official reports Of 458 with documented maltreatment, 13% cases of sexual abuse, 17% cases of physical, and 81% cases of neglect	Early childhood and middle childhood	Approximately 30 years	<u>Moderators measured</u> Abuse type (physical abuse, sexual abuse, and neglect) PTSD (National Institutes of Mental Health Diagnostic Interview Schedule Version III-R (Robins et al., 1989b)) <u>Moderators reported</u> Abuse type (physical abuse, sexual abuse, and neglect) PTSD <u>Moderators analyzed</u> PTSD	Measure of pain = self-reported pain symptoms Measure of pain interference? Yes All pain indices derived from the somatization module of the Diagnostic Interview Schedule III-R (Robins et al., 1989a) Chronic pain captured? No	Baseline and 10-year follow-up
Rimsza 1988	144	10 (with range of 2-17)	Clinical interview, with verification by	Early childhood, middle	Unknown (although it appears that	<u>Moderators measured</u>	Measure of pain = headaches,	2-year follow-up (with range

	Number of subjects with complete data	Age at baseline (mean (SD) or range in years) plus baseline pain status	Child maltreatment measure plus prevalence data	Develop-mental timing of maltreatment	Recency of maltreatment exposure	Measurement, reporting, and analysis of proposed moderators	Measures of pain and pain interference, and whether chronic pain was captured	Pain measurement timepoint(s)[1]
		Pain at baseline = unknown	physical examination for patients aged 2-4. Of 72 sexual abuse patients, 61% reported vaginal intercourse, 28% reported genital fondling, including nonpenile vaginal penetration, 12.5% reported sodomy, 19.4% reported oral-genital contact (categories are not mutually exclusive).	childhood, and adolescence	exposures were quite recent)	Abuse type (intercourse, no intercourse) Stable/prolonged abuse <u>Moderators reported</u> Abuse type (intercourse, no intercourse) Stable/prolonged abuse <u>Moderators analyzed</u> None	chest pain, back pain, abdominal pain, vaginal pain Measure of pain interference? No Measured via chart review, sometimes with the addition of phone interview with primary caregiver. Chronic pain captured? Unclear for all outcomes	from 9 to 48 months)
Sachs-Ericsson 2017	5001	33.03 (10.5) Pain at baseline -Pain experienced as a result of health problems	Semi-structured interview Items from the PTSD module of the Composite	Unspecified (<18 y.o. for verbal and physical abuse and neglect and <15 y.o. for sexual abuse)	30 - 40 years	<u>Moderators measured</u> Abuse type (sexual, physical, emotional/verbal) Frequent abuse PTSD (Composite	Measure of pain = self-reported number of painful medical disorders (arthritis or	Baseline pain severity Painful medical disorders from 10-year follow-up

	Number of subjects with complete data	Age at baseline (mean (SD) or range in years) plus baseline pain status	Child maltreatment measure plus prevalence data	Develop-mental timing of maltreatment	Recency of maltreatment exposure	Measurement, reporting, and analysis of proposed moderators	Measures of pain and pain interference, and whether chronic pain was captured	Pain measurement timepoint(s)[1]
		(scale ranging from 0 to 3) – mean baseline scores was 0.3 (SD=.77)	International Diagnostic Interview (World Health Organization, 1990) and the childhood history section of the National Comorbidity Survey (NCS-1) 4.1% of participants reported physical abuse that occurred "sometimes" or "often," 28.6% reported verbal abuse that occurred sometimes or often, and 2.9% reported sexual abuse that occurred more than once.			International Diagnostic Interview (World Health Organization, 1990)) <u>Moderators reported</u> Abuse type (sexual, physical, emotional/verbal) Frequent abuse PTSD <u>Moderators analysed</u> None	rheumatism, chronic back or neck problems, frequent or severe headache, or other chronic pain) Measure of pain interference? No Questions from the National Comorbidity Survey (Kessler, 1994) Chronic pain captured? Unclear	

Notes

[1]Given that some studies relied on retrospective reports of maltreatment, the timespan between the maltreatment exposure and pain measurement often exceeds that of study follow-up period.
[2]Indicates whether descriptive information and/or the association between the moderator and pain outcome(s) was reported.
[3]Indicates whether a moderation analysis was conducted and reported.

Table 2.3: *Grading of Recommendations, Assessment, Development and Evaluation (GRADE).*

Research question	Exposure variable	Number of studies (participants)	Unadjusted			Adjusted			Number of studies (participants) in meta-analysis	Odds ratio (95% CI) for adjusted analysis	GRADE Factors							Overall quality
			+	0	-	+	0	-			Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Moderate/large effect size	Dose effect	
What is the relationship between any child maltreatment and pain at follow-up?	**Any child maltreatment (sexual abuse, physical abuse, and/or neglect)**	3 (1,421)	2	0	0	1	2	0	0	NA	✓	✓	X	✓	X	X	X	+ +
What is the evidence regarding the proposed moderating variables?	**PTSD or PTSS**	1 (807)	0	0	0	1	0	0	0	NA	✓	NA	X	✓	X	✓	X	+ +
	Specific type of maltreatment																	
	Sexual	5 (6,203)	1	1	0	1	2	0	0	NA	X	X	X	X	X	X	X	+
	Physical	4 (15,150)	0	0	0	0	4	0	3 (14,723)	1.04 (0.99-1.10)	✓	✓	X	✓	X	X	X	+ +
	Emotional/verbal	1 (5,001)	0	0	0	1	0	0	0	NA	✓	NA	X	✓	X	X	X	+
	Neglect	3 (1,538)	1	0	0	0	3	0	0	NA	✓	✓	X	✓	X	X	X	++
	Exposure to violence	N/A																No evidence

Research question	Exposure variable	Number of studies (participants)	Unadjusted			Adjusted			Number of studies (participants) in meta-analysis	Odds ratio (95% CI) for adjusted analysis	GRADE Factors							Overall quality
			+	0	-	+	0	-			Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Moderate/large effect size	Dose effect	
	Presence of physical harm/injury	N/A																No evidence
	Frequent maltreatment	N/A																No evidence
	Chronic maltreatment	N/A																No evidence
	Developmental stage of maltreatment	N/A																No evidence

Note. For unadjusted and adjusted analyses: +, number of significant effects in expected direction; 0, number of non-significant effects; -, number of significant effects in unexpected direction. For GRADE factors, ✓, no serious limitations; X, serious limitations (or not present for moderate/large effect size, dose effect). For overall quality of evidence: +, very low; ++, low; +++, moderate; ++++, high.

Figure 2.1: *Study flow diagram.*

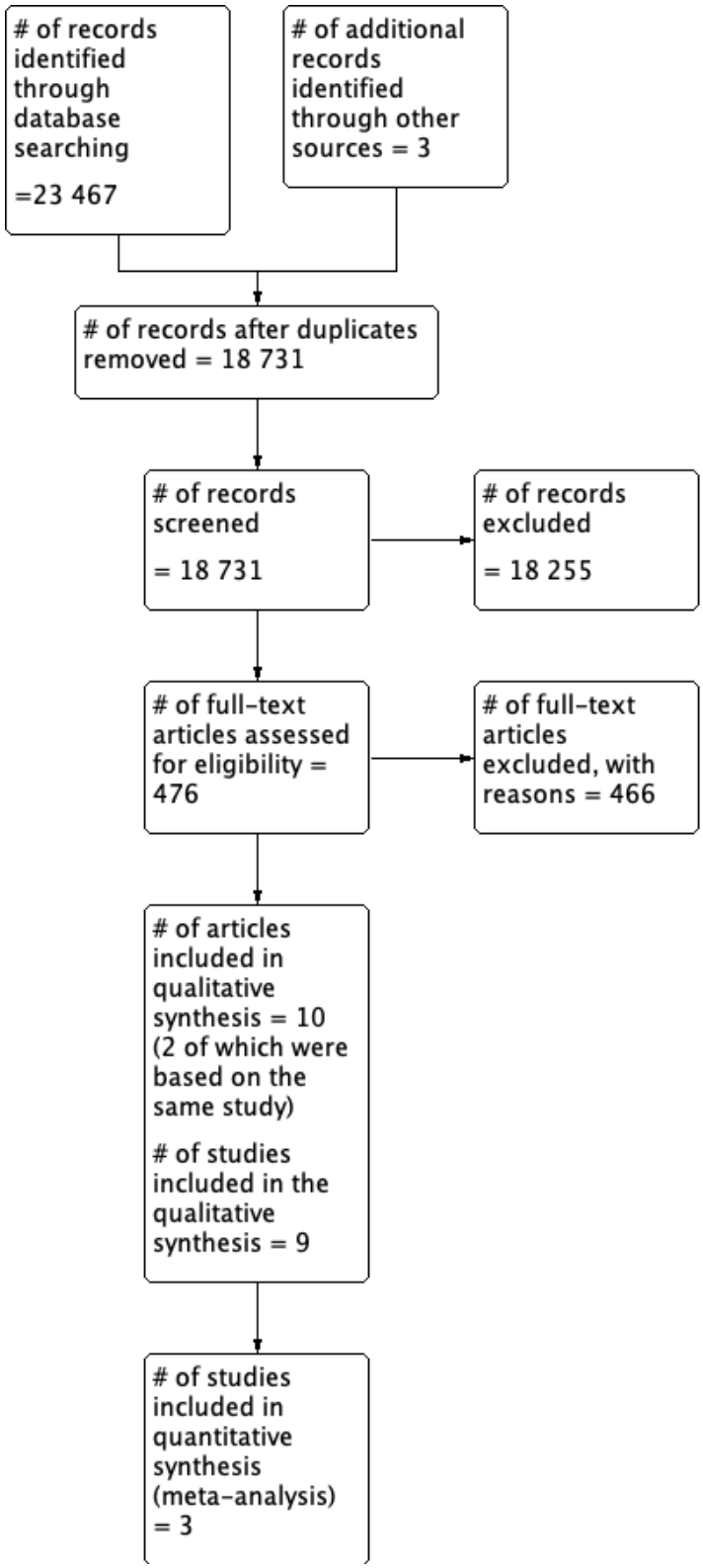


Figure 2.2: *QUIPS risk of bias summary: Review authors' judgments about each risk of bias domain (low, moderate or high) for each study and the overall rating for each study (low or high).*

Study	Study participation	Study attrition	Measurement of exposure	Measurement of outcome	Study confounding	Statistical analysis and reporting	Overall rating
Beal 2020	🟢	🟢	🟢	🟢	⚪	🟢	Low
Biskin 2014	⚪	⚪	⚪	🟢	⚪	🔴	High
Brown 2005	🟢	🟢	🟢	⚪	⚪	🟢	Low
Kopec 2005	🟢	🟢	⚪	⚪	⚪	🟢	Low
Lamers-Winkelman 2012[1]	⚪	N/A	⚪	🟢	🔴	🔴	High
Linton 2002[2]	🟢	🟢	⚪	⚪ 🟢	⚪	🟢	Low
Raphael 2011	🟢	⚪	🟢	🟢	⚪	⚪	Low
Rimsza 1988	⚪	🔴	🟢	🔴	⚪	🔴	High
Sachs-Ericsson 2017	🟢	🟢	⚪	⚪	⚪	🟢	Low

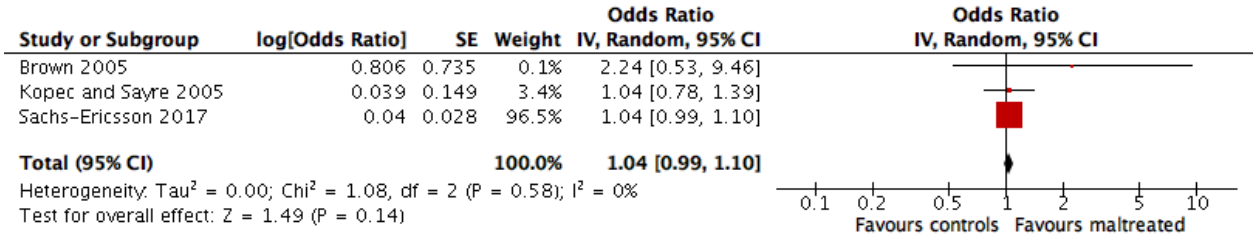
🟢 Low RoB

⚪ Moderate RoB

🔴 High RoB

Notes.
[1]The Lamers-Winkelman et al. (2012) study was <u>not</u> rated along the Study Attrition dimension because this was a cross-sectional study. Although the Brown et al. (2005) findings were also based on cross-sectional data, these data were from a larger cohort study, therefore study attrition remained a potential source of bias.
[2]Two risk of bias ratings are reported for the Measurement of Outcome domain because there were two reported outcomes with differing ratings (i.e., moderate for the measure of pain and low for the measure of pain interference). In cases of multiple outcomes reported in other studies, the risk of bias ratings were constant across outcomes.

Figure 2.3. *Forest plot depicting the results of a random-effects meta-analysis of longitudinal studies investigating the association between childhood physical maltreatment and pain at follow-up, adjusted for potential confounders.*



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Chapter 3: From Child Maltreatment to Bullying Victimization

There has been a longstanding interest in the relationship between child maltreatment and pain outcomes, especially in regard to pain experienced in adulthood (Davis et al., 2005). In contrast, there has been relatively little focus on the association between bullying victimization and chronic pain. For example, peer victimization was not captured as an Adverse Childhood Experience (ACE) as part of the original ACEs study (Dube et al., 2009), therefore it has been left out of studies analyzing the relationship between ACEs and later mental and physical health outcomes. However, it is known that peer victimization is a common experience in childhood (Lereya et al., 2015; Radford et al., 2013), and the evidence points to long-term consequences for health. For example, there is compelling data showing that the impact of peer victimization is *worse* than that of child maltreatment, at least in terms of mental health outcomes, such as depression, anxiety, and self-harm behaviours (Lereya et al., 2015). In the next chapter, this dissertation shifts focus away from the topic of victimization by caregivers and other adults to the topic of victimization by peers. As in Chapter 2, systematic review methods are used to examine the prospective relationship between early life adversity, in this case bullying victimization, and chronic pain.

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Chapter 4: A Systematic Review of the Prospective Relationship Between Bullying Victimization and Chronic Pain

Bullying victimization is a common adversity in childhood and adolescence. In a survey of children in nearly 40 countries conducted by the World Health Organization, approximately 13% of 11-year-olds reported being the victims of bullying (Currie et al., 2009). Not only does the experience of being bullied have negative consequences for mental health and psychosocial functioning, both in childhood (Bogart et al., 2014; Zwierzynska et al., 2013) and adulthood (Lereya et al., 2015; McDougall & Vaillancourt, 2015; Takizawa et al., 2014), but there is mounting evidence of its negative physical health consequences (Wolke et al., 2013; Wolke & Lereya, 2015), including increased risk of physical pain in school-aged children (Gini & Pozzoli, 2013; Gini et al., 2014). This is important because pain problems in young people can be intense and disabling, with the potential to track across childhood and adolescence and into adulthood (Brattberg, 2004; Stanford et al., 2008; Walker et al., 2012).

Despite the growing literature pointing to a relationship between bullying victimization and chronic pain, there is still much we don't know about the nature of this association. In particular, the majority of studies that have examined this relationship have relied on cross-sectional data (Gini & Pozzoli, 2013). Thus a positive association may indicate a causal relationship whereby bullying leads to chronic pain later in childhood or in adulthood, but it is also plausible that youth who experience pain are more likely to get bullied or that a third variable is driving the effect in which case the relationship between being bullied and chronic pain is indirect. Indeed, research evidence indicates that children who suffer from chronic health conditions are more vulnerable to being bullied (Nordhagen et al., 2005; Van Cleave & Davis, 2006), and the same may be true for youth with chronic pain (Forgeron et al., 2010). In regard to

potential confounding variables, we need to rule out such factors as reporting biases and other individual differences, which could drive both reports of bullying exposure and pain experiences, thereby creating a spurious association between the two.

In addition, recent evidence shows that the association between bullying victimization and pain may depend on key moderating factors, such as (1) the particular type of bullying, (2) its frequency and stability, and (3) whether it occurs within a critical developmental window. The following sections present evidence for these moderators.

Type of Bullying Victimization

There are two broad categories of bullying victimization; namely, direct and indirect. Direct victimization describes attacks on another child that are openly confrontational, including physical victimization (e.g., shoving, punching, beating up), verbal victimization (e.g., disparaging comments, taunting and/or mocking, name-calling), and attacks on property (e.g., stealing or damaging something). Indirect victimization (also referred to as relational victimization and social manipulation) describes attacks that are covertly manipulative, such as social exclusion, malicious gossip, and creating problems with other friends (Mynard & Joseph, 2000; Rosen et al., 2013). There is also a growing body of research on cyber-based bullying, and although it overlaps with relational victimization, it is treated as a distinct category of indirect victimization (Smith et al., 2008). It should also be noted that victims of bullying are often exposed to more than one type of victimization; for example, when physical victimization is present, verbal victimization is likely to be present as well (Atlas & Pepler, 1998; Craig & Pepler, 1998).

Most research to date has failed to examine whether the type (or types) of bullying victimization predicts psychosocial and health outcomes (McDougall & Vaillancourt, 2015). In

the case of chronic pain, it is especially important to distinguish between victimization that does and does not have a physical component. Physical victimization has the potential to cause bodily injury (Dukes et al., 2010); thus, it may contribute directly to the development of chronic pain. Despite research evidence showing a link between traumatic injury and chronic pain (Jenewein et al., 2009), the relationship between bullying victimization and related physical injury has not been examined, though one would expect such an association to be evident.

Also of interest is research evidence indicating that non-physical forms of bullying, such as relational victimization, are associated with increased somatic complaints, including headaches, stomachaches, fatigue and trouble sleeping (Baldry, 2004; Nixon et al., 2011). Such findings point to the relevance of psychological/stress-related pathways from victimization to chronic pain. For example, Eisenberger and colleagues (Eisenberger et al., 2003; Eisenberger, 2012) have hypothesized that "socially painful" situations (i.e., situations characterized by social rejection, exclusion, or loss) involve some of the same neurobiological substrates that underlie experiences of physical pain. According to this hypothesis, factors that increase or decrease social pain should have a similar effect on physical pain, and vice versa. The implication of this hypothesis is that social pain elicited by bullying victimization has the potential to impact physical pain independent of bodily injury. Clearly, models of bullying and pain need to specify the particular type or types of victimization and whether physical harm was involved to delineate the pathways from victimization to both the onset and persistence of pain in young people.

Frequency and Stability of Bullying Victimization

Consistent with models of chronic stress and health (McEwen, 1998), bullying victimization that is more frequent and/or stable over time may have a cumulative impact on pain outcomes (McDougall & Vaillancourt, 2015; Zarate-Garza et al., 2017). There is initial evidence

that the frequency of victimization has consequences for mental health outcomes. One study showed evidence of a dose-response effect on psychiatric outcomes, such that “frequent” childhood bullying victimization (i.e., parents indicated that their child was bullied “frequently” at age 7 or 11 or “sometimes” at both ages) was associated with an increased risk for depression, anxiety disorders, and suicidality at age 45 years, whereas “occasional" victimization (i.e., parents indicated that their child was bullied “sometimes” at age 7 or 11) was associated with depression only (Takizawa et al., 2014). Another study incorporated latent class analysis to better understand the construct of bullying victimization. Study results indicated that the frequency of victimization, as opposed to the specific type of victimization, best differentiated those youth who felt safe versus unsafe at school and predicted depression one semester later (Nylund et al., 2007).

Another way to conceptualize the intensity or “dose” of bullying victimization is to consider its stability over time. For example, Wolke and colleagues (2014) measured victimization status at ages eight and 11 years. They found that children who were classified as victims of bullying at both time-points were more likely to have psychotic experiences at 18 years compared to children who were classified as victims at only one time-point. Similarly, Bowes et al. (2013) found evidence for increased risk of mental health problems among “chronic victims” (i.e., children who were classified as bully victims in primary school *and* secondary school) as compared to never-bullied children and children bullied at only one time-point. Finally, Copeland et al. (2014) examined the longitudinal relationship between bullying victimization and the inflammatory marker, C-reactive protein (CRP), with up to nine waves of data per child. They found that recent victimization was unrelated to CRP changes, whereas the

number of study waves at which a child was classified as a victim of bullying was predictive of increasing levels of CRP, providing additional evidence for a cumulative impact of victimization.

Developmental Stage of Bullying Victimization

In contrast to chronic stress models which assume a cumulative impact of exposures (McEwen, 1998; Zarate-Garza et al., 2017), other models point to the importance of timing, with early life models receiving the most attention (Burke et al., 2017). For example, evidence shows that exposure to early adversity, such as maternal death or an automobile accident before the age of seven years, is a risk factor for chronic pain in adulthood (Jones et al., 2009). Although less is known about the impact of early life bullying exposures, there is some initial evidence that victimization in the early school years is associated with negative effects in children long after the exposure. For example, one study reported that victimization in kindergarten can "trigger" feelings of loneliness that remain stable even in the absence of further victimization (Kochenderfer-Ladd & Wardrop, 2001; McDougall & Vaillancourt, 2015). In addition to early life models, there may be other windows of vulnerability that are relevant to the victimization-pain relationship. For example, the adolescent years may represent a critical window during which youth experience heightened social vulnerability because of the importance of peer connections at this stage, as well as increased biological responses to stress related to pubertal maturation (Bingham et al., 2011; Sumter et al., 2010). Indeed, victimization may interact with developmental factors such as puberty to influence pain trajectories (Patton & Viner, 2007). Taken together, in order to delineate the relationship between victimization and pain, it is important to distinguish discrete episodes of bullying victimization from frequent or prolonged victimization and to account for the developmental context in which these exposures occur.

The Current Study

We conducted a systematic review of prospective studies on bullying and chronic pain in young people, with a focus on factors that are likely to shape this relationship. We sought to answer the following four research questions:

1. Is there evidence of a temporal relationship between bullying victimization and chronic pain in young people, and if so, what is the direction of the effect?
2. Is the type of victimization differentially associated with chronic pain outcomes? We were interested in four specific types of bullying; namely, physical victimization (with or without associated physical injury), verbal victimization, relational victimization, and attacks on property (Mynard & Joseph, 2000).
3. Does the intensity of bullying victimization have consequences for chronic pain? To answer this question, we examined the impact of victimization frequency (i.e., is it occurring at least weekly?) and stability (i.e., has it been persisting for at least six months?).
4. Does the stage of childhood during which bullying occurs (early childhood, childhood, or adolescence) have consequences for chronic pain?

Method

Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=133146 (Marin & Katz, 2019).

Inclusion Criteria

We included prospective cohort studies that showed the relationship between childhood bullying victimization and chronic pain. We included studies when a clearly defined measure of victimization was obtained in childhood and/or adolescence (i.e., 18 years or younger) and when

pain-related outcomes were measured at least three months after (whether that was in childhood, adolescence or adulthood). We also included studies in which the measurement of pain preceded the measurement of bullying victimization, again with a minimum three-month follow-up. We included studies when the full report was peer-reviewed.

Exclusion Criteria

We excluded (1) studies that induced pain in the laboratory, (2) intervention studies, and (3) case studies, review articles, dissertations, letters, editorials, book chapters, qualitative studies and conference abstracts, and (4) non-English articles.

Defining Bullying Victimization

Bullying victimization occurs when someone is the object of repeated aggression that is intentional and involves a disparity of power between the victim and perpetrators (Smith et al., 1999). For this review, we included bullying by peers and siblings, as well as cyberbullying. We included studies that measured bullying victimization using self-report questionnaires and interviews, other reports (e.g., parents or teachers reporting bullying), and behavioural ratings (e.g., being hit repeatedly).

Coding specific features of the bullying exposure. Where available, we coded for the following characteristics of bullying victimization:

Type of bullying victimization. We categorized bullying victimization based on the dimensions identified by Mynard and Joseph (2000); namely, (1) physical victimization (with an additional code for the presence/absence of bodily harm and documentation of the specific type of injury, e.g., fracture, laceration, bruising), (2) verbal victimization, (3) relational victimization, and (4) attacks on property. When different types of bullying were combined in a single measure, we coded it as (5) unclear. We also coded for the mode of bullying using the categories

(1) peer-, (2) sibling-, and (3) cyber-bullying, although it should be noted that cyber-bullying can occur with known peers. Moreover, peer bullying can be further differentiated based on sexual, religious, and racial victimization, thus we extracted this information where available. Given the co-occurrence of different types of bullying, we coded study measures for the presence of two or more types of bullying where available.

Frequency of bullying victimization. We coded for whether or not the bullying victimization occurred frequently. Frequent victimization was defined as victimization that occurred at least weekly or was rated as occurring "often" or "frequently." Given that bullying victimization is, by definition, repeated in nature (e.g., in the HBSC survey the victimization had to occur "more than two to three times a month" to qualify as bullying victimization (Freeman et al., 2016), this definition allowed us to identify cases of bullying victimization that exceeded this threshold in terms of frequency.

