

Child Maltreatment and Adult Psychopathology:  
Elucidating the Relationship Through Developmental and Biometric Research.

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## **Dedication**

*This dissertation is dedicated to my parents, Nina and Michael,  
for inspiring me to always seek the truth.*

## Abstract

**Objective:** While childhood maltreatment (CM) and psychopathology are strongly associated, the causality of their relationship is unclear. Existent research has interpreted the maltreatment effect as a causal one, where by CM increases the risk of subsequent psychopathology. In two studies, this dissertation explores the relationship between CM and externalizing psychopathology (EXT), and CM and Major Depressive Disorder (MDD). **Methods:** A co-twin control method, utilizing 1382 pairs of twins from two cohorts of the Minnesota Twin Family Study, was used to compare the difference in adult psychopathology symptoms between CM-positive, and CM-negative twins. MZ twins who are discordant for exposure provide a model (assumed to control for genetics and shared environment) allowing for the direct estimation of the effect of CM within discordant twin pairs. Models were fit to the twin data and study hypotheses were tested using mixed-level regression using SAS Proc Mixed (Littell, 1996). **Results:** Consistent group differences on level of psychopathology across maltreatment for both males and females were confirmed. The relationship between CM and psychopathology does not appear generally causal but instead reflects a combination of genetic and environmental confounding effects. The patterns of genetic influence vary across disorders. **Conclusion:** The results confirm the association between CM and psychopathology, but emphasize the significance of genetic mediation on the relationship in both the externalizing domain and MDD. These results challenge the belief that CM directly contributes to psychopathology. Further research into the mechanism underlying this genetic confounding is discussed.

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## Chapter 1. General Introduction

### 1.1. Introduction

Childhood maltreatment (CM) is one of the most adverse and traumatic experiences faced by children. With consistent findings showing a strong association between CM and later maladaptive outcomes such as internalizing psychopathology (mood and anxiety, INT), externalizing psychopathology (substance use and antisocial behavior, EXT), psychosis, and personality disorders (Bergen, Martin, Richardson, Allison, & Roeger, 2004; Cicchetti, 1989; Cohen, Brown, & Smailes, 2001; Erickson, Egeland, & Pianta, 1989; Kaplan, Pelcovitz, & Labruna, 1999; Teisl & Cicchetti, 2008; Verona & Sachs-Ericsson, 2005), CM is widely regarded as one of the most potent environmental risk factors for later psychological maladjustment (Dodge, Bates, & Pettit, 1990; English, 1998; Hussey, Chang, & Kotch, 2006; Lansford et al., 2002; McGloin & Widom, 2002; Widom, 1989; Widom & Maxfield, 2001).

In support of the relationship between CM and psychopathology, clinical research has shown that the prevalence of CM among psychiatric inpatients is significantly higher than the general population (Read, 1997). For example, the prevalence of child sexual abuse in female inpatients has been estimated to be around 51% in both the United States and United Kingdom, and 44% of female inpatients are estimated to have a history of physical abuse (Caelin & Ward, 1992; Wurr & Partridge, 1996). Furthermore, individuals with a history of CM have been shown to be more resistant to treatment and at a greater risk of recurrence of clinical symptoms (Harkness, Bagby, & Kennedy, 2012; Nanni, Uher, & Danese, 2012). Because of the above findings, the psychopathology of

individuals with a history of CM is frequently viewed by the clinical community as particularly difficult to treat and resistant to intervention (Morrison, 2007; Williams, 1994). This dissertation explores the relationship between CM and adult psychopathology and questions the nature of the underlying relationship within a longitudinal, biometrically-informed community sample.

### 1.1.1 *Psychopathology Correlates of Child Maltreatment*

Negative outcomes associated with CM include child and adult psychopathology, interpersonal relationship problems, violence, self-injury, and suicide (Bergen, et al., 2004; Cicchetti, 1989; Cohen, et al., 2001; Erickson, et al., 1989; Fergusson, Horwood, & Lynskey, 1996; Jaffee, Caspi, Moffitt, & Taylor, 2004; Kaplan, et al., 1999; Verona & Sachs-Ericsson, 2005) .

In childhood, the problems associated with CM may manifest as delayed play skills, attachment problems, deficits in prosocial behavior, hopelessness, depressive symptoms, suicidality, and low self-esteem. Maltreated children show an excessive degree of withdrawal and avoidance of social interaction (Mueller & Silverman, 1989) and secure attachment with primary caregiver is compromised (Carlson, Cicchetti, Barnett, & Braunwald, 1989) as is the ability to form peer relationships (Mueller & Silverman, 1989).

The psychological correlates of CM seem to range across all domains of psychopathology and social adjustment. In some children, the maladjustment appears to emerge as EXT psychopathology (McGloin & Widom, 2002). For example, 30% of children that experience CM will meet criteria for disruptive behavior disorders, such as

Oppositional Defiant and Conduct Disorders during their childhood (Kaplan, et al., 1999). In other children, INT problems appear more prevalent. Incredibly, 40% of physically maltreated children will meet criteria for Major Depressive Disorder (MDD) during their lifetime (Kaplan, et al., 1999) and prospective longitudinal studies exploring the significance of physical CM confirmed an increase of suicidal ideation, suicidal behavior, anxiety symptoms, depression symptoms, and PTSD in children with a history of physical CM (Brown, Cohen, Johnson, & Smailes, 1999; Dubner & Motta, 1999; U.S. Department of Health and Human Services, Administration for Children and Families, Administration on Children, Youth and Families, & Children's Bureau, 2011).

Problems associated with CM continue well into adulthood and can be characterized by self-destructive behavior, suicidal ideation and behavior, anxiety, hostility, dissociation, interpersonal difficulties, and poor self-concept. CM is linked to mood and anxiety psychopathology including unipolar and bipolar depression, panic disorder, phobias, generalized anxiety disorder, and posttraumatic stress disorder (Afifi, 2012; Famularo, Fenton, & Kinscherff, 1992; C. Heim, Shugart, Craighead, & Nemeroff, 2010; K. S. Kendler et al., 2000; Mullen, Martin, Anderson, Romans, & Herbison, 1996). For example, 36% of physical CM victims meet criteria for PTSD as adults (Famularo, Fenton, Kinscherff, Ayoub, & Barnum, 1994).

Problems within the externalizing domain, such as antisocial behavior, substance use, and violence are also strongly associated with CM (Dinwiddie et al., 2000; K. Kendler et al., 2000) and remain significant even when controlling for parental EXT (Verona & Sachs-Ericsson, 2005) or for childhood family problems such as divorce, and

conflict (Nelson et al., 2002). Victims of abuse and neglect are more likely to meet criteria for Antisocial Personality Disorder (ASPD) over their lifetime than individuals that were not maltreated (Cohen, et al., 2001; Luntz & Widom, 1994; Maxfield & Widom, 1996) and are more likely to be violent in relationships as adults (Marshall & Rose, 1990). Research shows a strong connection between CM, substance use, and heightened aggressiveness (Mueller & Silverman, 1989), and results of several longitudinal studies indicate a strong link between abuse and subsequent criminal behavior (Straus, Sugarman, & Giles-Sims, 1997; Widom, 1999; Widom & Maxfield, 2001).

Estimates of CM among prison inmates vary widely (Jespersen, Lalumière, & Seto, 2009; Johnson et al., 2006). A self-report study in New York prisons estimated that 35% of the male felons sampled reported severe physical CM, and 14% reported some form of sexual CM. Overall, the sample produced an overall prevalence of 68% (including neglect, emotional CM), with 23% of the men reporting more than one type of CM. Interestingly, violent offenders reported similar rates of childhood physical abuse but higher rates of childhood neglect than non-violent offenders, while sex offenders sex offenders were more likely to report sexual experiences before age 12 (Weeks & Widom, 1998).

Other domains of psychopathology such as psychosis (Larkin & Read, 2008; Sideli, Mule, La Barbera, & Murray, 2012) and eating disorders (Afifi, 2012; Chen et al., 2010a) have also been associated with CM. Within the domain of personality disorders, in addition to ASPD, borderline personality disorder (Bornovalova et al., 2013; Widom,

Czaja, & Paris, 2009), psychopathy (Gao, Raine, Chan, Venables, & Mednick, 2010), and schizotypal personality disorder (Powers, Thomas, Ressler, & Bradley, 2011) have also been documented at higher rates in individuals who were maltreated in childhood. In short, childhood maltreatment is consistently associated with negative outcomes across childhood and adult psychopathology.

### 1.1.2 *Neurobiological Correlates of Child Maltreatment*

Efforts to understand the link between CM and psychopathology have considered neurological deficits that may serve as intermediate factors. Differences in functional impairment have been reported in individuals with a history of CM across the cognitive and affective domains (Curtis & Cicchetti, 2011; Gould et al., 2012; Kaufman, 1991; McCrory, De Brito, & Viding, 2012). Maltreated children have been shown to use a less mature style of problem-solving, including violence (Kaufman, 1991) and have been shown to have decreased intellectual and cognitive functioning. Deficits in verbal abilities, memory, problem solving, perceptual motor skills, decreased reading and math skills, poor school achievement, and increased need for special education services are just some of the academic and social implications of CM (Miller-Perrin & Perrin, 2007; Mills et al., 2011; Pechtel & Pizzagalli, 2011).

Childhood physical abuse has been linked to compromised brain development, and alterations of the biological stress system (Glaser, 2000; Perry, 1997). Structural differences, including decreased brain volume in individuals with a history of emotional and sexual abuse (De Bellis et al., 1999) and cortical thinning in women reporting a history of childhood sexual and emotional maltreatment have been demonstrated, with

authors speculating that CM may lead to plastic reorganization as a protective measure for children experiencing abusive condition and potentially lead to behavioral disinhibition in adulthood (C. M. Heim, Mayberg, Mletzko, Nemeroff, & Pruessner, 2013).

Physiological differences also emerge, with maltreated children showing an increased startle response in adulthood (Jovanovic et al., 2009; Ornitz & Pynoos, 1989) as well as disruption in the function of neurotransmitters and hormones (De Bellis, 2001; C. Heim, et al., 2010). It has been hypothesized that CM exposes the victim to acute and chronic stress, which affects the development and function of multiple interconnected neurobiological systems that influence physical and cognitive development, as well as emotional and behavioral regulation. For example, physically and sexually abused children appear to have higher levels of urinary dopamine, norepinephrine and free cortisol than control children (De Bellis, et al., 1999). Abuse and neglect also appear to affect the hypothalamic-pituitary-adrenal axis as well as the parasympathetic and catecholamine responses resulting in deregulation of the stress response (Glaser, 2000). In a study comparing maltreated and control children, Hart et al (1995) found that the maltreated children “exhibited less cortisol reactivity than did controls and scored lower in social competence and higher in internalizing and externalizing behaviors.

Taken together, these findings suggest the relationship between maltreatment and significant delay in these systems is evident and may be related to increased rates of psychopathology in CM individuals. As a result, CM is not only associated with various

behavioral and psychopathology categories, but with differences in more “upstream” processes that involve neurological, neuro-endocrine, and cognitive function.

## **1.2. Interpretation of the Relationship**

The above overview suggests that CM is common and associated with multiple domains of negative outcomes. Given such strong connections between psychopathology and CM, the majority of existent research and clinical practice continues to interpret this relationship to be a causal one (Afifi, 2012), identifying psychological maladjustment as being the direct result of CM as opposed to other genetic or environmental factors.

Theories to account for the relationship between CM and psychopathology have included mechanisms related to difficulties in emotion recognition (Pollak, Cicchetti, Hornung, & Reed, 2000), stress-induced neuroregulatory dysfunction (Cicchetti & Rogosch, 2001; De Bellis, 2001), traumatic brain injury, modeling of aggression (Bandura & McClelland, 1977), and attachment (Carlson, et al., 1989), to name a few. In fact, many psychological theories - from psychoanalytic (Freud, 1933) and social to attachment (Bowlby, 1977), learning, and behavioral theories - incorporate childhood trauma as a trigger for later maladjustment and psychopathological sequelae. In other words, clinical and research psychology has long interpreted the relationship between CM and psychopathology to be causal.

Many questions remain regarding the mechanism by which CM is related to psychopathology across developmental stages. Despite overwhelming evidence of the negative sequelae of CM, many who are abused do not develop problems, appearing resilient to these environmental stressors (McGloin & Widom, 2002) and despite the

increased rates of psychological problems, history of childhood maltreatment does not appear necessary or sufficient for the development of psychopathology suggesting that the relationship — though present — is non-determinative.

An alternative explanation for the direct causal or diathesis-stress CM- psychopathology relationship may lie in the interplay of genetic and environmental factors in defining the relationship between CM and psychopathology. Recent attention to the importance of environmental factors has shifted interests from directly causal models to considering how the genes and environment work together to account for the variation in individual differences across the lifespan (Plomin & McGuffin, 2003), as well as the recognition that all risk factors (genetic and environmental) involve probabilistic not deterministic influences (Rutter, Moffitt, & Caspi, 2006).

If the relationship between CM and psychopathology is in fact causal, however, a better understanding of the underlying mechanism for this association may improve intervention and treatment as well as affect public policy. Unfortunately, CM is not a random event and certain individual and family characteristics are associated with higher risk of abuse. Parental impulse control problems and depression, for example, are consistently shown to be positively associated with child abuse and neglect as are characteristics of the parent-child relationship, and family conflict (Stith et al., 2009), as is physical disability of the victim (Kendall-Tackett, Lyon, Taliaferro, & Little, 2005; P. Sullivan & J. Knutson, 1998). In fact, According to the US Department of Human Services (1993), in nearly half of reported cases involving disability, the disability directly contributed to CM. Multiple disabilities are associated with increased risk of

physical and sexual abuse, as well as increased severity and duration of both (Kendall-Tackett, et al., 2005; P. Sullivan & J. Knutson, 1998), suggesting that individual differences do play a significant role in vulnerability to CM. Furthermore, genetically-informative research from normative samples has also demonstrated that life events are genetically mediated (Bemmels, Burt, Legrand, Iacono, & McGue, 2008; Kandler, Bleidorn, Riemann, Angleitner, & Spinath, 2012) suggesting that genetic factors may play a role not only in the heritability of psychopathology, but also in environmental stress.

### **1.3. Behavioral Genetics of Child Maltreatment**

The link between CM and adult psychopathology may be better accounted for by common genetic or environmental risk factors, which can be explored through genetically-informed samples and designs such as twin studies. Genes can contribute to the development of psychopathology in various ways. The most direct form of genetic influence occurs when genes increase the overall liability to a disorder, which represents a “main effect.” Because the expression of psychopathology involves diverse and complicated constellation of behaviors, it is unlikely that a single direct genetic main effect is responsible for the relationship between CM and adult psychopathology.

If the association between CM and psychopathology is genetically moderated, it could be due to a Gene-Environment interaction (G x E) or a relationship in which particular environmental factors increase the likelihood of gene expression. Another possible form of genetic and environmental interplay that may contribute to the association between CM and adult psychopathology is gene-environment correlation

(rGE). Because parents pass on both genes and a rearing environment, they may be passing on not only the genes for psychopathology but also a high-risk environment. In other words, parents may be contributing both - the genetic liability for psychopathology and an abusive environment – but independently, through a passive rGE. Though environmental factors have been shown to influence genetic expression, the reverse is also possible with genetic factors influencing the likelihood of exposure to environmental risk beyond parental contribution. Variability of stressful life events is influenced by an individual's genetic and environmental background (Bemmels, et al., 2008; Kandler, et al., 2012; Kendler, Neale, Kessler, Heath, & Eaves, 1993), and the child's temperament and conduct problems may contribute to parental discipline including corporal punishment through evocative rGE (Ge et al., 1996). In other words, the effects of risk environments may be genetically mediated.

As mentioned in previous sections, the likelihood of experiencing CM may vary from person to person based on individual differences such as behavior, personality, emotional and neurocognitive functioning. As a result, genetically mediated individual differences – such as emotional instability, physical disability, cognitive deficits, or behavioral outbursts – may place the individual at an increased risk of being maltreated. This type of rGE can take two forms; active where the individual selects or creates a particular environment and evocative where an environment is elicited by the individual's genetically-influenced traits. Given this theoretical framework, the relationship between CM and psychopathology may also be interpreted in the reverse, suggesting that early onset psychopathology or more severe cases of psychopathology may lead to an

increased likelihood of CM. In this scenario, psychopathology would be neither necessary nor sufficient for CM, and individuals would vary in the severity of both. This controversial perspective challenges the directionality of the association long assumed to be the cornerstone of childhood development research and suggests a more complicated interplay between individual differences and environmental stress.

Genetically informed research, in the form of biometric analysis and discordant twin studies, can explore the contribution of genetic factors that contribute to CM exposure, but also to the potential genetic mediation of the relationship between CM and psychopathology. Several such studies have demonstrated a genetic association between CM and childhood or adult psychopathology but to varying degrees.

Univariate biometric results show that the variation in children's experiences of CM is partially accounted for by genetic factors, with the remainder of the variance accounted for by environmental influences and error. The percent of variance attributed to genetic factors varies across measures and studies. A study from the Virginia Twin Registry evaluated parental and child report of physical discipline in female twins and estimated that child genetically-mediated effects accounted for 9-21% of parent reports and 33-40 % of child reports of physical discipline (Wade & Kendler, 2000). Other studies on corporal punishment have shown that as little as 11% (Plomin, Owen, & McGuffin, 1994) and as much as 25% (Jaffee et al., 2004) of the variance in exposure is due to genetic factors. Findings specific to CM show lower estimates of genetic effects, with 7% for physical CM (Jaffee, Caspi, Moffitt, Polo-Tomas, et al., 2004). Results from a recent study based on the same sample as this dissertation estimate the proportion of

variance accounted for by genetic factors to be 13% for emotional, 10% for physical, and 5% for sexual CM (Bornovalova, et al., 2013). Despite the low estimates of genetic influences, the findings do not exclude the possibility that the relationship between CM and psychopathology is genetically influenced and are encouraging of further investigation.

Bivariate behavioral genetic studies exploring the relationship between CM and childhood conduct problems have shown that most of the link between corporal punishment and childhood conduct problems is due to common genetic factors (Jaffee, Caspi, Moffitt, Polo-Tomas, et al., 2004), and, more specifically, showing that a non-passive gene environment correlation may account for the phenotypic correlation between CM and conduct problems (Schulz-Heik et al., 2010).

While biometric analysis estimates the amount of overlapping genetic and environmental variance between CM and psychopathology, discordant twin studies compare twins discordant for CM in an attempt to evaluate causal relationships. The logic of the discordant design – which compares members of monozygotic (MZ) and dizygotic (DZ) twin pairs that differ on exposure to CM – is that if the effect of CM on psychopathology is causal, then participants positive for CM will be significantly different on psychopathology symptoms regardless of MZ or DZ status. If genetic influences account for the association between CM and psychopathology, MZ twins discordant for CM should show similar levels of psychopathology whereas discordant DZ twins will show a greater difference between the CM positive and CM negative twin because DZ twin pairs only partially control for genetic influences. If non-shared

environment effects are responsible for the relationship between CM and psychopathology, both MZ and DZ pairs would have higher levels of psychopathology in the CM positive twin because both twins are matched on shared environment factors as part of twin study design.

Several discordant twin studies have attempted to look at the topic of CM. Kendler et al., (2000) considered odds ratio of psychopathology when comparing discordant twins, 30.4% of which reported sexual CM, concluding that twins with a history of sexual CM had higher rates of psychopathology than their CM-negative co-twins. The greatest differences between discordant co-twins were seen in bulimia and alcohol and drug dependence. The study did not have a large enough sample to carry out comparisons between MZ and DZ pairs. Dinwiddie et al (2000) considered life time diagnoses in discordant twins with particularly low rates of 5.9% of the women and 2.5% of the men reporting childhood sexual abuse. The study evaluated the degree to which sexual CM risk aggregates in families by comparing odds ratios of concordance of MZ and DZ pairs and found concordance for sexual CM was not significantly greater for female MZ than DZ twins. Logistic regression was used to calculate odds ratios for psychiatric diagnoses but the study failed to find significant odds ratios in any of the nine categories of psychopathology considered. The authors concluded that the pattern of odds ratios showed some support for the hypothesis of familial aggregation of risk for CM but reported that they lacked the sufficient power to exclude the possibility of genetic factors.

Increased risks of adverse psychological outcomes were noted in a study exploring the role of sexual CM with 16.7% of the women and 5.4% of the men reporting

CM (Nelson, et al., 2002) on a number of psychological disorders and outcomes. The study showed consistently higher odds ratios for individuals with a history of sexual CM but did not compare MZ and DZ pairs, concluding that “family background risk factors contribute increased negative outcome risk.”

A study by Jaffee et al. (2004) considered the relationship between physical maltreatment and antisocial behavior in children in the context of breaking the cycle of violence by looking at parental factors as well. The researchers found that the presence of physical CM was predictive of childhood antisocial behavior. Statistical models, however, showed that genetic factors did not account for significant variation in the experience of physical CM. The authors concluded that this eliminates the possibility that any heritable characteristic of the child provoked physical maltreatment. It is possible that these results are limited by considering only physical CM, and childhood as opposed to adult psychopathology. The study did find that parents who engaged in high levels of antisocial behavior were more likely to maltreat their children and that parents' history of antisocial behavior accounted for nearly half of the effect of physical CM on children's antisocial behavior at age 7, while the effect of physical maltreatment remained significant. Furthermore, regression analysis provided partial support for the genetic transmission hypothesis by estimating that genetic factors accounted for 56% of the effect of physical maltreatment on children's antisocial behavior, concluding that link between physical CM and victim antisocial behavior in children is partially genetically mediated.

More recently, a study looking at borderline personality disorder (BPD) in the context of childhood maltreatment (Bornovalova, et al., 2013) used a series of discordant

twin and biometric models to evaluate the genetic and environmental influences underlying the link between BPD and CM. The study demonstrated an absence of a direct causal relationship between CM and BPD traits at age 24. Discordant twin analyses revealed moderate to large genetic effects on the association between CM and BPD traits and were further supported by the biometric modeling results. The authors concluded that these results are consistent with genetic effects on the CM relationship on BPD and that CM does not cause BPD.

Overall, previous studies have confirmed higher rates of psychopathology in individuals with a history of CM (Jaffee, Caspi, Moffitt, & Taylor, 2004; K. Young-Wolff, Kendler, Ericson, & Prescott, 2011; K. C. Young-Wolff, Kendler, & Prescott, 2012), but the results did not support a pure environmental causal relationship between CM and psychopathology. Because, as discussed above, estimates of the influence of genetic factors on exposure to CM may not be very high, few studies have considered the genetic mediation involved in the relationship between CM and psychopathology. Instead, these findings have been interpreted as confirmation of the causal relationship or at the very best as being indicative of environmental and “familial” influences.

### 1.3.1 *Summary*

Despite a plethora of research devoted to the topic of CM, a number of limitations exist in the current literature that addresses the underlying mechanism of the association between CM and psychopathology. Because of the challenges associated with CM research and the power required to compare discordant pairs of MZ and DZ pairs, studies may fail to reach significant findings due to methodological and power limitations.

Previous studies have frequently considered only one type of CM (physical, emotional, neglect, or sexual) at a time as opposed to various forms of CM, separately and together. To our knowledge, none has considered an integrated index of CM which includes physical and sexual CM within a large longitudinal sample including males and females to evaluate the relationship to various forms of psychopathology by using discordant MZ and DZ pairs. The current studies attempt to fill this gap in the literature by further evaluating the complicated relationship between CM and psychopathology in adulthood.

As outlined in the previous sections, some of the most consistent associations between CM and psychopathology occur in the EXT domain (antisocial behavior, alcohol, nicotine, drugs disorders) and the INT domain (unipolar mood and anxiety disorders). INT and EXT have been documented to represent separate but related dimensions of multiple diagnoses, which share risk factors and clinical correlates, and are strongly associated with CM. In an attempt to address some of the previous research limitations, the current work focuses on the relationship between CM and EXT and MDD, two salient categories that represent some of the most relevant and common mental health concerns.

#### **1.4. Research in Child Maltreatment**

Research in CM presents some unique challenges. The prevalence of child maltreatment in the United States remains a topic of debate in the literature but most experts agree that public statistics present a significant underestimate (P. M. Sullivan & J. F. Knutson, 1998; US Government Accountability Office 2011). Estimation of CM is difficult as most cases are unreported. Out of the actual cases of CM only some come to

the attention of mandated reporters (doctors, teachers, etc). A fraction of these cases are actually reported to child protection agencies, smaller numbers of these are reported as crimes, and even fewer become substantiated cases of CM. The main methods of estimating CM in the United States are official statistics, and self-report surveys. Official statistics include the National Incidence Study (NIS, Sedlak & Broadhurst, 1996) a congressionally mandated survey of mandated reporters carried out by the National Center on Child Abuse and Neglect most recently conducted in 2008 and extrapolated from random samples to create national estimates; and the National Child Abuse and Neglect Data Systems (NCANDS), an index of official reports (representing a fraction of actual cases) of CM. According to NCANDS, approximately 3 million cases of CM (including sexual, physical, neglect, and psychological maltreatment) were reported to Child Protective Services in 2011 (U.S. Department of Health and Human Services, Administration for Children and Families, Administration on Children, Youth and Families, & Children's Bureau, 2012). Child neglect is the most common form of CM – an act of omission rather than of commission, followed by psychological and emotional maltreatment, and then by physical, and sexual maltreatment.

Self-report findings, which attempt to get a sense of the actual amount of CM as opposed to the amount reported, are even more disturbing. According to the National Family Violence Survey, approximately three quarters of parents surveyed admitted to having used at least one violent act in rearing their children. Victim and perpetrator data shows that most abuse occurs at the hands of the parents as opposed to an external figure. Shockingly, four-fifths (81.2%) of victims were maltreated by a parent either acting alone

or with someone else (U.S DHHS, 2012), and that the risk of victimization and injury is likely greater at home than on the most dangerous city streets with the exception of sexual abuse which often is perpetrated by nonfamily members (Miller-Perrin & Perrin, 2007). Though most think of child abusers as violent and malicious individuals that prey on the defenseless; more often, than not, abuse results from unfit parents. As a result, considering family relationships and the familial transmission of environmental factors and CM is critical.

Epidemiological studies have provided diverse prevalence estimates. Sexual CM, for example has been estimated anywhere from 3 to 36% (Finkelhor, 1994), with an aggregate of 25 studies on sexual CM reporting a 22% prevalence for woman and 8.5% prevalence for men (Gorey & Leslie, 1997). One study conducted on a representative sample of men and women in a metropolitan area estimated that overall CM ranged from approximately 30% for women, and over 40% for men, with 13% reporting more than one type of CM (Scher, Forde, McQuaid, & Stein, 2004). Physical maltreatment, emotional maltreatment, and neglect were the most common forms of CM reported by both men and women.

Though the prevalence of abuse varies based on the method of data collection (reported child protection cases, state estimates of documented cases, self-report) and definition of CM (Miller-Perrin & Perrin, 2007), certain patterns emerge across samples and studies. Overall rates of physical CM are almost equally distributed between males and females (U.S DHHS, U.S. Department of Health and Human Services, et al., 2012). The estimates also suggest that girls experience highest rates of physical CM between the

ages of 12 and 17; whereas boys experience highest rates of physical CM from infancy through age 11 (U.S DHHS, 2001). The highest rates of overall CM are seen in African-American children, American Indian or Alaska Native children, and children of multiple races in 2007, at 16.7, 14.2, and 14.0 per 1,000 children, respectively. Hispanic children and White children had rates of 10.3 and 9.1 per 1,000, respectively. The lowest rate was seen in Asian children with 2.4 per 1,000 children being reported victims of CM. (U.S DHHS, 2009).

#### 1.4.1 *Challenges of CM Research*

CM takes many forms presenting a challenge in researching its effects. The prevalence of CM is difficult to estimate because CM is difficult to define, frequently occurs behind closed doors, and occurs to individuals that are unable to speak for themselves. Usually different types of abuse coexist (Claussen & Crittenden, 1991; Scher, et al., 2004; U.S DHHS, 2012), making the unique contribution of each type of CM difficult to establish. For example, considering physical abuse, physical neglect, verbal abuse, emotional neglect, and sexual abuse, Ney et al (1994) found that less than 5% of these mistreatments occurred in isolation, a phenomenon that makes it more difficult to isolate the effects of particular forms of trauma. A study considering the interrelatedness of adverse childhood experiences, including various forms of CM, as well as household dysfunction including crime and violence in the home, showed that participants who had experienced at least one adverse experience in childhood, were more likely to report one additional type of adverse experience (median across types of experiences estimated at 87%). Additionally, reporting one type of CM resulted in an

odds ratio of 2 to 17 for reporting another (Dong et al., 2004). The strongest relationship was found between physical and emotional abuse and the lowest associations seen between sexual CM and neglect.

Overall, research on CM is inherently challenging as it often relies on retrospective self-report or the report of parents both of which are inevitably incomplete. Parents (whether perpetrators or not) and children alike may have multiple reasons for being unwilling to report cases of abuse; these include concerns with social desirability, measurement error, discrepant perception, and faulty recall. Moreover, because CM estimates are based on retrospective reporting they may be inaccurate for a number of reasons, including underestimation, or selective reporting, and incomplete reporting.

#### 1.4.2 *Current Sample*

The current studies employ a sample that may overcome some of the challenges of CM research described above. Because the CM data used were collected at two different time points and with several measures, each individual had multiple opportunities to disclose CM. Consistency of CM reporting was evaluated and confirmed in the current sample. For example: 86.5 % of individuals who reported sexual maltreatment on one measure also reported it on another at the same time point suggesting that information provided during self report was generally reliable. CM was assessed in terms of sexual and physical maltreatment of significant severity, and consistent with other studies, 22% reported CM by their most recent follow-up assessment. Repeated assessments, severity requirements, and rates consistent with other research point to this being a solid measure of CM in a genetically-informative

community sample, providing a unique opportunity for the evaluation of the relationship between CM and psychopathology.

### **1.5. Specific Study Objectives**

It has long been assumed that CM leads to psychological problems, and that the likelihood of developing problems is moderated by individual differences such as resilience. The current work explores the association between CM and psychopathology by considering the possible genetic mediation between these two factors. Is the difference between CM and non-CM people due to genetic differences or environmental trauma, or both? Is the association between CM and psychopathology directly causal or is it mediated by genetic factors?

Despite the robust association between CM and psychopathology presented in the above review, the mechanism of a direct relationship remains elusive. Instead, it is possible that rGE accounts for the association between CM and later negative outcomes. Considering the problem across the lifespan in the context of genetically-informative data should contribute to the literature by elucidating the relationship between CM and psychopathology.

In order to identify true causality, a counterfactual model of causation, a comparison of outcome with the presence of CM and without CM within the same individual, would be required but is not feasible for a variety of reasons. The co-twin control design is an analogue of the idealized counterfactual model of causation (McGue, Osler, & Christensen, 2010). MZ twins who are discordant for exposure provide a comparable model to the idealized counterfactual design (assumed to control for genetics

and shared environment). The co-twin design employs twin pairs discordant for CM to estimate what a twin with positive for a history of CM would have been like in terms of psychopathology had he or she not experienced CM. In this design, the difference in the level of psychopathology between discordant MZ twins would be consistent with a causal influence of CM, a direct estimate of the effect of maltreatment.

In two studies, this dissertation explores the relationship between childhood maltreatment and psychopathology. Specifically, the two discordant twin studies consider the difference in levels of psychopathology between CM positive and CM negative twins. These longitudinal twin-control method studies explore alternatives to the direct causation theory by evaluating the potential for environmental and genetic mediation underlying the association between CM and psychopathology. Participants for the two studies included 2764 twins (48.1% male) who were assessed as part of the Minnesota Twin Family Study (MTFS), an ongoing community-based longitudinal investigation of twins and their families (Iacono, Carlson, Taylor, Elkins, & McGue, 1999). The first study explores the relationship between two categories of CM and three EXT disorders – Antisocial Personality Disorder, Alcohol Dependence, and Nicotine Dependence. The second study explores the relationship between three categories CM and Major Depressive Disorder, two categories of common psychopathology.

It is predicted that there will be a positive association between CM and symptom counts for all disorders, with a higher level of adult symptoms reported by individuals with a history of CM regardless of sex. More specifically, it is hypothesized that, if the association between psychopathology and CM is consistent with a directly causal model,

then MZ twins positive for CM will have significantly higher levels of psychopathology symptoms than their co-twins. If the relationship between CM and adult psychopathology is completely genetically mediated, then MZ twins discordant for CM will not differ in their levels of adult psychopathology symptoms, but the discordant DZ twins will show significant differences in levels of psychopathology symptoms. It is predicted that the relationship between CM and psychopathology will be genetically mediated for both males and females, and for each of the disorders. It is predicted that these results will be consistent regardless of the type of CM.

In short, the present studies will answer the following questions: What is the relationship between CM and adult psychopathology symptoms? Is this relationship direct or mediated, partially or completely, by genetic factors? Does this relationship vary across sex? Does it vary across type of CM?

## **Chapter 2. Childhood Maltreatment and Externalizing Psychopathology**

### **2.1. Introduction**

The likelihood of developing externalizing spectrum (EXT) disorders such as antisocial personality disorder or substance dependence (Krueger et al., 2002) is influenced by multiple factors including neuro-cognitive deficits, personality traits, genetic risk, deviant peer relations, and other environmental risk factors such as stressful life events (Fergusson & Horwood, 1996; Frick & Morris, 2004; Krueger & Markon, 2008; Rutter, et al., 2006).

Adult Antisocial Personality Disorder (ASPD) is a pervasive pattern of disregard for, and violation of, the rights of others that begins in childhood or early adolescence with conduct disorder and continues into adulthood (American Psychiatric Association, 2000) with a prevalence estimated at 3% in males and 1% in females. Alcohol Dependence (ALD) is a disorder characterized by addiction to alcohol, physical or mental, with the continued use of alcohol despite significant areas of dysfunction, dependence, or hardship. It is estimated that as many as 12% of American adults have had an alcohol dependence problem at some time in their life (American Psychiatric Association, 2000). Nicotine dependence (NCD) is an addiction disorder defined by the use of nicotine products and cognitive, behavioral, and physiological consequences. The lifetime prevalence of nicotine dependence is estimated at 24% (Breslau, Johnson, Hiripi, & Kessler, 2001).

The strong comorbidity that exists among these disorder is best accounted for by an underlying, normally distributed, latent continuum of risk as well as specific genetic

and environmental factors that contribute to the heritability of each syndrome within the spectrum (Krueger, Markon, Patrick, & Iacono, 2005). The underlying structure appears to be similar in men and women, although men have higher mean liability (Hicks et al., 2007). Despite the high heritability estimates for the common EXT factor, estimated to be  $h^2=.81$  among adolescents (Krueger, et al., 2002), environment remains a critical component in the development of these disorders.

Child maltreatment (CM) is an environmental risk factor of particular interest with a well established association with antisocial behavior and substance abuse (Dodge, et al., 1990; Lansford, et al., 2002; McGloin & Widom, 2002; Widom, 1989; Widom & Maxfield, 2001). Despite the strong relationship, many who are abused do not become antisocial, appearing resilient to these environmental stressors (McGloin & Widom, 2002). In fact, some with a history of environmental stress show increased adaptive functioning (Cicchetti, Rogosch, Lynch, & Holt, 1993). Why is it that some people seem to be affected by abuse and others do not? What are the long-term sequelae of the different types of maltreatment, and how do different types of maltreatment relate to different forms of externalizing psychopathology?

The association between CM and EXT is robust. For example, 30% of children that experience CM will meet criteria for disruptive behavior disorders (Oppositional Defiant Disorder, Conduct Disorder) (Kaplan, et al., 1999) during their childhood. CM has been associated with heightened aggressiveness (Mueller & Silverman, 1989), ASPD and alcohol dependence (Horwitz, Widom, McLaughlin, & White, 2001), and increased rates of arrest as juveniles and adults (Widom & Ames, 2004), and prospective studies

have demonstrated a link between CM and childhood EXT (Manly, Kim, Rogosch, & Cicchetti, 2001). Victims of CM are also more likely to meet criteria for ASPD over their lifetime than individuals that were not abused or neglected (Luntz & Widom, 1994; Maxfield & Widom, 1996) and are more likely to show heightened aggressiveness (Mueller & Silverman, 1989) and be violent in relationships as adults (Marshall & Rose, 1990).

Studies have proposed a Gene-Environment interaction (G x E) between CM and psychopathology, suggesting that exposure to CM interacts with certain genetic predispositions to EXT. Research considering this relationship has shown a potential moderator of the effect of CM in the form of a functional polymorphism in the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (MAOA) (Caspi et al., 2002). The study proposed that antisocial behavior was more likely in males with the genotype for low MAOA activity who had been mistreated than in those who have high MAOA activity. Though results are intriguing, replicating efforts have been mixed with some studies confirming the hypothesis that MAOA moderates the relationship between adolescent maltreatment and adolescent or adult antisocial behavior (Beach et al., 2010; Foley et al., 2004) and not others (Derringer, Krueger, Irons, & Iacono, 2010; Haberstick et al., 2005; Huizinga et al., 2006; Young et al., 2006). Studies have similarly demonstrated mediation of impact of childhood sexual abuse on women's antisocial behavior through methylation at 5HTT (Beach, Brody, Todorov, Gunter, & Philibert, 2011) and more recently, indication that high levels of MAOA were associated

with increased vulnerability for certain types of maltreatment have been reported (Nikulina, Widom, & Brzustowicz, 2012).

Many genetic studies assume that the genes that lead to a particular phenotype do not also influence the environmental exposure. Perhaps for this reason, G x E findings have been difficult to prove and rarely replicated. The presence of an rGE can inflate the detection of a false G x E. To prevent this error, many studies have restricted the search for gene and environment interaction to environmental factors which are independent of the phenotype (ones that do not show an rGE). Unfortunately, many studies have demonstrated the influence of genes on environmental exposures such as life events (Bemmels, et al., 2008; Kendler & Baker, 2007) including trauma and CM, and considering these factors in isolation limits our understanding of these relationships. Additionally, high prevalence of parental CM (over 80%) (U.S. Department of Health and Human Services, et al., 2012) suggests that CM cannot be considered independently of familial, and possibly genetic, influence. Discordant twin design presents an alternative methodology to investigate the relationship between CM and EXT psychopathology.

## **2.2. Aims of Current Study**

The current study aims to elucidate the relationship between childhood maltreatment and Adult Antisocial Behavior (AAB), ALD, and NCD by evaluating the contribution of both genes and environment to these associations using the co-twin control method. It is predicted that a strong positive association will be seen between all categories of CM and all three of the disorders explored, with higher rates of symptoms

in individuals with a history of CM, but that these results will vary across discordant twin pairs with significant differences seen in discordant DZ but not MZ pairs. More specifically, it is hypothesized that, if the association between psychopathology and CM is consistent with a directly causal model, then MZ twins positive for CM, will have significantly higher levels of psychopathology symptoms than their co-twins who are negative for CM. If the relationship between CM and adult psychopathology is genetically mediated (completely or partially), then MZ twins discordant for CM will not differ in their levels of adult psychopathology symptoms, but the discordant DZ twins will show significant differences in levels of psychopathology symptoms. It is predicted that these results will be consistent regardless of the type of CM.

## **2.3. Methods**

### *2.3.1 Participants*

Eligible participants consisted of same-sex twins who were assessed as part of the Minnesota Twin Family Study (MTFS), an ongoing community-based longitudinal investigation of twins and their families (Iacono, et al., 1999). Participants were identified for intake assessment through public records of twin births in Minnesota between 1972 and 1984. Approximately 78% of those meeting eligibility criteria (living with at least one biological parent, within a day's drive of Minneapolis, and lacking a mental or physical disability that would preclude their completing the daylong intake assessment) agreed to participate (Iacono, et al., 1999). The sample is representative of the Minnesota population in terms of ethnicity and socioeconomic status (Holdcraft & Iacono, 2004). Reflecting the population of Minnesota during the target birth years, 96%

of the sample is Caucasian. Parents and children gave informed consent or assent as appropriate, and an institutional review board approved all research protocols.

Zygoty was determined by agreement among three estimates: MTFS staff evaluations of the twins' physical similarity; parents' completion of a standard zygoty questionnaire; and twin similarity on an algorithm of ponderal and cephalic indices and fingerprint ridge count. A serological analysis was performed if the 3 estimates did not agree. A previous validation study (N = 50) demonstrated 100% accuracy of zygoty determination when these three estimates agree. When disagreement among these estimates is noted, a blood sample is requested and a serological analysis is performed.

### 2.3.2 *Interview and Assessment Procedure*

The MTFS utilizes an accelerated longitudinal design with participants first entering the study at either age 11 or 17 and returning for follow-up assessments every three to six years (Table 1). The initial intake twin sample consisted of 2764 same-sex twins with 756 twin pairs from the 11-year old cohort, and 626 pairs from the 17-year old cohort. The younger of the two cohorts was initially assessed when the twins were approximately 11 years-old (M=11.72, SD = 0.43 years); and follow-up assessments were scheduled at ages 14-15, 17-18, 20-21, 24-25, 29-30. The older cohort was initially assessed when the twins were approximately 17 years-old (M=17.48, SD = 0.46 years), and follow-up assessments were scheduled at ages 20-21, 24-25, and 29-30. All assessments were designed to be in-person, although some individuals who could not complete an in-person assessment were interviewed by phone. Of the total 1382 pairs, 902 were MZ (50.9% female) and 480 DZ (53.8% female).

The current study utilized data from age 20, 24, and 29 assessments from both cohorts. The most recent data used in this sample was collected at the mean age of 29.41 (SD=0.64 years), with an average retention rate of 90% from intake. Maltreatment data were available for 2607 individuals (53% female) who comprise the CM subsample used in this study, with 1422 individuals from the younger cohort, and 1185 individuals from the older cohort. Table 1 shows the breakdown of twin pairs concordant and discordant for physical and sexual CM.

### 2.3.3 *Measures of Maltreatment*

CM before the age of 18 was evaluated retrospectively at age 20, 24, and 29 assessments (Table 1). The Trauma Assessment for Adult (TAA; Resnick, Falsetti, Kilpatrick, & Freedy, 1966) was administered for both cohorts at age 20 and 24, and the younger cohort males at age 29 and consisted of an interview to assess traumatic life events related to posttraumatic stress disorder. The assessment was preceded by the statement that unwanted sexual experiences can occur at any time in life, that they may not have been reported, and that they may have been committed by anyone including family members, or friends. The statement also encouraged participants to endorse past history of unwanted sexual experiences regardless of how long ago they happened. Two questions about sexual maltreatment were asked: whether the participant ever had sexual contact with anyone five or more years older before they reached the age of 13, and whether anyone, including a friend or relative, ever used pressure, force, or physical threats to engage in unwanted sexual contact. Sexual contact was defined as contact involving sexual organs—(penis or genital area for men; vagina, genital area, or breast

for women) of either individual. Age at which the endorsed maltreatment first occurred was reported.

The Childhood Experiences Questionnaire (CEQ) is a 26-item inventory consisting of items adapted from the Childhood Life Events Inventory (Sher, Gershuny, Peterson, & Raskin, 1997), the Colorado Adolescent Rearing Interview (Crowley, Mikulich, Ehlers, Hall, & Whitmore, 2003), and the Childhood Trauma Questionnaire (Bernstein et al., 2003). It was administered at age 24 for the younger cohort males and females and at age 29 for older cohort females to assess physical and sexual maltreatment occurring before the age of 18. The questionnaire included seven items about forceful sexual experiences such as unwanted sexual exposure, fondling, insertion, and intercourse as well as four items about physical maltreatment such as hitting and leaving a mark, hitting with an object such as a belt, using a weapon, kicking, biting, and burning as well as the age at which the endorsed maltreatment first occurred. For male twins in the older cohort, harsh discipline only was assessed as part of a larger Social Adjustment Interview (SAI) completed at age 20, in which participants were asked whether typical discipline while growing up included being “hit in the face” or “hit with an object.”

Sexual CM was defined as any endorsement of sexual exploitation, which occurred before the age of 18. A binary measure of sexual CM was comprised from the nine relevant items of the TAA and the CEQ. Sexual CM before the age of 18 was reported by 7% of participants.

Physical CM was defined as any endorsement of harsh discipline (e.g. leaving a mark) occurring before the age of 18. A binary measure was comprised of six relevant

items from the SAI and CEQ. Physical CM before the age of 18 was reported by 19% of participants. Emotional childhood maltreatment and neglect were not included in the analysis due to discontinuous data and low base rates.

Because preliminary analyses did not reveal significant differences in the association of sexual or physical CM with externalizing psychopathology ( $ps$  ranging from 0.12–1.00), a finding similar to other studies (Alink, Cicchetti, Kim, & Rogosch, 2009), a measure of overall maltreatment was comprised of the above mentioned measures of physical and sexual maltreatment to evaluate the effects of overall maltreatment in childhood on psychopathology. Participants were classified as having experienced any CM if they reported either physical or sexual CM before the age of 18. Overall, CM before the age of 18 was reported by 22% of participants (21 % males and 23% females). Rates of maltreatment by type and sex are presented in Table 2 and an overview of discordant pairs across sex and type of CM are presented in Table 3. Report of sexual CM was consistent across time and measure. For example, 85% of individuals reporting sexual CM on one measure at age 24, also reported it on another. Individuals reporting CM at age 24 were also likely to report it at a later assessment (75%).

#### 2.3.4 *Measured of Psychopathology*

Symptoms of adult antisocial behavior (AAB) were assessed with items from the Structured Clinical Interview for DSM-III-R Personality Disorders (R. L. Spitzer, Williams, J. B. W., Gibbons, M., & First, M. B., 1987). Alcohol dependence (ALD), and nicotine dependence (NCD) were assessed using a modified version of the expanded Substance Abuse Module of the Composite International Diagnostic Interview (Robins et

al., 1988). Data were collected at three time points for both cohorts (Table 1) with the exception the younger cohort females for whom, at the time of this study, age 29 assessment data was not yet available. The highest symptom count reported at any of the three assessments was retained for analysis as a measure of adult psychopathology for each of the three disorders.

AAB was assessed lifetime at ages 20 and 24, and since the previous assessment at age 29 for both cohorts. AAB was operationalized as the count of endorsed criterion “C” symptoms of DSM-III-R Antisocial Personality Disorder (ASPD), which include repeated illegal acts, irritability and aggressiveness, disregard for the truth, and lack of remorse. Because the full diagnosis of ASPD also requires three or more criterion “A” symptoms of conduct disorder, AAB alone does not constitute a DSM diagnosis. Rather, it presents an index of adult behavior characteristic of ASPD (including irritability and aggressiveness, irresponsibility, failure to conform to social norms, inconsistent work behavior, etc.), and previous studies have shown a high diagnostic reliability when comparing AAB to ASPD criteria ( $k=0.78$ ) (Burt et al., 2010).

ALD and NCD were operationalized as the highest value of DSM-III-R symptoms counts for ALD and NCD at each of the three time points. At each of the three assessments (ages 20, 24, and 29) symptom data were collected since the last time the participant was assessed except for older cohort males who were assessed for lifetime ALD and NCD symptoms at their age-20 assessment (as opposed to the last three years). Because the older cohort males were assessed lifetime, their symptom counts were adjusted to eliminate any possible childhood-limited data. Ages associated with

individual symptom counts were used to identify individuals who reported only symptoms which were childhood limited (starting and ending before the age of 18). This process identified no individuals who reported childhood isolated ALD symptoms and five individuals who did identify childhood limited NCD symptoms indicating that all of the symptoms that they endorsed ceased before the age of 18. These five individuals were recorded as having no adult symptoms for the age-20 assessment only.

All interview data were reviewed in a clinical case conference by at least two clinical psychology graduate students, with members of the review team required to reach consensus before assigning symptoms. A tape recording of the interview was consulted in ambiguous cases to reach consensus. Previous review of this process shows that this assessment process yielded uniformly high diagnostic reliabilities (greater than .91) (Iacono, et al., 1999). To adjust for positive skew, all symptom counts were log-transformed before analysis. Symptom and diagnostic prevalence rates are presented in Table 4.

### 2.3.5 *Statistical Design and Measures of Effects*

The analyses carried out in this study are predicated on the various sources of similarities and differences across reared-together twins. All of the twins in the study share their rearing environment. MZ twins share 100% of their genetic material, whereas DZ twins share 50% of their segregating genetic material. As a result, the differences between MZ twins are due solely to unique environmental influences (such as maltreatment), as well as measurement error. Differences between DZ twins, by

comparison, are due to both unique environmental influences, and the 50% of genes they do not have in common.

First, a series of analyses to examine the phenotypic association between CM and psychopathology was carried using correlations and regression. To adjust the analyses for correlated twin observations, these analyses use PROC MIXED in SAS 9.3 (SAS Institute Inc., 2011). Analyses were used to compare the relationship between the different categories of CM (any, sexual, physical) and AAB, ALD, NCD for the entire sample. Gender interaction regression models were used to evaluate the sex-differences present in these effects.

Next, the associations within twin pairs were evaluated using an analogue of the idealized counterfactual model of causation, the co-twin control design (McGue, et al., 2010). In order to identify true causality, a counterfactual model of causation, a comparison of outcome with the presence of CM and without CM within the same individual, would be required but is not feasible for a variety of reasons. MZ twins who are discordant for exposure provide a comparable model to the idealized counterfactual design (assumed to control for genetics and shared environment). The co-twin design employs twin pairs discordant for CM to estimate what a twin with a history of CM would have been like in terms of psychopathology had he or she not experienced CM. In this design, the difference in the level of psychopathology between discordant MZ twins would be attributed to a causal influence of CM, a direct estimate of the effect of maltreatment.

More specifically, let  $y_{ij}$  be the observed outcome for the  $j$ th twin ( $j = 1, 2$ ) in the  $i$ th twin pair ( $i = 1, 2, \dots, N$ ) and let  $x_{ij}$  be the corresponding exposure index (in this case, childhood maltreatment) for this individual. The overall, or individual-level, regression of the outcome on the exposure is given by the regression model

$$y_{ij} = \beta_0 + \beta_1 x_{ij} + \varepsilon_{ij},$$

where  $\beta_1$  is the individual-level effect of exposure (childhood maltreatment) on outcome (psychopathology),  $\beta_0$  is the intercept term, and  $\varepsilon_{ij}$  is the residual (correlated across the 2 members of the twin pair). The overall regression effect can be further represented in terms of within-pair ( $\beta_W$ ) and between-pair ( $\beta_B$ ) effect using the regression model

$$y_{ij} = \beta_0 + \beta_W(x_{ij} - \bar{x}_i) + \beta_B \bar{x}_i + \varepsilon_{ij},$$

where  $\bar{x}_i$  is the mean exposure index for the  $i^{\text{th}}$  twin pair. The individual-level effect is estimated with the between-pair regression coefficient and the within-pair regression coefficient serves as a direct estimate of the effect of exposure on the outcome (maltreatment on psychopathology) within discordant twin pairs.

This regression model can be further conceptualized within a genetically-informed design (McGue, et al., 2010). Individual-level associations reflect potential confounding of genetic effects, shared environmental effects, and non-shared environmental effects. Associations within DZ twin pairs discordant for exposure control for shared environmental effects and partially for genetic effects. Associations within MZ twin pairs discordant for exposure control for shared environmental and genetic effects. Any remaining associations within discordant MZ pairs, therefore, directly index nonshared environmental effects. Accordingly, should maltreatment be causally linked to

increases in psychopathology, one would expect to observe this association at the individual level, within DZ twin pairs discordant for exposure and within MZ twin pairs discordant for exposure (Figure 1, scenario A). By contrast, the failure to observe an association within discordant MZ twin pairs would imply that the association of exposure with outcome is solely attributable to selection processes (i.e. the process is mediated by genetic and/or shared environmental effects rather than nonshared environmental effects given that there is no association between exposure and outcome in discordant MZ twins). In particular, if exposure was associated with outcome at the individual level and in discordant DZ twins (scenario B), we would infer that the selection process was genetic in origin. If the exposure was associated with outcome only at the individual level (scenario C), we would infer that the selection process was shared environmental in origin. While the failure to detect a within-pair association would invalidate the existence of causality, the opposite (presence of association between exposure and outcome) cannot confirm causality because without a longitudinal context it does not rule out that discordance is related to outcome by some other factors.

To evaluate whether, after controlling for sex, twins who had reported a history of CM showed higher rates of psychopathology, regression analyses were conducted using PROC MIXED in SAS for each category of CM and psychopathology. The entire sample, regardless of concordance status, was used to estimate the between-pair effects, while only discordant pairs were used for the within-pair effects.

## **2.4. Results**

### 2.4.1 *Phenotypic Analyses*

Rates of CM are presented in Table 2. Physical CM before the age of 18 was reported by 19% of participants, with a significantly greater percentage of men than women, 21% and 17% respectively, reporting childhood physical CM,  $X^2(1, N = 2311) = 7.273, p = .007$ . Sexual CM before the age of 18 was reported by 7% of participants, with a significantly greater percentage of women than men, 11% and 3% respectively, reporting sexual CM  $X^2(1, N = 2607) = 62.095, p = <.001$ . Overall CM before the age of 18 was reported by 22% of participants, with no significant differences across gender, 21% males and 23% females reporting maltreatment,  $X^2(1, N = 2607) = 2.104, p = .147$ .

Correlations among the variables showed significant relationships (Table 5) Tetrachoric correlations revealed a weak relationship between sexual and physical CM ( $r=.20, p<.001$ ) and a strong relationship between the index of any CM and physical CM ( $r=.99, p<.001$ ) and sexual CM ( $r=.95, p<.001$ ). Correlations between gender and CM showed a weak relationship between having either CM and gender, a weak relationship between physical CM and gender, and a moderate relationship between sexual CM and gender. Biserial correlations between CM and psychopathology showed generally weak but statistically significant ( $r= .05 - .18$ ) relationships. Pearson correlations among the three disorders showed moderate relationships ( $r=.43-.59$ ).

Estimates of main effects and gender interactions were calculated using mixed-level regressions (Table 6) for each type of CM and disorder. None of the CM by gender interactions proved to be significant. Main effect calculations were conducted for the entire sample and for males and females separately. Main gender effect and interaction

with CM were computed only in the combined sample. Each type of CM had a significant main effect on AAB, ALD, and NCD, and regardless of whether the sample was split by gender, individuals with a history of any type of CM showed higher levels of symptom counts in each of the three disorders. In the combined sample, gender was also a significant predictor of psychopathology, with males reporting significantly more symptoms of AAB, ALD, and NCD.

#### 2.4.2 *Discordant Twin Analyses*

Nine discordant twin models were fit to evaluate the differences in the three symptoms counts (AAB, ALD, NCD) for MZ and DZ twins discordant for each of the three categories of CM (Any, Physical CM, Sexual CM). The results are presented in Table 7. As expected, all nine models showed significant individual level effects, meaning that significant differences in symptom counts were seen when comparing individuals with and without a history of CM for each of the disorders and for each type of maltreatment. All nine models had non-significant MZ within-pair effects, suggesting that identical twins discordant for each type of CM did not differ significantly in their level of psychopathology symptoms regardless of their history of maltreatment. In other words, the symptom expression in identical twins did not vary as a factor of CM, suggesting that the association of CM and the three categories of psychopathology symptoms cannot be attributed simply to causal effect of CM on symptoms.

DZ within-pair effects on CM on symptom counts were significant for all of the symptoms categories and CM types except for Physical CM on NCD. These results suggest that within discordant DZ pairs, individuals with and without a history of CM

varied significantly in their level of symptoms. These results, taken together with the non-significant discordant MZ pair differences, are consistent with a genetic mediation effect of CM on psychopathology symptom counts. These results, including relative magnitude and significance of standardized within-pair differences are presented in Figure 2 to facilitate understanding. Overlapping confidence intervals are interpretable only for statistically significant values such as the individual and DZ bars. With the exception of NCD physical results, all individual effects and DZ effects are significant. Because of non-significant MZ results, the models follow the genetic-confounding scenario (scenario B in Figure 1). The NCD and Physical CM result is more consistent with genetic and environmental confounding (scenario C in Figure 1).

## **2.5. Discussion**

The aim of the current study was to clarify the nature of the association between CM and EXT psychopathology. This study used three measures of CM including physical, sexual, and any maltreatment reported to have occurred before the age of 18. DSM-III-R diagnostic criteria symptom counts for Adult Antisocial Behavior (AAB), Alcohol Dependence (ALD), and Nicotine Dependence (NCD) were collected at three time points. The maximum value of adult psychopathology symptoms for each disorder at any one time point was retained for analysis. Co-twin control analyses (within and between-pair effect) of the relationship between maltreatment and symptom counts associated with three EXT disorders were conducted in SAS.

The results, consistent with previous findings (Afifi, 2012; K. S. Kendler, et al., 2000; Nelson, et al., 2002), confirmed the prediction that adults with a history of CM

show increased rates of psychopathology symptoms later in life. No significant gender differences were noted in the relationship between CM and any of the three symptom counts.

Co-twin control analysis offered support for selection explanations underlying the relationship between CM and EXT. Differences among individual-level, MZ within-pair effects, and DZ within-pair effects indicated that the relationship was genetically mediated, with the exception of NCD and Physical CM, which was both genetically and environmentally mediated. In other words, the results confirm that CM is not a random event and individuals who demonstrated higher levels of adult EXT psychopathology, were also at a higher risk of a history of CM, consistent with other research (Bemmels, et al., 2008; Kandler, et al., 2012) that shows that individual differences may play a role in the likelihood of CM.

Potential explanation for the mechanism underlying these genetic-mediation findings, include non-passive gene-environment correlation where genetically-influenced individual differences such as behavioral problems may increase the risk of being maltreated, or passive gene-environment correlation in which the same genetic influences are responsible for both the maltreatment by the parents and the later psychopathology of the offspring.

Because the genetic mediation and environmental mediation results varied across disorder, with NCD and Physical CM showing both, it may be possible that CM does not affect all psychopathology equally, despite the fact that it significantly increases the risk

for all three disorders tested. This may explain variation among other studies regarding the effect of CM on psychopathology.

### 2.5.1 *Limitations*

The current study had a number of limitations. Assessment of psychopathology was conducted using DSM-III-R diagnostic criteria, which conceptualize behaviors in terms of symptoms, and may not be the best measure of these behaviors. Furthermore, symptom counts, though a good indicator of lifetime prevalence, do not reflect the frequency, severity, or duration of psychopathology, and measures that incorporate some or all of these factors that are associated with CM will be of benefit to future research.

As with most maltreatment studies, the current data were reported retrospectively, across several measures and time points, and may be an underestimate of CM due to participants' reluctance to disclose. Though self-report is considered a reliable and valid form of assessment, it is not faultless. The current study used several self-report measures of CM, which potentially overcame some of these limitations. This provided some convergent validity in estimating CM, and allowing participants multiple opportunities to disclose a history of CM. Furthermore, the categorization of CM was restricted to severe and specific cases of reported CM, and with rates and correlations consistent with previous research, this appears to be a valid and reliable measure of CM.

Another limitation is that though the study considered several CM categories, it did not include neglect, emotional CM, psychological CM, or characteristics of the relationship between the victim and the perpetrator. Though CM severity was established through careful item selection, future studies may benefit from evaluating CM on a

continuum of both severity and frequency. Other measures of EXT-related psychopathology, such as drug dependence and psychopathy, as well as childhood EXT such as Conduct Disorder may be useful in evaluating the life-course relationship between CM and EXT.

Sample-specific limitations must also be considered, including the predominantly Caucasian sample, as well as potential attrition of subjects due to either CM or psychopathology, resulting in a skewed sample. However, the high participation rate, which exceeded 90%, suggests that such effects would not be likely to have a major impact on the results. Furthermore, because the most recent data represents psychopathology through the age of 29, it is possible that individuals will report problems in the future, and a follow up study considering this effect may be beneficial.

### 2.5.2 *Overall Summary*

Despite robust associations between CM and adult EXT in existing literature, the nature of the relationship has been poorly understood. This study employed a co-twin control analysis design to evaluate potential genetic mediation of the relationship between CM and adult symptom counts associated with three disorders (AAB, ALD, NCD). Results confirm the positive association between CM and all three of the psychological symptom counts used with this sample. Individuals with a history of CM show higher adult symptom counts when compared to individual with no history of CM. The relationship between CM and the three symptom counts did not vary for men and women.

Discordant twin analyses revealed significant differences in DZ but not in MZ pairs for all comparisons between symptoms counts (AAB, ALD, NCD) and types of CM (Any, Sexual, Physical); a pattern of results consistent with genetic-confounding suggested by other research (Bornovalova, et al., 2013; Jaffee et al., 2005b). The only analysis to indicate a different relationship was the NCD and Physical CM analysis, which revealed non-significant DZ and MZ differences, suggestive of both genetic and environmental mediation. As a whole, none of the results was consistent with the directly causal relationship between CM and psychopathology.

These results provide additional evidence that the relationship between environmental trauma and psychopathology must be further evaluated in the context of genetic factors. The genetic mediation demonstrated by this study may take the form of passive, and/or evocative gene-environment correlations (McGue, et al., 2010). In the case of passive gene-environment correlation, the parents contribute both the genotype and rearing environment. In the case of CM and EXT, the parents may pass on the genetic predisposition for antisocial behavior and provide the environmental exposure to child to maltreatment. In the case of evocative gene-environment correlation, the genetically-influenced traits may elicit particular responses from others. In the case of CM, a child prone to emotional instability or behavioral outburst may place greater demands on the parent's coping abilities and lead to harsher forms of discipline.

Future studies devoted to identifying factors that account for the genetic mediation between CM and EXT, and controlling for parental psychopathology, could contribute to a better understanding of the link between these two phenomena.

Furthermore, shifting the current clinical framework from a directly causal interpretation of CM and psychopathology may be beneficial to case conceptualization and intervention.

This work has contributed to an improved understanding of the relationship between CM and adult psychopathology by identifying that the underlying relationship is not directly causal in nature. Phenotypic results are consistent with the large body of research that links CM to negative outcomes including psychopathology, and more specifically EXT (Afifi, 2012). The co-twin control findings are consistent with other research that has suggested that genetic mediation may be at play in other psychopathology at other life stages (Bornovalova, et al., 2013; Jaffee, Caspi, Moffitt, & Taylor, 2004; Schulz-Heik, et al., 2010) but extended these findings to EXT disorders in adulthood. These results are inconsistent with odds-ratio discordant twin research, (without co-twin control), that suggests that CM directly causes psychopathology with no genetic mediation at play (Dinwiddie, et al., 2000; Nelson, et al., 2002) a difference in findings that may be due to limitations of the samples used including low sample size and insufficient rates of CM. Overall, the current work, using a large genetically informative sample with strong measures of CM, and rates of both CM and psychopathology consistent with other research suggests that the association between CM and adult EXT disorders is not directly causal. The second study of this dissertation extends this line of work in to the domain of Major Depressive Disorder.

Table 1. Schedule of Assessments

	Age						Total Twin Pairs
	11	14	17	20	24	29	
<i>Younger Cohort</i>	<i>Intake</i>	<i>FU1</i>	<i>FU2</i>	<i>FU3</i>	<i>FU4</i>	<i>FU5</i>	
Males				TAA, SCID-II, SAM	TAA, CEQ, SCID-II, SAM	TAA, SCID-II, SAM	376
Females				TAA , SCID-II, SAM	TAA, CEQ, SCID-II, SAM		380
<i>Older Cohort</i>			<i>Intake</i>	<i>FU1</i>	<i>FU2</i>	<i>FU3</i>	
Males				TAA, SAI, SCID-II, SAM	TAA, SCID-II, SAM	SCID-II, SAM	289
Females				TAA, SAI, SCID-II, SAM	TAA, SCID-II, SAM	CEQ, SCID- II, SAM	337

FU = study follow-up assessment; TAA = Trauma Assessment for Adults; SAI = Social Adjustment Interview; CEQ = Childhood Experiences Questionnaire; SCID-II = The Structured Clinical Interview for DSM-III-R, Personality Disorders. SAM = Substance Abuse Module of the Composite International Diagnostic Interview

*Table 2. Rates of Reported Childhood Maltreatment by Type*

	Total N	Sexual CM			Physical CM			Any CM		
		n	yes	%	n	yes	%	n	yes	%
Male	1330	1219	37	3.0	1072	229	21.4	1219	254	20.8
Female	1434	1388	154	11.1	1239	210	16.9	1388	322	23.2
Total	2764	2607	191	7.3	2311	439	19.0	2607	576	22.1

CM = Child Maltreatment

Table 3. Twin Pairs Discordant for Child Maltreatment.

	MZ Pairs				DZ Pairs			
	Neither	Discordant	Both	Total	Neither	Discordant	Both	Total
<b>Sexual CM</b>								
Males	374	13	2	389	186	16	1	203
Females	372	53	14	439	193	40	16	249
All	746	66	16	828	379	56	17	452
<b>Physical CM</b>								
Males	231	66	29	326	112	37	22	171
Females	274	66	33	373	156	43	13	212
All	505	132	62	699	268	80	35	383
<b>Any CM</b>								
Males	271	86	32	389	129	51	23	203
Females	300	89	50	439	150	66	33	249
All	571	175	82	828	279	117	56	452

Neither = neither member of the pair reports maltreatment, Discordant = one member of the pair reports maltreatment, Both = both members of the pair report maltreatment.

*Table 4. Symptom Counts and Diagnostic Prevalence of Adult Psychopathology.*

	Males				Female				Both			
	N	Symptom Count		Diagnostic Prevalence	N	Symptom Count		Diagnostic Prevalence	N	Symptom Count		Diagnostic Prevalence
		Mean	SD	%		Mean	SD	%		Mean	SD	%
AAB	1263	1.77	1.40	11.2	1393	0.92	1.03	3.2	2656	1.33	1.29	7.0
ALD	1272	2.13	2.08	36.9	1400	0.82	1.50	11.4	2672	1.44	1.91	23.6
NCD	1272	1.93	2.18	39.3	1400	1.28	1.94	25.1	2672	1.59	2.08	31.9

Note: Data based on maximum values of three assessments (age 20, 24, 29). AAB = Adult Antisocial Behavior; ALD = Alcohol Dependence; NCD = Nicotine Dependence; MDD = Major Depressive Disorder. Assessments occurred at age 20, 24, and 29.

Table 5. Variable Correlations

	Any CM	Physical CM	Sexual CM	AAB	ALD	NCD
Sex	.05	.10***	.38**	-.35**	-.38**	-.16**
Any CM		.99**	.95**	.18**	.10**	.16**
Physical CM			.20**	.18**	.10**	.14**
Sexual CM				.08**	.05*	.14**
AAB					.59**	.48**
ALD						.43**

Note: CM = Childhood Maltreatment; AAB = Adult Antisocial Behavior symptoms; ALD = Alcohol Dependence symptoms; NCD = Nicotine Dependence symptoms; MDD = Major Depressive Disorder symptoms. Sex coded 1= male, 2 = female.  
 \*\*p<.001 \* p<.01

Table 6. Regression Models of the Effect of Sex and Child Maltreatment on Adult Psychopathology.

Criterion		Males			Females			Both		
		Any CM	Physical CM	Sexual CM	Any CM	Physical CM	Sexual CM	Any CM	Physical CM	Sexual CM
AAB	Sex	–	–	–	–	–	–	.39(.02)**	.36(.02)**	.39(.02)**
	CM	.17(.03)**	.16(.04)**	.28(.08)**	.24(.03)**	.20(.03)**	.23(.04)**	.24(.03)**	.20(.04)**	.22(.04)**
	Int	–	–	–	–	–	–	-.06(.04)	-.03(.05)	.06(.09)
ALD	Sex	–	–	–	–	–	–	.55(.03)**	.51(.03)**	.54(.03)**
	CM	.11(.05)**	.11(.05)*	.32(.11)**	.23(.04)**	.11(.05)**	.24(.05)**	.22(.04)**	.18(.05)**	.24(.05)**
	Int	–	–	–	–	–	–	-.11(.06)	-.08(.07)	.09(.11)
NCD	Sex	–	–	–	–	–	–	.27(.04)**	.22(.04)**	.29(.04)**
	CM	.22(.05)**	.21(.06)**	.44(.12)**	.26(.05)**	.19(.05)**	.39(.06)**	.26(.05)**	.20(.06)**	.40(.06)**
	Int	–	–	–	–	–	–	-.04(.07)	.00(.08)	.04(.13)

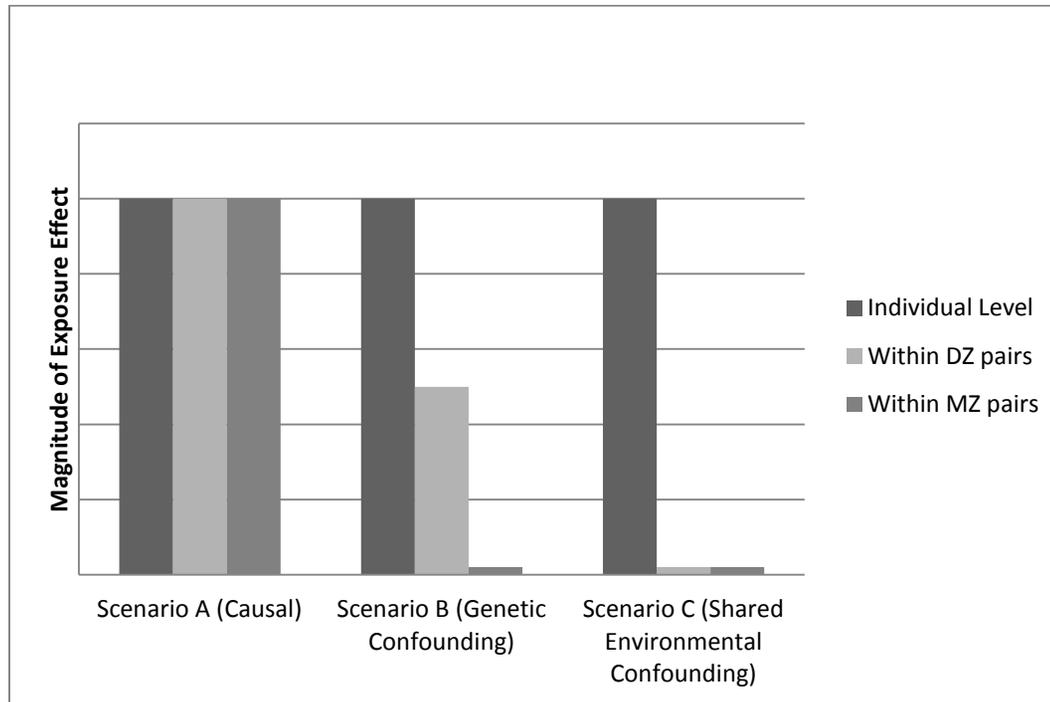
Note: Unstandardized Regression Coefficients B(SE) are presented. CM= Child Maltreatment; Int = gender interaction; AAB = Adult Antisocial Behavior symptoms; ALD = Alcohol Dependence symptoms; NCD = Nicotine Dependence symptoms; MDD = Major Depressive Disorder symptoms. Each column represents the type of CM, specifically Any, Physical, or Sexual CM. \*\*p<.001 \* p<.01

Table 7. Twin Control Analysis Evaluating the Associations Between Externalizing Psychopathology and Childhood Maltreatment

	Fixed Effect Estimates (SE)				
	Individual	Within Pair		Between Pair	
		DZ	MZ	DZ	MZ
AAB Any CM	.51 (.05)***	.66 (.13)***	.25 (.11)	.76 (.15)***	.82 (.12)***
AAB Sexual CM	.57 (.08)***	.68 (.19)***	.33 (.17)	.86 (.22)***	.95 (.21)***
AAB Physical CM	.45 (.05)***	.61 (.16)***	.13 (.12)	.61 (.17)***	.79 (.13)***
ALD Any CM	.29 (.05)***	.43 (.13)***	.20 (.11)	.27 (.14)*	.48 (.11)***
ALD Sexual CM	.44 (.08)***	.68 (.19)***	.23 (.17)	.45 (.20)*	.80 (.19)***
ALD Physical CM	.23 (.05)***	.41 (.16)**	.20 (.12)	.13 (.16)	.37 (.12)***
NCD Any CM	.41 (.05)***	.37 (.13)***	.11 (.11)	.71 (.15)***	.76 (.12)***
NCD Sexual CM	.64 (.08)***	.87 (.19)***	.16 (.17)	.93 (.22)***	1.28 (.22)***
NCD Physical CM	.35 (.05)***	.13 (.16)	.14 (.12)	.50 (.17)***	.69 (.13)***

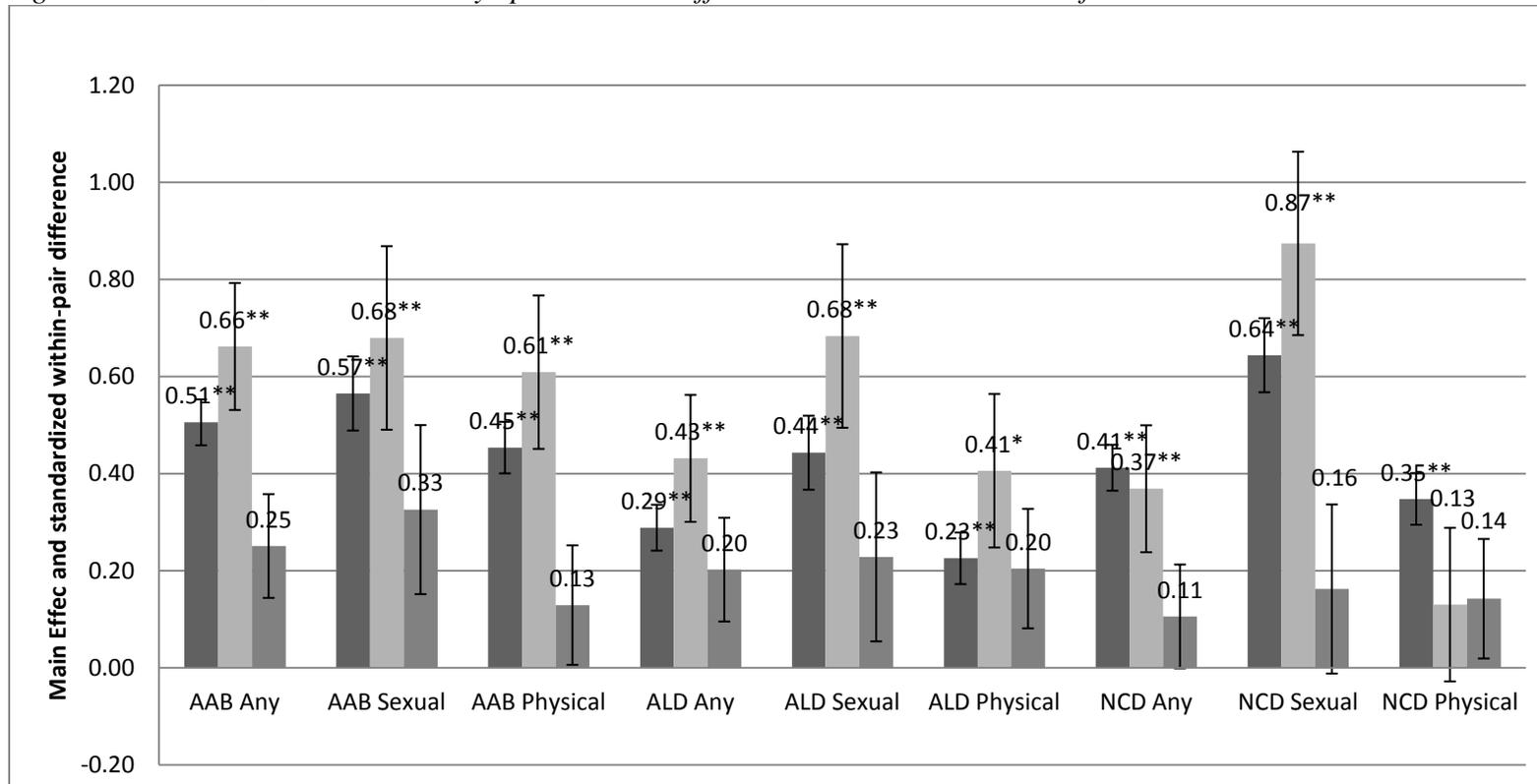
Note: Regression coefficients presented. CM= Child Maltreatment; AAB = Adult Antisocial Behavior symptoms; ALD = Alcohol Dependence symptoms; NCD = Nicotine Dependence symptoms; MDD = Major Depressive Disorder symptoms. Any = Either Physical or Sexual CM. \*p < .05. \*\*p < .01 \*\*\*p<.001

Figure 1. Interpretation of Co-Twin Results



Interpretation of co-twin results. Scenario A: Association is seen at the individual level, within DZ twin pairs discordant for exposure, and within MZ twin pairs discordant for exposure. Failure to observe an association within discordant MZ twin pairs implies the selection process is mediated by genetics effects (scenario B). Failure to observe an association within discordant MZ and DZ twin pairs implies the selection process is mediated by shared environmental effects (scenario C).

Figure 2. Standardized Within-Pair Symptom Count Differences in Twins Discordant for CM



Standardized regression weights, B(SE) presented. Within-pair differences in psychopathology symptoms for twin pairs discordant for child maltreatment. Data based on the first three columns of Table 7. MZ = Monozygotic; DZ = Dizygotic; AAB = Adult Antisocial Behavior symptoms; ALD = Alcohol Dependence symptoms; NCD = Nicotine Dependence symptoms; MDD = Major Depressive Disorder symptoms. \* $p < .01$ . \*\* $p < .001$ .

### **Chapter 3. Childhood Maltreatment and Major Depressive Disorder**

#### **3.1. Introduction**

Major Depressive Disorder (MDD) is a significant public health concern because of its association with excessive mortality, disability, and high comorbidity with other psychopathology. Research has consistently shown that both genetic and environmental factors are etiologically significant to this complex disorder (Dinwiddie, et al., 2000; McGue, et al., 2010). Among identified contributing factors are neuro-cognitive deficits, personality traits, genetic risk, peer relations, and other environmental risk factors such as stressful life events (Fergusson & Horwood, 1996; Frick & Morris, 2004; Krueger & Markon, 2008; Rutter, et al., 2006).

Childhood Maltreatment (CM) is an environmental stressor of particular interest to MDD research, and studies from diverse samples have consistently indicated that a history of CM is associated with an increased risk of MDD symptoms in childhood and adolescence (D. Cicchetti, F.A. Rogosch, M. Sturge-Apple, & S.L. Toth, 2010; Sullivan, Neale, & Kendler, 2000). Furthermore, maltreated children show an excessive degree of withdrawal and avoidance of social interaction (Buzi, Weinman, & Smith, 2007), their ability to form secure attachments with primary caregivers is compromised (Mueller & Silverman, 1989), as is their the ability to form peer relationships (Carlson, et al., 1989).

The association between CM and MDD extends into adulthood (Mueller & Silverman, 1989) with lifelong prevalence rates suggesting that as many as 40% of maltreated children meet criteria for MDD during their lifetime (Cutajar et al., 2010; Gibb, Chelminski, & Zimmerman, 2007) as compared to approximately 17% in the

general population (Kaplan, et al., 1999). Longitudinal studies have confirmed the CM and MDD relationship (Kessler et al., 2005) and it has been shown to remain significant even when controlling for social factors such as childhood socioeconomic status, marital status, and education (Cohen, et al., 2001; Cutajar, et al., 2010). CM has also been linked with increased risk of suicide attempts (Herrenkohl, Hong, Klika, Herrenkohl, & Russo, 2013), increased severity of MDD symptoms (Afifi, Boman, Fleisher, & Sareen, 2009; Dante Cicchetti, Fred A Rogosch, Melissa Sturge-Apple, & Sheree L Toth, 2010), and increased comorbidity with anxiety disorders (Wiersma et al., 2009). Thus, this association is particularly important to understand in the context of clinical treatment.

Gender differences in the relationship between CM and MDD are not as clearly understood as the relationship itself. Some studies have reported differences in the magnitude of the effect (Spinhoven et al., 2010) and others have detected no gender differences (Buzi, et al., 2007; Fletcher, 2009). This variation may be due to individual studies frequently focusing on either physical or sexual maltreatment, which do not have equal prevalence rates between men and women. It is possible that one type of CM may have a unique relationship to MDD in males but not in females, and the other way around.

Despite overwhelming evidence of the negative sequelae of CM across social, psychological, behavioral, and biological domains, CM is neither necessary nor sufficient for MDD, and many questions remain regarding the mechanism by which CM is related to MDD across developmental stages. Recent attention to the importance of environmental factors has shifted interests from directly causal models to considering

how the genes and environment work together to account for the variation in individual differences across the lifespan (Cutajar, et al., 2010), and in particular to factors that contribute to resilience from trauma. Evidence of gene-environment interaction has been proposed as a potential explanation of why some people develop MDD in the presence of environmental stress, and others do not (Plomin & McGuffin, 2003).

Research with genetically-informative samples has been inconclusive in identifying the nature of the relationship between CM and MDD. For example, a study of sexual abuse in a sample of female discordant CM twins (Caspi et al., 2003) found higher levels of MDD symptoms in twins with a history of CM but the authors were not able to analyze differences within pairs of monozygotic and dizygotic twins due to small sample size. They concluded, based on increased odds ratios of psychopathology in adulthood for twins with a history of CM, that the relationship was causal in nature. A similar discordant twin study (K. S. Kendler, et al., 2000) that included both men and women evidenced no genetic effects when comparing the agreement of reported sexual CM. Models used to evaluate genetic factors focused on the heritability of CM, and not the relationship between CM and MDD and further analyses were carried out on a collapsed sample of MZ and DZ evaluated together. On the whole, the findings have been inconclusive in either establishing proof of direct causation or providing support for genetic mediation.

If the relationship between CM and MDD is in fact causal, a better understanding of the underlying mechanism for this association may improve intervention and treatment as well as affect public policy. Given the fact that adverse life events are not random

(Bemmels, et al., 2008; Kendler & Baker, 2007) and the association between CM and MDD remains unclear, a discordant twin design investigation into potential genetic mediation in this relationship is warranted and presents an alternative methodology to investigate the relationship between CM and MDD.

The previous study focused on EXT psychopathology and revealed that the effects between CM and Alcohol Dependence, Adult Antisocial Behavior, and Nicotine Dependence are not directly causal but involve genetic mediation. The current study extends this research by exploring the relationship between the same CM measures and symptoms of MDD within the same twin sample. The study contrasts and compares the EXT findings with a disorder outside of the EXT spectrum to evaluate whether a similar relationship exists in other psychopathology, and specifically in MDD.

### **3.2. Aims of Current Study**

The current study aims to elucidate the relationship between childhood maltreatment and adult MDD by evaluating the contribution of both genes and environment to these associations using the co-twin control method. It is predicted that a strong positive association will be seen between CM and MDD, with higher rates of symptoms in individuals with a history of CM. It is expected that this relationship will be the same for males and females, but that it will vary across twin pair membership. More specifically, it is hypothesized that, if the association between psychopathology and CM is consistent with a directly causal model, then MZ twins positive for CM, will have significantly higher levels of adult MDD symptoms than their unexposed co-twins. If the relationship between CM and MDD is genetically mediated (completely or partially),

then MZ twins discordant for CM will not differ in their levels of adult psychopathology symptoms, but the discordant DZ twins will show significant differences in levels of psychopathology symptoms. It is predicted that these results will be consistent regardless of the type of CM.

### **3.3.Methods**

#### *3.3.1 Participants*

Eligible participants consisted of same-sex who were assessed as part of the Minnesota Twin Family Study (MTFS), an ongoing community-based longitudinal investigation of twins and their families (Iacono, et al., 1999). Participants were identified for intake assessment through public records of twin births in Minnesota between 1972 and 1984. Approximately 78% of those meeting eligibility criteria (living with at least one biological parent, within a day's drive of Minneapolis, and lacking a mental or physical disability that would preclude their completing the daylong intake assessment) agreed to participate (Iacono, et al., 1999). The remaining sample is representative of the Minnesota population in terms of ethnicity and socioeconomic status (Holdcraft & Iacono, 2004). Reflecting the population of Minnesota during the target birth years, 96% of the sample was Caucasian. Parents and children gave informed consent or assent as appropriate, and an institutional review board approved all research protocols.

Zygosity was determined by agreement among three estimates: MTFS staff evaluations of the twins' physical similarity; parents' completion of a standard zygosity questionnaire; and twin similarity on an algorithm of ponderal and cephalic indices and

fingerprint ridge count. A serological analysis was performed if the 3 estimates did not agree. A previous validation study ( $N = 50$ ) demonstrated 100% accuracy of zygosity determination when these three estimates agree. When disagreement among these estimates is noted, a blood sample is requested and a serological analysis is performed.

### 3.3.2 *Interview and Assessment Procedure*

The MTFS utilizes an accelerated longitudinal design with participants first entering the study at either age 11 or 17 and returning for follow-up assessments every three to six years (See table 1). The initial intake twin sample consisted of 2764 same-sex twins with 756 twin pairs from the 11-year old cohort, and 626 pairs from the 17-year old cohort. The younger of the two cohorts was initially assessed when the twins were approximately 11 years-old ( $M=11.72$ ,  $SD = 0.43$  years); and follow-up assessments were scheduled at ages 14-15, 17-18, 20-21, 24-25, 29-30. The older cohort was initially assessed when the twins were approximately 17 years-old ( $M=17.48$ ,  $SD = 0.46$  years), and follow-up assessments were scheduled at ages 20-21, 24-25, and 29-30. All assessments were designed to be in-person, although some individuals who could not complete an in-person assessment were interviewed by phone. Of the total 1382 pairs, 902 were MZ (50.9% female) and 480 DZ (53.8% female).

The current study utilized data from age 20, 24, and 29 assessments from both cohorts. The most recent data used in this sample was collected around at an average age of 29.41 ( $SD=0.64$  years), with an average retention rate of 90% from intake.

Maltreatment data were available for 2607 individuals (53% female) who comprise the CM subsample used in this study, with 1422 individuals from the younger cohort, and

1185 individuals from the older cohort and the final subsample. Table 3 shows the breakdown of twin pairs concordant and discordant for physical and sexual CM.

### 3.3.3 *Measures of Maltreatment*

Childhood maltreatment was evaluated retrospectively at ages 20, 24, and 29 assessments (Table 1) for CM that occurred before the age of 18. The Trauma Assessment for Adult (TAA; Resnick, et al., 1966) was administered for both cohorts at age 20 and 24, and the younger cohort males at age 29 and consisted of an interview to assess traumatic life events related to posttraumatic stress disorder. The assessment was preceded by the statement that unwanted sexual experiences can occur at any time in life, that they may not have been reported, and that they may have been committed by anyone including family members, or friends. The statement also encouraged participants to endorse past history of unwanted sexual experiences regardless of how long ago they happened. Two questions are about sexual maltreatment and the age at which the maltreatment occurred were asked: whether the participant ever had sexual contact with anyone five or more years older before they reached the age of 13, and whether anyone, including a friend or relative, ever used pressure, force, or physical threats to engage in unwanted sexual contact. Sexual contact was defined as contact involving sexual organs—(penis or genital area for men; vagina, genital area, or breast for women) of either individual. Age at which the endorsed maltreatment first occurred was reported.

The Childhood Experiences Questionnaire (CEQ) is a 26-item inventory consisting of items adapted from the Childhood Life Events Inventory (Sher, et al., 1997), the Colorado Adolescent Rearing Interview (Crowley, et al., 2003), and the

Childhood Trauma Questionnaire (Bernstein, et al., 2003). It was administered at age 24 for the younger cohort males and females as well as older cohort females at age 29 to assess physical and sexual maltreatment occurring before the age of 18. The questionnaire included seven items about forceful sexual experiences such as unwanted sexual exposure, fondling, insertion, and intercourse as well as four items about physical maltreatment such as hitting and leaving a mark, hitting with an object such as a belt, using a weapon, kicking, biting, and burning as well as the age at which the endorsed maltreatment first occurred. For male twins in the older cohort, harsh discipline only was assessed as part of a larger Social Adjustment Interview (SAI) completed at age 20, in which participants were asked whether typical discipline while growing up included being “hit in the face” or “hit with an object.”

Sexual CM was defined as any endorsement of sexual exploitation, which occurred before the age of 18. A binary index of sexual CM was determined from the nine relevant items of the TAA and the CEQ. Sexual CM before the age of 18 was reported by 7% of participants. Physical CM was defined as any endorsement of harsh discipline (e.g. leaving a mark) occurring before the age of 18. A binary index of was comprised of six relevant items from the SAI and CEQ. Physical CM before the age of 18 was reported by 19% of participants.

Because preliminary analyses did not reveal significant differences between sexual and physical CM with externalizing psychopathology ( $ps$  ranging from 0.12–1.00), a finding similar to other studies (Alink, et al., 2009), an index of overall maltreatment was comprised of the above mentioned measures of physical and sexual

maltreatment to evaluate the effects of overall maltreatment in childhood on psychopathology. Participants were classified as having any CM if they reported either physical or sexual CM before the age of 18. Overall CM before the age of 18 was reported by 22% of participants (21 % males and 23% females) reporting maltreatment. Rates of maltreatment by type and sex are presented in Table 2 and an overview of discordant pairs across sex and type of CM are presented in Table 3. Report of sexual CM was consistent across time and measure. For example, 85% of individuals reporting sexual CM on one measure at age 24, also reported it on another. Individuals reporting CM at age 24 were also likely to report it at a later assessment (75%).

#### 3.3.4 Measures of Psychopathology

Symptoms of MDD were assessed using a modified version of the Structural Clinical Interview (SCID) for DSM-III-R (R. Spitzer, Williams, Gibbon, & First, 1992) which was the diagnostic system in use at the start of the study. Data were collected at three time points for both cohorts (Table 1) with the exception the younger cohort females for whom, at the time of this study, age 29 assessment data for was not yet available. MDD was operationalized as the highest count of endorsed symptoms of DSM-III-R MDD criteria assessed as a single episode at any of the three time points. Per standard skip-out rules, participants had to report at least sub threshold level of depressed mood or anhedonia for MDD to complete the remaining part of the interview. At each of the three assessments (ages 20, 24, and 29) symptom data were collected for each diagnostic category since the last time that the participant was assessed except for older cohort males who were assessed for lifetime MDD at their age-20 assessment. Because

the older cohort males were assessed lifetime, there was a possibility that some individuals could have reported symptoms, which started and ceased before the age of 18, reflecting childhood MDD. For the older cohort males, to eliminate the presence of clinical symptoms that did not reflect adult psychopathology, ages associated with individual symptoms counts were used to identify individuals who reported that their assessed MDD episode was childhood limited (starting and ending before the age of 18). This process identified three individuals who reported childhood isolated MDD symptoms. These three individuals were recorded as having no adult MDD symptoms for that assessment only (age 20). The highest symptom count recorded at any of the three time points was used to represent the highest lifetime adult MDD symptom count achieved at age 29, with 33% of individuals reporting at least one symptom, and 21% reporting five or more symptoms.

All interview data were reviewed in a clinical case conference by at least two clinical psychology graduate students, with members of the review team required to reach consensus before assigning symptoms. A tape recording of the interview was consulted in ambiguous cases to reach consensus. Based on previous research, this assessment process yielded high diagnostic reliabilities ( $\kappa = .82$ ) (Iacono, et al., 1999). To adjust for positive skew, all symptom counts were log-transformed before analysis. Symptom and diagnostic prevalence rates are presented in Table 4.

### 3.3.5 *Statistical Design and Measures of Effects*

The analyses carried out in this study are predicated on the various sources of similarities and differences across reared-together twins. All of the twins in the study

share their rearing environment. MZ twins share 100% of their genetic material, whereas DZ twins share 50% of their segregating genetic material. As a result, the differences between MZ twins are due solely to unique environmental influences (such as maltreatment), as well as measurement error. Differences between DZ twins, by comparison, are due to both unique environmental influences, and the 50% of genes they do not have in common.

First, a series of analyses to examine the phenotypic association between CM and psychopathology was carried using correlations and regression. To adjust the analyses for correlated twin observations, these analyses use PROC MIXED in SAS 9.3 (SAS Institute Inc., 2011). Analyses were used to compare the relationship between the different types of CM (any, sexual, physical) and MDD for the entire sample. Gender interaction regression models were used to evaluate the sex-differences present in these effects. If the regression weights indicated significant sex-differences further analyses were carried out separately for males and females.

Next, the associations within twin pairs were evaluated using an analogue of the idealized counterfactual model of causation, the co-twin control design (McGue, et al., 2010). In order to identify true causality, a counterfactual model of causation, a comparison of outcome with the presence of CM and without CM within the same individual, would be required but is not feasible for a variety of reasons. MZ twins who are discordant for exposure provide a comparable model to the idealized counterfactual design (assumed to control for genetics and shared environment). The co-twin design employs twin pairs discordant for CM to estimate what a twin with positive history of

CM would have been like in terms of psychopathology had he or she not experienced CM. In this design, the difference in the level of psychopathology between discordant MZ twins would be attributed to a causal influence of CM, a direct estimate of the effect of maltreatment.

More specifically, let  $y_{ij}$  be the observed outcome for the  $j$ th twin ( $j = 1,2$ ) in the  $i$ th twin pair ( $i = 1,2,\dots,N$ ) and let  $x_{ij}$  be the corresponding exposure index (in this case, childhood maltreatment) for this individual. The overall, or individual-level, regression of the outcome on the exposure is given by the regression model

$$y_{ij} = \beta_0 + \beta_1 x_{ij} + \varepsilon_{ij},$$

where  $\beta_1$  is the individual-level effect of exposure (childhood maltreatment) on outcome (psychopathology),  $\beta_0$  is the intercept term, and  $\varepsilon_{ij}$  is the residual (correlated across the 2 members of the twin pair). The overall regression effect can be further represented in terms of within-pair ( $\beta_W$ ) and between-pair ( $\beta_B$ ) effect using the regression model

$$y_{ij} = \beta_0 + \beta_W(x_{ij} - \bar{x}_i) + \beta_B \bar{x}_i + \varepsilon_{ij},$$

where  $\bar{x}_i$  is the mean exposure index for the  $i^{\text{th}}$  twin pair. The individual-level effect is estimated with the between-pair regression coefficient and the within-pair regression coefficient serves as a direct estimate of the effect of exposure on the outcome (maltreatment on psychopathology) within discordant twin pairs.

This regression model can be further conceptualized within a genetically-informed design (McGue, et al., 2010). Individual-level associations reflect potential confounding of genetic effects, shared environmental effects, and non-shared environmental effects. Associations within DZ twin pairs discordant for exposure control

for shared environmental effects and partially for genetic effects. Associations within MZ twin pairs discordant for exposure control for shared environmental and genetic effects. Any remaining associations within discordant MZ pairs, therefore, directly index nonshared environmental effects. Accordingly, should maltreatment be causally linked to increase in psychopathology, one would expect to observe this association at the individual level, within DZ twin pairs discordant for exposure and within MZ twin pairs discordant for exposure (Figure 1, scenario A). By contrast, the failure to observe an association within discordant MZ twin pairs would imply that the association of exposure with outcome is solely attributable to selection processes (i.e. the process is mediated by genetic and/or shared environmental effects rather than nonshared environmental effects given that there is no association between exposure and outcome in discordant MZ twins). In particular, if exposure was associated with outcome at the individual level and in discordant DZ twins (scenario B), one would infer that the selection process was genetic in origin. If the exposure was associated with outcome only at the individual level (scenario C), one would infer that the selection process was shared environmental in origin. While the failure to detect a within-pair association would invalidate the existence of causality, the opposite (presence of association between exposure and outcome) cannot confirm causality because without a longitudinal context as it does not rule out that discordance is related to outcome by some other factors.

To evaluate whether twins who had reported a history of CM showed higher levels of MDD symptoms, regression analyses were conducted using PROC MIXED in SAS for each category of CM and psychopathology. The entire sample, regardless of

concordance status, was used to estimate the between-pair effects, while only discordant pairs were used for the within-pair effects.

### 3.4. Results

#### 3.4.1 Phenotypic Analyses

Rates of CM are presented in Table 2. Physical CM before the age of 18 was reported by 19% of participants, with a significantly greater percentage of men than women, 21% and 17% respectively, reporting physical CM,  $X^2(1, N = 2311) = 7.273, p = .007$ . Sexual CM before the age of 18 was reported by 7% of participants, with a significantly greater percentage of women than men, 11% and 3% respectively, reporting sexual CM  $X^2(1, N = 2607) = 62.095, p < .001$ . Overall CM before the age of 18 was reported by 22% of participants, with no significant differences across gender, 21% males and 23% females reporting maltreatment,  $X^2(1, N = 2607) = 2.104, p = .147$ .

Correlations among the variables showed significant relationships (Table 5). Tetrachoric correlations revealed a weak relationship between sexual and physical CM for males ( $r = .21, p < .01$ ) and females ( $r = .25, p < .001$ ) and strong relationships between any CM and physical and sexual CM for both males and females ( $r = .88$  to  $r = .99$ ). Biserial correlations between CM and MDD showed generally weak to moderate but significant relationships with stronger correlations seen in the females ( $r = .13$  to  $.19$ ) than the males ( $r = .07$  to  $.10$ ).

Estimates of main effects of CM, sex, and gender interactions were calculated using mixed-level regressions (Table 6) for each type of CM and MDD. Main effect calculations were conducted for the entire sample and for males and females separately.

Main sex effect and interaction with CM were computed only in the combined sample. Each type of CM had a significant main effect on MDD, and regardless of whether the sample was split by gender, individuals with a history of each type of CM or with any type of CM showed higher levels of MDD symptom counts.

Regression analysis revealed that, in the combined sample, gender was also a significant predictor of MDD for Sexual and Physical CM but gender was not a significant predictor for the any CM measure. The CM-gender interaction terms are significant for the any CM measure and physical CM, but not for sexual CM, suggesting that the association between different types of CM and MDD varies across gender. The association between sexual CM and MDD appears to be the same for men and women, but the relationship between physical CM and MDD shows different trajectories (Figure 2) with females showing a greater increase in adult MDD symptoms than males if they report a history of CM. This trend is carried over when physical and sexual CM are considered together, and for this reason, in the context of MDD, physical and sexual CM should be considered separately for males and females, and males and females should be considered separately in the context of physical CM association with MDD.

### 3.4.2 *Discordant Twin Analyses*

Nine discordant twin models were used to evaluate the differences in MDD symptoms counts of MZ and DZ twins discordant for each of the three categories of CM (Any, Physical CM, Sexual CM) within the combined sample and separately for males and females (Table 7). To facilitate understanding, the results, including relative magnitude and significance of standardized within-pair differences are also presented in

Figure 3. Overlapping confidence intervals are interpretable only for statistically significant values.

As expected, all nine models showed significant individual level (between-pair) effects, meaning that significant differences in MDD symptom counts were seen when comparing individuals with and without a history of CM for each type of maltreatment regardless of whether males and females were analyzed together or apart. All nine models had non-significant MZ within-pair effects, suggesting that identical twins discordant for each type of CM did not differ significantly in their level of MDD symptoms regardless of their history of maltreatment. In other words, the symptom expression in identical twins did not vary as a factor of CM, suggesting that the association of CM and MDD symptoms may be attributable to a selection process, a finding which remains consistent regardless of whether the sample is split by gender or not. In the context of non-significant MZ differences, the relationship between CM and MDD is generally consistent with some level of genetic confounding.

For Sexual CM, the combined sample showed significant DZ within-pair differences, indicative of a selection process mediated by genetic effects (Figure 1 scenario B). While both males and females produced significant main effects, and non-significant MZ within-pair differences, the female sample showed a significant DZ within-pair difference while the male sample only approached significance ( $p=0.09$ ). The DZ difference in males ( $\beta=0.59$ ,  $SE=0.35$ ,  $p=.09$ ), however, though non-significant, is close in magnitude to the individual effect of sexual CM ( $\beta=0.58$ ,  $SE=0.17$ ,  $p<.001$ ),

appearing more consistent with genetic mediation and suggesting that the non-significance is likely the result of lower rates of both MDD and sexual CM in males.

Physical CM and MDD results showed a pattern of non-significant DZ and MZ pair differences in the combined sample as well as for males and females separately. This pattern of results is consistent with shared environmental mediation (Scenario C). Regression results did reveal a gender by physical CM interaction (Table 6, Figure 2) that approached significance ( $\beta = 0.18$ ,  $SE = .09$ ,  $p = .06$ ) and appears to reflect the strength of the relationship between MDD and physical CM, with a stronger association in females than in males.

When sexual and physical CM were considered together, MDD symptom within-pair effects in DZ twin pairs were significant for males but not females. Because neither males or females had significant MZ differences, the difference in the DZ results suggests that in males, the relationship between CM and MDD is mediated by genetic effects only (scenario B in Figure 1). In females, the DZ within-pair result is nonsignificant; however, the DZ effect is considerably greater, suggestive of genetic influences (scenario B). Because regression results indicated significant sex-CM interaction, this is interpreted as a sex difference in the effect of any CM on MDD. Given that no significant gender interaction was seen in sexual CM and that the gender interaction in physical CM was significant, the presence of a gender interaction in the any CM measure suggests that gender-specific effects may be involved in the relationship of childhood trauma and adult MDD that are specific to CM type and require further investigation.

### **3.5. Discussion**

The aim of the current study was to clarify the nature of the association between CM and adult MDD symptoms. This study used sexual and physical maltreatment reported to have occurred before the age of 18, as well as a summary measure of any reported CM. DSM-III-R diagnostic criteria symptom counts for MDD collected at three time points and aggregated into an estimate of lifetime adult MDD. Co-twin control analyses (within and between-pair effect analyses) of the influence of maltreatment on MDD symptoms were conducted in SAS.

As predicted, the results confirmed that individuals with a history of CM showed increased rates of MDD symptoms later in life. This result was similar for males and females and for all three CM variables. These findings are consistent with previous research (Afifi, 2012).

Discordant twin analyses produced several differences across gender and type of CM. Significant sex-interaction appears in the relationship between MDD and physical CM but not between MDD and sexual CM. The ordinal interaction between sex and the relationship between CM and MDD appears to lie in the magnitude of the relationship, with a larger increase in MDD symptoms seen in women with a history of physical CM than in men. The relationship between physical CM and MDD appears more consistent with both genetic and environmental mediation (in males, females, and the combined sample) as opposed to the complete genetic mediation seen in the relationship between sexual CM and MDD.

When combined, the measure of any CM suggested that the relationship with MDD may be characterized by both genetic and environmental factors in females but not

in males. Because of significant sex-interaction regression results, these findings suggest that combining across type of CM may have varying consequences on female and male samples, and that future research should aim to differentiate between types of CM and gender in the context of MDD.

These results indicate that further research into how types of CM co-occur and interact with psychopathology across gender may be important to understanding more about the underlying mechanism of how childhood trauma is related to psychopathology. This distinction may also be a characteristic of additional factors such as frequency of CM, duration of CM, onset and offset of CM. These factors may also be gender or maltreatment-type specific, as is suggested by prevalence statistics: physical CM is more likely to occur than sexual CM, and rates of sexual CM are higher in females than males within the general population.

Results of the twin-control method indicate that the differences seen across CM status are not attributable to direct influence from childhood trauma, but may be genetically mediated. Potential explanations for this relationship may include non-passive gene-environment correlations where genetically influenced individual differences such as behavioral problems may increase the risk of being maltreated, or passive gene-environment correlation in which the same genetic influences are responsible for both the maltreatment on the behalf of the parents, and the later psychopathology of the offspring. The findings are encouraging of further research into the significance of genetic differences in the context of environmental events and how such events and individual differences are related to psychopathology.

### 3.5.1 *Limitations*

Limitations of the current research include the use of DSM-III-R diagnostic criteria that conceptualize behaviors in terms of MDD symptoms. Because of the DSM criteria “A” which requires the presence of either depressed mood or anhedonia and at least one of the five required symptoms, diagnostic skip out rules were used if neither of the two symptoms was present. As a result, the remaining seven MDD symptoms were not assessed in the absence of depressed mood and anhedonia. Despite this, 33% of individuals reported at least one lifetime MDD symptom across three assessments by age 29, and 21% reported five or more symptoms (within a single episode) by age 29 indicating that the assessment was able to capture significant psychopathology. Furthermore, symptom counts, though a good indicator of lifetime prevalence, do not reflect the frequency, severity, or duration of psychopathology, and measures that incorporate some or all of these factors that are associated with CM will be of benefit to future research. Though the overall diagnostic rates of the sample are consistent with the literature on MDD, subclinical symptoms may have been underestimated, a problem potentially reduced by aggregating data from three assessments.

As with most maltreatment studies, the current data were reported retrospectively, across several measures and time points, and may be an underestimate of CM due to participants’ reluctance to disclose. Though self-report is considered a reliable and valid form of assessment, it is not faultless. The current study used several self-report measures of CM, which potentially overcame some of these limitations. This provided some convergent validity in estimating CM, and allowing participants multiple

opportunities to disclose a history of CM. Furthermore, the categorization of CM was restricted to severe and specific cases of reported CM, and with rates and correlations consistent with previous research, this appears to be a valid and reliable measure of CM.

The study considered several CM categories, but did not include neglect, emotional CM, psychological CM, or characteristics of the relationship between the victim and the perpetrator, specific age of CM, or duration of CM. Though CM severity was established through careful item selection, future studies may benefit from evaluating CM on a continuum of severity and frequency as well as incorporating related INT psychopathology.

Despite the powerful model presented by the counterfactual methodology employed in this study to test causality, MZ twins do not provide a perfect counterfactual pair due to non-shared environmental effects that make them psychologically unique. As a result, within MZ pair association may reflect true causality or the effect of non-shared environmental experiences that led to differences in exposure.

Sample-specific limitations must also be considered, including the predominantly Caucasian participants, as well as potential attrition of subjects due to either CM or psychopathology, resulting in a skewed sample, though high participation rates argue against this. Furthermore, because the most recent data represents psychopathology through the age of 29, it is possible that individuals will report problems in the future, and a follow up study considering this effect may be beneficial.

### 3.5.2 *Overall Summary*

This study employed the co-twin control analysis design to evaluate the mediation of the relationship between CM and adult MDD symptom counts. Results confirm the positive association between CM and MDD symptom counts used with this sample regardless of the category of CM, but indicated significant sex-CM interactions any CM and physical CM categories. Analyses were carried out separately for males and females as well as the entire sample.

Analysis of discordant twin effects revealed no significant discordant MZ twin differences regardless of CM category. In the context of significant between-group differences, this finding is indicative of partial or complete genetic mediation. Specific to the type of CM and gender, analysis revealed partial genetic mediation in the relationship between sexual CM and MDD in the combined sample of men and women. The significance of within-pair differences in the Physical CM and MDD relationship was most consistent with complete genetic mediation.

The pattern of results in the relationship between any CM and MDD showed genetic confounding in males and genetic or shared environmental mediation in females. Due to possible concerns with statistical power, these results require further evaluation, but are generally consistent with some level of genetic confounding. The variability in the results, however, underlines the importance of considering these relationships independently across sex and type of CM.

The genetic mediation demonstrated by this study may take the form of passive, evocative or active gene-environment correlations. In the case of passive gene-

environment correlation, the parents contribute both the genotype and rearing environment. In the case of CM and MDD, the parents may pass on the genetic predisposition for mood disorders and provide the environmental exposure to maltreatment. In the case of evocative gene-environment correlation, an individual's genotype may elicit particular responses from others. In the case of CM and MDD, a child prone to emotional instability or behavioral withdrawal may place greater demands on the parent's coping abilities and lead to harsher forms of interaction.

Future directions may include efforts to identify factors that account for the genetic mediation between CM and MDD and the sex differences in this relationship. Related outcomes such as other mood disorders, anxiety disorders, and suicidality as well as underlying childhood internalizing traits, and personality precursors may also help in identifying the link between CM and negative outcomes. Combining resilience research to evaluate the interplay of traits that may be related to the genetic overlap between CM and MDD may be beneficial. Incorporating data from parents, including history of CM and psychopathology may also provide additional insight.

Beyond research, the current results have clinical implications, including the potential benefit of shifting the current clinical framework from a directly causal and inflexible interpretation of CM and MDD. Clinical conceptualization of individuals with a history of CM may instead begin to consider CM as a correlate of psychopathology, instead of its cause, and an environmental stressor that reflect a much more complicated and dynamic interplay between environment and individual differences.

Table 1. Schedule of Assessments

	Age						Total Twin Pairs
	11	14	17	20	24	29	
<i>Younger Cohort</i>	<i>Intake</i>	<i>FU1</i>	<i>FU2</i>	<i>FU3</i>	<i>FU4</i>	<i>FU5</i>	
Males				TAA, SCID	TAA, CEQ, SCID	TAA, SCID	376
Females				TAA, SCID	TAA, CEQ, SCID		380
<i>Older Cohort</i>			<i>Intake</i>	<i>FU1</i>	<i>FU2</i>	<i>FU3</i>	
Males				TAA, SAI, SCID	TAA, SCID	SCID	289
Females				TAA, SAI, SCID	TAA, SCID	CEQ, SCID	337

FU = study follow-up assessment; TAA = Trauma Assessment for Adults; SAI = Social Adjustment Interview; CEQ = Childhood Experiences Questionnaire; SCID = The Structured Clinical Interview for DSM-III-R.

*Table 2. Rates of Reported Childhood Maltreatment by type*

	Total N	Sexual CM		Physical CM			Any CM			
		n	yes	%	n	yes	%	n	yes	%
Male	1330	1219	37	3.0	1072	229	21.4	1219	254	20.8
Female	1434	1388	154	11.1	1239	210	16.9	1388	322	23.2
Total	2764	2607	191	7.3	2311	439	19.0	2607	576	22.1

CM= Childhood Maltreatment

*Table 3. Twin Pairs Discordant for Child Maltreatment.*

	MZ Pairs				DZ Pairs			
	Neither	Discordant	Both	Total	Neither	Discordant	Both	Total
<b>Sexual CM</b>								
Males	374	13	2	389	186	16	1	203
Females	372	53	14	439	193	40	16	249
All	746	66	16	828	379	56	17	452
<b>Physical CM</b>								
Males	231	66	29	326	112	37	22	171
Females	274	66	33	373	156	43	13	212
All	505	132	62	699	268	80	35	383
<b>Any CM</b>								
Males	271	86	32	389	129	51	23	203
Females	300	89	50	439	150	66	33	249
All	571	175	82	828	279	117	56	452

Neither = neither member of the pair reports maltreatment, Discordant = one member of the pair reports maltreatment, Both = both members of the pair report maltreatment.

*Table 4. Symptom Counts and Diagnostic Prevalence of MDD.*

	MDD			
	N	Symptom Count		Diagnostic Prevalence %
		Mean	SD	
Males	1263	1.53	2.61	18.4
Females	1393	1.92	2.89	23.8
Both	2656	1.73	2.77	21.2

Note: Data based on maximum values of three assessments at ages 20, 24, and 29. MDD = Major Depressive Disorder. Assessments occurred at age 20, 24, and 29.

*Table 5. Variable Correlations*

	Any CM	Physical CM	Sexual CM	MDD
Any CM		.99**	.88**	.09**
Physical CM	.99**		.21*	.07*
Sexual CM	.97**	.25**		.10**
MDD	.19**	.13**	.17**	

Note: Results for males appear above the diagonal, results for females below the diagonal. CM = Childhood Maltreatment; MDD = Major Depressive Disorder. \*\*p<.001 \* p<.01

*Table 6. Regression Models of the Effect of Sex and Child Maltreatment on MDD*

Model	Criterion	B(SE)		
		Any	Sexual	Physical
Males	CM	.17(.06)**	.48(.14)**	.14(.06)*
Females	CM	.39(.06)**	.48(.08)**	.32(.07)**
Both	Sex	-.06(.04)	-.07(.04)*	-.10(.04)**
	CM	.39(.06)**	.48(.07)**	.32(.07)**
	Int	-.22(.08)**	.00(.16)	-.18(.09)*

Note: Unstandardized Regression Coefficients B(SE) are presented. CM= Child Maltreatment; Int = gender interaction; MDD = Major Depressive Disorder symptoms. Each column represents the type of CM, specifically Any, Physical, or Sexual CM.

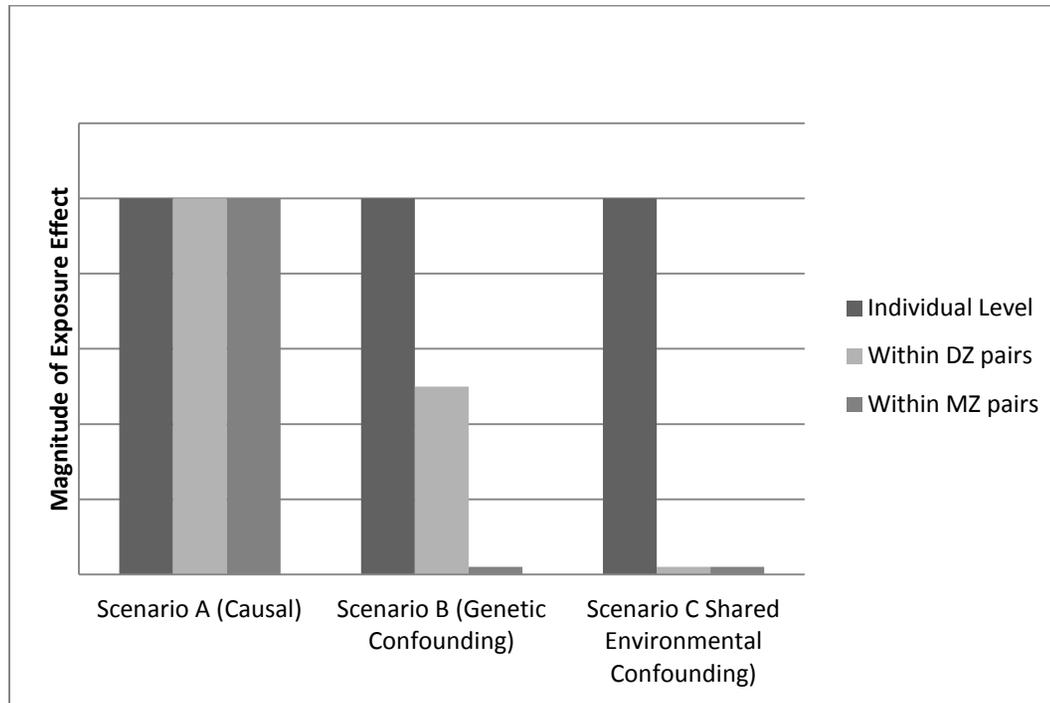
\*\*p<.001 \* p<.01

Table 7. Twin Control Analysis Evaluating the Associations between MDD and Childhood Maltreatment

		Fixed Effect Estimates (SE)				
		Individual	Within Pair		Between Pair	
			DZ	MZ	DZ	MZ
Both	Any CM	.34 (.05)***	.35 (.13)**	.10 (.11)	.53 (.12)***	.46 (.09)***
	Sexual CM	.55 (.08)***	.51 (.19)**	-.04 (.17)	.80 (.17)***	.90 (.16)***
	Physical CM	.27 (.05)***	.25 (.16)	.24 (.12)	.27 (.13)*	.36 (.10)***
Males	Any CM	.21 (.07)**	.38 (.20)*	.07 (.15)	.33(.18)	.25(.14)
	Sexual CM	.58 (.17)**	.59 (.35)	-.16 (.39)	1.22(.39)**	.70(.37)
	Physical CM	.17 (.07)*	.43 (.23)	.11 (.17)	.19(.18)	.16(.14)
Females	Any CM	.44 (.06)***	.32 (.17)	.13 (.15)	.66(.16)***	.62(.12)***
	Sexual CM	.53 (.09)***	.47 (.22)*	-.01 (.19)	.64(.19)**	.97(.18)***
	Physical CM	.37 (.08)***	.09 (.22)	.36 (.17)	.41(.20)*	.55(.14)**

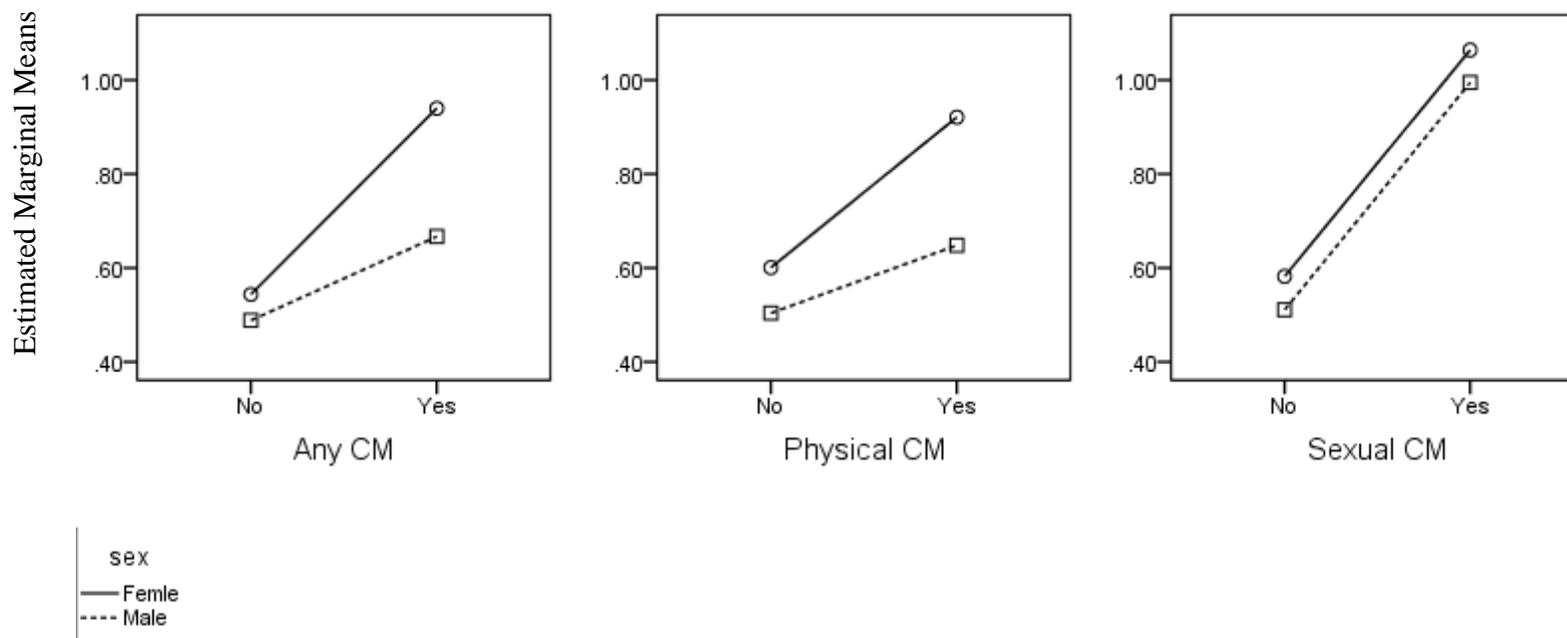
CM= Child Maltreatment; MDD = Major Depressive Disorder symptoms. Any = Either Physical or Sexual CM. MZ = Monozygotic, DZ =Dizygotic. \*p < .05. \*\*p < .01 \*\*\*p<.001

Figure 1 Interpretation of Co-Twin Control Results



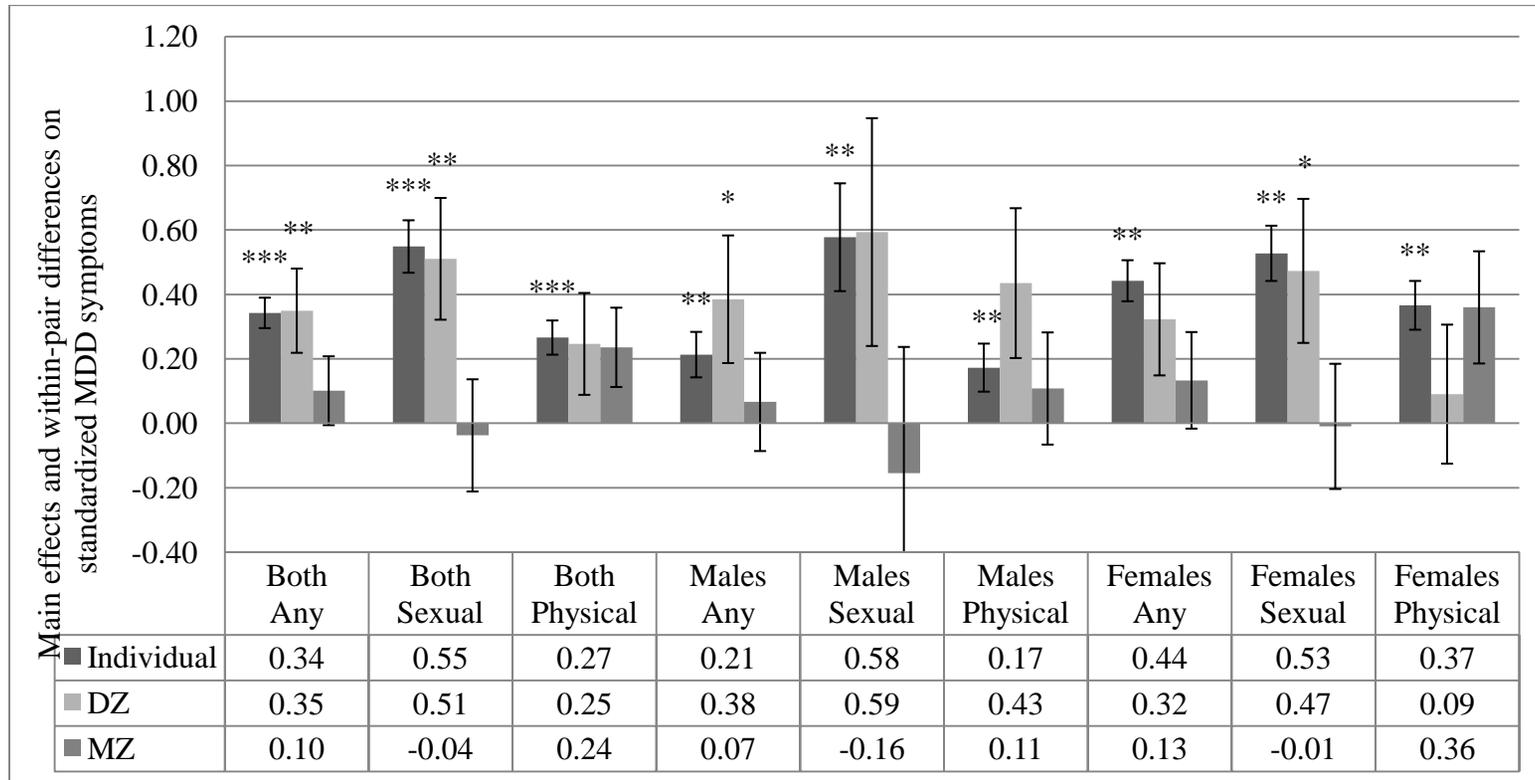
Interpretation of co-twin results. Scenario A: Association is seen at the individual level, within DZ twin pairs discordant for exposure, and within MZ twin pairs discordant for exposure. Failure to observe an association within discordant MZ twin pairs implies the selection process is mediated by genetics effects (scenario B). Failure to observe an association within discordant MZ and DZ twin pairs implies the selection process is mediated by shared environmental effects (scenario C).

Figure 2. Estimated Marginal Means of MDD lifetime symptoms across sex.



Note: MDD = Major Depressive Disorder, CM = Child Maltreatment. Lifetime symptoms of MDD were log transformed. Females are represented as circles and solid lines, males as squares and dotted lines for each category of CM. Results for Any CM and Physical CM suggest ordinal interaction, while the results for Sexual CM do not suggest an interaction between CM and gender.

Figure 3. Standardized Within-Pair MDD Symptom Count Differences in Twins Discordant for CM



Note: Within-pair differences in psychopathology symptoms for twin pairs discordant for child maltreatment. Data based on the first three columns of Table 7. MZ = Monozygotic; DZ = Dizygotic; MDD = Major Depressive Disorder symptoms. \*p < .01. \*\*p < .001. Although significant sex differences were found only for Any CM and Physical CM models, all models are presented here.

## Chapter 4. General Conclusions

### 4.1. Overview

Despite strong associations between child maltreatment (CM) and various forms of psychopathology, a comprehensive model to support causality or to explain the underlying mechanism is absent from the current literature. The goals of the current work were to explore the relationship between CM and adult psychopathology by evaluating this relationship across longitudinal co-twin control models.

The two studies confirmed the positive association between CM and adult psychopathology by evaluating symptom counts of various disorders in representative samples of male and female twins reared together. As suggested by previous research and predicted by this work, the results confirm the presence of significantly higher levels of reported psychopathological symptoms in individuals also reporting a history of CM before the age of 18 (Afifi, 2012). (Chen, et al., 2010a; Chen et al., 2010b; Cutajar, et al., 2010)

Despite the fact that all analyses were carried out on the same sample with the same methodology, differences in the way that CM is related to adult psychopathology did emerge, including the presence of sex differences in MDD for physical but not sexual CM. The significant sex-interaction reflects the magnitude of the relationship between physical CM and MDD, with a stronger relationship in females than in males. This suggests that the relationship between CM and MDD is different for men and women and somehow different from the other disorders explored and that the relationship between

CM and psychopathology is not universal across disorders associated with CM, deserving further exploration.

Co-twin control design analysis in both studies indicated that the relationship between CM and psychopathology is not directly causal - a finding replicated across all disorders explored within this dissertation – but that the relationship is completely or partially genetically mediated varied across disorders. These findings suggest, that the relationship between CM and psychopathology is better explained by genetic (and in some cases, environmental) confounding than direct causation and is in line with other studies that suggest genetic processes involved in this relationship (Caspi, et al., 2002; Derringer, et al., 2010; Jaffee et al., 2005a). At the same time, the variation in these results across the four disorders explored with the same sample and methodology underline the difference in this relationship across gender and diagnosis and may help to explain the inconsistency in findings from other studies (Dinwiddie, et al., 2000; Jaffee, et al., 2005a; Jaffee, Caspi, Moffitt, Polo-Tomas, et al., 2004; Jaffee, Caspi, Moffitt, & Taylor, 2004; K. Kendler, et al., 2000; Nelson, et al., 2002) . More specifically, since the underlying mediation of the relationship between CM and psychopathology may not be consistent across type of CM and disorder, a study limited to only males and physical CM may provide different conclusions than a study looking at sexual CM and females. Future research will benefit from representative longitudinal samples that incorporate multiple measures of CM.

#### **4.2. Genetic Mechanisms**

One potential explanation for the relationship between CM and adult psychopathology is genetic mediation in the form of passive or evocative gene-environment correlations. Genotypic influences have been shown to influence behaviors that affect environmental factors including stressful life events, social support, marriage, and others .

In the case of passive gene-environment correlation, the parents contribute both the genotype and rearing environment. In the case of CM and psychopathology, the parents may pass on both the genetic predisposition for psychopathology and an environment which may be exposing the child to maltreatment. A scenario involving AAB may mean that a child, who shares a genetic predisposition for negative emotionality, aggression, or violence with his parents, is also more likely to be reared in an environment that is hostile, violent, and abusive. In the case of evocative gene-environment correlation and genetically-influenced traits may elicit particular responses from others. For example, a child prone to depression and emotional withdrawal may place greater demands on the parent's coping abilities. A child who is loud, moody, impulsive, or hyperactive may be more likely to elicit negative attention from adults or peers including harsher discipline from the parents.

In other words, early signs of genetically mediated psychopathology and related characteristics may predispose an individual to childhood maltreatment, as opposed to the other way around. This dynamic may at least partially account for the relationship between CM and psychopathology. This work supports this relationship across four disorders.

### 4.3. Future Directions

Further research into the gene-environment correlation and interaction demonstrated between CM and psychopathology may be useful in preventing, and treating psychopathology across the lifespan. It is important to explore the role of resilience, distress tolerance, emotional regulation, personality, and other factors that may serve as precursors to psychopathology and explain the genetic relationship between CM and adult psychopathology.

An exploration of individual traits in childhood rather than psychiatric symptoms may shed some light on this relationship. Characteristics associated with CM include disruptive-aggressive, withdraw, and internalized behavior problems as well as lower ego-resilience and intelligence than non-maltreated children (Cicchetti et al., 1993), while “above average cognitive abilities, high self-esteem, internal locus of control, external attribution of blame, presence of spirituality, ego-resilience, and high ego control” are associated with better outcomes (Kendler & Baker, 2007). Though the current literature regards these traits as consequences of CM or factors protective of negative outcomes, it is important to consider them as characteristics that may both predispose or decrease the likelihood of CM and later psychopathology.

Resilience research is particularly relevant to understanding long-term outcomes in the context of CM, psychopathology, and other traumatic and adverse events (Wright, Masten, & Narayan, 2013). Identifying characteristics and processes that differentiate individuals who show successful adaptation may also clarify the relationship between CM and psychopathology in those who do not. These mechanisms may also prove

relevant to other types of trauma, and psychopathology. For example, the relationship between combat trauma and psychopathology remains unclear (Afifi, Asmundson, Taylor, & Jang, 2010) and with as much as 35% to 47% of the variance on exposure to combat related trauma attributed to genetic effects (Lyons et al., 1993), genetically-informative studies may prove useful in disentangling the relationships between trauma, psychopathology, and individual differences.

Future efforts to consider how CM is genetically related to early manifestations of psychopathology, including the internalizing and externalizing dimensions, and how these may relate to adult psychopathology is important. For example, an exploration of the biometric relationship between CM and psychopathology, in the form of discrete diagnostic categories, and as underlying internalizing and externalizing factors, may be useful. Identifying characteristics of CM that may explain some of the variation in results may also be of great benefit. For example, differences in exposure to physical CM and sexual CM for men and women, chronicity, age of onset, and frequency of CM, as well as severity, and co-occurrence with other forms of CM are important factors to consider in future studies.

#### **4.4. Implications**

Individuals with a history of CM are assumed by the clinical community to have life-long and irreversible negative consequences specific to the maltreatment they experiences as children. This is viewed in the clinical community as particularly difficult and stigmatizing, and treatment strategies oftentimes emphasize and reinforce this connection.

While there is a consistent association between CM and various negative outcomes including psychopathology, physical wellbeing, and social adjustment, the causality is not established, and the current work suggests that the relationship between CM and adult psychopathology is not direct. This is in line with various lines of research that suggest that genetic factors contribute to trauma exposure (Afifi, et al., 2010; Kandler, et al., 2012; Lyons, et al., 1993), interact with environmental stress (Caspi, et al., 2002), and mediate the relationship between trauma and psychopathology (Jaffee, Caspi, Moffitt, Polo-Tomas, et al., 2004; Jaffee, Caspi, Moffitt, & