Bridging the Gap Between Chronic Pain and Mental Health in Childhood: A Genetically-Informed Study Examining the Etiology Underlying Co-occurring Symptomologies and Mechanisms of Intergenerational Transmission

by

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ABSTRACT

Pediatric chronic pain is pervasive and associated with myriad adverse consequences, yet due consideration has not been given to the mental health disturbances that often present alongside chronic pain and the etiological mechanisms that potentially underlie both. The current study examined the etiology underlying chronic pain and internalizing symptomology in middle childhood, considering both independent and co-occurring symptom presentations. Phenotypic parent-offspring associations across chronic pain and internalizing symptomology were also examined. Lastly, nuclear twin family models were tested to determine the extent to which genetic and environmental factors underlie parent-offspring transmission. The sample comprised 795 children (399 families; M_{age}= 9.7 years; SD = 0.92) and their parents drawn from the Arizona Twin Project. Results indicated that chronic pain was highly heritable (78%), whereas internalizing symptomology was modestly heritable (32%) and further subject to moderate shared environmental influence (50%). Moreover, 9% of the variance in chronic pain was explained by additive genetic factors shared with internalizing symptomology. Maternal chronic pain and internalizing symptomology were positively associated with both child chronic pain and internalizing symptomology. The association between maternal chronic pain and child chronic pain was more pronounced for girls than boys, whereas the association between maternal internalizing symptomology and child internalizing symptomology was more pronounced for boys than girls. Paternal chronic pain was not significantly associated with child chronic pain but was unexpectedly associated with lower child internalizing symptomology. The negative association between paternal chronic pain and child internalizing symptomology was more

pronounced for boys than girls. Paternal internalizing symptomology was not significantly associated with child chronic pain but was positively associated with child internalizing symptomology. Lastly, the best fitting reduced nuclear twin family models for both chronic pain and internalizing symptomology retained additive genetic, sibling-specific shared environmental, and nonshared environmental parameters, where parent-offspring transmission was solely explained by shared genetics and sibling-specific shared environmental factors further accounted for co-twin resemblance. Results provide novel insight into common liabilities underlying chronic pain and internalizing symptomology in middle childhood, parent-offspring associations across chronic pain and internalizing symptomology, and the etiological mechanisms that explain symptom aggregation across generations.

DEDICATION

Para Martha Isabel Cáceres Zapata. Siempre, tu muñeca de trapo.

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INTRODUCTION AND BACKGROUND LITERATURE

The familial aggregation of chronic pain, defined as recurrent or persistent pain lasting more than three months (Merskey, 1994), is well-documented, primarily by studies examining intergenerational transmission from parents to their adult offspring (Edwards et al., 1985). However, growing evidence highlights substantial prevalence rates for pediatric chronic pain, ranging from 4 to 88% across pain types in the epidemiological literature (King et al., 2011). More research is needed to examine the intergenerational transmission of chronic pain from parents to younger offspring and to elucidate etiological mechanisms, particularly in childhood. An improved understanding of these mechanisms is critical to identifying points of intervention in an effort to disrupt developmental cascades associated with early-onset chronic pain and potentially mitigate suffering. However, an examination of chronic pain in isolation discounts complex patterns of symptom co-occurrence across the physical and mental health domains. This symptom co-occurrence is well-characterized in adult populations, but less is known regarding patterns of symptom co-occurrence in childhood. The anachronistic biomedical model of health, which perpetuates a reductionistic view that "true" pain and mental health operate independently, has been rejected in favor of a biopsychosocial perspective which acknowledges that physiological, psychological, and sociocultural factors converge to dynamically influence multiple domains of health (Gatchel, 2004). Research that bridges these often-siloed health domains will lead to a more thoughtful examination of nuanced patterns of symptom presentation in childhood and the mechanisms that contribute to co-occurrence.

The present study approached comorbidity as a substantive focus, rather than a nuisance confounder, in order to elucidate mechanisms through which susceptibilities for *both* chronic pain and mental health disturbances unfold in childhood. Given high rates of co-occurring symptomology across the two domains, liabilities for either pain or psychopathology are not likely to entirely operate independently; rather, there is likely some shared liability partially underlying variance in both. Furthermore, the present study examined phenotypic parent-offspring associations across chronic pain and internalizing symptomology and elucidated the extent to which genetic and environmental factors mediate these associations. Research examining the intergenerational conferral of susceptibilities to chronic pain and internalizing symptomology through gene-environment transactions stands to inform interventions targeting putative mechanisms from a multisystems approach toward a more comprehensive mitigation of risk for vulnerable youth.

Theoretical Background

Efforts to understand pain and alleviate suffering are well-documented in historical texts and have been traced back millennia, however it was not until the 19th century that the elucidation of pain mechanisms converged to inform treatment. Following this shift, biomedical reductionism, the theory that mind and body function independently, prevailed. This failure to acknowledge the mind-body dynamic impeded efforts to understand and treat pain (Gatchel, 1999). However, perspectives began to transition toward a more dynamic framework in the second half of the 20th century after Melzack and Wall (1965) introduced the gate control theory of pain, in which they challenged extant reductionist approaches and presented evidence of psychological influence on pain

experiences. This gave way to a biopsychosocial approach to the study of pain, emerging in the late 20th century and predominating current research. The biopsychosocial model of pain emphasizes complex transactions across biological, psychological, and social processes with current research attempting to elucidate the nature of these transactions (Gatchel, 2004). For example, Varni's biobehavioral model of pediatric pain (1995) adopts a biopsychosocial perspective to illustrate the intervening roles of biological predisposition, psychological processes, and social factors on the pathway from precipitant (i.e., disease, injury, medical procedure, and/or psychological stress) to pain and co-occurring impairments, including symptoms of psychopathology. In an extension of Palermo and Chamber's (2005) integrative model of pediatric chronic pain, which incorporated operant-behavioral and family systems theories to emphasize psychosocial influences across multiple levels (i.e., parent, parent-child dyad, and broader familial environment), Palermo (2012) further integrates the role of biological factors and broadens the social context beyond the family to provide a more comprehensive, biopsychosocial framework of pediatric chronic pain. Emphasizing complex transactions across the biological, psychological, and social levels, they also focus on the role of health habits (e.g., sleep and physical activity) that emerge in the context of these transactions and further impact pediatric chronic pain. Palermo and colleagues (2014) acknowledge that these interactions are dynamic and shaped by developmental processes. In further integrating a consideration of development, they highlight a need to examine such transactions in various developmental stages as well as longitudinally. The reviewed models provide a general framework. However, in order to specifically test such models and elucidate the dynamic, intergenerational, biopsychosocial processes underlying pain

and psychopathology symptom co-occurrence, modeling strategies must be revisited to better capture liability transmission.

Stone and Wilson (2016) proposed a conceptual model of intergenerational transmission where they posit that parental chronic pain is a specific risk factor for the development of children's chronic pain, disability, and poor psychological functioning. They emphasize important moderators of this risk, including a second parent experiencing chronic pain, timing, course, and location of the parent's pain, and children's characteristics, such as sex and temperament. These factors modify risk to indirectly influence children's pain related outcomes via transactions between mechanisms of transmission and children's vulnerabilities. Proposed mechanisms are genetic propensities, early neurobiological development, social learning of pain-related behaviors, parenting, family functioning, and stressful environments, and child vulnerabilities include altered pain processing, cognitive and emotional responses to pain, coping behaviors, physical health, and deficits in emotion regulation. Stone and Wilson emphasize that children are vulnerable to both chronic pain and poor psychological functioning, however, they appear to neglect the psychological functioning of the parents. Parent mental health is likely a key moderator of risk associated with parent chronic pain; moreover, it likely exerts main effects on the proposed mechanisms of transmission and child vulnerabilities. Thoughtful consideration of parental psychological functioning will provide a more comprehensive intergenerational framework of chronic pain. An integration of existing models of comorbidity is a means of reinforcing this framework.

Krueger and Markon's (2006) review of liability models of comorbid psychopathology can be aptly extended to co-occurring pain and psychopathology. They

first review associated liabilities models, whereby latent propensities to develop different psychiatric disorders vary in the extent to which they are correlated. Under the chance model, liabilities are uncorrelated and comorbidity is a stochastic phenomenon. Under the correlated liabilities model, liabilities are correlated (but not perfectly) and manifest comorbid diagnoses. Lastly, under the alternate forms model, liabilities are perfectly correlated and comorbidity reflects alternate forms of the same underlying condition. They then describe multiformity models, whereby liabilities are uncorrelated but can cause symptoms of multiple conditions. Next, they review causation models, whereby disorders influence the development of other disorders via directional or reciprocal means. The penultimate model discussed is the independence model, whereby putative comorbidity is actually explained by the manifestation of a distinct disorder characterized by symptoms shared with the presumed disorders; all are subject to independent liabilities. Lastly, spurious association models implicate external variables that may explain comorbid conditions, such as socioeconomic status.

Though Krueger and Markon's (2006) review focuses on comorbid psychiatric disorders, these models can be extended to comorbid pain and psychiatric symptomology and tested within a biopsychosocial framework to elucidate the extent to which liabilities for both are linked. Multivariate twin designs are well-suited to testing these competing models of comorbidity and elucidating the independence or commonality of liabilities for pain and psychopathology, though there is a dearth of research applying these strategies in childhood. The present study elaborated upon foundational phenotypic, family-based, and genetically-informed research toward more comprehensive, theoretically-informed model testing. Specifically, the present study leveraged twin data to test the correlated

liabilities model across chronic pain and internalizing symptom phenotypes and determine whether co-occurrence is explained by shared genetic and/or environmental liabilities and the degree to which latent genetic and environmental influences on the two phenotypes are correlated.

Childhood Chronic Pain: Epidemiological Findings

Empirical investigations on the origins and consequences of pediatric chronic pain remain understudied, despite mounting epidemiological research attesting to its prevalence. The personal and economic costs associated with pediatric chronic pain have not been quantified to the extent that they have been in the adult chronic pain literature, perhaps explaining this relative dearth of research (Goodman & McGrath, 1991). However, studies elucidating the underlying mechanisms contributing to pediatric chronic pain and its mental health comorbidities stand to enhance our understanding of early-onset trajectories and inform preventative and intervening care, ultimately mitigating personal suffering and economic burden.

In their foundational review paper, Goodman and McGrath (1991) summarize epidemiological studies examining the prevalence of specific pain conditions in childhood and adolescence. They highlight inconsistencies across the studies and posit methodological limitations that might explain the mixed reports. They first reference issues regarding measurement reliability and validity, stating that pain is a subjective experience and asserting the superiority of self-report. The reviewed studies include samples with participants as young as three years old and yet parental report is still criticized. Goodman and McGrath do not address the potential inaccuracy of self-reported data acquired from young children and instead advocate for the development of age-

appropriate pain measures; this recommendation side-steps tenuous evidence for the reliability of young children's self-reported chronic pain (Birnie et al., 2019). Alternatively, psychometric validation of parent-report measures of pediatric pain may be a more effective pursuit when conducting research with this demographic. They then criticize assessments of pain that only address presence or absence and advocate for the measurement of severity, frequency, and duration. Next, they discuss limitations regarding the timing of retrospective reports, yet they do not provide recommendations for optimal time frames. They also suggest expanding breath of measurement by assessing more than one type of pain, including measures of disability and handicap, measuring pain across generations, and designing longitudinal studies. Though they acknowledge potentially co-occurring pain types, they do not specifically call for measurement of psychological functioning which stands to provide a more comprehensive assessment of children's pain experiences. Lastly, they call for samples that are well-described, representative of the general population, large, and inclusive of a sufficient range of ages.

Twenty years after the publication of Goodman and McGrath's seminal paper, King and colleagues (2011) provided an updated review of epidemiological studies of *chronic* pain in childhood and adolescence. Chronic pain is defined as recurrent or persistent pain lasting more than three months (Merskey, 1994). By including only studies of chronic pain, the authors minimize inconsistencies that stem from a failure to distinguish acute and chronic pain presentations. Included studies were screened for quality based on criteria influenced in large part by the methodological recommendations set forth by Goodman and McGrath (1991). Their review is enhanced by significant improvements to

epidemiological studies of chronic pain made in the two decades since the first review was published as well as their examination of individual factors influencing pain prevalence, including psychological factors. A total of 58 studies reporting on the prevalence of headache, abdominal pain, back pain, and musculoskeletal/limb pain in childhood and/or adolescence were included and systematically reviewed.

Prevalence rates for headache varied across frequency categories (i.e., monthly, weekly, and daily occurrence of headache). Monthly headache prevalence estimates ranged from 26 to 69%, weekly from 6 to 31%, and daily from 1 to 9%. Migraine prevalence estimates ranged from 3 to 10% and tension-type headache from 1 to 73%. Generally, prevalence increased with age and tended to be higher among girls. Depression, anxiety, and low self-esteem were also associated with increased headache prevalence. Prevalence rates for recurrent abdominal pain (at least three episodes that limit functioning over at least three months) ranged from 4 to 41% and weekly abdominal pain from 8 to 22%. Age effects were mixed, with some studies reporting increases in abdominal pain and others decreases as age increased. Chronic abdominal pain was more prevalent among girls. Children's anxiety, depression, and stress were also associated with increased abdominal pain prevalence. Additionally, maternal anxiety was identified as a risk factor. Monthly back pain prevalence estimates ranged from 18 to 24% and weekly from 9 to 25%. Prevalence consistently increased with age. There was minimal evidence of sex differences, with only one study reporting greater prevalence among girls. The prevalence rate for monthly musculoskeletal and/or limb pain was approximately 38.9% and weekly prevalence rates ranged from 8.5 to 32.1%. Overall, rates tended to increase with age and be higher among girls. The prevalence rate for

monthly multisite pain (complaints of pain occurring at 2 or more sites) was approximately 16% and weekly prevalence rates ranged from 4 to 11%. Associations with age varied as a function of the number of symptoms reported and pain site, and symptoms were greater among girls. The monthly prevalence rate for general or nonspecific pain was approximately 60%. Overall, general pain tended to increase with age and be higher among girls.

These epidemiological findings highlight the overwhelming prevalence of pediatric chronic pain; however, there is a dearth of research examining immediate and long-term functional consequences (Palermo, 2000). More studies are needed in order to fully ascertain the impact of this often overlooked, yet major health concern.

Co-occurring Academic, Social, Health, and Psychiatric Problems

Existing studies have primarily examined impairment in academic and social domains. For example, school absenteeism is a well-documented consequence of pediatric chronic pain that may place vulnerable children at greater risk for cognitive and psychosocial delays relative to their chronic pain-free peers (Sato et al., 2007). Moreover, this phenomenon is not specific to clinical cases of pediatric chronic pain; community-based studies also report evidence of school absenteeism, with 48.8% of students experiencing chronic pain missing school “sometimes” or “always” (Roth-Isigkeit et al., 2005). However, chronic pain does not act alone to influence school absenteeism. In fact, Logan and colleagues (2009) reported that pain intensity was not correlated with school absenteeism in a sample of clinically referred adolescents, but rather depressive symptoms were. These findings indicate that psychological correlates of pediatric chronic pain, such as depression, anxiety, and stress, should be examined as factors that place

children experiencing chronic pain at greater risk for school absenteeism and academic impairment more broadly. The family context also warrants further attention, as parental behaviors in response to children's chronic pain have been found to play a role in school absenteeism. For example, parental pain catastrophizing, or negative thinking related to children's pain, and parental protective behaviors, including protectiveness, pain minimization, encouraging, and monitoring, have been associated with greater rates of school absence in a clinical sample of children and adolescents, controlling for children's pain intensity and depressive symptoms. Furthermore, parental behavioral responses were found to mediate the association between parental cognitive responses and school absenteeism (Logan et al., 2012). These findings highlight the importance of considering the role of the familial context in modifying risk for functional consequences associated with pediatric chronic pain. Beyond examining parental cognitive and behavioral responses to their children's pain, studies should also consider the role of parental pain experiences and/or mental health symptoms in exacerbating offspring impairment. The familial aggregation of chronic pain and mental health disturbances is well-established, yet little is known regarding the extent to which this clustering impacts children's functional impairment.

Few studies of pediatric chronic pain examine academic impairment beyond collecting school absence rate data at a single time point, highlighting a need to acquire more in-depth, longitudinal assessments of academic and functional outcomes. For example, Logan and colleagues (2008) found that 44.3% of adolescents experiencing clinically-treated chronic pain were subject to declines in academic performance, as assessed by parent report of current grades and retrospective report of pre-onset grades.

In addition to examining academic performance, they collected data on school absence rates, self- and teacher-perceptions of academic competence, and accommodations provided due to pain. An average of 4.5 days (*SD* = 5.6) were missed per month according to school records. Self-reports of academic competence were comparable to those of chronic pain-free peers, whereas teacher-reports were higher than average. Lastly, one or more accommodations were provided to 67.4% of the sample. These findings indicate that adolescents experiencing chronic pain are at risk for declining academic performance, despite self- and teacher-perceived ability. However, the cross-sectional design precludes the ability to decipher transactional pathways and whether perceived academic competence is sustained across persistent declines in academic performance.

In addition to schooling, peer relationships are another formative influence on children's development impacted by chronic pain. In a systematic review of studies examining the impact of chronic pain on peer relationships in childhood and adolescence, only nine studies examined peer relationships as a primary focus with an additional 33 studies assessing peer relationships secondary to quality of life, mental health, and other factors (Forgeron et al., 2010). Greater rates of peer victimization, social isolation, and social anxiety/phobia were reported among children and adolescents experiencing chronic pain. The authors point out that a large proportion of children and adolescents experiencing comorbid chronic pain and mental health conditions also experience negative peer relationships, however so do those without comorbid mental health conditions. As such, they posit that mental health difficulties may not be the primary mechanism linking chronic pain to peer difficulties. The authors also highlight studies

examining peer relationships as a moderator of the association between chronic pain and mental health outcomes, with negative peer relationships exacerbating associations and positive peer relationships serving a protective function. These findings highlight the importance of examining individual and contextual factors, peer-related and beyond, as moderators of the association between chronic pain and mental health difficulties.

Beyond the impact of pediatric chronic pain on academic and social functioning, studies have also demonstrated functional consequences in other health domains, such as sleep. Children experiencing chronic pain have been found to exhibit clinically significant sleep disturbances which have, in turn, been found to predict impaired daytime functioning while controlling for demographic factors, pain characteristics, and depression (Long et al., 2008). However, these findings do not examine the potentially reciprocal relation between chronic pain and sleep. Interestingly, a review by Finan and colleagues (2013) examining the directionality of this relationship found that sleep disturbances are a more potent predictor of chronic pain in both clinical and population-based samples primarily consisting of adults. A relative dearth of research has examined these directional relations in children, however. For example, Incledon and colleagues (2016) examined associations between child and family factors and pain in a longitudinal, community-based study focused on the transition into adolescence. A history of pain symptoms was the strongest predictor of pain in adolescence; maternal chronic pain, adverse life events, and child-reported mental health and sleep disturbances were also significant predictors. Furthermore, in a model accounting for all predictors, a history of pain symptoms maintained the strongest association; however, sleep deficiency was the only additional predictor to maintain a unique association with pain problems in

adolescence above and beyond the effect of past pain. These findings suggest that research should examine the bidirectional relationship between sleep and pain but perhaps rethink assignment of temporal precedence, as it may be that sleep difficulties precede pain problems. Moreover, the influence of mental health disturbances on the dynamic relationship between pediatric pain and sleep warrants further attention. For example, symptoms of anxiety and depression have been found to partially mediate the association between sleep quality and pain interference and intensity in a clinical sample of children and adolescents (Pavlova et al., 2017).

Many of the reviewed studies examining the functional consequences of pediatric chronic pain include controls for mental health disturbances, particularly depression. This effort to eliminate confounds introduced by psychiatric symptomology when examining outcomes associated with pediatric chronic pain highlights the near axiomatic relationship that exists between chronic pain and mental health. However, the cursory inclusion of depressive symptoms as a covariate treats this comorbidity as nuisance rather than acknowledging the meaning and impact of their co-occurrence. Both clinical and population-based studies have documented the co-occurrence of various chronic pain types with depression and anxiety in childhood and adolescence (Anttila et al., 2000; Balottin et al., 2013; Blaauw et al., 2014; Feldman et al., 2010; Gordon et al., 2004; Skrove et al., 2014; Vaalmo et al., 2002). However, the cross-sectional designs of these studies preclude the ability to draw directional inferences and examine developmental trajectories underlying the progression of chronic pain and co-occurring psychiatric symptomology over time. In fact, several cross-sectional studies have corroborated chronic pain and mental health comorbidities in samples with rather large age ranges,

spanning from infants as young as less than a year old to adolescents 18 years of age (Coffelt et al., 2013; Kaczynski et al., 2016; Little et al., 2007). Aggregating effects across such a wide range of ages masks important, developmentally-salient nuance.

Longitudinal studies have attempted to elucidate directional relations between pediatric chronic pain and internalizing symptoms over time. Wolff and colleagues (2012) examined concurrent and prospective associations between chronic pain (e.g., ear, abdominal, and arm/leg pain) and internalizing problems in a population based study of toddlers. The authors tested prospective associations between chronic pain at 2 years of age and internalizing problems at 3 years, while controlling for internalizing problems at 1.5 years. They also tested prospective associations between internalizing problems at 1.5 years of age and new-onset chronic pain at 3 years, excluding children with persistent pain. Prevalence rates for chronic pain at 2 and 3 years of age were 1.3 and 2.3%, respectively, and a negligible percentage of children experienced persistent chronic pain from 2 to 3 years. Concurrent associations indicated that toddlers with chronic pain were more likely to exhibit simultaneous anxious and depressive symptoms. However, there were no significant longitudinal associations between chronic pain and internalizing problems or the reversed association. These findings suggest that onsets of both chronic pain and internalizing problems are directly linked and simultaneous in toddlerhood. The authors caution against generalizing these findings to other developmental stages and recommend expanding analyses to include older ages in order to determine when prospective relations emerge.

Larsson and Sund (2007) examined longitudinal associations between pain (i.e., headache, stomach, back, and limb pain) and internalizing problems within a similarly

constrained time frame (1 year), however the population-based sample comprised adolescents ranging in age from 12 to 15 years-old. In this much older sample, chronic pain predicted internalizing symptoms, with effect sizes increasing as frequency and number of pain sites increased. However, these prospective analyses were not as stringent as those conducted by Wolff and colleagues (2012); there were no controls for prior internalizing symptoms nor were there for subsequent pain, precluding the ability to fully decipher directional associations. Mikkelsson and colleagues (2008) utilized this more stringent approach in a population-based study of children's widespread pain and depressive symptoms. Ages ranged from 10 to 12 years-old at the inception of the study and follow-ups were conducted 1 and 4 years later. Depressive symptoms at baseline were found to predict new-onset widespread pain at follow-up, suggesting that internalizing problems are a risk factor for widespread pain in adolescence. They did not, however, assess whether widespread pain at baseline predicted later internalizing problems with the appropriate concurrent controls (i.e., internalizing at baseline and widespread pain at follow-up). It is possible that both patterns of prospective associations exist.

More research is needed to examine mechanisms underlying these comorbidities; as such, thorough assessments of relevant family and contextual factors (e.g., family history, dysfunction, socioeconomic status) as well as biologically-based mechanisms are needed to elucidate the contexts within which susceptibilities for co-occurring pediatric chronic pain and mental health disturbances unfold. Vinall and colleagues (2016) posit a number of neurobiological mechanisms that are influenced by gene-environment transactions and underlie comorbid presentations of chronic pain and psychopathology in childhood.

These include prolonged activation of the hypothalamic-pituitary-adrenal axis, serotonin availability, modified brain-derived neurotrophic factor expression, inflammation and immune system dysregulation, and activation of brain networks, particularly the limbic system. Examining the complex transactions that occur across these mechanisms requires methodologies, such as developmental behavioral genetic designs, that can elucidate causal pathways contributing to both early-presenting and *persistent* chronic pain and mental health comorbidities.

Continuity from Childhood to Adulthood

A call for more longitudinal research in the area of pediatric chronic pain should not be limited to early development; rather, a lifespan perspective should imbue the research as a means of elucidating long-term trajectories associated with early-presenting symptoms. For example, in both population-based and clinical samples, pediatric headache and back pain have been found to persist into adulthood (Brattberg, 2004; Fearon & Hotopf, 2001; Knook et al., 2012). Alternatively, evidence for the persistence of recurrent abdominal pain into adulthood emerges in clinical but not population-based samples (Hotopf et al., 1998; Magni et al., 1987; Shelby et al., 2013; Walker et al., 2012). Moreover, psychiatric symptoms have been found to both prospectively predict and be predicted by chronic pain symptoms from childhood to adulthood in longitudinal, population-based studies (Brattberg, 2004; Fearon & Hotopf, 2001; Hotopf et al., 1998). In contrast to studies examining the independent, prospective effects of chronic pain and psychiatric symptomology, a 6-year, clinical follow-up study of chronic headache in childhood and adolescence examined the effect of comorbid symptomology on the persistence of both pain and psychiatric symptoms into adulthood. They found that

comorbid symptomology did not predict persistence of chronic headache into young adulthood but did predict psychiatric disorder (Knook et al., 2011). These studies convey the dynamic processes involved in the manifestation of chronic pain and mental health symptoms over time, providing critical insight into the long-term outcomes associated with early onset of comorbid chronic pain and mental health disturbances. Moreover, studies have shown that adolescent chronic pain is prospectively associated with deficits in educational, vocational, social, and psychological aspects of young adult life, evidencing long-term functional impairments that potentially dampen quality of life and amplify suffering (Murray et al., 2020; Noel et al., 2016).

Family History of Chronic Pain

More research is need to identify risk factors associated with early-onset and persistent chronic pain as well as protective factors associated with the mitigation of chronic pain over time in an effort to derail these deleterious trajectories. A relatively simple, yet potent means of assessing risk for chronic pain is collection of family history data. Population-based studies examining the familial aggregation of pain indicate that odds of offspring pain increase when parents and other relatives experience pain themselves (Antilla et al., 2000; Boey & Goh, 2001a; Lester et al., 1994; Wilson et al., 2019). Evidence of site-specific pain parent-child associations has been found using parent-report of their own and their children's pain, though it has been suggested that these findings may be due to rater bias and therefore spurious (Grøholt et al., 2003). However, studies relying on independent reports of chronic pain from parents and offspring further bolster evidence of the familial aggregation of chronic pain, with parent-

offspring associations in both site-specific and multisite pain emerging (Hoftun et al., 2013; Saunders et al., 2007).

These studies consider diverse pain sites and account for the effects of important covariates, like age, sex, and sociodemographic factors. However, more studies should consider the moderating role of these variables rather than simply including them as covariates in order to identify contexts that potentially amplify or attenuate parent-child associations. For example, Stanford and colleagues (2008) reported a significant interaction between parent headache and child sex, such that girls who had a parent experiencing chronic headaches were more likely than boys to have high frequencies of chronic headaches in late adolescence. Studies have also considered the influence of parent sex on children's chronic pain experiences; results indicate that there are no significant differences in offspring reports of pain when contrasting maternal and paternal chronic pain experiences (Grøholt et al., 2003; Higgins et al., 2015). Moreover, odds of pediatric chronic pain increase when both parents are afflicted, indicating a dose-response relationship. Family structure has also been found to influence parent-child associations, with stronger relations emerging between children and the parent with whom they primarily reside. Specifically, Hoftun and colleagues (2013) found that significant mother-child but not father-child associations emerged when children resided with their mothers primarily. However, when children resided with their fathers primarily, both father-child and mother-child associations were significant, though the former was stronger. These findings implicate shared, familial environmental factors in the etiology of pediatric chronic pain, suggesting that there are common experiences contributing to clustering of chronic pain within families beyond shared genetic susceptibilities. More

studies are needed to elucidate potential mediators or underlying mechanisms contributing to this familial aggregation.

Importantly, other studies report no significant associations between parent and child chronic pain experiences (Borge & Nordhagen, 2000; Brattberg, 2004; Jones et al., 2004; Kovacs et al., 2003). Methodological explanations for these mixed findings include definition and assessment of pain at diverse sites, the age of the samples examined and other sample characteristics, such as whether they are community-based or clinical, and varying reporters of generational pain (i.e., use of parent report of child pain, offspring report of parent pain, or independent self-reports). Additionally, the studies vary in the extent to which they account for the effects of important covariates, particularly sociodemographic factors. Moreover, a paucity of studies considers the role of children's psychiatric symptomology in contributing to their chronic pain. Studies have demonstrated that children whose parents experience chronic pain exhibit more internalizing and externalizing problems than children whose parents do not (Higgins et al., 2015). Even fewer studies consider the effect of parents' psychiatric symptomology on children's chronic pain experiences. Cross-sectional research shows that mothers of children who experience chronic pain are more likely to have a lifetime history of depressive and anxious disorders (Campo et al., 2007). Integrating comprehensive assessment of family risk for *both* chronic pain and mental health disturbances into studies of pediatric chronic pain will help to elucidate the manner in which predispositions for chronic pain and psychiatric comorbidities are expressed in childhood and aid in the identification of targets that may be amenable to early intervention.

Putative Familial Environmental Factors

Studies have demonstrated that intergenerational pain associations are stronger when parents and offspring reside together, suggesting that shared environmental factors exert a substantive influence on the familial aggregation of symptomology (Grøholt et al., 2003). An abundance of phenotypic research has attempted to identify putative familial environmental factors that contribute to pediatric chronic pain, though the range of contexts examined is quite limited and there are areas of research that are ripe with opportunity for expansion. Parental modeling and reinforcement of chronic pain has garnered considerable attention, given parents' proximal and salient influence on children's development. Walker and Zeman (1992) were the first to study parental encouragement of children's pain. They found that when parents frequently attended to their children's pain and granted permission to avoid regular activities, children experiencing gastrointestinal symptoms were more likely to adopt the sick role. This seminal work laid the foundation for other studies to examine the role of parental behaviors in perpetuating children's chronic pain symptoms. Parental worries and catastrophic thinking about their children's pain and physical health have been associated with children's chronic pain symptoms and disability (Goubert et al., 2006; Guite et al., 2009; Wilson et al., 2014). Moreover, when parents experience chronic pain themselves, parental modeling of pain behavior and reinforcement of child pain have been associated with their children's chronic pain and internalizing symptoms. For example, Higgins and colleagues (2019) found that the association between parental pain interference and children's internalizing symptoms was mediated through child pain catastrophizing and

that the association between parental attending to children's pain and their children's pain intensity was mediated through children's pain-attending. The findings implicate parental modeling and reinforcement mechanisms, respectively. While the role of parents' pain related behaviors certainly warrants further attention, recommendations have been made to couch these effects within the broader context of other dyadic and family variables, like family functioning (Palermo & Chambers, 2005). An integrative contextual framework is needed in order to attain a comprehensive understanding of the environments within which pediatric chronic pain manifests.

The impact of family functioning (e.g., conflict, cohesion, communication, enmeshment) on pediatric chronic pain has also attracted substantial attention. Lewandowski and colleagues (2010) conducted a systematic review of both community-based and clinical studies examining the impact of family functioning on chronic pain and pain-related disability in childhood and adolescence. They identified 16 studies representing various pain conditions, including headache, abdominal pain, and musculoskeletal pain, and utilizing various measures of family functioning, both general and specific. Four of seven studies revealed that youth with chronic pain experienced worse family functioning compared to healthy or normative controls. Six of nine studies found that higher pain disability was associated with more family dysfunction. Lastly, findings from studies examining associations between family functioning and pain (e.g., frequency, intensity, duration, number of pain sites) were mixed, with some corroborating hypothesized associations between better family functioning and reduced pain and others producing unexpected results in the opposite direction. The authors speculate that there may be contexts where pain unites families and reduces relational

distress but posit that variable measurement of chronic pain could also underlie the mixed findings, advocating for the assessment of multiple pain characteristics in future studies. They also call for the validation of use of family functioning measures in pain populations. Additionally, they acknowledge limitations associated with the cross-sectional designs of the reviewed studies and highlight a need for more longitudinal research in order to elucidate trajectories of family functioning in the context of pain over time. In the decade since the publication of this review, a lack of longitudinal research examining the role of family functioning in pediatric chronic pain persists. In a population-based study of physical symptoms in adolescence (e.g., headache, stomachache, and musculoskeletal pain characterized as somatic rather than chronic) participants were assigned to non-symptomatic, moderate, high, or extreme symptom clusters. Those is the latter two clusters were more likely to report low parental affection and greater involvement, a pattern indicative of enmeshment, and to exhibit stability in cluster membership one year later (Rhee et al., 2005). Despite the longitudinal design, examinations of parental affection and involvement with cluster membership were correlational, highlighting a critical need for studies examining the role of family functioning in the stability of pain symptoms over time.

Stressful family events have also been associated with pediatric chronic pain. For example, population-based studies indicate that change in occupational status, hospitalization, and death of a family member are linked to prevalence of recurrent abdominal pain in children (Boey & Goh, 2001b) and physical abuse and parental divorce are linked to chronic daily headache in adolescence (Juang et al., 2004). When examining such phenomena, a biopsychosocial perspective would call for an examination of the

sociodemographic context in which families are embedded in order to attain a more comprehensive understanding of these processes. However, despite an established association between socioeconomic status (SES) and family functioning and stressful events (Brady & Matthews, 2002; Mansfield et al., 2013), studies have not consistently taken this effect into account. Moreover, relations between SES and pediatric chronic pain have been established in the epidemiological literature. In their review, King and colleagues (2011) report that only 12 of the 41 studies reviewed presented demographic information, including SES. In the studies that did, low SES was found to be associated with higher prevalence of pediatric chronic pain across various types, particularly headache. Thoughtful integration of sociodemographic context into research examining environmental influences on pediatric chronic pain and the familial aggregation of symptomology stands to present a more nuanced depiction of the contexts within which susceptibilities for pediatric chronic pain unfold.

More phenotypic research considering the influence of familial factors on pediatric chronic pain and the familial aggregation of symptomology is no doubt warranted. However, there are assumptions and potential confounds attached to this research that must be acknowledged if these findings are intended to ultimately inform targets of intervention. Genetically-informed studies present a means of testing these assumptions and identifying the pathways (genetic and/or environmental) by which these familial factors exert their influence on pediatric chronic pain.

(Shared) Genetic Etiology of Pain and Psychopathology

Studies of pediatric chronic pain and parent-offspring transmission have implicated various family level factors, however the assumption that these factors exert their

influence solely through environmental pathways is short-sighted and does not consider the possibility of genetic confounding, which presents when families share both common environments and genetic propensities. One potential source of confounding is gene-environment correlation (*r*GE), the process by which likelihood of environmental exposure is influenced by, or associated with, an individual's genotype (Plomin et al., 1977). There are three *r*GE processes: passive, evocative, and active. In passive *r*GE, associations between environmental exposures and individual traits are explained by the parental genotype, which underlies both parental provision of the environmental exposure and inheritance of the trait. In evocative *r*GE, heritable traits evoke reactions from an individual's environment. Lastly, in active *r*GE, an individual's genotype influences their tendency to seek out certain environments. Studies that do not acknowledge the possibility of genetic confounding via *r*GE when examining parent-offspring chronic pain transmission likely inflate the role of environmental mechanisms of transmission. Measured gene and quantitative genetic studies confer the ability to estimate the degree to which variance in a trait, like chronic pain, is genetically and/or environmentally influenced. Furthermore, there are measured gene and quantitative genetic methods that elucidate mechanisms of parent-offspring transmission while accounting for the effect of passive *r*GE, providing more precise estimates of genetic and environmental contributions to the familial aggregation of traits.

Measured gene research on chronic pain conditions is predominated by candidate gene or gene panel studies conducted with samples of less than 1000, whereby hypothesized associations with a single gene or a limited panel of genes are tested (Zorina-Lichtenwalter et al., 2016). However, these methods do not accommodate

polygenicity, meaning that several common single nucleotide polymorphisms (SNPs) underlie complex traits, like chronic pain, with each exerting a very small effect on the phenotype. Considering these small effect sizes, these studies are likely underpowered to detect true signals. In their review of genetic predictors of chronic pain conditions, including but not limited to migraine, low back pain, and fibromyalgia, Zorina-Lichtenwalter and colleagues (2016) aggregated over 150 genetic variants linked to chronic pain. The functional pathways associated with these genetic loci involved metabolism, immune response, cellular growth, apoptosis, protein structure and degradation. However, across all reviewed chronic pain conditions, an enrichment for genes involved in neurotransmission pathways was overwhelmingly observed. It is posited that genetic variants involved in neurotransmission and more pathophysiologically-specific secondary pathways interact with environmental factors to influence the development of specific chronic pain conditions. More large-scale, genome-wide association studies that are sufficiently powered to detect these small effects are needed to bolster findings from candidate gene and gene panel studies of chronic pain.

In contrast to candidate gene and gene panel studies, genome-wide association studies (GWAS) are not hypothesis-driven; rather, the effect of each individual SNP across the genome on the phenotype is tested. There are very few GWAS and GWAS meta-analyses of chronic pain, most of which feature migraine (Antilla et al., 2013; Chasman et al., 2011; Freilinger et al., 2012; Gormley et al., 2015; I.H.G. Consortium, 2010; Ligthart et al., 2011) and another two of which feature fibromyalgia (Docampo et al., 2014) and widespread chronic pain (Peters et al., 2013). Up to 44 independent SNPs have been associated with migraine across studies (Gormley et al., 2016). Conversely, the GWAS

for fibromyalgia produced no genome-wide significant hits (Docampo et al., 2014) and that of chronic widespread pain produced only one (Peters et al., 2013). Larger consortia are needed across various chronic pain conditions in order to attain the power needed to yield results comparable to those found in GWAS of migraine. Furthermore, measured gene research is plagued by many of the methodological limitations encountered in the phenotypic literature. Definitions of chronic pain vary across studies and measurement is often cursory. Ill-defined and poorly measured phenotypes likely impede the ability to detect significant effects. Additionally, measured gene studies rarely consider comorbid conditions, including psychiatric symptomology, despite robust phenotypic evidence that chronic pain and mental health disturbances often co-occur. Measured gene research can be harnessed to elucidate the extent to which these comorbidities are genetically mediated. For example, cross-trait linkage disequilibrium score regression analyses have produced significant and positive genetic correlations between pain phenotypes (e.g., headache, facial pain, neck or shoulder pain, stomach or abdominal pain, back pain, and widespread pain) and depressive symptoms, meaning that a significant proportion of the cross-trait covariance is genetically influenced (Meng et al., 2020). Put simply, these analyses entail regressing the product of SNP effect sizes for two traits (retrieved from GWAS summary statistics) onto scores indexing linkage disequilibrium (refers to nonrandom associations among alleles at different loci; Reich et al., 2001) in order to account for the bias introduced when the likelihood of inheriting certain blocks of alleles is greater than chance. These findings suggest pleiotropic effects, meaning that there are genetic variants that influence both pain and mental health disturbances, indicating a common genetic liability that may explain their comorbidity.

Other methods used to estimate the influence of genetic and environmental factors include quantitative genetic studies that consider the degree of phenotypic resemblance between individuals that vary in the extent to which they are genetically related (such as identical and fraternal twins) in order to estimate the proportion of variance in a trait that is genetically and/or environmentally influenced (Knopik et al., 2017). Specifically, structural equation modeling is used to parse the phenotypic variance for a selected trait into multiple latent factors: additive genetic influence (A, the sum of the average effects of individual genes across the genotype), nonadditive genetic influence (D, the interaction of alleles at the same or different loci), shared environmental influence (C, environmental factors common to co-twins and contributing to their similarity), and non-shared environmental influence (E, environmental factors specific to one co-twin and contributing to within-pair differences, as well as measurement error). Twins present a unique, methodological advantage in that they are genetically related and subject to many of the same environmental exposures while also obtaining unique experiences of their own. Beyond this, twins can vary in the degree to which they are genetically related. Monozygotic (MZ) twins share 100% of their genes. MZ twin similarities can be compared to dizygotic (DZ) twins who share, on average, 50% of their segregating genes. If a trait is uniquely influenced by genetic factors, MZ twins are expected to exhibit phenotypic correlations which are twice those of DZ twins (or greater than twice the correlation of DZ twins in the case of nonadditive genetic influence). Conversely, if DZ twins exhibit phenotypic correlations that exceed half of the MZ correlations, shared environmental influences are implicated. The univariate twin model can be extended to a bivariate framework, whereby the covariance between two traits is parsed into latent A, C

or D, and E factors, estimating the degree to which genetic and environmental influences on one trait are shared with a second. If cross-twin, cross-trait correlations are higher for MZ twins, shared genetic influence across the two traits is implicated. If correlations are comparable across zygosity groups, shared environmental influence is implicated.

Despite their strengths, classical twin models are subject to certain addressable limitations. First, the classical twin model assumes that there is no assortative mating on the phenotypic trait. Assortative mating is the tendency for individuals to partner with mates matched similarly on phenotype. Under assortative mating, DZ twins appear more similar than would be expected in its absence, inflating shared environmental estimates and attenuating heritability estimates. Additional limitations include inabilities to simultaneously estimate A, C, D, and E, to account for passive *r*GE, and to parse C into twin specific versus family level influences. As stated previously, MZ twin correlations greater than twice those of DZ twins indicate presence of nonadditive genetic influence. When evidence of nonadditivity emerges, the classical twin model is limited to estimating only three latent effects. ACE or ADE models can both be estimated, however when they fit the data equally well, there is no empirical means of selecting one over the other. This is problematic, given that the models are subject to distinct interpretations. Next, a failure to account for passive *r*GE inflates shared environmental estimates and attenuates heritability estimates, again limiting precision. Finally, an inability to distinguish shared environmental influences experienced specifically by twin siblings from those that operate more broadly at the family level provides us with a limited understanding of trait-relevant contexts.

The nuclear twin family model is an extension of the classical twin model that addresses the aforementioned limitations. It incorporates parental data, presenting additional information from which parameter estimates are derived. The classical twin model utilizes covariance between MZ and DZ twins to acquire these estimates; the twin family model is able to additionally base parameter estimates on the covariance between parents and the covariance between parents and offspring. This allows the model to account for the effect of assortative mating, to simultaneously estimate A, C, D, and E influences, and to differentiate passive *r*GE from true shared environmental influence by modeling the covariance between genetic and family level environmental factors. This model differentiates shared environmental influence which is common to parents and twins from that which is specific to the twin siblings. It can also determine whether true familial transmission from parents to offspring, accounting for the effect of *r*GE, significantly accounts for the intergenerational resemblance on a phenotypic trait above and beyond the influence of shared genes (Keller et al., 2009). Evidence of familial transmission is of particular interest in that it presents a promising window for intervention, free from genetic confounds encountered in non-genetically informed research. The nuclear twin family model has also been extended to a bivariate framework (Keller et al., 2013). Despite these strengths, the model is rarely utilized and has only been applied to the study of psychopathology, personality traits, cognitive outcomes, and values.

Despite an abundance of epidemiological research indicating high prevalence rates of pediatric chronic pain and a need for studies that elucidate underlying mechanisms which can be targeted by preventative and intervening care, there are just four classical twin

studies that examine genetic and environmental influences on pediatric chronic pain. Relying on parent-report of recurrent headaches in eight to nine-year-old Swedish twins, Svensson and colleagues (1999) tested univariate twin models with and without sex-limitation effects. The prevalence rate for recurrent headache in the full sample was 13.7%. They reported no significant differences between boys and girls, despite evidence from epidemiological research indicating that headache is more prevalent among girls (King et al., 2011). An AE model was the best-fitting model without sex-limitation effects, with additive genetic factors explaining 70% of the variance in recurrent headache and nonshared environmental factors explaining 30%. AE models with sex limitation effects were then tested, and a model freely estimating the additive genetic correlation between boys and girls fit the data best. The additive genetic correlation was estimated at zero, suggesting distinct genetic etiologies for boys and girls. Considering a greater susceptibility for headache and other chronic pain conditions among girls, this finding suggests that the genetic etiology of chronic pain conditions should not be assumed to be equal across sexes, as such an assumption may perpetuate sex disparities in preventive and intervening care.

Mikkelsson and colleagues (2001) acquired self-reports of widespread pain among 11-year-old Finnish twins, estimating genetic and environmental effects. Classification of widespread pain required a frequency of pain at least once a week over a period of approximately 3 months. Pain had to occur above and below the waist, on both sides of the body, and in the axial skeleton. The prevalence rate was 9.9% in the full sample and did not differ significantly between boys and girls. A CE model was the best-fitting sex-limited model; C and E parameters could not be equated across boys and girls. For boys

and girls, 35 and 56% of variance in widespread pain was explained by shared environmental factors, respectively, with the remaining variance explained by nonshared environmental factors. These findings suggest that shared environmental factors, like family dysfunction, are perhaps more salient to widespread pain experiences among girls, whereas factors outside of the family environment may be a more potent influence among boys. Consequently, sex-specific routes of environmental intervention for widespread pain may be necessary.

Relying on the same cohort of 11-year-old Finnish twins, El-Metwally and colleagues (2008) estimated the degree of genetic and environmental influence on twin-reported, non-specific low back pain. The prevalence rates for low back pain occurring once a month and at least once a week during the previous 3 months were 15.7 and 6.7%, respectively. Boys endorsed weekly low back pain at a significantly higher rate than girls. Again, sex-limited twin models were tested; however, there was no evidence of sex-specific genetic variance and parameter estimates could be equated across boys and girls. A CE model was the best-fitting model, with 41 and 59% of the variance explained by shared and nonshared environmental influences, respectively. In contrast to findings from twin models on recurrent headache and widespread pain, there were no sex differences in genetic etiology or in the extent to which low back pain was environmentally influenced, suggesting that preventative and intervening care for non-specific low back pain may generalize to both sexes.

Finally, in another study relying on the same cohort of 11-year-old Finnish twins, Ståhl and colleagues (2013) estimated the degree of genetic and environmental influence on twin-reported, non-specific neck pain. The prevalence rates for neck pain occurring

once a month and at least once a week during the previous 3 months were 38.3 and 16.3%, respectively. There were no significant differences between boys and girls. Again, sex-limited models were tested; there was no evidence of sex-specific genetic variance and parameter estimates could be equated across boys and girls. An AE model fit the data best, with 68% of the variance in neck pain explained by additive genetic factors. Findings suggest no sex differences in the source and magnitude of effect for genetic etiology or in the extent to which neck pain is influenced by the nonshared environment, implying that intervening and preventative efforts targeting genetic liabilities and unique environmental factors may generalize to both sexes.

The current state of twin research on pediatric chronic pain conditions falls grossly short of a need to identify etiological mechanisms of pain phenotypes that are both prevalent and associated with myriad adverse outcomes. In these studies, widespread and low back pain were environmentally mediated, whereas headache and neck pain were subject to additional genetic influence. There are blatant needs for more twin research across various chronic pain conditions in childhood and for recruitment of more diverse samples in order to corroborate these findings and determine whether they generalize across samples and methodologies. The reviewed studies all relied on samples of Nordic ancestry, with 3 of the 4 studies utilizing the same Finnish cohort. Assuming that these findings generalize to more diverse populations could be a risky oversight that may function to exacerbate health inequities among populations that are severely underrepresented in quantitative genetic research. Moreover, multivariate twin studies examining the etiology underlying covariation of chronic pain conditions and mental health disturbances are needed to elucidate sources of common liability.

Unfortunately, there are no studies examining shared genetic and/or environmental influences underlying co-occurring pain and mental health symptomology in childhood or adolescence. To date, such analyses have only been conducted with adult samples. In a systematic review of 23 twin studies examining covariation of pain with depression and anxiety in adulthood, Khan and colleagues (2020) found that covariation was genetically mediated or both genetically and environmentally mediated in nearly all studies. These findings held across various chronic pain sites, including headache, lower back, neck, gastrointestinal, and chronic wide spread pain. However, these findings cannot be assumed to generalize to younger samples; as such, parallel methods examining the shared etiology across chronic pain and mental health symptomology should be applied in childhood in order to advance our understanding of the mechanisms that explain early-onset comorbidity.

Both chronic pain and psychiatric conditions have been found to cluster within families and are transmitted from parents to offspring, however little is known regarding mechanisms which contribute to the intergenerational transmission of chronic pain and its mental health comorbidities. The nuclear twin family model has been used to determine whether true familial environmental transmission from parents to offspring, controlling for the effects of *r*GE and assortative mating, significantly accounts for the intergenerational resemblance on phenotypes above and beyond the influence of shared genes. Nuclear twin family studies of conduct disorder, antisocial behavior, social aggression, delinquent behavior, ADHD, and alcohol use have found that shared genetic proclivities primarily account for parent-offspring resemblance (Burt & Klump, 2012; Burt et al., 2012; Kendler et al., 1994; Koopmans & Boomsma, 1996; Maes et al., 2007;

Meyer et al., 2000; Slawinski et al., 2019; Taylor et al., 2000). Two studies have considered the etiology of parent-offspring similarity in internalizing, utilizing extended pedigrees of parent, offspring, spouse, and sibling data for panic-phobia, somatization, and depressive symptomology. Both studies reported substantial genetic influence and significant assortative mating with little to no evidence of familial environmental influence. For panic-phobia only, modest evidence emerged for familial environmental transmission from mothers and twin-specific environmental influence for females (Kendler et al., 1994; Kendler et al., 1995). Also, Rice, Harold, and Thapar (2005) employed a sample of mothers and their twin offspring aged 8 to 17 years to elucidate mother-offspring transmission of depression. They observed evidence of familial environmental transmission above and beyond the influence of shared genes when maternal ratings of adolescent symptomology were utilized, but the finding did not generalize to offspring self-report. These studies suggest strong genetic influences on internalizing psychopathology, with significant assortative mating, and some inconsistent evidence of shared familial environmental influence. Nuclear twin family studies of chronic pain are needed to determine whether these traits are also primarily transmitted via genetic pathways or if the familial environment contributes to symptom clustering within families above and beyond shared genetics.

Overall, very little is known regarding the etiology of pediatric chronic pain, its mental health comorbidities and potential mechanisms of intergenerational transmission, as measured gene, univariate, multivariate, and nuclear twin family studies have tended to focus on adult conditions. Applying these methods to child and adolescent samples stands to elucidate the etiology of early-onset conditions and may ultimately shed light on

means of prevention and intervention to disrupt intergenerational cycles of chronic pain and mental health transmission and ultimately mitigate personal suffering.

The Current Study

Research examining the intergenerational transmission of chronic pain has tended to focus on adult populations, despite epidemiological findings that indicate childhood chronic pain is pervasive and associated with myriad adverse consequences (King et al., 2011). Moreover, due consideration has not been given to the widespread mental health disturbances that often accompany chronic pain conditions. By assessing twin-sibling resemblance across chronic pain and internalizing symptomology, the current study elucidated the etiological mechanisms that mediate their co-occurrence in middle childhood. Moreover, the current study examined parent-offspring associations across chronic pain and internalizing symptomology, investigating patterns of familial aggregation and the etiological mechanisms that mediate them. Specifically, the current study tested the following aims:

Aim 1. The first aim of the current study was to determine the degree to which genetic and environmental factors explain variation in childhood chronic pain and internalizing symptomology (univariate twin analyses) as well as the extent to which these factors contribute to unique and shared variation across them (bivariate twin analyses). Based on the few extant studies of chronic pain in twin children (El-Metwally et al., 2008; Mikkelsson et al., 2001; Ståhl et al., 2013; Svensson et al., 1999), it was hypothesized that additive genetic, shared environmental, and nonshared environmental influences would underlie childhood chronic pain symptomology. Based on adult twin studies examining covariation of pain and internalizing symptoms (Khan et al., 2020), it

was hypothesized that most of the shared variance would be accounted for by additive genetic influences.

Aim 2. The second aim of the current study was to determine whether maternal and paternal chronic pain and internalizing symptoms are associated with children's chronic pain and internalizing symptoms. Given the higher rates of chronic pain symptomology observed among girls and substantiated moderation of parent-offspring pain associations by child sex (King et al., 2011; Stanford et al., 2008), interactions with child sex were also tested. It was hypothesized that both maternal and paternal chronic pain and internalizing symptoms would be positively associated with children's chronic pain and internalizing symptoms. It was also expected that these associations would be more pronounced for girls than boys.

Aim 3. The final aim was to determine the degree of genetic and environmental influence on the familial aggregation of chronic pain and internalizing symptoms using the nuclear twin family design. Based on phenotypic studies examining influences of parental chronic pain and mental health on family functioning (Herr et al., 2007; Higgins et al., 2019), it was hypothesized that family level environmental influences would significantly contribute to parent-offspring covariance above and beyond shared genetics. However, a developmental lens necessitates the consideration of possible generational differences in etiology; therefore, sibling-specific and nonshared environmental influences were also hypothesized. As such, models estimating additive genetic, family level-, sibling specific-, and nonshared environmental influences were expected to best represent the familial aggregation of both chronic pain and internalizing symptoms.

CHAPTER 2

METHOD

Participants

The sample comprised 795 children (399 families) who participated in the age 9 assessment of the Arizona Twin Project, 755 (381 families) for whom either chronic pain or internalizing symptom data were available (Lemery-Chalfant et al., 2019). Specifically, 372 and 364 twin pairs were included in univariate twin modeling of chronic pain and internalizing symptomology, respectively. For bivariate twin modeling, a total of 359 twin pairs were included. Maternal and paternal chronic pain and/or internalizing symptom data were available for 353 and 221 families, respectively. For multilevel regressions examining phenotypic parent-offspring associations, data from all 399 families were included using full information maximum likelihood. For nuclear twin family models of chronic pain and internalizing symptomology, data from 194 and 187 intact families were included, respectively. For families with both maternal and paternal data available (N = 199), mothers were older (M = 39.72, SD = 4.96 versus M = 38.60, SD = 6.27, $t(586) = -2.43$, $p < .05$), twins were younger (M = 9.54, SD = 0.89 versus M = 9.86, SD = 0.90, $t(701) = 4.77$, $p < .001$), and socioeconomic status was higher (M = 0.10, SD = 0.74 versus M = -0.13, SD = 0.82, $t(683) = -3.84$, $p < .001$) when compared with families for whom only maternal data were available (N = 154). Additionally, families with and without paternal data did not differ on levels of maternal chronic pain (M = 2.99, SD = 2.94 versus M = 2.64, SD = 2.53, $t(701) = -1.69$, $p = .09$) and internalizing symptomology (M = 0.28, SD = 0.28 versus M = 0.32, SD = 0.34, $t(653) = 1.60$, $p = .11$) nor did they differ on levels of twin chronic pain (M = 1.38, SD = 1.66

versus M = 1.32, SD = 1.68, $t(691)$ = -0.42, p = .67) and internalizing symptomology (M = 1.25, SD = 0.18 versus M = 1.28, SD = 0.21, $t(697)$ = 1.68, p = .09). Twins were 9.7 years old (SD = 0.93) at data collection. The sample was evenly split between males and females (51.2% female) and was racially/ethnically diverse (59.8% Non-Hispanic White, 28.0% Hispanic/Latinx, 3.4% Asian, 3.9% Black, and 4.9% Mixed Race/Other). 31% of twins were MZ, 35% same-sex DZ, and 34% opposite-sex DZ. Families were socioeconomically diverse, such that 7.3% of families were considered to be living below the poverty line for a family of their size, 22.9% at or near the poverty line, 15.9% in lower middle class, and 53.9% in middle to upper class based on income-to-needs ratios. 1.2% of mothers did not complete high school, 9.7% obtained a high school or equivalent degree, 24.4% attended some college but did not graduate, 41.5% obtained college degrees, 2.4% completed 2 or more years of graduate school, and 20.9% obtained graduate or professional degrees.

Procedure

Prior to the start of the study, Institutional Review Board approval was obtained for all procedures. Parental written informed consent and child assent were obtained. Families completed a home visit and parents completed online surveys. Mother and father reports of chronic pain and internalizing symptoms and primary caregiver reports of twin chronic pain and internalizing symptoms were obtained via online surveys.

Measures

Chronic Pain. Primary caregivers (90% mothers, 6% fathers) reported on their own and each twin's chronic pain. Secondary caregivers (50% fathers, 4% mothers) provided separate reports of their own chronic pain. Reports of pain occurring at 15 different body

locations in the last three months on a 1 (rarely/never) to 5 (about every day) scale were obtained for primary caregivers and twins, and reports across 7 body locations were obtained for secondary caregivers. The pain assessments were recoded, such that sites with pain endorsed at least "once a month or more" were given a value of "1" and sites with pain "rarely/never" were coded as 0. The sites were then summed to obtain a total number of body sites with pain recurring at least once a month (possible range 0–15 for primary caregivers and twins and 0-7 for secondary caregivers). Pain assessment using the same 1-5 scale has been validated in child and adolescent samples (Mikkelsson et al., 1997; Stanford et al., 2008).

Internalizing Symptoms. Twins' internalizing symptoms were assessed via primary caregiver report using the mental health scales of the Health and Behavior Questionnaire (HBQ; Armstrong et al., 2003). The internalizing composite is comprised of depression (7 items; α= .58), overanxious (13 items; α= .73), and separation anxiety (10 items; α= .69) scales. From this 30-item composite (α= .82), 3 items that are related to pain were removed to ensure associations were not driven by overlap in constructs. All 3 pain items were from the overanxious scale. Caregivers responded to all items on a 1 (never or not true) to 3 (often or very true) scale, with higher scores indicating more internalizing symptoms. An HBQ internalizing symptom composite threshold of 1.72 has been found to predict clinical diagnoses (Lemery-Chalfant et al., 2007). Based on this threshold, 3.1% of twins in the current sample experienced clinically significant internalizing symptoms.

Parent internalizing symptoms were assessed via self-report on the Center for Epidemiologic Studies Depression Scale (CESD; Radloff, 1977) and the Depression

Anxiety Stress Scales (DASS; Lovibond & Lovibond, 1995a). The CESD is a self-report measure of adult depressive symptoms designed for use in the general population. Respondents rate the frequency with which 20 depressive symptoms have manifested over the past week (α= .90 and .82 for mothers and fathers, respectively). Response categories are 0- "rarely or none of the time (less than 1 day)", 1- "some or a little of the time (1-2 days)", 2- "occasionally or a moderate amount of time (3-4 days)," and 3- "most or all of the time (5-7 days)." A sum score of 16 or higher is considered to have clinical significance. In the current sample, CESD sum scores of 16 or higher were obtained for 12.5% and 11% of mothers and fathers, respectively, indicating likely presence of clinically significant depression. The CESD has demonstrated very high internal consistency, and adequate test-retest reliability across a wide variety of samples with different demographic characteristics (Radloff, 1977) and across White, Black, and Mexican American samples (Vernon & Roberts, 1981). The DASS is a self-report measure of adult depressive, anxious, and stress symptoms. In the current study, only the anxiety subscale was utilized. Respondents rated the extent to which symptoms apply to them for 14 items assessing physiological arousal, perceived panic, and fear (α= .80 and .71 for mothers and fathers, respectively). Response categories are 0- "Did not apply to me at all", 1- "Applied to me some degree, or some of the time", 2- "Applied to me to a considerable degree, or a good part of the time," and 3- "Applied to me very much, or most of the time." DASS anxiety subscale sum scores ranging from 0 to 7, 8-9, 10-14, 15-19, and 20 or above are indicative of normal, mild, moderate, severe, and extremely severe symptom levels, respectively. 91 and 92.1% of mothers and fathers experienced normal symptoms, 2.6 and 3.7% experienced mild symptoms, 4.6 and 3.2% experienced

moderate symptoms, 1.3 and 0.5% experienced severe symptoms, and 0.6 and 0.5% experienced extremely severe symptoms. The DASS has demonstrated high internal consistency and good test-retest reliability (Brown et al., 1997; Lovibond & Lovibond, 1995b). A mean composite characterizing internalizing symptoms broadly was formed using the CESD depression and DASS anxiety scores.

Zygosity. The Zygosity Questionnaire for Young Twins (Goldsmith, 1991) is a 32-item measure designed to assess the zygosity of twin pairs ($\alpha = .95$). Caregivers responded to questions regarding their pregnancy and the presence of observable differences between the twins. The agreement of this particular questionnaire with genotyping has been estimated at 96% (Forget-Dubois et al., 2003), rendering it a less burdensome and more cost effective alternative. The questionnaire was administered on multiple occasions, and photographs were also examined. Ambiguous cases were resolved with genotyping.

Pubertal Status. The Pubertal Development Scale (Petersen et al., 1988) is a 10-item measure designed to assess pubertal status in developing children and adolescents. Primary caregivers reported on their twins' growth in height, body hair, and skin changes over the past 2 months. Questions regarding breast growth and menstruation were asked of female twins, and questions regarding growth of facial hair and voice changes were asked of male twins. Response categories range from 1 to 4, with 1 indicating that growth has not begun or changes have not been observed and 4 indicating that growth or change is complete. Mean composites were formed, with higher scores indicating more advanced pubertal development. A PDS score of 1.5 indicates pubertal onset and a score of 2.5 represents mid-puberty, corresponding to Tanner stage 3 (Beltz et al., 2014).

Accordingly, 54.5% of twins in the current sample were considered prepubertal, 41.6% had reached pubertal onset, and 4% had reached mid-puberty.

Covariates. Sex and age effects were regressed out of twin phenotypes and residual scores utilized in subsequent twin model fitting, following standard practice (McGue & Bouchard, 1984). In phenotypic analyses testing parent-child associations, twin sex, age, ethnicity and pubertal status, mother and father age, and family socioeconomic status (a composite of income-to-needs ratio and primary and secondary caregiver education level) were included as covariates.

Statistical Approach

Preliminary Analyses. Descriptive statistics including means, standard deviations, minimums, maximums, skew, and kurtosis for all study variables were conducted in Mplus 8 (Muthén & Muthén, 1998-2017; version 8.4) and are reported in Table 1. Univariate outlier analyses, skew, and kurtosis were examined to determine whether any variables had significant outlying values that may bias estimates. Variables with significant outliers, skew, and/or kurtosis were windsorized to +/- 3 *SD*s. Specifically, mother and father internalizing symptoms exceeded the recommended cutoff for skew, and mother, father, and twin chronic pain and internalizing symptoms contained outlying values that were windsorized to +/- 3 *SD*s. No variables exceeded the recommended cutoff for skew (+/- 2) or kurtosis (+/- 7; Muthén & Kaplan, 1985) after windsorizing. Zero-order correlations between all study variables were conducted in Mplus 8 (Muthén & Muthén, 1998-2017; version 8.4) using the type = complex command to account for twin interdependence, and twin intraclass correlations (ICCs) for child chronic pain and internalizing were computed in OpenMx (Boker et al., 2011; Table 2). If MZ twin ICCs

are more similar than those of DZ twins, additive genetic influence is implicated. When MZ twin ICCs exceed more than double those of DZ twins, this suggests additional nonadditive genetic influence. Conversely, when MZ and DZ twin ICCs are comparable, shared and nonshared environmental influences are implicated.

Aim 1. Univariate and bivariate ACE models estimating genetic and environmental influences on child chronic pain and internalizing symptomology were conducted in OpenMx (Boker et al., 2011), an R-based program that implements maximum likelihood estimation to estimate genetic and environmental variance and covariance using structural equation modeling. First, saturated models were tested to determine the presence of twin order, rater contrast, and/or assimilation effects in the data. Fully saturated multigroup models freely estimating means and variances for MZ and DZ twins were tested against a series of models constraining means and variances to be equal across twin order and zygosity. Higher DZ vs. MZ twin variance suggests that reporters may be inflating DZ twin differences (contrast effects) or MZ twin similarities (assimilation effects), whereas lower DZ twin variance suggests possible sibling cooperation or imitation effects (Neale & Cardon, 1992). Once the assumptions of the twin model were examined, univariate ACE models were tested. The ACE model is a multigroup structural equation model that utilizes observed phenotypic variances and covariances of MZ and DZ twins to estimate latent factors A (or additive genetic influence, representing the sum of the average effects of individual genetic variants across the genome), C (or shared environmental influence, representing environmental exposures shared by both cotwins that contribute to cotwin similarity), and E (or non-shared environmental influence, representing environmental

exposures uniquely experienced by one cotwin, contributing to intrapair differences, as well as measurement error; Figure 1).

MZ twins share 100% of their segregating genes, and DZ twins share, on average, 50%; as such, the A factor correlation is fixed to 1 for MZ twins and to .5 for DZ twins. C is fully shared by cotwins; as such, the C factor correlation is fixed to 1, regardless of zygosity. Lastly, the E factor correlation is fixed to zero for both MZ and DZ twins. First, full models estimating latent A, C, and E factors were fit. Next, parameters were systematically dropped and the fits of reduced, nested models compared against the full model using the –2 log likelihood chi-square test of fit to determine the most parsimonious solution. A nonsignificant difference in fit suggests that the reduced model represents the observed data as well as the full model, whereas a significant change in fit indicates that the dropped parameter should be retained, as it is required to accurately represent the observed data. E is always retained because it contains measurement error.

Bivariate twin models were fit to determine the genetic and environmental contributions to shared etiology across child chronic pain and internalizing symptomology. The bivariate Cholesky decomposition estimates unique additive genetic (A22), shared environmental (C22), and nonshared environmental influences (E22) on phenotype 2 while accounting for shared additive genetic (A21), shared environmental (C21), and nonshared environmental (E21) influences with phenotype 1. Estimates from the bivariate Cholesky decomposition can be used to calculate the proportion of shared variance explained by A, C, and E influences as well as the proportion of total variance in phenotype 2 that is explained by shared and independent A, C, and E influences. When MZ cross-twin cross-trait correlations are higher than those of DZ twins, additive genetic

effects are implicated as underlying co-occurrence. When there are no differences between MZ and DZ cross-twin cross-trait correlations, shared environmental influences are implicated. Additionally, the bivariate twin model can estimate the degree to which genetic (*r*G), shared environmental (*r*C), and nonshared environmental factors (*r*E) for two traits are correlated (Figure 2).

Aim 2. Multilevel regression analyses testing associations between parent and child chronic pain and internalizing symptoms were conducted in Mplus (Muthén & Muthén, 1998-2017; version 8.4) to account for the nested data structure (i.e., twins [Level 1] within families [Level 2]) and using full information maximum likelihood (FIML) to account for missing data. In total, 4 models were tested. Maternal chronic pain and internalizing symptoms were included as separate predictors in models testing associations with 1) child chronic pain and 2) internalizing symptoms. Models with paternal chronic pain and internalizing symptoms included as separate predictors were tested in turn. The following is an example set of equations for one model. ChildChronic*Pain*$_{ij}$ represents the number of body sites with monthly pain persisting for 3 months or more for child *i* in family (cluster) *j*. Maternal chronic pain and internalizing were measured at Level 2 and twin sex and its interaction with maternal chronic pain were measured at Level 1.

Level 1: ChildChronic*Pain*$_{ij}$ = β_{0j} + β_{1j}ChildSex$_{ij}$ + β_{2j}MaternalChronicPainXChildSex$_{ij}$ + β_{3j}ChildPubertalStatus$_{ij}$ + e_{ij}.

Level 2: β_{0j} = Υ_{00} + Υ_{01}MaternalChronicPain$_{1j}$ + Υ_{02}MaternalInternalizing$_{2j}$ + Υ_{03}ChildAge$_{3j}$ + Υ_{04}ChildEthnicity$_{3j}$ + Υ_{05}MaternalAge$_{5j}$ + Υ_{06}SES$_{6j}$ + u_{0j}

β_{1j} = Υ_{10} + u_{1j}

$$\beta_{2j} = \Upsilon_{20} + u_{2j}$$

$$\beta_{3j} = \Upsilon_{30} + u_{3j}$$

Twin sex, age, ethnicity and pubertal status, parental age, and family socioeconomic status (a composite of income-to-needs ratio and primary and secondary caregiver education level) were included as covariates. Interactions between maternal or paternal chronic pain and internalizing symptoms and twin sex were tested. Significant interactions were probed using simple slopes analysis for hierarchical linear modeling (Preacher et al., 2006).

Aim 3. Prior to model fitting, reports of mother, father, and twin chronic pain and internalizing symptomology were z-scored. Nuclear twin family models were conducted in OpenMx (Boker et al., 2011). The model utilizes observed covariances between mothers, fathers, and twins (both MZ and DZ) and their degree of genetic relatedness (MZ twins share 100% of their segregating genes with each other and 50% with each parent where DZ twins share 50% of their segregating genes with each other and with each parent) to estimate the proportion of phenotypic variance attributable to genetic and environmental influences. The covariances between parents and between parents and offspring allow for the simultaneous estimation of variance attributed to additive genetic factors (A), nonadditive or dominant genetic factors (D), twin-specific shared environment (S), familial environmental transmission from parents to offspring (F), and nonshared environment (E). However, a single model is only able to estimate three out of the four A, D, S, and F components (E is always included because it includes measurement error), requiring one of the estimates to be fixed at zero. The model can account for assortative mating, or the covariance between mothers and fathers, as it

impacts the estimation of A and F. Passive rGE is represented by the covariance between the A and F. An assumption of the NTF design is that genetic variance components are equal in the parent and offspring generations. (Figure 3; See Keller et al., 2009, for a NTF model review.)

First, all possible full models with variances, covariances, and means freely estimated were tested (i.e., ADSE, ADFE, and ASFE). The best-fitting full model was then selected as the base model against which the fits of reduced, nested models were compared (i.e., ADE, ASE, AFE, and AE). D, S, and F parameters were systematically dropped, and reduced models were evaluated for fit. The Akaike's Information Criterion (AIC; Akaike, 1987), the Bayesian Information Criteria (BIC; Raftery, 1995), and the sample-size adjusted Bayesian Information Criterion (SABIC; Sclove, 1987) fit indices were used to determine the most parsimonious fit to the data. A significant change in fit after dropping a parameter indicates that the reduced model fits significantly worse than the full model. In this case, the parameter should be retained, as the pathway contributes significantly to the phenotypic variance. These fit indices do not consistently agree; as such, best fitting model criteria required lower or more negative values for at least two of the three fit indices.

CHAPTER 3

RESULTS

Preliminary Analyses

Descriptive Statistics. Means, standard deviations, minimums, maximums, skewness, and kurtosis for all study variables are presented in Table 1. On average, mothers experienced chronic pain at 2.84 sites (*SD* = 2.77), fathers at 1.79 sites (*SD* =

1.60), and twins at 1.37 sites (*SD* = 1.75). On scale of 0 to 3, mothers reported an average of .30 internalizing symptoms (*SD* = .30) and fathers an average of .25 symptoms (*SD* = .31). On a scale of 1-3, twins experienced an average of 1.26 internalizing symptoms (*SD* = .20).

Correlations. Zero-order correlations are presented in Table 2. Chronic pain and internalizing symptoms were positively associated within mothers, fathers, and twins. Mother and father internalizing symptoms were positively associated, but chronic pain was not. The correlation between chronic pain and internalizing symptoms was higher for fathers ($r = .39$, $p < .01$) than mothers ($r = .29$, $p < .01$), though a Fisher's *r*-to-*z* transformation indicated no significant difference in the correlations ($z = -1.82$, $p = .07$). Mother chronic pain was positively associated with both twin chronic pain and internalizing symptoms, as were mother internalizing symptoms. Father chronic pain was not significantly associated with either twin chronic pain or internalizing symptoms. Father internalizing symptoms were positively associated with twin internalizing symptoms but not chronic pain.

Regarding demographic variables, age was not significantly associated with chronic pain or internalizing symptoms in either mothers, fathers, or twins. Twin sex, ethnicity, and pubertal status were not significantly associated with either twin chronic pain or internalizing symptoms. Finally, SES was negatively associated with both mother and father internalizing symptoms.

Twin ICCs. Twin intraclass correlations (ICCs) are presented in Table 2. MZ twins were more similar than DZ for both chronic pain (ICCs = .79 vs. .45) and internalizing symptoms (ICCs =.81 vs. .67).

Aim 1: Genetic and Environmental Influences on Children's Chronic Pain and Internalizing Symptomology

Saturated models were fit for both chronic pain and internalizing symptoms. Means and variances could be equated across twin order and zygosity, indicating no evidence of twin order, rater contrast, or assimilation effects. Standardized A, C, and E squared parameter estimates and fit statistics for the full and best fitting reduced univariate models of chronic pain and internalizing are presented in Table 3. For chronic pain, the best fitting model was the reduced AE model, with 78 and 22% of the variance explained by additive genetic and nonshared environmental influences, respectively. For internalizing symptoms, the best fitting model was the full ACE model, with 32, 50, and 18% of the variance explained by additive genetic, shared environmental, and nonshared environmental influences, respectively.

Fit statistics for the full and best fitting reduced bivariate models of internalizing symptoms and chronic pain, as well as A, C, and E squared parameter estimates are given in Table 4. The best fitting model was an ACE-AE model. Shared additive genetic factors explained all of the covariance between the two phenotypes. The A1 factor explained 34% of the variance in internalizing symptoms and 9% of the variance in chronic pain. An additional 69% of the variance in chronic pain was explained by the specific, A2 factor. The C1 and E1 factors explained 48 and 18% of the variance in internalizing symptoms. Finally, the E2 factor explained 22% of the variance in chronic pain. Genetic correlations indicated that additive genetic influence on internalizing symptoms and chronic pain were correlated at .34.

Aim 2: Phenotypic Parent-Offspring Associations for Chronic Pain and Internalizing Symptomology

Results of the multilevel regressions predicting twin chronic pain and internalizing from mother chronic pain and internalizing are reported in Tables 5 and 6. The main effects only model indicated that mother chronic pain and internalizing symptoms were positively associated with twin chronic pain ($\beta = .10$, $p < .01$ and $\beta = 1.01$, $p < .01$, respectively). The model including an interaction between mother chronic pain and twin sex also indicated that mother internalizing symptoms were positively associated with twin chronic pain ($\beta = 1.02$, $p < .01$). Additionally, the interaction between mother chronic pain and twin sex was a significant predictor ($\beta = .08$, $p < .05$). Simple slopes analyses revealed that the association between mother and twin chronic pain was significant for female ($\beta = .14$, $p < .001$) but not male twins ($\beta = .06$, $p = .10$; Figure 4). The main effects only model indicated that mother chronic pain and internalizing were positively associated with twin internalizing symptoms ($\beta = .01$, $p < .01$ and $\beta = .14$, $p < .01$, respectively). The model including an interaction between mother internalizing symptoms and twin sex also indicated that mother chronic pain and internalizing symptoms were positively associated with twin internalizing symptoms ($\beta = .01$, $p < .01$ and $\beta = .19$, $p < .01$, respectively). Additionally, the interaction between mother internalizing symptoms and twin sex was a significant predictor ($\beta = -.09$, $p < .01$). Simple slopes analyses revealed that the association between mother and twin internalizing symptoms was stronger for male ($\beta = .19$, $p < .001$) than female twins ($\beta = .10$, $p < .05$; Figure 5).

Results of the multilevel regressions predicting twin chronic pain and internalizing from father chronic pain and internalizing are reported in Tables 7 and 8. The main effects only model indicated that neither father chronic pain nor internalizing symptoms were positively associated with twin chronic pain. There were no significant interactions between father chronic pain or internalizing symptoms and twin sex in the prediction of twin chronic pain symptoms. The main effects only model indicated that father chronic pain and internalizing symptoms were negatively and positively associated with twin internalizing symptoms, respectively (β = -.02, p < .01 and β = .19, p < .01). The model including an interaction between father chronic pain and twin sex also indicated that that father chronic pain and internalizing symptoms were negatively and positively associated with twin internalizing symptoms, respectively (β = -.03, p < .01 and β = .19, p < .01). Additionally, the interaction between father chronic pain and twin sex was a significant predictor (β = .01, p < .05). Simple slopes analyses revealed that the negative association between father chronic pain and twin internalizing symptoms was stronger for male (β = -.03, p < .001) than female twins (β = -.02, p < .01; Figure 6).

Aim 3: Genetic and Environmental Influences on the Familial Aggregation of Chronic Pain and Internalizing Symptomology

Nuclear twin family (NTF) models were examined to estimate the degree of genetic and environmental influence on the familial aggregation of chronic pain and internalizing symptoms. Model fitting results for a series of nested NTF models of chronic pain and internalizing symptoms are presented in Tables 9 and 10. First, the three plausible 4-latent-variable models (all contain E due its incorporation of measurement error) were fit. The models vary in which pair of dominant genetic variance (D), sibling-specific

environmental variance (S), and family level environmental variance (F) is included. The best fitting full model for chronic pain was the ADSE model, indicating that parent-offspring transmission and twin similarity were accounted for by A and D influences as well as environmental influences that rendered twins more similar to one another but did not increase similarity of parents and offspring. For internalizing symptoms, the ADSE and ASFE full models fit equally well; as such, we were unable to distinguish whether modeling dominant genetic effects or family level environmental influence best represented the etiology underlying parent-offspring internalizing symptom resemblance. Next, more parsimonious (reduced) 3-latent-variable models were tested by systematically dropping D, S, and F from their respective full models. The best fitting reduced model for both chronic pain and internalizing symptoms was the ASE model; the dominance genetic factor in the full ADSE model could be dropped, with improved model fit, as could the family level environmental variance factor in the ASFE model for internalizing symptomology. Next, we estimated an AE model, dropping sibling-specific shared environmental influence, which resulted in poorer model fit. Final ASE model estimates for chronic pain indicated that additive genetic influences were moderate in magnitude (46%), sibling-specific shared environmental influences were modest (29%), and nonshared environmental influences were also modest (23%). There was no evidence of assortative mating for chronic pain. Final ASE model estimates for internalizing symptoms indicated that additive genetic influences were modest in magnitude (35%), sibling-specific shared environmental influences were moderate (47%), and nonshared environmental influences were modest (18%). Lastly, modest evidence of positive

assortative mating for internalizing symptoms emerged (μ = .19). Overall, genetics was the primary mechanism for parent-offspring transmission.

CHAPTER 4

DISCUSSION

The current study contributes to a growing body of literature examining parent-offspring associations in chronic pain, advancing a more comprehensive understanding of the chronic pain experience in middle childhood and the mechanisms through which susceptibility is transmitted and unfolds by examining comorbid internalizing symptomology as a substantive focus and leveraging twin family data to elucidate the etiology underlying comorbidity and parent-offspring transmission. Specifically, the current study aimed to 1) examine the degree to which genetic and environmental influences explain variance in chronic pain and internalizing symptomology in middle childhood, as well as covariance across the two phenotypes, 2) examine phenotypic parent-offspring associations across chronic pain and internalizing symptomology, and 3) examine the degree to which genetic and environmental factors underlie parent-offspring transmission of chronic pain and internalizing symptomology using nuclear twin family models. Findings from the current study indicated that chronic pain was highly heritable (78%), whereas internalizing symptomology was modestly heritable (32%) and further subject to moderate shared environmental influence (50%). Moreover, 9% of the variance in chronic pain was explained by additive genetic factors shared with internalizing symptomology. Maternal chronic pain and internalizing symptomology were positively associated with both child chronic pain and internalizing symptomology. The relation between maternal chronic pain and child chronic pain was more pronounced for girls than

boys, whereas the relation between maternal internalizing symptomology and child internalizing symptomology was more pronounced for boys than girls. Paternal chronic pain was not significantly associated with child chronic pain but unexpectedly associated with decreased child internalizing symptomology. The negative association between paternal chronic pain and twin internalizing symptomology was more pronounced for boys than girls. Paternal internalizing symptomology was not significantly associated with child chronic pain but was positively associated with child internalizing symptomology. Lastly, the best fitting reduced nuclear twin family models for both chronic pain and internalizing symptomology retained additive genetic, sibling-specific shared environmental, and nonshared environmental parameters, where parent-offspring transmission was solely explained by shared genetics and sibling-specific shared environmental factors further accounted for co-twin resemblance and contributed to trait variability.

By examining early-onset chronic pain through a genetically-informed lens, the current study provides unique insight into common liabilities underlying chronic pain and internalizing symptomology in middle childhood and the etiological mechanisms that explain symptom aggregation across generations. These findings advance our understanding of the mechanisms that connect mind and body and those that perpetuate intergenerational cycles of suffering— knowledge that can ultimately be leveraged in efforts to disrupt these cycles. Results are contextualized within the broader literature, and strengths, limitations, and future directions are discussed.

Aim 1 Findings and Interpretation

Only four twin studies have previously examined the genetic and environmental etiology of pediatric chronic pain, with findings indicating that widespread and low back pain are environmentally mediated (El-Metwally et al., 2008; Mikkelsson et al., 2001), whereas headache and neck pain are subject to genetic influence (Ståhl et al., 2013; Svensson et al., 1999). Notably, the studies relied solely on samples of Nordic ancestry. Specifically, three of the four relied on the same Finish cohort. Not only is there a critical dearth of research examining the etiology of pediatric chronic pain, but these findings are also limited in the extent to which they can be generalized to other populations. Assuming that these findings generalize to more diverse populations could be a risky oversight that may function to exacerbate health inequities among populations that have been traditionally excluded from quantitative genetic research. Moreover, no twin studies to date have examined shared etiology across chronic pain and internalizing symptomology in childhood, despite ample evidence that the two frequently co-occur (Vinall et al., 2016). However, results from adult twin studies indicate that covariation among pain and anxious/depressive symptoms tends to be genetically or both genetically and environmentally mediated (Khan et al., 2020). The current study contributes to this limited area of research in a number of ways. First, this is one of only five twin studies examining genetic and environmental influences on pediatric chronic pain. Second, the current study utilizes data from one of only three twin cohorts in which this research is being conducted. Moreover, the current sample characterizes a population that has not yet been represented in this area of research and is more diverse in its racial/ethnic and

sociodemographic composition. Finally, this is the first study to examine shared etiology across chronic pain and internalizing symptomology in childhood.

It was hypothesized that variance in pediatric chronic pain would be explained by additive genetic, shared environmental, and nonshared environmental influences, though the best-fitting reduced univariate twin model indicated that 78% of the variance in chronic pain was explained by additive genetic factors, with the remaining 22% of the variance explained by nonshared environmental factors. These findings indicate that chronic pain is highly heritable in middle childhood and that relevant environmental influences are those that are uniquely experienced by twin siblings, rendering them dissimilar. Though the chronic pain phenotypes considered differ, these findings mirror those examining the etiology of recurrent headache in middle childhood (70% heritable; Svensson et al., 1999) and neck pain in early adolescence (68% heritable; Ståhl et al., 2013), where no evidence of shared environmental influence emerged. This stands in contrast to studies examining the etiology of non-specific low back pain (El-Metwally et al., 2008) and widespread pain (Mikkelsson et al., 2001), implicating shared and nonshared environmental influences only.

Comparing findings from the current study with these few extant results is complicated by the fact that twin model estimates are population-specific. As alluded to previously, generalizing findings from Nordic populations to the current sample, which is far more diverse in its ethnic/racial and sociodemographic composition, is a cautionary pursuit. For example, it is possible that certain trait-relevant contexts that may amplify shared environmental influences are pertinent to some populations and not others. Furthermore, given the young age of the sample and limited endorsement of chronic pain

at certain body sites, the chronic pain phenotype considered in the current study is an aggregate of chronic pain endorsed across various body sites. For example, headache was more frequently endorsed than low back pain in the current sample; hence, the current findings may mirror those of Svensson et al. (1999) more closely than El-Metwally et al. (2008) due to better phenotype-match across the studies. Moreover, the variable findings across pain types may indicate distinct etiologies.

Importantly, this is the only study to examine shared etiology across chronic pain and internalizing symptomology in childhood. First, univariate twin analyses indicated that 32%, 50%, and 18% of the variance in internalizing symptomology was explained by additive genetic, shared environmental, and nonshared environmental factors, respectively. Twin studies relying on parent-reported anxious and depressive symptoms have shown modest to high heritability estimates, which tend to be higher than estimates for self-reported symptoms where shared environmental influence is more pronounced (Murray et al., 2009; Rice et al., 2002). Second, bivariate twin models examining the common etiology across internalizing symptomology and chronic pain in the current sample were tested to ascertain the extent to which liabilities underlying the two phenotypes are shared or distinct. Findings indicated that 9% of the variance in chronic pain was explained by additive genetic factors shared with internalizing symptomology, and genetic correlations indicated that additive genetic influences on internalizing symptoms and chronic pain were correlated at .34.

The hypothesis based on adult twin studies examining covariation of pain and internalizing symptoms (Khan et al., 2020) and positing that most of the shared variance would be accounted for by additive genetic influences was corroborated. Notably, the

current study was uniquely equipped to test the associated liabilities models proposed by Krueger and Markon (2006), extending the models to characterize the degree to which underlying liabilities for chronic pain and internalizing symptomology in middle childhood are correlated. Under the chance model, liabilities are uncorrelated and comorbidity is a stochastic phenomenon. Under the correlated liabilities model, liabilities are correlated (but not perfectly) and manifest comorbid diagnoses. Lastly, under the alternate forms model, liabilities are perfectly correlated and comorbidity reflects alternate forms of the same underlying condition. The current study lends supports to the correlated liabilities model, though it should be noted that the association between chronic pain and internalizing in the current sample was modest (r = .19); as such, the degree of covariance parsed into additive genetic, shared environmental, and nonshared environmental components was modest at 9%. Specifically, 91% of the variance in chronic pain was explained by independent liabilities. These results are comparable to those at the lower range of estimates for shared variance across depression and pain in the adult twin literature (.10 - .30; Burri et al., 2015; Gasperi et al., 2017; Schur et al., 2009; Yang et al., 2016). Findings suggest that, overall, chronic pain and internalizing symptomology in middle childhood are primarily distinct phenotypes with independent etiologies.

Aim 2 Findings and Interpretation

Population-based studies examining the familial aggregation of pain indicate that odds of offspring pain increase when parents and other relatives experience pain themselves (Antilla et al., 2000; Boey & Goh, 2001a; Lester et al., 1994; Wilson et al., 2019). Overall, studies suggest that there are no significant differences in offspring

reports of pain when contrasting maternal and paternal chronic pain experiences (Grøholt et al., 2003; Higgins et al., 2015). However, one study considering differential parent-offspring associations as a function of family structure found that mother-child but not father-child associations were significant when children resided with their mothers primarily. When children resided with their fathers primarily, both father-child and mother-child associations were significant, though the former was stronger (Hoftun et al., 2013). These findings not only suggest that shared environments contribute to the familial aggregation of pain but also that maternal influences may be more potent, perhaps through the nature of sustained contact despite separate residences. Furthermore, research also indicates that parent-offspring pain associations may be more pronounced for girls than boys (Stanford et al., 2008). Taken together, the extant research examining phenotypic parent-offspring associations provided a foundation for the analyses conducted in the second aim of the current study. However, existing studies often fail to acknowledge the fact that chronic pain frequently co-occurs with internalizing symptomology, which has also been found to aggregate within families (Connell & Goodman, 2002). The current study aimed to treat this co-occurrence as a substantive focus by examining phenotypic parent-offspring associations both within and across chronic pain and internalizing phenotypes.

It was hypothesized that both maternal and paternal chronic pain and internalizing symptoms would be positively associated with children's chronic pain and internalizing symptoms. It was also expected that these associations would be more pronounced for girls than boys. Hypotheses were partially corroborated. Maternal chronic pain and internalizing symptomology were indeed positively associated with both child chronic

pain and internalizing symptomology, and the effect of maternal chronic pain on child chronic pain was more pronounced for girls than boys. However, the effect of maternal internalizing symptomology on child internalizing symptomology was more pronounced for boys than girls; this interaction was unexpected. Furthermore, paternal chronic pain was not significantly associated with child chronic pain but unexpectedly negatively associated with child internalizing symptomology. The negative association between paternal chronic pain and twin internalizing symptomology was more pronounced for boys than girls. Lastly, paternal internalizing symptomology was not significantly associated with child chronic pain but was positively associated with child internalizing symptomology; the association did not vary as a function of child sex.

Studies have demonstrated that children whose parents experience chronic pain exhibit more internalizing problems than children whose parents do not (Higgins et al., 2015). The current study corroborates this finding in demonstrating independent main effects of maternal chronic pain on child internalizing symptomology. Even fewer studies consider the effect of parents' psychiatric symptomology on children's chronic pain experiences. Cross-sectional research shows that mothers of children who experience chronic pain are more likely to have a lifetime history of depressive and anxious disorders (Campo et al., 2007). The current study bolsters this scant research by demonstrating that maternal internalizing symptomology exerted a main effect on child chronic pain. The significant mother-child associations across chronic pain and internalizing phenotypes observed in the current study attest to the importance of integrating parental psychological functioning into models conceptualizing the intergenerational transmission of chronic pain, such as that posited by Stone and Wilson

(2016). In doing so, future studies will be better equipped to conduct comprehensive examinations that fully characterize the complex ways in which these symptoms tend to cluster within families. Notably, the unexpected negative association between paternal chronic pain and child internalizing symptomology defied expectations based on previous research and requires further replication before implications can be drawn.

Stone and Wilson (2016) proposed several key moderators of intergenerational risk for chronic pain, including timing, course, and location of parental chronic pain. The current study did not consider these facets of parental chronic pain which may account for our failure to detect significant father-child chronic pain associations. A primary consideration is pain site match across generations. For both mothers and children, headache was the most commonly reported pain site. For fathers, however, backache was most common; it is possible that this mismatch underlies the absence of father-child chronic pain associations in the current study. Accounting for timing and course of parental chronic pain may further illuminate these findings. Specifically, the current study did not consider onset of parental chronic pain and whether it preceded the children's births or emerged at an alternative point in their development. Early and sustained exposure to parental chronic pain likely exerts differential effects on children's chronic pain experiences when compared to delayed exposures of shorter duration. Furthermore, prevalence rates for pediatric onset of monthly headache and backpain range from 26 to 69% and 18 to 24%, respectively (King et al., 2011). Considering pain type match and the earlier age of onset for headache versus backpain, it possible that father-child chronic pain associations entail smaller effects that may emerge later in development. Moreover, it is likely that pain types with earlier onset, like headache, are

more heritable than those with later onset, like backache, which may be subject to more environmental, lifestyle factors. It is possible that with prolonged exposure to these factors, father-child chronic pain associations may emerge.

Studies indicate that chronic pain is more prevalent among girls than boys (King et al., 2011) and that parent-offspring pain associations may be stronger for girls than boys (Stanford et al., 2008). While the current study did not find a significant correlation between child sex and chronic pain, it did corroborate the latter finding, demonstrating stronger associations between maternal chronic pain and child chronic pain for girls than boys. In fact, the association between maternal chronic pain and child chronic pain for boys was non-significant. These findings suggest that girls are particularly vulnerable when their mothers experience chronic pain. Unexpectedly, the association between maternal internalizing symptomology and child internalizing symptomology was more pronounced for boys than girls, though still significant for both. The literature examining sex differences in internalizing symptomology prior to adolescence is mixed, with some studies suggesting that boys may exhibit slightly higher internalizing symptoms prior to pubertal onset (Angold & Worthman, 1993), others finding that girls do (Sterba et al., 2007), and still others indicating no sex differences (Colder et al., 2002). In terms of the effect of maternal internalizing symptomology on child internalizing symptomology, studies of maternal depression, for example, have shown stronger associations with internalizing problems for girls than boys (Goodman et al., 2011). However, there is some evidence that suggests that boys are more susceptible than girls to suboptimal caregiving (Shaw et al., 1998). Furthermore, parental depressive symptoms have been associated with increased intrusive parenting for boys but not girls (Gruhn et al., 2016). It

may be that boys' sensitivity to suboptimal caregiving within the context of increased intrusive parenting associated with parental depression places them at greater risk for internalizing symptomology. More research is needed with large samples to examine potential 3 way interactions between maternal depression, parenting behaviors, and child sex in order to support this hypothesis. Overall, prevention and intervention efforts should consider the heightened risk incurred by girls whose parents experience chronic pain and identify potential mediating mechanisms. In terms of prevention and intervention for internalizing symptomology, a closer look at the parenting context within which these associations emerge is needed to determine for whom risk is greatest.

Aim 3 Findings and Interpretation

The nuclear twin family design is a potent yet underutilized extension of the classical twin model. By accounting for the effect of assortative mating, estimating A, C, D, and E influences simultaneously, differentiating passive *r*GE from true shared environmental influence, and distinguishing familial environmental transmission from that which is specific to siblings, the model provides parameter estimates that are more accurate and specific than those ascertained from classical twin models. Despite these advantages, no nuclear twin family studies have examined the etiology underlying the familial aggregation of chronic pain and those that have examined psychopathology focus primarily on externalizing psychopathology. As such, the current study makes an important contribution to this small, yet promising area of research.

Based on phenotypic studies examining influences of parental chronic pain and mental health on family functioning (Herr et al., 2007; Higgins et al., 2019), it was hypothesized that family level environmental influences would significantly contribute to

parent-offspring covariance above and beyond shared genetics. Sibling-specific and nonshared environmental influences were also hypothesized upon consideration of potential generational and individual differences in environmental exposures that could lead to twin-sibling resemblance and family member individuation. As such, models estimating additive genetic, family level, sibling-specific, and nonshared environmental influences were expected to best represent the familial aggregation of chronic pain and internalizing symptoms. Hypotheses were partially corroborated, with results indicating that the best fitting reduced nuclear twin family models for both chronic pain and internalizing symptomology were ASE models. There was no evidence of familial environmental transmission; as such, parent-offspring resemblance was entirely accounted for by shared genetics. There was also no evidence of passive *r*GE. Genetic influences on chronic pain and internalizing symptomology were moderate in magnitude and additive in nature. For chronic pain, the effect of sibling-specific environmental influence was modest whereas the effect was moderate for internalizing symptomology. Lastly, there was modest evidence of positive assortative mating on internalizing symptomology but not chronic pain.

Though the current study examined the etiology underlying the familial aggregation of chronic pain and internalizing symptomology, the failure to detect familial environmental transmission is consistent with nuclear twin family models examining externalizing and general psychopathology and extended pedigree studies examining internalizing symptomology. Overall, nuclear twin family studies of conduct disorder, antisocial behavior, social aggression, delinquent behavior, ADHD, alcohol use, and general psychopathology and extended pedigree studies of panic-phobia, somatization,

and depressive symptomology have found that shared genetic proclivities primarily account for parent-offspring resemblance (Burt & Klump, 2012; Burt et al., 2012; Kendler et al., 1994; Kendler et al., 1995; Koopmans & Boomsma, 1996; Maes et al., 2007; Oro et al., 2019; Rice et al., 2005; Slawinski et al., 2019; Taylor et al., 2000). This suggests that environmental influences shared by both parents and twins, such as sociodemographic factors, family emotional climate, and cultural values, do not contribute to parent-offspring chronic pain and internalizing associations above and beyond shared genetics. Moreover, the current findings suggest that there are environmental exposures uniquely experienced by twin siblings that render them more similar to one another but not their parents. While we can only speculate regarding the specific environmental exposures that contribute to chronic pain and internalizing symptomology based on twin modeling results, it is possible that certain exposures and lifestyle factors are uniquely relevant in middle childhood as opposed to adulthood, accounting for the sibling-specific environmental effect. For example, sleep habits, nutrition, hydration, physical activity, and screen use are lifestyle factors that have been implicated in pediatric headache (Langdon & DiSabella, 2017), and these experiences may be more similar among same-aged siblings that share multiple contexts, including home and school, than among children and parents whose daily routines are more likely to differ.

The current study also found modest evidence of positive assortative mating on internalizing symptomology ($\mu = .19$) but not chronic pain. The ability to account for the effect of assortative mating in nuclear twin family models is an advantage in that a failure to do so functions to inflate estimates of shared environmental influence and attenuate

heritability. Evidence of nonrandom mating has been documented both within and across diagnoses of depression and anxiety (Nordsletten et al., 2016). Moreover, extended twin-pedigree studies of panic-phobia, somatization, and depressive symptomology have also reported significant assortative mating (Kendler et al., 1994; Kendler et al., 1995). Findings from the current study further corroborate patterns of spousal resemblance on internalizing symptomology, yet relatively little is known regarding whether the same phenomenon underlies mate selection when considering chronic pain. In a sample of nearly 24,000 couples, McIntosh and colleagues (2016) found evidence of significant spousal concordance on chronic pain. They also reported that the presence of chronic pain in one partner increased the likelihood of major depressive disorder in the other partner. The current study did not replicate these findings either within chronic pain phenotypes or across chronic pain and internalizing phenotypes. It is likely that these associations are not as robust as those documented in the psychiatric domain, necessitating larger studies that are powered to detect assortative mating on chronic pain.

Overall, findings from the nuclear twin family models of chronic pain and internalizing symptomology provide a more nuanced depiction of the etiology underlying familial aggregation in pediatric offspring populations. This insight provides focus for the development of preventative and intervening care aimed at disrupting the perpetuation of risk for chronic pain and internalizing symptoms across generations, potentially putting an end to cycles of suffering. Specifically, these findings suggest that the development of prevention and interventions efforts that show promise in buffering against genetic risk for chronic pain and internalizing symptomology should be prioritized for at-risk children with afflicted parents.

Strengths, Limitations, and Future Directions

The current study presents a number of methodological and conceptual strengths. First, the sample is rich in both racial/ethnic and socioeconomic diversity. As described previously, behavior genetic research has traditionally been conducted with ethnically homogenous samples of European ancestry. In fact, ours is the first twin study of pediatric chronic pain conducted outside of Scandinavia, making a small but meaningful push towards narrowing health disparities perpetuated by systemic exclusion in the sciences. Second, ours is the first study to examine shared etiology across pediatric chronic pain and internalizing symptomology and the first to implement nuclear twin family modeling of chronic pain. Use of novel and rigorous quantitative genetic methods makes a significant contribution to the scant, extant research. Lastly, inclusion of both maternal and paternal data within both phenotypic and genetic frameworks not only allowed us to circumvent several limitations of the classical twin design, it also provided a more comprehensive assessment of familial risk for chronic pain.

Despite these strengths, a number of limitations should be acknowledged. Generalizability of the findings is a primary concern. This is a community sample and parent-offspring associations for both chronic pain and internalizing symptomology may vary as a function of symptom severity. For example, severity of parental depression has been associated greater child depressive symptoms (Mars et al., 2012). More research should assess whether parent-offspring associations for chronic pain and internalizing symptomology differ as a function of symptom features, including severity. However, this does not negate the importance of examining intergenerational associations at sub-clinical levels. Additionally, nuclear twin family modeling requires data from two

biological parents and twin offspring. As such, results may not generalize to other family structures, where different trait-relevant contexts may come into play. For example, there may be important family level environmental influences that are uniquely relevant to single-parent families. While rates of maternal and twin chronic pain and internalizing symptomology in the current study did not differ between intact families and those for whom only maternal data were available, there were significant differences in socioeconomic status across the groups. More research is needed to determine whether the etiology underlying familial aggregation of chronic pain and internalizing symptomology varies as a function of family structure. The generalization of twin study results of psychopathology to singleton populations has also been challenged, with studies examining disorder-specific rates in twins and singletons producing mixed results; though overall, rates appear to be generally equitable (Kendler et al., 1995). However, more research is needed to ascertain whether rates of chronic pain are different in twin and singleton samples. Preliminarily, rates of chronic pain in the current twin study are comparable to those reported by epidemiological studies conducted in singleton populations (King et al., 2011).

Final limitations concern design, measurement and the confound of heterotypic continuity when examining parent-child associations. Assessments of parental and child chronic pain and internalizing symptomology were concurrent; as such, interferences regarding direction of effect and nuance regarding timing and change of symptom presentations cannot be ascertained. Mothers also reported on their own and their children's chronic pain and internalizing symptomology, introducing shared reporter bias and possibly inflating mother-child associations. It is important, however, to recall that

children are not accurate reporters of their own pain (Birnie et al., 2019). Notably, this is an ongoing, longitudinal twin study and self-report of twin chronic pain in adolescence can be leveraged by future studies. Lastly, heterotypic manifestations of symptomology and differential etiology across development may dampen parent-offspring associations and introduce potential additive genetic-by-age interaction effects.

Future studies should examine patterns of comorbidity across chronic pain and internalizing symptomology at various developmental stages in order to ascertain dynamic changes in both the magnitude of the correlation over time and in the degree of overlapping etiology. The current study indicated that there is, in fact, modest co-occurrence in middle childhood and that chronic pain and internalizing symptomology have primarily distinct etiologies. Longitudinal research is needed to determine how this might change across the transition into adolescence. Furthermore, longitudinal assessments of parental and child chronic pain and internalizing symptomology will allow for more dynamic examinations of familial clustering. There are likely transactional processes at work, which quantitative approaches like the actor-partner interdependence model (Cook & Kenny, 2005) can help to illuminate. To circumvent issues of heterotypic continuity and developmental change in etiology, future nuclear twin family studies of chronic pain should acquire retrospective reports of parents' childhood symptoms. Lastly, future studies should prioritize elucidating the diverse contexts within which co-occurring chronic pain and internalizing symptomology manifest. By considering measured environmental moderators of the shared genetic and environmental influence across chronic pain and internalizing symptomology, we stand to acquire a more nuanced understanding of the extent to which co-occurrence is

mediated by heritable and/or environmental factors in certain contexts. Specifically, by utilizing culturally relevant measured environmental moderators, future research can further narrow health disparities suffered by populations that have been traditionally excluded from twin research and the sciences more broadly.

Conclusion

Overall, this study makes a significant contribution to the literature examining co-occurring chronic pain and internalizing symptomology in middle childhood and parent-offspring transmission of risk, providing novel insight into shared and independent liabilities, patterns of phenotypic parent-offspring transmission, and the etiological mechanisms underlying familial aggregation. Findings suggest that the development of prevention and interventions efforts that show promise in buffering against genetic risk for chronic pain and internalizing symptomology should be prioritized in order to disrupt intergenerational cycles of suffering both in mind and body.

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APPENDIX A

TABLES

Table 1

Descriptive Statistics for Study Variables

Continuous	Mean	SD	Min.	Max.	Skewness	Kurtosis	N
Mother Age	39.27	5.65	25	53	.098	-.568	296
Father Age	41.67	5.90	25	58	.127	-.221	169
Twin Age	9.71	.93	7.70	12.09	.312	-.004	795
Pubertal Status	1.55	.45	1	3.6	1.262	2.205	729
Socioeconomic Status	-.01	.78	-1.53	3.33	.578	.554	358
Mother Chronic Pain	2.84	2.77	0	14	1.362	1.926	353
Father Chronic Pain	1.79	1.60	0	7	.652	-.315	221
Twin Chronic Pain	1.37	1.75	0	11	1.872	4.632	750
Mother Internalizing	.30	.30	0	2	2.170	6.550	350
Father Internalizing	.25	.31	0	1.85	2.400	6.667	218
Twin Internalizing	1.26	.20	1	2.15	1.043	1.214	731
Dichotomous							N
Twin Sex	48.8% Male						795
	51.2% Female						
Twin Ethnicity	59.8% Non-Hispanic Caucasian						763
	28% Hispanic						
	12.2% Other						
Twin Zygosity	30.8% Monozygotic						779
	34.8% Same-Sex Dizygotic						
	34.4% Opposite-Sex Dizygotic						

Note. Min. = minimum; Max. = maximum; N = sample size.

Table 2

Zero-Order Correlations for Covariates, Maternal, Paternal, and Twin Chronic Pain and Internalizing Symptoms (N = 795) and Twin Intraclass Correlations for Chronic Pain (N = 372 twin pairs) and Internalizing (N = 364 twin pairs)

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.
1. Mother Age	-													
2. Father Age	.78**	-												
3. Twin Age	.19**	.19*	-											
4. Twin Sex	.04	-.02	.02	-										
5. Caucasian	.17*	.22*	-.18**	-.09	-									
6. Hispanic	-.27**	-.30**	.08	.02	-.98**	-								
7. Pubertal Status	.08	.05	.35**	.47**	-.15**	.10	-							
8. SES	.39**	.31**	-.02	.07	.31**	-.41**	-.09*	-						
9. Mother CP	-.08	-.10	.00	.01	.00	-.07	.04	-.08	-					
10. Mother INT	.03	-.09	-.03	-.04	-.03	.02	.01	-.15**	.29**	-				
11. Father CP	.06	-.06	.05	-.09	.15	-.18	.07	-.09	-.07	.02	-			
12. Father INT	.04	-.03	-.04	-.05	.08	-.05	-.01	-.14*	-.03	.18**	.39**	-		
13. Twin CP	-.07	-.06	.01	.01	.06	-.13	.04	-.08	.23**	.22**	.05	.07	-	
14. Twin INT	.05	.05	.03	.05	.07	-.03	.07	.06	.19**	.23**	-.07	.18**	.19**	-
MZ ICC													.79	.81
DZ ICC													.45	.67

Note. * $p < .05$; ** $p < .01$; Twin sex coded 0 = male, 1 = female; Caucasian = dummy coded twin ethnicity where 1 = Non-Hispanic Caucasian, 0 = Other; Hispanic = dummy coded twin ethnicity where 1 = Hispanic, 0 = Other; SES = socioeconomic status; CP = chronic pain; INT = internalizing symptomology; Sample size (N = 795) uses full information maximum likelihood.

Table 3

Univariate ACE Model Fit and Parameter Estimates

Phenotype	Model	-2LL	*df*	Δ-2LL	Δ*df*	*p*	AIC	A	C	E
Chronic Pain	ACE	2640.55	730	-	-	-	1180.55	.63 (.43-.87)	.14 (.01-.41)	.23 (.17-.29)
	AE	**2642.23**	**731**	**1.68**	**1**	**.19**	**1180.23**	**.78** (.66-.90)	-	**.22** (.17-.28)
	CE	2668.90	731	28.34	1	<.001	1206.90			
	E	2807.39	732	166.84	2	<.001	1343.39			
Internalizing	**ACE**	**-590.35**	**711**	**-**	**-**	**-**	**-2012.35**	**.32** (.19-.49)	**.50** (.35-.68)	**.18** (.13-.23)
	AE	-558.24	712	32.1	1	<.001	-1982.24			
	CE	-575.48	712	14.86	1	<.001	-1999.48			
	E	-324.37	713	265.98	2	<.001	-1750.37			

Note. A, C, and E are standardized squared parameter estimates for additive genetic, shared environmental, nonadditive genetic, and nonshared environmental factors, respectively. Standardized confidence intervals are reported in parentheses. The most parsimonious final model is indicated in bold. -2LL = - 2 log likelihood; df = degrees of freedom; Δ = change; AIC = Akaike's information criterion; Sample size for chronic pain model, *N* = 372 twin pairs; Sample size for internalizing model, *N* = 364 twin pairs.

Table 4

Bivariate Model Fit and Parameter Estimates

	Model	-2LL	*df*	Δ-2LL	Δ*df*	*p*	AIC
INT - CP	Bivariate Cholesky (full)	2027.83	1438	-	-	-	-848.17
	Bivariate Cholesky (final)	**2031.85**	**1441**	**4.02**	**3**	**.26**	**-850.15**

	Phenotype	A1	C1	E1	A2	C2	E2
Full Model	INT	.32 (.19-.49)	.50 (.35-.68)	.18 (.13-.23)	-	-	-
	CP	.01 (.01-.12)	.02 (.00-.11)	.00 (.00-.02)	.62 (.42-.86)	.11 (.00-.40)	.23 (.17-.29)
Final Model	INT	.34 (.20-.51)	.48 (.33-.66)	.18 (.14-.23)	-	-	-
	CP	.09 (.03-.19)	-	-	.69 (.56-.83)	-	.22 (.17-.28)

Note. Standardized squared parameter estimates for A, C, and E are reported. Standardized confidence intervals are reported in parentheses. The most parsimonious final model is indicated in bold. INT = internalizing symptomology; CP = chronic pain; -2LL = - 2 log likelihood; df = degrees of freedom; Δ = change; AIC = Akaike's information criterion; Sample size, *N* = 359 twin pairs.

Table 5

Multilevel Regression Main Effects Only Model Coefficients Estimating Child Chronic Pain and Internalizing from Mother Chronic Pain and Internalizing

	Child Chronic Pain			Child Internalizing		
	Est.	SE	95% CI	Est.	SE	95% CI
Twin Age	.03	.09	-	.01	.01	-
Sex	.03	.11	-	.00	.01	-
Caucasian	-.07	.25	-	.04	.03	-
Hispanic	-.46	.26	-	.04	.03	-
Pubertal Status	.12	.15	-	.03	.02	-
Mother Age	-.02	.02	-	.00	.00	-
SES	-.07	.11	-	.03*	.01	.002, .05
Mother CP	.10**	.03	.04, .16	.01**	.00	.003, .02
Mother INT	1.01**	.31	.41, 1.61	.14**	.04	.07, .22

Note. * $p < .05$; ** $p < .01$; Sex coded 0 = male, 1 = female; Caucasian = dummy coded twin ethnicity where 1 = Non-Hispanic Caucasian, 0 = Other; Hispanic = dummy coded twin ethnicity where 1 = Hispanic, 0 = Other; SES = socioeconomic status; CP = chronic pain; INT = internalizing symptomology; CI = confidence interval; Sample size (N = 795) uses full information maximum likelihood.

Table 6

Multilevel Regression Full Model Coefficients Estimating Child Chronic Pain and Internalizing from Mother Chronic Pain and Internalizing

	Child CP			Child CP			Child INT			Child INT		
	Est.	SE	95% CI	Est.	SE	95% CI	Est.	SE	95% CI	Est.	SE	95% CI
Twin Age	.02	.09	-	.03	.09	-	.01	.01	-	.01	.01	-
Sex	.03	.11	-	.03	.11	-	.00	.01	-	.00	.01	-
Caucasian	-.08	.24	-	-.07	.25	-	.04	.03	-	.05	.03	-
Hispanic	-.46	.26	-	-.46	.26	-	.04	.03	-	.04	.03	-
Pubertal Status	.13	.15	-	.12	.15	-	.03	.02	-	.03	.02	-
Mother Age	-.02	.02	-	-.02	.02	-	.00	.00	-	.00	.00	-
SES	-.07	.11	-	-.07	.11	-	.03*	.01	.002, .05	.03	.01	-
Mother CP	.06	.04	-	.10**	.03	.04, .16	.01*	.00	.002, .02	.01**	.00	.003, .02
Mother INT	1.02**	.30	.43, 1.62	1.01**	.38	.26, 1.77	.14**	.04	.07, .22	.19**	.04	.11, .27
Mother CP x Sex	.08*	.03	.01, .14	-	-	-	.00	.00	-	-	-	-
Mother INT x Sex	-	-	-	-.01	.35	-	-	-	-	-.09*	.04	-.16, -.02

Note. * $p < .05$; ** $p < .01$; Sex coded 0 = male, 1 = female; Caucasian = dummy coded twin ethnicity where 1 = Non-Hispanic Caucasian, 0 = Other; Hispanic = dummy coded twin ethnicity where 1 = Hispanic, 0 = Other; SES = socioeconomic status; CP = chronic pain; INT = internalizing symptomology; CI = confidence interval; Sample size (N = 795) uses full information maximum likelihood.

Table 7

Multilevel Regression Main Effects Only Model Coefficients Estimating Child Chronic Pain and Internalizing from Father Chronic Pain and Internalizing

	Child Chronic Pain			Child Internalizing		
	Est.	SE	95% CI	Est.	SE	95% CI
Twin Age	.02	.09	-	.01	.01	-
Sex	.02	.11	-	.00	.01	-
Caucasian	-.14	.26	-	.04	.03	-
Hispanic	-.58*	.27	-1.11, -.04	.01	.03	-
Pubertal Status	.13	.15	-	.03	.02	-
Father Age	-.02	.02	-	.00	.00	-
SES	-.14	.12	-	.03	.02	-
Father CP	.00	.06	-	-.02**	.01	-.04, -.01
Father INT	.42	.44	-	.19**	.05	.09, .29

Note. * $p < .05$; ** $p < .01$; Sex coded 0 = male, 1 = female; Caucasian = dummy coded twin ethnicity where 1 = Non-Hispanic Caucasian, 0 = Other; Hispanic = dummy coded twin ethnicity where 1 = Hispanic, 0 = Other; SES = socioeconomic status; CP = chronic pain; INT = internalizing symptomology; CI = confidence interval; Sample size (N = 795) uses full information maximum likelihood.

Table 8

Multilevel Regression Full Model Coefficients Estimating Child Chronic Pain and Internalizing from Father Chronic Pain and Internalizing

	Child CP			Child CP			Child INT			Child INT		
	Est.	SE	95% CI	Est.	SE	95% CI	Est.	SE	95% CI	Est.	SE	95% CI
Twin Age	.02	.09	-	.02	.09	-	.01	.01	-	.01	.01	-
Sex	.01	.12	-	.03	.12	-	.00	.01	-	.00	.01	-
Caucasian	-.14	.26	-	-.14	.26	-	.04	.03	-	.04	.02	-
Hispanic	-.57	.27	-1.10, -.03	-.58	.27	-1.11, -.05	.01	.03	-	.01	.03	-
Pubertal Status	.14	.15	-	.11	.16	-	.02	.02	-	.03	.02	-
Father Age	-.02	.02	-	-.02	.02	-	.00	.00	-	.00	.00	-
SES	-.14	.12	-	-.15	.12	-	.03	.02	-	.03	.02	-
Father CP	.03	.07	-	.00	.06	-	-.03**	.01	-.04, -.01	-.02**	.01	-.04, -.01
Father INT	.42	.45	-	.23	.49	-	.19**	.05	.09, .29	.19**	.05	.09, .30
Father CP x Sex	-.04	.04	-	-	-	-	.01*	.00	.001, .01	-	-	-
Father INT x Sex	-	-	-	.45	.31	-	-	-	-	.00	.03	-

Note. * $p < .05$; ** $p < .01$; Sex coded 0 = male, 1 = female; Caucasian = dummy coded twin ethnicity where 1 = Non-Hispanic Caucasian, 0 = Other; Hispanic = dummy coded twin ethnicity where 1 = Hispanic, 0 = Other; SES = socioeconomic status; CP = chronic pain; INT = internalizing symptomology; CI = confidence interval; Sample size (N = 795) uses full information maximum likelihood.

Table 9

Nuclear Twin Family Model of Chronic Pain Fit Statistics and Parameter Estimates

Model	-2Lnl	df	AIC	BIC	SABIC	%A	%D	%S	%E	%H
ADSE	3494.369	1294	906.369	-4281.035	3519.890	38	16	23	23	54
ASFE	3497.210	1294	909.210	-4278.194	3522.731	-	-	-	-	-
ADFE	3505.009	1294	917.009	-4270.395	3530.530	-	-	-	-	-
ASE	3497.210	1295	907.210	-4284.203	3519.896	46	-	29	25	46
ADE	3505.009	1295	915.009	-4276.404	3527.695	-	-	-	-	-
AFE	3542.241	1295	952.241	-4239.172	3564.927	-	-	-	-	-
AE	3542.241	1296	950.241	-4245.180	3562.091	-	-	-	-	-

Note. Best fitting full model in bold type. -2Lnl = negative two log likelihood; df = degrees of freedom; AIC = Akaike's information criterion; BIC = Bayesian information criterion; SABIC = sample-size adjusted Bayesian information criterion; A= additive genetic variance; D= dominant genetic variance; S= sibling-specific environmental variance; F= family level environmental variance; E= unique (nonshared) environmental variance; H = broad sense heritability, a sum of A and D; Sample size, N = 194 intact twin families.

Table 10

Nuclear Twin Family Model of Internalizing Fit Statistics and Parameter Estimates

Model	-2Lnl	df	AIC	BIC	SABIC	%A	%D	%F	%S	%E	%H
ADSE	3319.348	1272	775.348	-4323.863	3344.869	35	0	-	47	18	35
ASFE	3319.348	1272	775.348	-4323.863	3344.869	27	-	20	39	14	27
ADFE	3375.344	1272	831.344	-4267.867	3400.865	-	-	-	-	-	-
ASE	3319.348	1273	773.348	-4329.872	3342.033	35	-	-	47	18	35
ADE	3375.344	1273	829.344	-4273.876	3398.029	-	-	-	-	-	-
AFE	3444.365	1273	898.365	-4204.854	3467.050	-	-	-	-	-	-
AE	3444.365	1274	896.365	-4210.863	3464.214	-	-	-	-	-	-

Note. Best fitting full and reduced models in bold type. -2Lnl = negative two log likelihood; df = degrees of freedom; AIC = Akaike's information criterion; BIC = Bayesian information criterion; SABIC = sample-size adjusted Bayesian information criterion; A= additive genetic variance; D= dominant genetic variance; S= sibling-specific environmental variance; F= family level environmental variance; E= unique (nonshared) environmental variance; H = broad sense heritability, a sum of A and D; Sample size, *N* = 187 intact twin families.

APPENDIX B

FIGURES

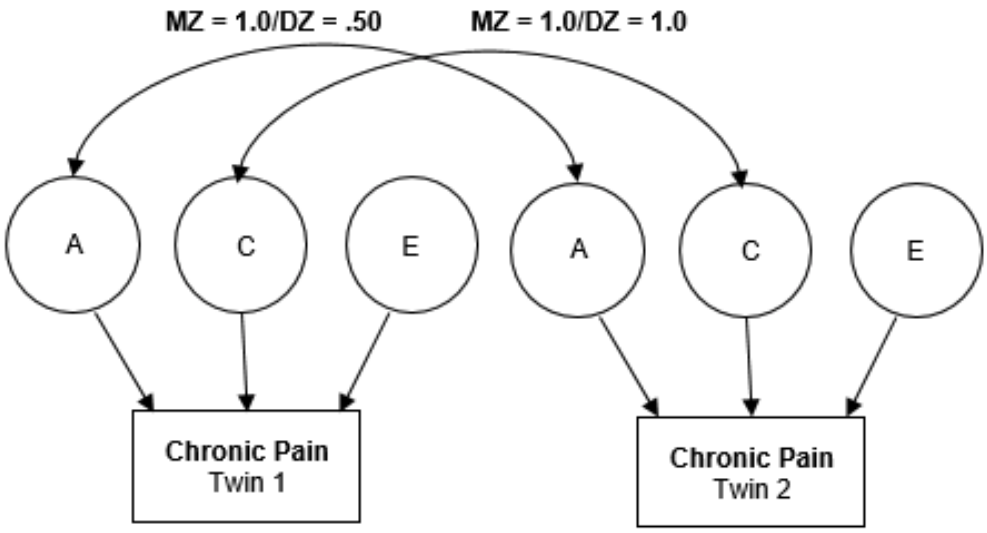

Figure 1. Example Univariate ACE Model. The model demonstrates genetic and environmental influences on variance in chronic pain. A represents additive genetic influence (path between MZ twins constrained to 1.0, path between DZ twins constrained to .5). C represents shared environmental influence (path constrained to 1.0 for both MZ and DZ twins). E represents nonshared environmental influence.

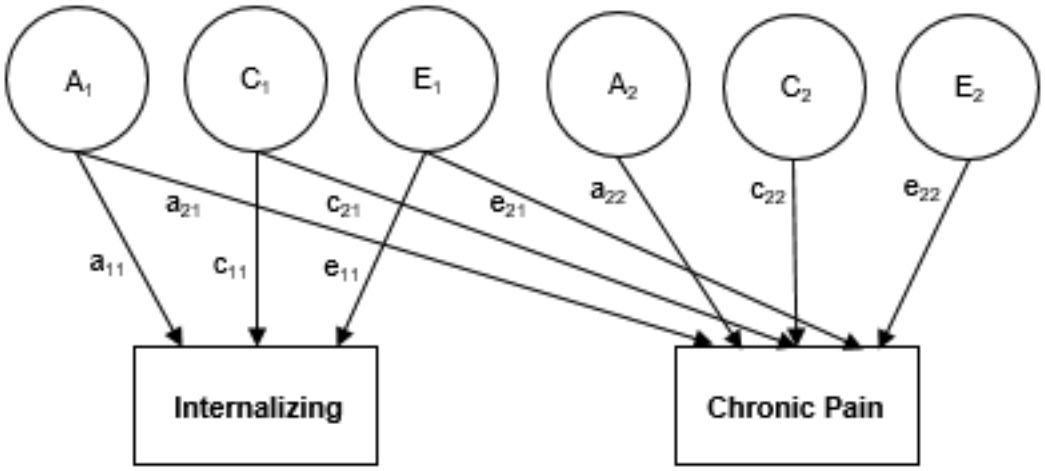

Figure 2. Example Bivariate ACE Model. The model demonstrates genetic and environmental influences on unique and shared variance in internalizing and chronic pain (for 1 twin only). A_1, C_1, and E_1 factors represent additive genetic, shared environmental, and nonshared environmental influences on internalizing, which may also be shared with chronic pain. The degree of genetic, shared and nonshared environmental influence that underlies covariance across the phenotypes is represented by the a_{21}, c_{21}, and e_{21} path estimates. A_2, C_2, and E_2 factors represent additive genetic, shared environmental, and nonshared environmental influences on chronic pain that are independent of internalizing.

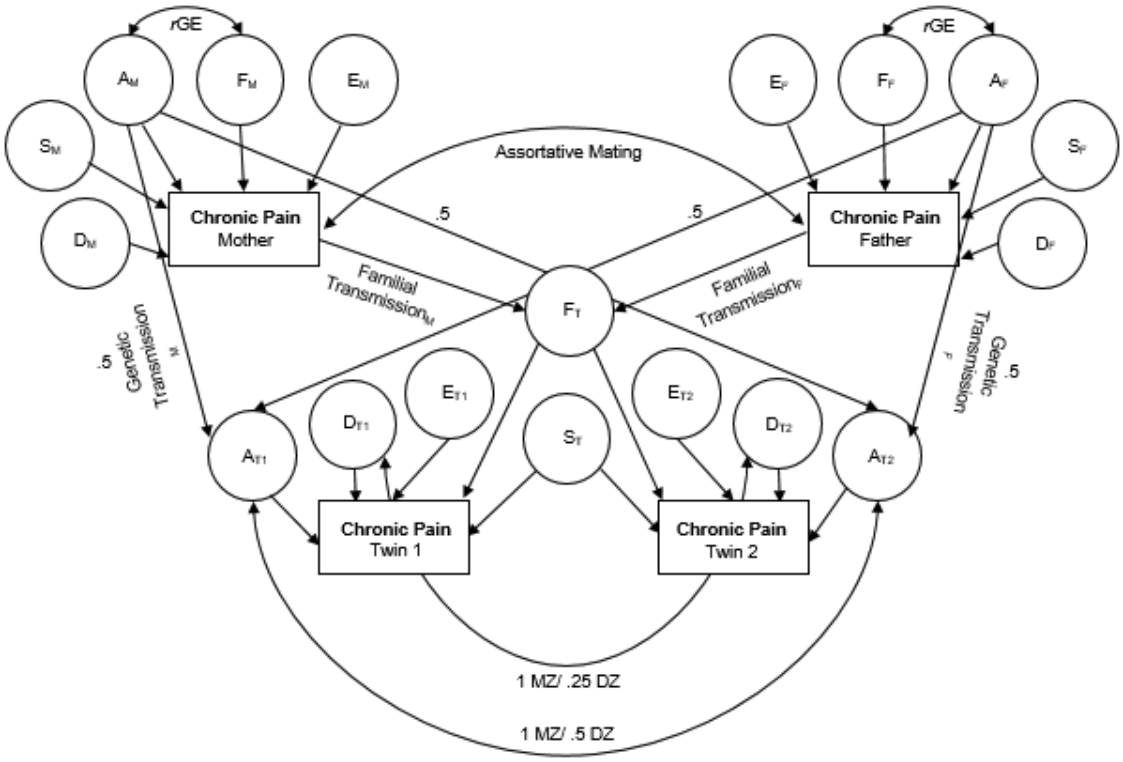

Figure 3. Nuclear Twin Family Model. Variance in the phenotype is parsed into that which is due to additive genetic influence, dominant genetic influence, sibling-specific environmental influence, family level environmental influence, and nonshared environmental influence. D, S, and F cannot be estimated simultaneously, requiring one of the three to be dropped. Note: A= additive genetic variance; D= dominant genetic variance; S= sibling-specific environmental variance; F= family level environmental variance; E= unique (nonshared) environmental variance.

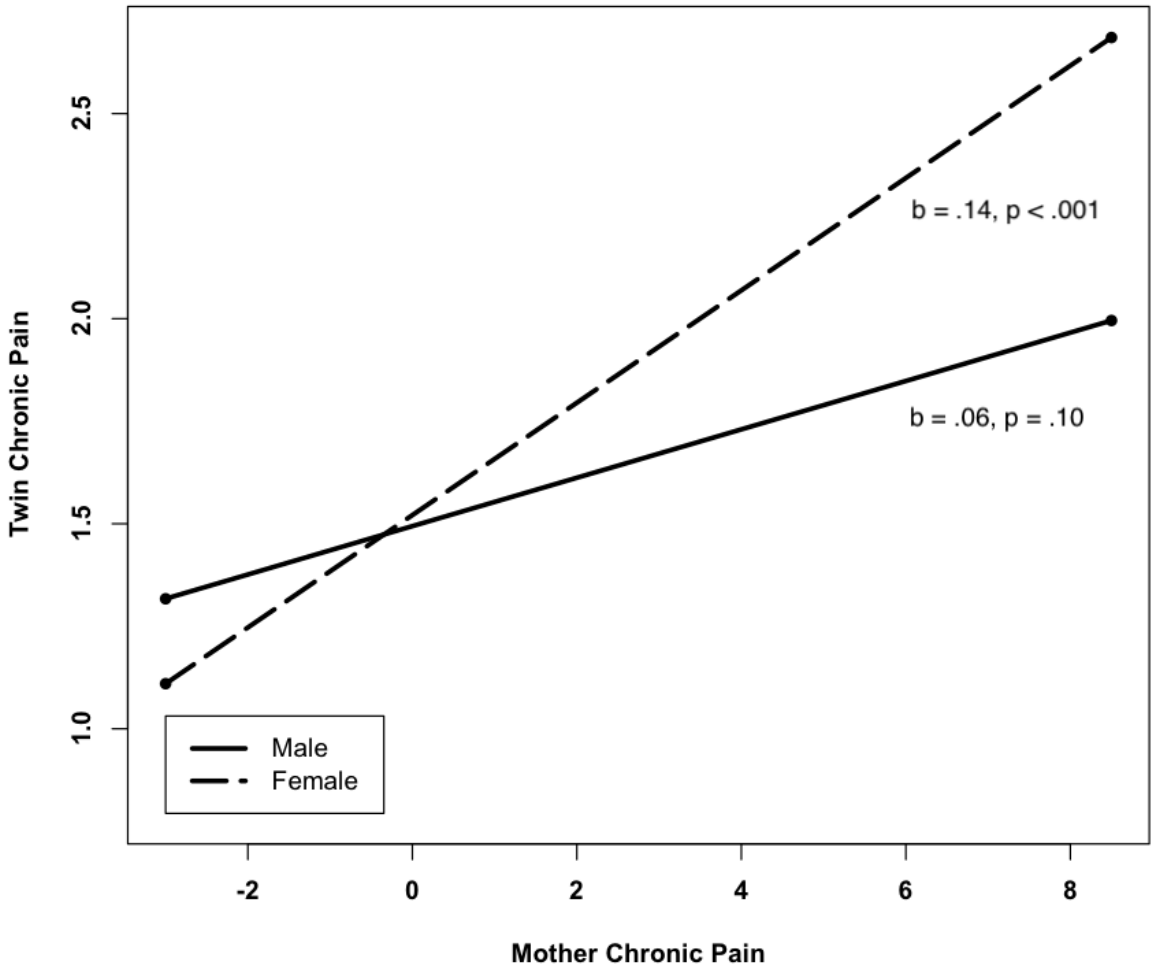

Figure 4. Simple slopes plot of the interaction between mother chronic pain and twin sex on twin chronic pain symptoms. b = unstandardized regression coefficient.

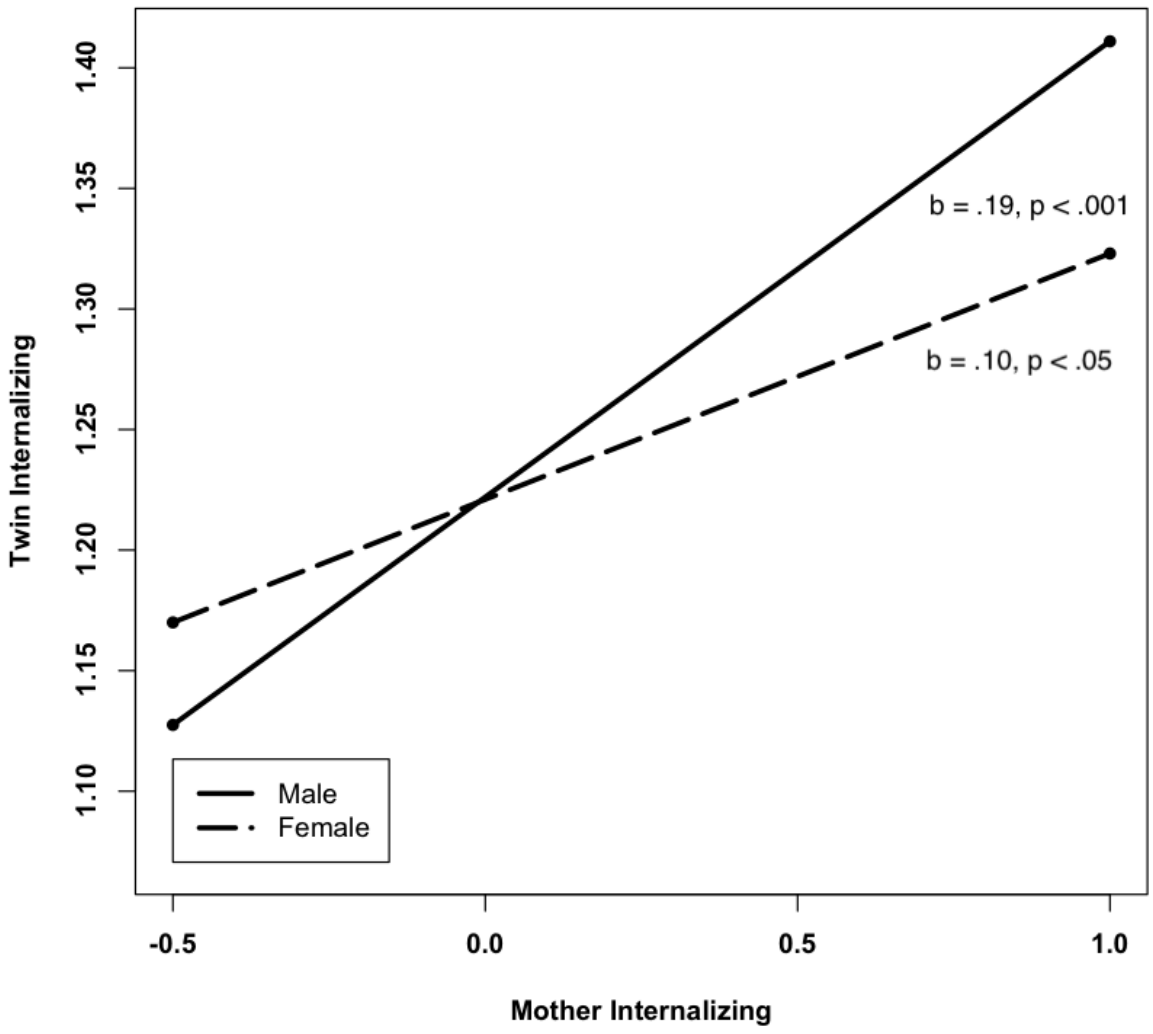

Figure 5. Simple slopes plot of the interaction between mother internalizing and twin sex on twin internalizing symptoms. b = unstandardized regression coefficient.

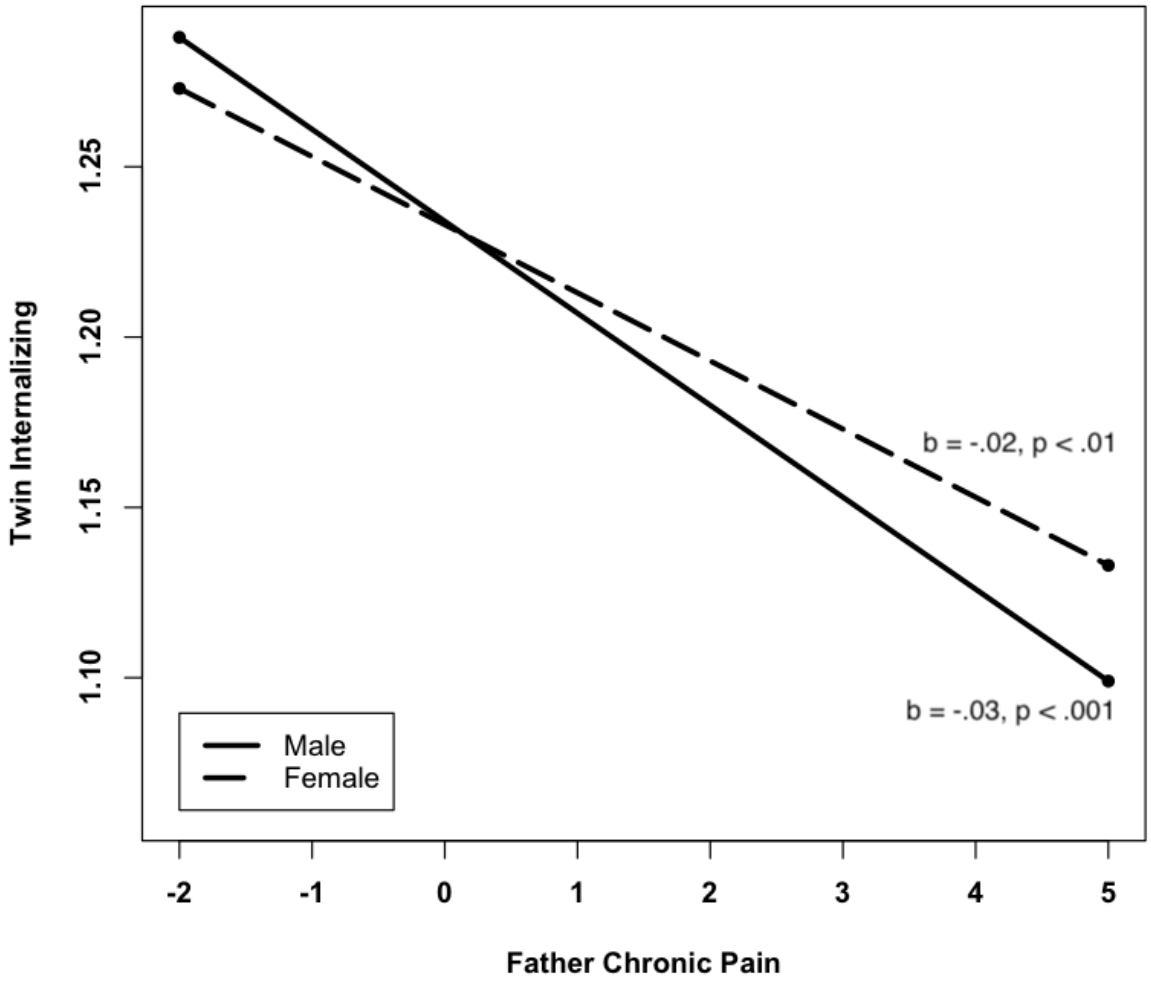

Figure 6. Simple slopes plot of the interaction between father chronic pain and twin sex on twin internalizing symptoms. b = unstandardized regression coefficient.