Stability of bullying victimization. We coded for the stability of bullying victimization over time. Stable/prolonged bullying victimization was defined as victimization that persisted for at least six months or was reported to be present at two measurement points spaced at least six months apart. This definition is consistent with definitions of chronic stress, where the stressor needs to be present for at least six months (Hammen & Rudolph, 1999).

Developmental stage of bullying victimization. We coded the stage of childhood during which participants had been exposed to bullying victimization. Consistent with previous research examining the impact of developmental timing of trauma exposure on health, we defined early childhood as age up to 5 years, middle childhood as age 6 to 10 years, and adolescence as 11 to 18 years (Dunn et al., 2013; Dunn et al., 2017; Kaplow & Widom, 2007).

Defining Pain Outcomes

Our primary outcome was chronic pain, defined as pain lasting longer than 3 months (Treede et al., 2019). In addition to including studies that captured pain intensity or frequency, we included studies that reported the outcome as presence of a chronic pain condition (e.g., migraine, chronic musculoskeletal, or abdominal pain). We included studies that measured pain in childhood, adolescence or adulthood via self-report (e.g., visual analogue scale, numeric rating scale, McGill Pain Questionnaire (Melzack, 1975)), parental report, or clinician examination or interview.

Many studies that report pain outcomes fail to specify the duration, thus it is unclear whether the study is actually measuring chronic pain. We therefore made an a priori decision to include studies regardless of duration, and if possible, account for any such measurement issues in our analysis.

In regard to secondary outcomes, we included studies that reported pain-related outcomes, such as pain-related disability or interference. Where possible, we also coded for information regarding pain medication use.

Search and Screening Strategy

Electronic searches of Medline (OVID), EMBASE (OVID), PsycINFO (OVID, Proquest[1]), and CINAHL (EBSCO) were conducted by an experienced librarian (QM) and last updated June 30, 2019. The search strategy was adapted from a previous systematic review examining risk factors for chronic pain (Higgins et al., 2015). Search terms cover three broad categories: (1) Bullying victimization, (2) Chronic pain, and (3) Study design: captured by terms such as "risk" and "association" (see search terms for Medline presented in Appendix 2). The searches were customized for each database, using a combination of index and free text terms.

[1] PsycInfo was originally run in OVID but due to an institutional change was only available through Proquest when the search was last updated.

The searches were limited to human studies. To identify studies for inclusion, we screened the citations from these searches for relevance through title/abstract and full-text review. Recognizing potential limitations of electronic search strategies (Hayden et al., 2014), we also searched references of previously published reviews of bullying victimization and pain (Forgeron et al., 2010; Gini & Pozzoli, 2013; Gini et al., 2014) and conducted a review of references for all included studies and citation searches of key articles in the field (Copeland et al., 2014; McDougall & Vaillancourt, 2015; Reijntjes et al., 2010).

Data Extraction

Two independent reviewers (TM and RL) extracted data and reached consensus using pre-defined electronic extraction forms. A consensus method was used and a third reviewer (JK) consulted in the case of disagreements. See Table 4.1 for a list of variables extracted.

Assessing Risk of Bias

We assessed each study's risk of bias using an approach based on the Quality in Prognosis Studies (QUIPS) tool (Hayden et al., 2013) for studies examining prognostic or risk factors. This involved consideration of six important domains: study participation, study attrition, measurement of the risk factor of interest, outcome measurement, confounding, and analysis/reporting. For each of the six domains, responses to the prompting items were taken together to inform the risk of bias judgment (low, moderate, or high). To judge risk of bias for the confounding domain, we considered whether statistical analyses were unadjusted, minimally adjusted (i.e., controlled for participant age and sex) or adequately adjusted (i.e., controlled for age, sex, baseline pain, a measure of social status, such as family income or parental education, and a measure of negative affect, such as neuroticism or symptoms of anxiety or depression). Unadjusted studies were rated as having high risk of bias, minimally adjusted studies were rated

as having moderate risk of bias, and adequately adjusted studies were rated as having low risk of bias. Finally, we judged overall study validity by defining studies with a low risk of bias as those in which at least half of bias domains were rated to be low risk and there were no domains rated as high risk of bias. This assessment was conducted in duplicate by the first and last author, and any disagreements were resolved through discussion.

Measures of Association Extracted

Using methods described by Hayden and colleagues (2019), we extracted unadjusted and adjusted measures of the association between bullying victimization and pain and used odds ratios (ORs) in the natural log scale as the common measure of the relationship. We converted effect sizes to the natural log scale and calculated standard errors (SEs) by log-transforming confidence intervals and then converting using an appropriate formula. We converted standardized regression coefficients for continuous outcomes to natural log ORs (Borenstein et al., 2009; Peterson & Brown, 2005).

Data Synthesis

We conducted a meta-analysis when three or more sufficiently homogenous studies assessed the relationship between bullying victimization or a proposed moderator variable and chronic pain. Data were analyzed using Review Manager software (RevMan version 5.3, the Cochrane Collaboration) with a random-effects generic inverse variance meta-analysis model, which allows for between-study heterogeneity in the exposure effect. The meta-analysis was summarized by the pooled estimate (the average exposure effect) and its 95% CI. We conducted these analyses separately using both unadjusted statistics and values adjusted for potential confounders.

To further test the proposed moderation models, we planned to use subgroup analyses to explore between-study differences in the specific nature of bullying victimization, including the type of victimization, presence of bodily injury and the frequency, stability and timing of exposure. We also planned to use subgroup analysis to explore the impact of differences in the timing of outcome measurement, specifically whether the assessment was conducted in early childhood (age 0-5 years), middle childhood (age 6 to 10 years), or adolescence (11 to 18 years).

We planned to use sensitivity analysis to explore the impact of other study factors on the relationship between victimization and chronic pain. In particular, we planned to examine the impact of the measurement of chronic pain, RoB, and adjustment for confounders by limiting our analyses to studies that (1) clearly captured chronic pain, (2) were assessed as having low RoB, and (3) adequately adjusted for confounders.

Interpretation of Results

The strength of observed associations was defined, for binary factors, based on effect size as small (OR < 1.5), moderate (1.5 ≥ OR ≤ 2), or large (OR > 2) (Hartvigsen et al., 2004; Hayden et al., 2019). We considered moderate or large effect sizes (OR ≥ 1.5) to be clinically important. Statistical heterogeneity between studies was assessed using the I^2 test; heterogeneity was considered important if I^2 was greater than 50%. In cases where it was not appropriate to combine results using meta-analysis due to the small number (fewer than 3) of sufficiently homogeneous studies with available data, the results were presented qualitatively as follows:

(1) Strong evidence of effect: Consistent findings (defined as greater than 75% of studies showing the same direction of effect) in multiple low risk of bias studies

(2) Moderate evidence of effect: Consistent findings in multiple high risk of bias and/or one study with low risk of bias

(3) Limited evidence of effect: One study

(4) Conflicting evidence: Inconsistent findings across studies

(5) No evidence: No association between bullying victimization and the outcome of interest.

We used an approach modified from the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework (Guyatt et al., 2011; Hayden et al., 2014) to assess overall quality of evidence on the relationship between bullying victimization and chronic pain. We rated the overall strength of evidence as high, moderate, low or very low considering internal validity, size and precision of effect, heterogeneity, generalizability, and potential reporting bias.

Results

Description of Studies

Results of the search. Our extensive literature search identified 2,535 citations for appraisal against our inclusion and exclusion criteria. We retrieved 59 full-text articles for further assessment and study selection. We initially identified five longitudinal studies examining associations between bullying victimization and pain. Two of these studies reported findings based on cross-sectional aspects of the study data (Biebl et al., 2011; Lien & Welander-Vatn, 2013), thus we requested additional data from the study authors to satisfy our inclusion criteria. Biebl and colleagues (2011) provided a subset of their data,[2] whereas Lien and colleagues (2013) no longer had access. Ultimately, four studies were included. The search was last updated on June 30, 2019. See Figure 4.1 for the study flow diagram and Table 4.2 for the characteristics of included studies.

[2] At our request, the authors provided bullying victimization data from the second timepoint and pain data from the third timepoint.

Included studies. We included a total of four prospective cohort studies in the review. Two studies were conducted in Europe, one was conducted in Australia, and one was conducted in the United States of America. Sample sizes ranged from 70 to 3,821. The studies included mixed samples of male and female participants (% female ranged from approximately 49 to 56.7). The mean age of participants at baseline ranged between 10 and 14 years. Follow-up periods ranged from 6 months to 12 years, with two studies following participants into adulthood (Biebl et al., 2011; Sigurdson et al., 2014).

Three included studies examined peer victimization as a risk factor for pain (Biebl et al., 2011; Incledon et al., 2016; Sigurdson et al., 2014), and one study examined bidirectional relations between victimization and pain (Fekkes et al., 2006).

Excluded studies. We excluded 55 articles after full-text screening. The most common reasons for exclusion were: (1) study design other than prospective cohort study, (2) no measure of bullying victimization, and (3) no measure of pain or pain was not included as an outcome in the bullying victimization analyses.

Measurement of bullying victimization. Each of the included studies measured bullying victimization using self-report questionnaires. One measure comprised a single question (e.g., "How often did other children bully you in recent months?" (Fekkes et al., 2006), while others tapped the frequency of different types of bullying victimization, such as verbal insults, taunting and/or mocking, physical assault, and being frozen out of friendship groups (Sigurdson et al., 2014; Biebl et al., 2011). In contrast, the Incledon et al. study (2016) tapped exposure to different types of bullying rather than frequency per se. One study also used behavioural observations of a 20-minute play session to capture early victim-type behaviours (e.g., experiencing repetitive hitting, punching or kicking) among five-year-olds (Biebl et al., 2011),

although these observational data were not available for meta-analysis. The prevalence of bullying victimization in the included studies ranged from 12.5 to 23.5%. This variability may be accounted for by heterogeneity in the populations studied and important differences in the bullying measures used.

Type of bullying victimization. Three studies used measures that captured different types of bullying victimization, including physical victimization, verbal victimization, and relational victimization (Biebl et al., 2011; Incledon et al., 2016; Sigurdson et al., 2014). The measure used by Biebl and colleagues (2011) also tapped stealing and other attacks on property. None of these studies reported descriptive statistics broken down by the type of victimization in the published manuscripts; however these data were available in the Biebl et al. (2011) dataset sent to us. They found that 17.6% of their sample reported more than one incident of physical victimization, 14.1% reported more than one incident of verbal victimization, 5.8% reported more than one incident of relational victimization, and none of the participants reported attacks on property. None of the studies that measured physical victimization provided information regarding the presence of associated physical harm or specific injuries incurred. None of the included studies measured specific types of verbal victimization (sexual, religious, and racial victimization) or cyberbullying.

Frequency of bullying episodes. Only the Sigurdson et al. study (2014) measured "frequent victimization," defined in our protocol as victimization that occurred at least weekly or was rated as occurring "often" or "frequently." Frequent victimization was reported by 12.5% of the sample. Two studies used measures of bullying victimization that also captured victimization at lower thresholds (e.g., a few times a month or more often) (Fekkes et al., 2006; Lien & Welander-Vatn, 2013), and one study did not measure frequency (Incledon et al., 2016).

Stability of bullying victimization. Two studies captured "stable victimization" (Biebl et al., 2011; Sigurdson et al., 2014), defined in our protocol as victimization that persisted for at least six months or was reported to be present at two measurement points spaced at least six months apart. The study by Sigurdson and colleagues (2014) captured stable bullying victimization over six months (i.e., their measure captured both "frequent" and "stable" victimization, with 12.5% falling into this category). In contrast, the Biebl et al. study (2011) measured victimization at multiple timepoints. Results indicated that 24.6% of participants had been exposed to victimization at each of the three study time-points (which started at age 5 years and ended between the ages of 12 and 20 years). However, the trajectory data from the published paper could not be used for the purpose of our synthesis given that the final victimization measure and the pain measure were taken cross-sectionally, and the raw data provided to the authors included time 2 victimization scores and time 3 pain scores only.

Developmental stage of bullying victimization. Studies measured the occurrence of victimization in early childhood (Biebl et al., 2011), middle childhood (Fekkes et al., 2006; Incledon et al., 2016) and adolescence (Biebl et al., 2011; Sigurdson et al., 2014). Only the Biebl study captured victimization at different stages of childhood. However, given the nature of the data we requested from Biebl et al. (2011) we did not have the data to examine whether the timing of the exposure was associated with chronic pain outcomes.

The measurement of pain. Two studies measured site-specific pain, such as headache (Biebl et al., 2011; Fekkes et al., 2006; Sigurdson et al., 2014) and abdominal pain (Fekkes et al., 2006), and two studies included a measure of bodily pain (i.e., unspecified location of pain) (Incledon et al., 2016; Sigurdson et al., 2014). They used self-report measures (Biebl et al., 2011; Fekkes et al., 2006; Sigurdson et al., 2014) or parental report (Incledon et al., 2016). Three

studies measured pain using validated questionnaires (Biebl et al., 2011; Fekkes et al., 2006; Sigurdson et al., 2014), including The Physical Health Questionnaire (Schat et al., 2005), the Short Indicative Questionnaire for Psychosocial Problems among Adolescents (KIVPA) (Reijneveld et al., 2003) and the problem scale of the Adult Self Report (Achenbach & Rescorla, 2003), while other pain questions were developed specifically for the study (Incledon et al., 2016; Sigurdson et al., 2014).

One study captured chronic pain (i.e., pain lasting three months or more) (Sigurdson et al., 2014), one study reported pain over the past four weeks (Fekkes et al., 2006), and in the two remaining studies, either the duration or frequency of pain was not reported or it was unclear. The prevalence of pain was reported in two studies. Incledon and colleagues (2016) reported 5.2% for pain symptoms, and Sigurdson et al. (2014) reported 26.2% and 31.3% for bodily pain and headache, respectively. Two studies included a measure of pain at baseline (Fekkes et al., 2006; Incledon et al., 2016).

The Risk of Bias in Included Studies

We judged two studies to have low risk of bias overall (Fekkes et al., 2006; Incledon et al., 2016). Although both studies suffered from moderate risk of bias in up to three categories, they were determined to have low risk of bias across all other categories and in no case was a rating of high risk of bias made. The results of the 'risk of bias' assessment are summarized in Figure 4.2.

Study participation. We classified three of the studies as having low risk of bias due to study participation (Fekkes et al., 2006; Incledon et al., 2016; Sigurdson et al., 2014). Two of these studies reported a high participation rate (>80%) and the other was based on a nationally representative sample. In each of these studies there was no indication that the recruitment

strategies used were likely to encourage or discourage certain types of people to participate in the study. We classified the study by Biebl and colleagues (2011) as having high risk of bias due to study participation. The concern here was that there was a 70% dropout rate between the first and second timepoints (and we treated the second timepoint as baseline). Due to this high level of attrition, there is a high risk that the sample at the second timepoint was not representative of the population from which the initial sample was initially drawn.

Study attrition. We classified the study by Biebl et al. (2011) as having low risk of bias due to study attrition. In this study the attrition rate between the second timepoint (when victimization was measured) and third timepoint (when pain was measured) was low (<20%), and there were no obvious differences between those who completed the study and those who dropped out. We classified the studies by Incledon et al. (2016), and Fekkes et al. (2006) as having moderate risk of bias due to attrition. In the case of Incledon et al. (2016), the attrition rate was relatively low (<20%), but the researchers failed to report comparisons between full participants and those who dropped out. In contrast, the Fekkes et al. study (2006) had higher attrition (>20%), but this was mitigated by the fact that comparisons made on demographic and outcome variables did not reveal significant differences between those who did and those who did not participate in follow up. Finally, the Sigurdson study (2014) was rated as having high risk of bias in this category due to very high attrition (49%) and evidence of differences in demographic characteristics between those who did versus did not complete the study follow-ups.

Measurement of the exposure. We classified three of the studies as having low risk of bias related to measurement of the exposure (bullying victimization) (Biebl et al., 2011; Fekkes et al., 2006; Sigurdson et al., 2014). These studies provided clear definitions of bullying

victimization, used reliable and valid measures (Alsaker, 2003; Mynard & Joseph, 2000; Olweus, 1994), and when dichotomized scores were used, reported the cut-off point. In contrast, the Incledon study (2016) was classified as having moderate risk of bias in this area due to the low face validity of the victimization measure, which captured exposure to multiple types of bullying (i.e., severe bullying was defined as exposure to three or more types of bullying) rather than the frequency of incidents. Exposure to different types of bullying may or may not be associated with the frequency or severity of incidents.

Outcome measurement. To determine risk of bias due to outcome measurement, we made ratings at the level of the outcome rather than the study. We classified outcomes from two of the studies as having low risk of bias. This was the case for the measurement of abdominal pain and headache in the Fekkes study (2006) and headache in the Sigurdson study (2014). For these outcomes, the study authors provided a clear definition of the pain outcome, specified the timeframe of interest (e.g., pain in the last four weeks), used a reliable and valid measure, and specified the cut-off used to create dichotomized scores. We rated the other pain outcomes as having moderate risk of bias due to measurement concerns in one or two areas.

Study confounding. We classified one study as having low risk of bias due to study confounding (Incledon et al., 2016). This study statistically controlled for all pre-specified potential confounders (i.e., age, sex, baseline pain, social status and a measure of negative affect) plus additional factors, such as pubertal stage, sleep difficulties, and family risk variables (e.g., angry parenting and the mother having chronic pain). We classified one study as having moderate risk of bias due to study confounding (Fekkes et al., 2006). This study statistically controlled for two of the pre-specified confounders (age and sex), and it controlled for baseline pain by limiting the analysis of the victimization-pain relationship to participants free of pain at

baseline. However, this study failed to control for social status and negative affect and was therefore considered to be minimally adjusted. The other two studies did not meet the criteria for adequate or minimal adjustment and were therefore classified as having high risk of bias due to study confounding (Biebl et al., 2011; Sigurdson et al., 2014).

Statistical analysis and reporting. We assessed all but one study in the review as having low risk of bias in this category. The one exception was the study by Fekkes et al. (2006), which was considered to have moderate risk of bias due to the use of multiple comparisons without adjusting the Type I error rate.

Findings

Zero to four studies provided sufficiently similar data regarding each of our research questions, and zero to four studies were available for each of our planned meta-analyses. Given the small number of studies, we were unable to conduct the planned subgroup and sensitivity analyses. Overall, the level of evidence was assessed to be very low quality. See Table 4.3 for a summary of the GRADE analysis for each of the main analyses.

Is baseline exposure to bullying victimization associated with pain at follow-up?

Very low quality evidence from four studies (total of 6,275 participants) examined the relationship between baseline bullying victimization and pain outcomes at follow-up (Biebl et al., 2011; Fekkes et al., 2006; Incledon et al., 2016; Sigurdson et al., 2014). Both unadjusted and adjusted results were available for each of these studies. When a study reported findings for more than one pain outcome (e.g., abdominal pain and headache), the effect size was combined before inclusion in the meta-analysis.

Meta-analysis of unadjusted statistics showed that victimized individuals were 1.58 times more likely than non-victims to report pain at follow-up (OR [95% CI] = 1.58 [1.23-2.02], n = 4)

(statistically significant and clinically important). See Figure 4.3. There was notable heterogeneity across the studies, with an I^2 of 57%. Meta-analysis revealed a similar finding for pooled adjusted results, but with a smaller effect size (OR [95% CI] = 1.45 [1.06-1.97], n = 4) (statistically significant but not clinically important). See Figure 4.4. Again, there was considerable heterogeneity across the studies (I^2=68%). We had planned to explore heterogeneity across studies with *a priori* defined subgroup analyses, but this was not possible given the small number of included studies in the review. See Table 4.3 for GRADE summary.

Is baseline pain associated with bullying victimization at follow-up? There was very low quality evidence from one study (947 participants) examining the relationship between baseline pain and bullying victimization at follow-up (Fekkes et al., 2006). Both unadjusted and adjusted analyses showed no difference in risk of bullying victimization at follow-up when comparing children with and without pain symptoms at baseline. This finding should be interpreted with caution given the limited evidence available. See Table 4.3 for GRADE summary.

Does the type of bullying victimization and the presence/absence of physical harm influence the victimization-pain relationship? There was very low quality evidence from one study (70 participants) with information about the associations between different types of victimization and pain (Biebl et al., 2011). In multiple regression models including both relational and physical victimization, adjusted and unadjusted analyses showed that relational victimization but not physical victimization was significantly associated with pain at follow-up (p=.002). This finding was in the expected direction, such that increased relational victimization at baseline was associated with more frequent headaches two years later even after statistically adjusting for sex and age. Although this analysis is not a direct test of moderation, it suggests

that victimization type may influence the victimization-pain relationship. However, this finding should be interpreted with caution given the limited evidence available. In regard to physical injury as a potential moderator, there was no evidence available with information about the association between physical injury and pain. See Table 4.3 for GRADE summary.

Do the frequency and/or stability of bullying victimization influence the victimization-pain relationship? There was not enough evidence available to conduct a meaningful synthesis of whether victimization frequency or stability was related to pain outcomes. Specifically, only one of the included studies provided usable information about the relationship between frequent/stable victimization and pain (Sigurdson et al., 2014). Therefore, there was not enough evidence to meaningfully compare pain outcomes between victimization that occurred at high versus low doses. See Table 4.3 for GRADE summary.

Does the developmental stage of bullying victimization influence the victimization-pain relationship? Although the included studies captured victimization at different stages of development (early childhood, middle childhood and adolescence), there were too few included studies to conduct a meaningful analysis of the relationship between developmental stage of the exposure and later pain. See Table 4.3 for GRADE summary.

Discussion

The goal of this review was to provide evidence on the relationship between bullying victimization and pain. We aimed to examine the nature of the victimization-pain relationship, including the temporal ordering of events (i.e., does victimization precede pain or does pain precede victimization?) and potential moderators of this relationship (i.e., does the type of victimization; presence or absence of bodily injury; frequency and stability of victimization; and developmental stage of victimization relate to pain outcomes?).

The review included four longitudinal studies, with data from 6,275 participants. Each of the included studies provided unadjusted and adjusted results for meta-analysis; however, these results were limited in scope and only provided evidence on the relationship between baseline bullying victimization and pain at follow-up. In contrast, only one included study examined the relationship between baseline pain and bullying victimization at follow-up, and for each of our questions about moderating factors, there was either no available evidence or evidence from only a single study.

Summary of the Main Results

We found very low quality evidence that bullying victimization was associated with increased risk of pain at follow up. However, after adjusting for potential covariates, the effect size was small and not clinically important. Moreover, there was substantial heterogeneity across the studies, thereby limiting our ability to interpret the results. Indeed, the variability in effect sizes may be explained by between-study variability in clinical and/or methodological factors, including our pre-specified moderators and the timing of outcome measurement (i.e., whether pain was assessed in early childhood, middle childhood, adolescence, or adulthood). However, we were unable to explore these factors due to the small number of included studies, and a dearth of information on the specific nature of bullying victimization. Additional high quality studies are needed to identify factors that accentuate versus dampen the magnitude of this association.

We found very low quality evidence from one study that youth who experience pain were at no greater risk of bullying victimization at follow up compared to their pain-free counterparts. Additional high quality studies are needed to delineate the temporal ordering of events.

Summary of Additional Findings

Regarding potential moderators of the victimization-pain relationship, we found very low quality evidence from one study that relational victimization, but not physical victimization, was associated with pain at follow up. Additional work is needed to replicate this finding and to examine whether the relationship holds true when bullying-related bodily injury is accounted for. If so, it would add to mounting evidence showing that emotional injury can be more painful than physical injury (Atlas & Pepler, 1998).

None of the included studies examined the association between the frequency, stability, or timing of victimization and pain outcomes, and there were too few studies to conduct comparisons across studies using subgroup analysis. Clearly, high quality studies that measure and report the nuances of bullying victimization and the presence or absence of bodily harm are needed to test the proposed moderator models. None of the included studies measured secondary outcomes.

Strengths and Limitations of the Review

This review has a number of strengths. First, the methods were planned and registered with PROSPERO a priori. This included a pre-specified set of potential moderating variables related to the specific nature of bullying victimization and the presence or absence of physical injury, as well as other factors potentially related to heterogeneity, such as the timing of outcome measurement. Similarly, we considered what it would mean for a model to be minimally versus adequately adjusted and then accounted for the level of control in the risk of bias assessment. Second, we conducted a comprehensive literature search, including an electronic search and a review of references of key articles in the field (e.g., previously published reviews) to identify included studies. Third, we judged the overall quality of the evidence, accounting for such

factors as risk of bias, size and precision of effect, heterogeneity, generalizability, and potential reporting bias.

This review also has some limitations. First, there is unexplained heterogeneity with many potential sources. In addition to the proposed moderators (which we would expect to account for some of the heterogeneity), there is substantial (1) between-study variability in the measurement of bullying victimization and pain and (2) differences in covariate measurement and adjustment, thereby raising more questions than answers. For example, the Incledon et al. (2016) findings differed from those of the other studies because they revealed no association between baseline bullying victimization and pain at follow-up. However, this pattern of findings could be interpreted in several ways. On the one hand, this is a lower risk of bias study that was well controlled in regard to potential confounders, so it may reflect the true state of affairs (i.e., there is no direct relationship between victimization and pain). On the other hand, this study's ability to detect an association between victimization and pain may have been limited by measurement issues, as we had some concerns about the validity of the bullying victimization measure used. In particular, children in this study were classified into the victimization group if they endorsed 3 or more types of bullying over the past 12 months. Although this construct is likely to correlate with the frequency of victimization, it fails to capture repeated victimization that is limited to one or two types (e.g., repeated verbal victimization or repeated verbal and physical victimization). In fact, someone who experienced one or two types of victimization repeatedly would have been classified as "non-victimized," possibly leading to relevant cases of bullying being classified as controls. Conversely, someone who was exposed to three types of bullying in a single episode would have been classified as victimized, leading to less relevant

cases of bullying being classified as "victimized." Clearly, there are many factors and too few studies to accurately pinpoint the sources of variation in the data.

Second, this review may not reflect the full body of work on this topic. Given that this is a prognostic factor review, we suspect the presence of reporting and publication biases due to difficulty publishing findings showing no connection between bullying victimization and pain. Moreover, we excluded non-English studies, thereby limiting the pool of published studies for inclusion in the review. Third, we had concerns about the internal validity (risk of bias) of included studies. In particular, we cannot rule out the impact of study attrition and potential confounding on the study results reported.

Overall Completeness and Applicability of the Evidence

This review provides initial evidence regarding the relationship between baseline bullying victimization and pain at follow-up. However, the literature failed to cover all relevant types of participants, risk factors, and outcomes. The evidence represents community and school samples in the United States, Australia, and Europe, thus it's unclear whether the findings generalize to people outside of these geographic areas, including in developing nations, as well as youth in healthcare settings. In regard to our questions about the direction of the effect and the proposed moderators, the evidence was incomplete. As shown in the GRADE table (Table 4.3), only one study examined the potential impact of pain on bullying victimization, and of the five proposed moderators, only one study analysed one of these moderators, so there was a dearth of evidence pertaining to the majority of our questions. Finally, only one of the four included studies actually measured chronic pain, which was our primary outcome variable. The other studies either failed to specify the duration of pain or examined pain occurring for a shorter duration. Therefore, the applicability of our findings to chronic pain is unclear.

Agreements and Disagreements with Other Studies and Reviews

Other reviews in the field have also suggested a positive association between bullying victimization and pain, but these reviews have generally pointed to a more robust association compared to the current findings. There are a number of factors that may account for these inconsistencies, such as the inclusion of cross-sectional versus longitudinal studies and the particular outcome being studied (e.g., pain versus somatic symptoms). In some cases, we excluded studies based on their cross-sectional design while other reviews classified them as longitudinal.

The review on bullying victimization and headaches by Gini and colleagues (2014) is most directly comparable to the present review. These authors found that bullied children and adolescents were at higher risk for headache compared with non-bullied peers, a finding that held up across two meta-analyses, one of 17 cross-sectional studies and the other of three longitudinal studies. In both cases the effect sizes were large and clinically relevant. However, it is unclear how to interpret the cross-sectional findings, especially in regard to the direction/temporality of the effect, and although the longitudinal findings begin to address this question, we have some concerns about the validity of these results. In particular, of the three studies classified as longitudinal by Gini and colleagues (2014), our team classified only one as longitudinal (i.e., Fekkes et al., 2006). We excluded the Kshirsagar et al. study (2007) based on its cross-sectional design, and we included Biebl et al. (2011) in our review only after receiving longitudinal data from the study authors. Given that cross-sectional studies are subject to higher risk of bias compared to longitudinal studies, it is possible that the longitudinal finding reported by Gini et al. (2014) reflects an overestimate of the true effect.

Two other reviews examined the relationship between bullying victimization and various symptoms in children and adolescents, with one focusing on somatic symptoms (Gini & Pozzoli, 2013) and the other focusing on "internalizing" problems (Reijntjes et al., 2010). The Gini and Pozzoli review (2013) showed evidence of increased risk of somatic symptoms among bullying victims compared to non-victims, yielding large and clinically relevant effects in meta-analyses of both 24 cross-sectional studies and six longitudinal studies. Again, we disagreed with the classification of Biebl et al. (2011) and Kshirsagar et al. (2007) as longitudinal studies, calling into question the validity of this meta-analysis, especially concerning the magnitude of the effect. The Reijntjes et al (2010) meta-analysis of 18 longitudinal studies on bullying victimization and "internalizing" symptoms (including somatic symptoms) also points to more conservative effects, with effect sizes in the small to moderate range. Moreover, their findings suggest a bi-directional association between these variables. Taken together, findings across the reviews point to a significant relationship between bullying victimization and bodily symptoms, but comparison of findings from longitudinal studies and cross-sectional studies point to more conservative estimates of the magnitude of the effect, and more work is needed to determine the temporal relationship between exposure and outcome measures.

Similar to the current findings, previous reviews in the field showed evidence of variability in results across studies. In addition to the potential moderators proposed in the current review, other reviews in the field have pointed to peer and family support, including having a best friend, as important moderating factors (Forgeron et al., 2010; McDougall & Vaillancourt, 2015). Some reviews point to gender as a key moderator (Gini & Pozzoli, 2013; Gini et al., 2014), while others suggest uniform associations across gender (McDougall & Vaillancourt, 2015). These effects may be difficult to pin down due to interactions between

various moderators. For example, the role of peer and family support may depend on the developmental stage (McDougall & Vaillancourt, 2015), and gender may interact with the type of bullying to shape outcomes (Kim et al., 2018). Indeed, well-powered studies are needed to do a comprehensive test of theoretically grounded moderator models.

Implications for Research

The findings from this review suggest that there is a small but statistically significant longitudinal relationship between bullying victimization and pain in youth, yet there remain many unanswered questions about the nature of this relationship. For example, we cannot say whether victimization precedes pain, pain precedes victimization, or if there is a bidirectional relationship between the two. Moreover, not only were we unable to answer our questions about the proposed moderator models and whether there are specific contexts that magnify versus dampen the victimization-pain relationship, but the findings from our meta-analysis raised additional questions. For example, the attenuated effect in the adjusted compared to the unadjusted meta-analyses suggests that victimization may exert its effects through indirect pathways. Indeed, the findings reported by Incledon and colleagues (2016) suggest that factors such as "at-risk child mental health" and sleep difficulties are directly associated with children's pain outcomes and may therefore represent key pathways from victimization to pain.

In order to further delineate the psychological and emotional pathways from victimization to pain, we recommend direct tests of mediation models, including symptoms of anxiety, depression, and posttraumatic stress disorder (PTSD). Symptoms of PTSD have been linked to both bullying victimization and chronic pain and therefore may be particularly relevant (Idsoe et al., 2012; Noel et al., 2016). Moreover, given that health behaviours may represent an important pathway to pain in youth, factors such as the sleep difficulties identified by Incledon

and colleagues (2016), as well as cigarette smoking and drug and alcohol use, should also be examined as potential mediators (Ghandour et al., 2004; Hoftun et al., 2012). Finally, we suggest that future studies include measures of both biological sex and gender, especially given the high prevalence of victimization and mental health concerns, including symptoms of PTSD, among transgender and gender non-conforming youth (Earnshaw et al., 2016; Mustanski et al., 2016; Roberts et al., 2013).

Ideally, data from large prospective cohort studies with long follow-ups would be available to tackle these questions directly, but it is likely to be years or decades before such data become available. Therefore, we suggest the use of alternative methods to begin to illuminate the nature of the victimization-pain relationship. One possibility would be to use a postsurgical pain model to examine whether victimization status prior to surgery predicts pain trajectories across the recovery period and beyond (Katz & Seltzer, 2009). This type of study could shed light on the role of bullying victimization in the development of chronic pain following physical insult (i.e., the surgical intervention). Another possibility would be to examine the relationship between bullying histories (taken retrospectively) and longitudinal pain outcomes, such as the emergence and persistence of pain in adolescence. For example, Bogart and colleagues (2014) have shown that trajectories of victimization across the transition from elementary school to high school are differentially associated with health outcomes among adolescents. Thus, by comparing different trajectories (e.g., those bullied in elementary school only versus those bullied in both elementary school and high school), it would be possible to examine whether factors such as the developmental timing and stability of victimization contribute to the development of chronic pain, either directly or via the proposed mediators detailed above.

Regardless of the research design, future work in this area would benefit from in depth measurement of bullying victimization and pain. Bullying victimization should be measured using standardized measures and multiple informants (e.g., teachers, parents, siblings) to capture different types of bullying (e.g., physical versus verbal victimization) and different modes of bullying (e.g., school bullying versus cyberbullying) at multiple time points (McDougall & Vaillancourt, 2015). Similarly, we recommend measurement of bullying-related physical harm, including the mechanism, frequency, and type of injury. In regard to the measurement of pain, we urge the use of well-validated and reliable measures that provide information about pain severity and pain interference (e.g., Brief Pain Inventory-Short Form [BPI-SF] (Chapman & Loeser, 1989; Cleeland & Ryan, 1994)) as well as pain quality (e.g., Short Form-McGill Pain Questionnaire [SF-MPQ] (Melzack, 1987)). These measures are typically used with adults, but they can also be used with children and adolescents (Turk & Melzack, 2011). Information from these questionnaires must be supplemented with a detailed pain history including, at a minimum, important pain-related variables, such as pain duration, diagnosis, body location, and pain medication use (Birnie et al., 2019; Breivik et al., 2008; Manworren & Stinson, 2016).

We know that the quality of life of victimized youth can be jeopardized over decades (Takizawa et al., 2014). Future work must take a nuanced approach to delineate factors that shape risk and resilience in the context of peer relationships and bullying, both in regard to chronic pain and mental and physical health outcomes more broadly.

Table 4.1: *Variables extracted from articles included in the review.*

Variable information extracted
Patient characteristics
Sample size
Study setting
Follow-up period
Bullying victimization (yes/no)
Type of bullying victimization (physical, verbal, relational victimization, and attacks on property)
Mode of bullying victimization (peer, sibling, and cyber)
Specific type of peer bullying (sexual, religious, and racial)
Co-occurrence of different types of bullying
Frequency and stability of bullying victimization
Developmental stage during which bullying occurred
Presence and type of bullying-related physical harm
Pain at baseline
Pain outcome measures used to determine pain intensity and incidence
Presence of a chronic pain condition

Table 4.2: *Characteristics of included studies.*

Author/ year	Number of subjects with follow-up data	Age at baseline (range in years)	Direction of effect(s) examined	Bullying victimization measure and timeframe	Develop-mental timing of victimization	Measurement, reporting, and analysis of proposed moderators	Pain outcome/measure and whether chronic pain was captured	Pain measurement timepoint(s)
Biebl 2011	70	10 – 18	V to P	Multi-dimensional Peer Victimization Scale (MPVS) (Mynard & Joseph, 2000). Timeframe not specified	Adolescence	<u>Moderators measured</u> Victimization type Stable/prolonged victimization <u>Moderators reported</u>[1] Victimization type[2] Stable/prolonged victimization <u>Moderators analyzed</u>[3] None	Self-reported headache The Physical Health Questionnaire (Schat et al., 2005) Chronic pain captured? Unclear	2 years
Fekkes 2006	1118	9 – 11	V to P P to V	Question from the Olweus Bully/Victim Questionnaire (Olweus, 1994). Captures victimization	Middle childhood	<u>Moderators measured</u> None <u>Moderators reported</u> None	Self-reported abdominal pain and headache Items from the KIVPA, a Dutch instrument to measure psychosocial problems among	Baseline and 6 months

Author/ year	Number of subjects with follow-up data	Age at baseline (range in years)	Direction of effect(s) examined	Bullying victimization measure and timeframe	Develop-mental timing of victimization	Measurement, reporting, and analysis of proposed moderators	Pain outcome/measure and whether chronic pain was captured	Pain measurement timepoint(s)
				over past 1-2 months		Moderators analyzed None	children (Reijneveld et al., 2003) Chronic pain captured? No, focus was on past 4 weeks	
Incledon 2016	3821	10 – 11	V to P	Self-report measure that appears to have been developed for the study Captures victimization over the past 12 months	Middle childhood	Moderators measured Victimization type Moderators reported None Moderators analyzed None	Parent reports of pain problems (abdominal, headache or other) Appears that pain items were developed for current study. Chronic pain captured? Unclear	Baseline and 2 years

Author/ year	Number of subjects with follow-up data	Age at baseline (range in years)	Direction of effect(s) examined	Bullying victimization measure and timeframe	Develop-mental timing of victimization	Measurement, reporting, and analysis of proposed moderators	Pain outcome/measure and whether chronic pain was captured	Pain measurement timepoint(s)
Sigurd-son 2014	1266	12 – 15	V to P	Self-report questionnaire (Alsaker, 2003). Captures victimization over the past 6 months	Adolescence	<u>Moderators measured</u> Victimization type Frequent victimization Stable victimization <u>Moderators reported</u> Frequent victimization Stable victimization <u>Moderators analysed</u> None	Self-reported bodily pain and headache Bodily pain item appears to have been developed for study. Headache item taken from reliable measure (Achenbach & Rescorla, 2003). Chronic pain captured? Yes	12 years

Note. V = Victimization, P = Pain
[1]Indicates whether descriptive information and/or the association between the moderator and pain outcome(s) was reported.
[2]Analysis of association between victimization type and pain was possible with data provided by authors.
[3]Indicates whether a moderation analysis was conducted and reported.

Table 4.3: *Grading of Recommendations Assessment, Development and Evaluation (GRADE).*

Research question	**Exposure variable**	**Number of studies (participants)**	**Unadjusted**			**Adjusted**					**GRADE Factors**							
			+	**0**	**-**	**+**	**0**	**-**	**Number of studies (partici-pants) in meta-analysis**	**Odds ratio (95% CI) for adjusted analysis**	**Study limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Moderate/large effect size**	**Dose effect**	**Overall quality**
What is the temporal relationship between victimization and pain?	Victimization	4 (6275)	3	1	0	3	1	0	4 (6275)	1.45 (1.06-1.97)	X	X	X	✓	X	X	X	+
	Pain	1 (947)	0	1	0	0	1	0	0	N/A	✓	N/A	X	✓	X	X	X	+
Do characteristics of victimization moderate the victimization-pain relationship?	Victimization type	1 (70) (relational vs. physical victimization)	1	0	0	1	0	0	0	N/A	X	N/A	X	X	X	X	X	+
	Presence of physical harm	N/A																No evidence
	Frequent victimization	N/A																No evidence
	Stable victimization	N/A																No evidence

	Developmental stage of victimization	N/A	No evidence

Note. For unadjusted and adjusted analyses: +, number of studies with a positive value; 0, number of non-significant effects; -, number of significant effects with a negative value. For GRADE factors, ✓, no serious limitations; X, serious limitations (or not present for moderate/large effect size, dose effect). For overall quality of evidence: +, very low; ++, low; +++, moderate; ++++, high.

Figure 4.1: *Study Flow Diagram*

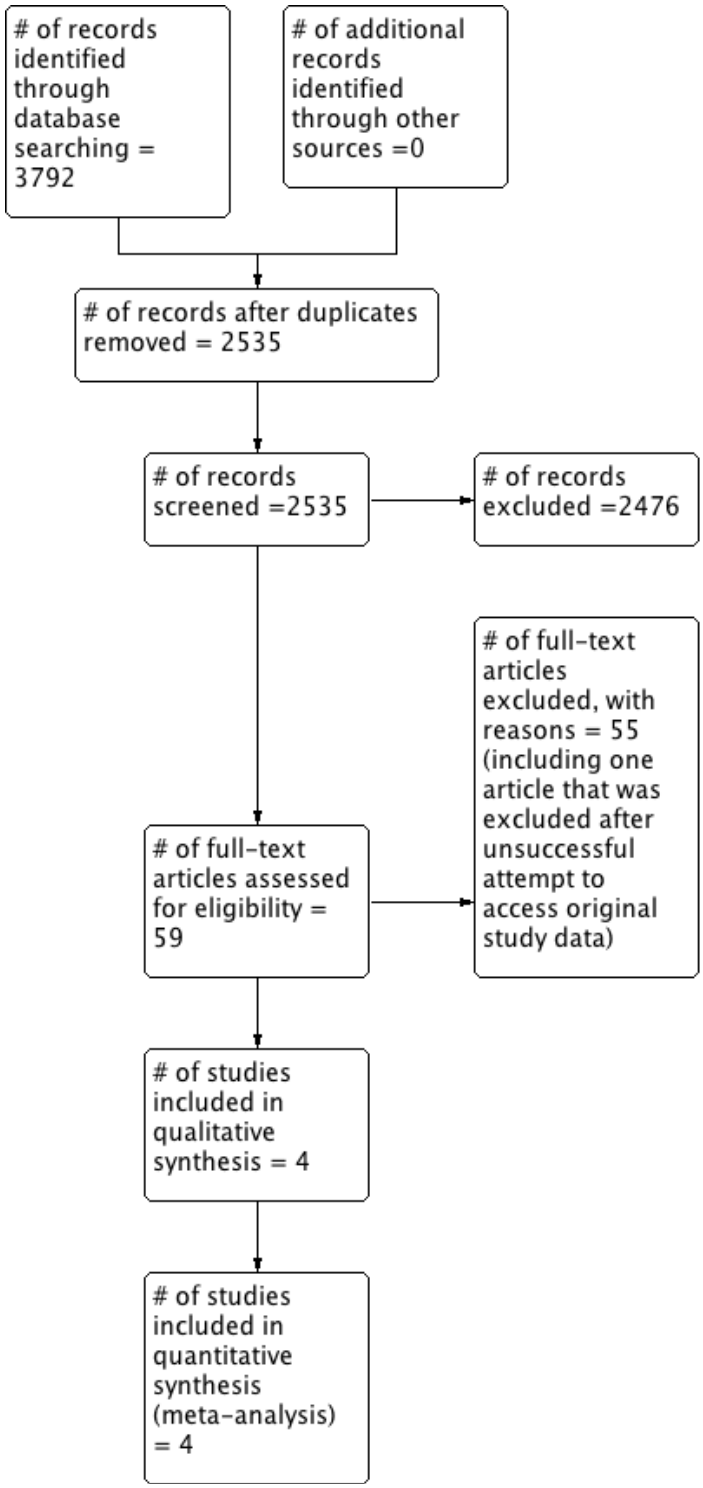


Figure 4.2: *QUIPS risk of bias summary. Review authors' judgments about each risk of bias domain (low, moderate or high) for each study and outcome and the overall rating for each study (low or high).*

Study	Study participation	Study attrition	Measurement of exposure	Measurement of outcome	Study confounding	Statistical analysis and reporting	Overall rating
Biebl 2011							High
Sigurdson 2014				 			High
Incledon 2016							Low
Fekkes 2006				 			Low

 Low RoB

 Moderate RoB

 High RoB

Note. Biebl 2011 and Fekkes 2006 each reported two pain outcomes.

Figure 4.3. *Forest plot depicting the results of a random-effects meta-analysis of longitudinal studies investigating the association between baseline bullying victimization and pain at follow-up, unadjusted for potential confounders.*

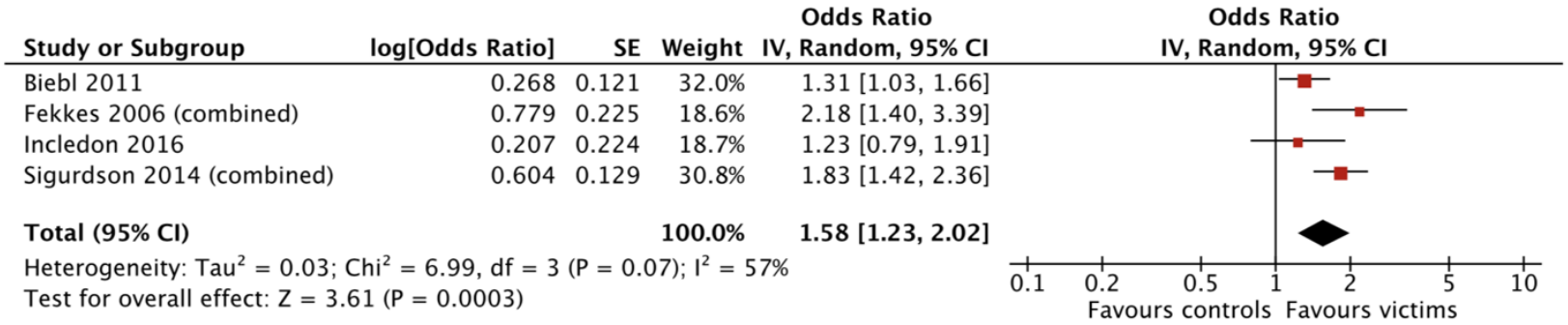
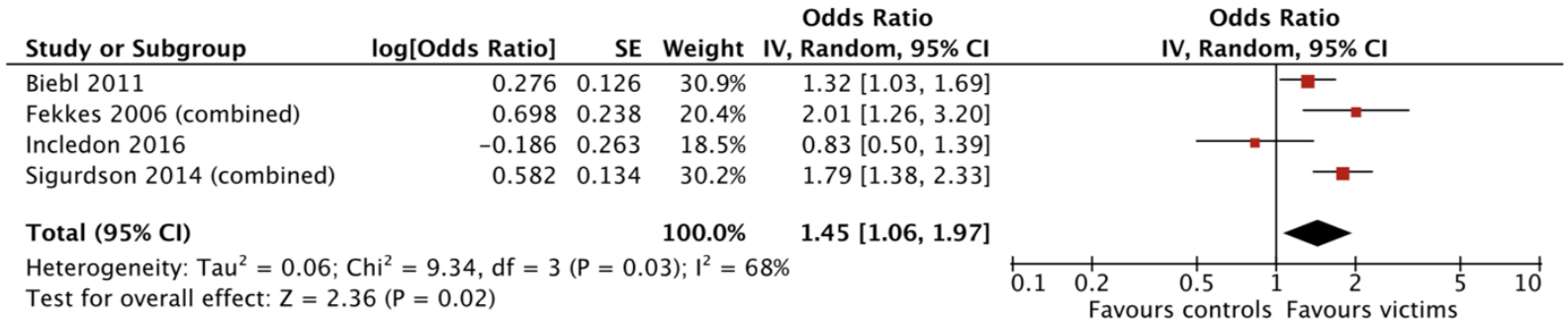


Figure 4.4: *Forest plot depicting the results of a random-effects meta-analysis of longitudinal studies investigating the association between baseline bullying victimization and pain at follow-up, adjusted for potential confounders.*



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Chapter 5: General Discussion

There is mounting evidence that adverse experiences in the early years of life have longstanding consequences for general health and wellbeing in later years, with exposure to multiple types of adversity being particularly impactful (Hughes et al., 2017; Miller et al., 2011; Norman et al., 2012; Wegman & Stetler, 2009). The empirical literature also points to early life adversity as an important risk factor for chronic pain, but methodological challenges have limited the interpretability of study findings in this field. Specifically, due to concerns about reporting biases and other possible alternative explanations for observed associations (e.g., psychological distress as a potential confounding variable), most studies have been unable to convincingly demonstrate temporal (let alone causal) effects or draw definitive conclusions about the nature of the adversity-pain relationship. Moreover, there are features of early life adversity that may be particularly relevant to pain outcomes, including the presence of physical injury and PTSD, yet these factors have been largely ignored in the extant literature.

The current dissertation therefore used systematic review methods to examine the relationship between early life adversity and chronic pain, with a focus on two types of adversity that were expected to be particularly relevant to the emergence of chronic pain; namely, child maltreatment and bullying victimization. There were two main objectives. The first was to examine the temporal nature of the relationship between each of these early life adversities and chronic pain by limiting the reviews to primary studies with prospective research designs or cross-sectional designs in which the adverse exposure was documented and occurred at least months before the outcome. The second was to examine whether specific features of these adversities (i.e., type, timing, and intensity (frequency or chronicity/stability) of adversity,

presence of PTSD, and presence of physical harm) shape the relationship between adversity and chronic pain.

The Temporal Relationship Between Early Adversity and Chronic Pain

My first objective for the reviews of child maltreatment and bullying victimization was to examine whether the evidence demonstrated a temporal association between the adversities and chronic pain. Findings from the child maltreatment review pointed to a lack of a direct association between maltreatment and pain at follow up. However, evidence from two high quality studies showed that when PTSD, or subsyndromal PTSD, was included in the statistical model as a mediator (Beal et al., 2020) or moderator (Raphael & Widom, 2011), documented history of maltreatment did indeed predict pain at long-term follow-up (with a 9-year follow up in the Beal et al. (2020) study and a 30-year follow-up in the Raphael and Widom (2011) study). Although future work is needed to replicate these findings, including more rigorous control for potential confounding variables (i.e., baseline pain and negative affect), they provide initial evidence that the maltreatment exposure precedes the onset of pain.

The bullying victimization review revealed evidence of a small yet statistically significant increased risk of pain among victimized compared to non-victimized youth, yet no temporal inferences can be drawn. The evidence, based on four studies (two rated as having low risk of bias (Fekkes et al., 2006; Sigurdson et al., 2014) and two rated as having high risk of bias (Biebl et al., 2011; Incledon et al., 2016)), was generally deemed to be of very low quality, in part due to inadequate control for potential confounding variables. Moreover, only one study tested the inverse association (baseline pain predicting victimization at follow up) (Fekkes et al., 2006), therefore the possibility of pain as an antecedent to bullying victimization could not be ruled out. Finally, in comparison to the child maltreatment review, the follow-up periods were

relatively short (<2-year follow-ups for three studies and a 12-year follow-up for one study), with only one study capturing pain outcomes in adulthood (Sigurdson et al., 2014). Therefore, additional evidence from high quality studies is needed before any definitive conclusions can be drawn about the temporal nature of the relationship between bullying victimization and pain.

Limitations and future directions. The systematic reviews presented in this dissertation were specifically designed to address questions of temporality. By limiting the review to studies that used prospective measures of adversity and through careful consideration of potential confounding factors, I planned to conduct rigorous tests of the temporal nature of the observed associations. However, my ability to examine these associations according to the pre-planned methods was limited by the dearth of available evidence. Across the two reviews, only 13 prospective studies met the inclusion criteria, of which only four studies measured and reported chronic pain as a primary outcome. The other studies either failed to specify the duration of pain or examined pain occurring for a shorter duration. The lack of evidence linking early life adversities to later pain outcomes exemplifies the challenges of conducting methodologically sound research in this field. Given that prospective cohort studies are resource-intensive, future work should consider novel research designs, such as post-surgical pain models (Katz & Seltzer, 2009; Salberg et al., 2020), to test prospective relationships between early life adversity and the emergence of chronic pain in youth and adult populations.

The Role of PTSD

One of my objectives for the child maltreatment review was to examine the role of PTSD as a moderating factor in the maltreatment-pain relationship. Consistent with empirical findings showing a significant overlap between symptoms of PTSD and chronic pain (Katz et al., 2014;

Noel et al., 2016), I expected that the presence of PTSD would magnify the association between child maltreatment and pain.

Only one included study conducted a formal test of moderation by PTSD (Raphael & Widom, 2011). Consistent with my hypothesis, the authors reported that the combination of a maltreatment history *and* PTSD was associated with risk of pain in adulthood. Interestingly, neither maltreatment history nor PTSD alone showed a significant association with pain. Replication of this finding with additional high quality studies (i.e., studies with low risk of bias) is needed to increase our understanding of, and confidence, in this moderation effect. However, another included study also reported a key role of PTSD in the maltreatment-pain relationship, but this time as a mediator (Beal et al., 2020). Although I did not have an *a priori* hypothesis about mediator models, this pattern of findings points to the importance of measuring and accounting for PTSD. It is unclear whether the role of PTSD is best explained by a mediator model, a moderator model, or a combination of the two, yet it seems quite clear that a complete model of child maltreatment and pain must account for PTSD.

Limitations and future directions. Given the limited evidence on the role of PTSD in the maltreatment-pain relationship, the findings on PTSD raise more questions than answers. Where is PTSD positioned in the temporal ordering of events? Does child maltreatment bring about symptoms of PTSD, which in turn, increase risk for chronic pain (as would be suggested by the Beal et al. (2020) findings)? Or does early life adversity activate a vulnerability to both pain and PTSD (Asmundson et al., 2002)? Finally, does the relationship between PTSD and chronic pain depend on the presence of early life adversity, or do other sources of PTSD also drive associations with pain? There are challenges associated with testing these research questions in clinical samples. For example, given that the relationship between PTSD and

chronic pain is likely to unfold over years or decades, the possibility of additional traumatic events and/or physical injury must be accounted for (Burke et al., 2017; Katz et al., 2014). Raphael and Widom (2011) reported that almost 80% of their sample reported lifetime PTSD that was *not* related to the documented child maltreatment (which was the focus of the empirical study). Future work must include comprehensive diagnostic assessments of lifetime exposures to PTSD, including the presence and timing of all Criterion A traumatic events.

In addition, for the review on bullying victimization, I did not include research questions related to PTSD. However, symptoms of PTSD may play an important role in the relationship between peer victimization and the emergence of chronic pain in young people, especially given the high prevalence of both victimization and mental health concerns in vulnerable populations, such as transgender and gender non-conforming youth (Earnshaw et al., 2016; Mustanski et al., 2016; Roberts et al., 2013). Future work on bullying victimization would benefit from consideration of symptoms of PTSD because, even in the absence of a Criterion A trauma, there may be clinically relevant symptoms present (Katz et al., 2014). For example, the Eisenberger et al. (2012) model of social pain would predict that social rejection is a particularly threatening form of adversity, especially during stages of development when concerns about belonging are already salient, such as during the adolescent period (Masten & Eisenberger, 2009). Does the pathway to later pain among the socially-rejected youth require the presence of PTSD symptoms and, if so do these symptoms have to be related to social rejection?

Finally, in regard to both reviews, I did not consider research questions related to post-traumatic growth and other constructs capturing resilience and protective factors. Such constructs may be particularly relevant in light of my findings suggesting that PTSD moderates the relationship between child maltreatment and later pain. In other words, for children who

experience maltreatment but do *not* develop symptoms of PTSD, there may be no increased risk of chronic pain. In fact, some evidence is suggestive of post-traumatic growth and pain-resilience in the aftermath of adversity. For example, a study of patients recovering from total knee replacement showed that patients with a history of trauma experienced *less* severe pain and functional limitations at one- and three-month follow-up compared to patients without a trauma history (Cremeans-Smith et al., 2015). Additional research is needed to further delineate these findings and identify contextual factors associated with risk versus resilience in the aftermath of adversity. For example, there is clear evidence from the mental health literature showing the buffering effect of social support on psychopathology among individuals with histories of maltreatment (Jaffee, 2017). From the bullying victimization literature, family support (i.e., family contact and support (Elgar et al., 2014)) and supportive friendships (Brendgen & Poulin, 2018) have been identified as key protective factors.

The Role of the Particular Type of Adversity

Another objective of the current review papers was to specify the relationships between particular types of adverse experiences and later chronic pain. The evidence was again limited in this regard. For child maltreatment, the findings on specific maltreatment types (sexual, physical, and emotion/verbal abuse and neglect, and exposure to domestic violence) pointed to a lack of a direct association between maltreatment and pain, especially in adjusted models and when the exposure involved physical abuse or neglect. For bullying victimization, there was evidence from a single study that relational victimization, but not physical victimization, was associated with pain at follow up (Biebl et al., 2011), although future research is needed to replicate this finding.

Limitations and future directions. One of the challenges of the current systematic reviews has to do with the heterogeneity across included studies, which limited my ability to conduct meaningful between-study comparisons. For example, the maltreatment review revealed evidence from one high quality study that self-reported verbal abuse in childhood was associated with increased risk of pain at follow-up (Sachs-Ericsson et al., 2017). In contrast, other high quality studies in the review did not capture verbal/emotional abuse because they relied on official reports of maltreatment (Beal et al., 2020; Brown et al., 2005; Raphael & Widom, 2011), which do not document this type of maltreatment. Therefore, it is unclear whether there is something unique about verbal abuse or if this finding is driven by reporting biases in the measurement of both child maltreatment and pain. Future work would benefit from the use of multiple informants, including sibling reports, to improve the reliability and validity with which early life adversities are measured (Gilbert et al., 2009; McDougall & Vaillancourt, 2015), as it is only when consistent measurement strategies are used across exposure types and studies that meaningful comparisons can be drawn both within and between studies. In this regard, there has been a call in the literature for the standardization of measures of child maltreatment (Wegman & Stetler, 2009).

The Role of Physical Harm

Another objective of this dissertation was to examine the role of physical injury in the relationship between early life adversity and later chronic pain. Empirical findings from preclinical (animal models) and clinical research point to critical windows during which the impact of pain and physical injury may be particularly profound (Burke et al., 2017), as well as a synergistic relationship between stressful environments and physical injury in the prediction of pain outcomes (Burke et al., 2017; Salberg et al., 2020). It was therefore hypothesized that

exposures to maltreatment or peer victimization that involved physical harm or injury would be more strongly related to long-term pain compared to exposures without a physical component. Unfortunately, none of the included studies reported on the presence or absence of physical harm or injury; therefore, there was no available evidence for testing this hypothesis.

Limitations and future directions. When I set out to conduct the reviews for this dissertation, I was interested in the differential impact of adverse experiences that did versus did not incur physical harm. Although this remains an important question (that has yet to be answered), future work should take a broader perspective. Physical injuries can occur across childhood and adolescence, and although some injuries may result directly from adverse experiences (as in the case of injury during a physical or sexual assault or a motor vehicle accident), others may be only indirectly related, such as an injury (stovetop burn or fracture from a fall) that occurs in the context of a chronically neglectful home environment because the child is not being appropriately monitored. In both of these situations (defined by the combination of physical harm and psychological stress) the physical harm may have consequences for pain later in life, but it is only in the case of the former that the injury would be classified as "trauma-related." Therefore, efforts should be made to assess for lifetime physical injuries regardless of whether they are directly linked to adversity or trauma, especially when they occur in the context of chronic background stress (e.g., a risky family environment (Repetti et al., 2002)). Moreover, in addition to capturing perpetrated and accidental injuries, intentional self-injury (e.g., self-inflicted cutting or burning) should also be accounted for, as maltreated and bullied children are at increased risk of engaging in self-injurious behavior (Lereya et al., 2015; Srabstein & Piazza, 2008), which could have implications for later pain.

The Roles of the Frequency, Chronicity, and Developmental Timing of Adversity

An additional aim of this dissertation was to examine the roles of the frequency and chronicity of adversities and the developmental stage(s) of exposure. Based on a cumulative adversity model, I hypothesized that frequent and/or chronic exposures to child maltreatment or bullying victimization would "add up" to predict later pain. Moreover, consistent with a critical period model, I expected exposures occurring in very early childhood and/or adolescence to be particularly detrimental. Unfortunately, I was not able to test these hypotheses in either of the reviews due to the small number of included studies and the general lack of information regarding the duration of the exposure or whether it was a single occurrence or a repeated event. Certainly, one of the most surprising findings from this review was the lack of attention to the "dose" of adverse experiences, whether it was in regard to child maltreatment or bullying victimization.

Limitations and future directions. For both review papers I took a systematic approach to examining the impact of frequency, chronicity, and timing of adversity on pain outcomes; however, less attention was given to other aspects of timing, including the span of time between the adverse experience and the measurement of pain (referred to as the recency of exposure). This is important because there was a great deal of variability across the included studies in both reviews, with one study measuring pain six months after the exposure to peer victimization (Fekkes et al., 2006) and another study measuring pain 30 years after documented child maltreatment (Raphael & Widom, 2011). The recency of the exposure could have implications for the adversity-pain relationship. Future work examining pathways from adversity to chronic pain should elucidate how these processes are expected to unfold over time. In a similar regard, a distinction should be made regarding the measurement of pain in childhood, adolescence, or

adulthood. For example, findings from a meta-analysis of childhood adversities and adult-onset chronic physical conditions showed that the relationship between early life adversity and spinal pain did not emerge until middle adulthood (at approximately age 40 years) (Scott et al., 2011). Therefore, studies must not only consider the recency of the exposure but the age of participants at follow up (when pain assessments are conducted).

Also, in regard to the cumulative impact of adversity on chronic pain, it may be important to consider the additive effects of both maltreatment and peer victimization. Children who experience maltreatment at home are at increased risk of bullying by peers (Radford et al., 2013), therefore, from a cumulative risk or "poly victimization" perspective, victimization by both caregivers and peers should be considered (Finkelhor et al., 2009). In a study of "potentially traumatic interpersonal events," including child maltreatment and peer victimization, there was a dose-response relationship between the number of types of interpersonal events and recurrent headache among adolescents (Stensland et al., 2013). Therefore, future work on early life adversity should capture all forms of victimization, whether it is inflicted by parents, other caregivers, siblings, and/or peers.

Clinical Implications

Although more work is needed to further examine the association between early adversity and risk for the development of chronic pain, our findings suggest that the association is not as robust as would be expected. In fact, it may be only in the presence of PTSD that risk for chronic pain increases. This suggests that it is the presence of symptoms of PTSD rather than the exposure to adversity that is most important from an early intervention perspective. In this regard, it has been suggested that screening for PTSD should include screening for shared vulnerabilities to PTSD and chronic pain (Asmundson, 2014). One shared vulnerability that has

received increasing attention from an intervention perspective is anxiety sensitivity, which is defined as the fear of anxiety symptoms based on the belief that they will have harmful consequences (Reiss, 1991). Anxiety sensitivity has been successfully targeted using interoceptive exposure (exposure to feared bodily sensations associated with arousal) (Boswell et al., 2013) and cognitive therapy (Short et al., 2017). Moreover, interventions targeting anxiety sensitivity have proven effective in the treatment of PTSD symptoms (Short et al., 2017) and pain severity among individuals with chronic pain (Olthuis & Asmundson, 2019). Therefore, from an early intervention perspective, anxiety sensitivity may be a promising target for chronic pain prevention among maltreated youth with symptoms of PTSD.

The lack of evidence for a robust, direct effect of child maltreatment and bullying victimization on chronic pain may also point to psychological resilience among some youth. Clearly, we still need to define resilience to chronic pain in the context of maltreatment and peer victimization, as well as to clarify its associations with environmental factors that are likely to bolster resilience (e.g., family, peer, and community supports (Brendgen & Poulin, 2018; Elgar et al., 2014; Jaffee, 2017). For example, factors such as emotional awareness, emotion regulation, and distress tolerance may mitigate the relationship between early adversity and chronic pain, with social support bolstering emotion regulation processes (Koechlin et al., 2018). Although we still have a long way to go, enhanced understanding of these factors could open up intriguing possibilities from an intervention perspective. Is it possible to bolster psychological and emotional resilience to chronic pain among youth who are at increased risk of victimization or re-victimization within the family and/or peer group? And if so, could this set the stage for enhanced mental health and decreased risk of chronic pain among those who may otherwise be considered vulnerable to PTSD and chronic pain?

Limitations of the Dissertation

This dissertation has some limitations. As highlighted in the sections above, the main limitation relates to the dearth of evidence available to answer my research questions. However, to the extent that I was able to draw some conclusions regarding the relationship between early life adversity and pain, these findings are limited by the pain measures used in the primary research studies. Across the two review papers, only four of the 13 included studies actually measured chronic pain, which was the primary outcome variable. The other studies either failed to specify the duration of pain or examined pain occurring for a shorter duration. Therefore, the applicability of the findings to chronic pain (and related outcomes such as pain interference and disability) is unclear. In a similar regard, there are some concerns related to the measurement of child maltreatment using data abstracted from official reports. Although the use of official reports minimizes the impact of reporting biases on study findings, evidence indicates that only a small portion of children who are maltreated receive official attention (Gilbert et al., 2009). This means that findings from this review may not represent unreported cases of maltreatment and it is not known what, if any biases, are associated with unreported cases.

There are some addition limitations related to the systematic review methods used. First, the review papers may not reflect the full body of work on this topic. Given that I conducted reviews of prognostic/risk factors, it is likely that there exist reporting and publication biases due to difficulty publishing findings showing no connection between early life adversity and pain. Moreover, I excluded non-English studies, thereby limiting the pool of published studies for inclusion in the reviews. A final limitation relates to concerns about the internal validity (risk of bias) of studies included in the reviews. As discussed in the sections above, I cannot rule out the

impact of potential confounding variables (baseline pain, current/adult abuse, and co-occurring abuse types) on the study results reported.

Strengths of the Dissertation

This dissertation has a number of strengths. The two systematic reviews were based on theoretically derived research questions which were specified in advance and registered with an online systematic review database (PROSPERO). Methodological rigour was prioritized throughout the review process using tools to judge the overall quality of the evidence, accounting for such factors as risk of bias, size and precision of effect, heterogeneity, and generalizability (Guyatt et al., 2011; Hayden et al., 2013). Although the available evidence did not allow me to draw definitive conclusions about the nature of the relationships between both child maltreatment and bullying victimization and chronic pain, the reviews make a number of contributions to the field. First, they provide a framework for organizing the literature on early adversities and pain that is specific to the study of chronic pain, with a focus on the roles of physical injury and PTSD. This framework is novel in regard to the study of early life adversity and pediatric and adult pain. Second, the review papers provide comprehensive descriptions and analysis of the current literature, including judgments of the overall quality of the evidence, thereby providing a roadmap for other investigators with interest in this field. This is important because previous reviews (mainly of cross-sectional studies) suggest that the evidence for both child maltreatment (Afari et al., 2014; Häuser et al., 2011; Paras et al., 2009) and bullying victimization (Gini & Pozzoli, 2013; Gini et al., 2014) is much stronger and more definitive than our findings revealed it to be. Finally, the systematic reviews identify priorities for future work in this field, including recommended study designs and measurement strategies to capture the nuances of child maltreatment, bullying victimization, and chronic pain.

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Appendix I

Search Terms and Yields for Review of Traumatic Events and Chronic Pain

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

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1 (adverse adj3 event?).ti,ab. (133405)
2 (adverse adj3 incident?).ti,ab. (556)
3 Stress Disorders, Post-Traumatic/ (28447)
4 stress disorders, traumatic/ or battered child syndrome/ or combat disorders/ or stress disorders, traumatic, acute/ (4799)
5 post-traumatic stress.ti,ab. (9750)
6 posttraumatic stress.ti,ab. (17510)
7 PTSD.ti,ab. (19269)
8 (severe adj3 accident$).ti,ab. (864)
9 (severe adj3 injur$).ti,ab. (27141)
10 Survivors/px [Psychology] (8397)
11 trauma$.ti,ab. (310084)
12 Bullying/ (2376)
13 Child Abuse/ (20906)
14 Child Abuse, Sexual/ (9644)
15 Rape/ (6197)
16 Sex Offenses/ (7656)
17 (abus$ adj3 (child or physical or sexual)).ti,ab. (23042)
18 or/1-17 (521868)
19 Chronic Pain/ (8151)
20 (chronic adj3 pain).ti,ab. (50977)
21 Chronic Disease/ (255754)
22 chronic condition?.ti,ab. (13894)
23 Pain/ and (recur$ or chronic or persistent).ti,ab. (22437)
24 (pain? adj5 (recur$ or chronic or persistent)).ti,ab. (69710)
25 Pain/ep, et, px [Epidemiology, Etiology, Psychology] (54311)
26 Pain, intractable/ (6144)
27 Fibromyalgia/ (7686)
28 Irritable Bowel Syndrome/ (6044)
29 Arthritis/ (35406)
30 exp back pain/ and (recur$ or chronic or persistent).ti,ab. (8981)
31 neck pain/ and (recur$ or chronic or persistent).ti,ab. (1542)
32 Osteoarthritis/ (35175)
33 Arthritis, Rheumatoid/ (94135)
34 Headache/ and (recur$ or chronic or persistent).ti,ab. (3966)
35 Migraine/ and (recur$ or chronic or persistent).ti,ab. (3746)
36 Neuralgia/ (11475)
37 Peripheral Nervous System Diseases/ (22216)

38 Complex Regional Pain Syndromes/ (1172)
39 Whiplash Injuries/ and (recur$ or chronic or persistent).ti,ab. (705)
40 Cumulative Trauma Disorders/ and (recur$ or chronic or persistent).ti,ab. (488)
41 Somatoform Disorders/ and (recur$ or chronic or persistent).ti,ab. (1549)
42 (somat$ adj3 pain).ti,ab. (1961)
43 or/19-42 (557592)
44 impact$.ti,ab. (834620)
45 Influen$.ti,ab. (1411837)
46 predict$.ti,ab. (1315420)
47 factor$.ti,ab. (2952954)
48 association?.ti,ab. (1128022)
49 Association/ (3869)
50 cross-sectional.ti,ab. (263712)
51 risk.mp. (2144345)
52 Risk/ (118699)
53 (related or relation$).ti,ab. (3392028)
54 correlat$.ti,ab. (1649023)
55 aggregat$.ti,ab. (215239)
56 or/44-55 (9704939)
57 18 and 43 and 56 (11035)
58 animals/ not humans/ (4636441)
59 57 not 58 (10634)

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APPENDIX II

Search Terms and Yields for Review of Bullying Victimization and Chronic Pain

Database: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® <1946-Present>
Search Strategy:

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1 Bullying/ (2931)
2 bully$.ti,ab. (4307)
3 bullie?.ti,ab. (1426)
4 cyberbull$.ti,ab. (447)
5 cyber-bull$.ti,ab. (82)
6 cyberharass$.ti,ab. (4)
7 cyber-harass$.ti,ab. (7)
8 frozen out.ti,ab. (80)
9 freeze? out.ti,ab. (157)
10 freezing out.ti,ab. (86)
11 tease?.ti,ab. (2093)
12 teasing.ti,ab. (1094)
13 taunt$.ti,ab. (123)
14 Social Isolation/ (12391)
15 Social Distance/ (2428)
16 (social$ adj2 exclusion?).ti,ab. (1444)
17 (social$ adj2 exclud$).ti,ab. (302)
18 victimization?.ti,ab. (6845)
19 victimisation?.ti,ab. (457)
20 victimi?ed.ti,ab. (1396)
21 (physical$ adj2 assault$).ti,ab. (1133)
22 Sibling relations/ (2729)
23 ostraci$.ti,ab. (525)
24 Harassment, Non-Sexual/ (25)
25 (harass$ not sexual$).ti,ab. (1404)
26 or/1-25 (36298)

27 Chronic Pain/ (10359)
28 (chronic adj3 pain).ti,ab. (53977)
29 Chronic Disease/ (249746)
30 chronic disease?.ti,ab. (53189)
31 chronic condition?.ti,ab. (14749)
32 Pain/ (125774)
33 pain?.ti,ab. (556985)
34 Pain/ep, et, px [Epidemiology, Etiology, Psychology] (53195)
35 Pain, intractable/ (6051)
36 Fibromyalgia/ (7727)
37 fibromyalgia.ti,ab. (9084)

38 Irritable Bowel Syndrome/ (6294)
39 irritable bowel syndrome.ti,ab. (11285)
40 IBS.ti,ab. (7549)
41 Arthritis/ (34431)
42 arthritis.ti,ab. (157900)
43 exp back pain/ (35555)
44 neck pain/ (6103)
45 Osteoarthritis/ (34125)
46 osteoarthritis.ti,ab. (53125)
47 Arthritis, Rheumatoid/ (93448)
48 Headache/ (25996)
49 (headache? or head-ache?).ti,ab. (75386)
50 Migraine/ (23361)
51 migraine?.ti,ab. (30950)
52 Neuralgia, Postherpetic/ (929)
53 postherpetic neuralgia.ti,ab. (1797)
54 post-herpetic neuralgia.ti,ab. (770)
55 Herpes Zoster/ (9655)
56 herpes zoster.ti,ab. (8374)
57 shingles.ti,ab. (1135)
58 Complex Regional Pain Syndromes/ (1242)
59 complex regional pain syndrome?.ti,ab. (2642)
60 Somatoform Disorders/ (8939)
61 (somat$ adj3 pain).ti,ab. (1987)
62 stomachache?.ti,ab. (292)
63 stomach ache?.ti,ab. (357)
64 or/27-63 (1189079)

65 impact$.ti,ab. (898081)
66 Influen$.ti,ab. (1430306)
67 predict$.ti,ab. (1355997)
68 factor$.ti,ab. (2961285)
69 association?.ti,ab. (1136191)
70 Association/ (3825)
71 cross-sectional.ti,ab. (285291)
72 Cross-Sectional Studies/ (272809)
73 risk.mp. (2205664)
74 Risk/ (115810)
75 (related or relation$).ti,ab. (3455121)
76 correlat$.ti,ab. (1667337)
77 aggregat$.ti,ab. (217177)
78 or/65-77 (9856961)

79 26 and 64 and 78 (1071)

80 animals/ not humans/ (4456014)

81 79 not 80 (991)
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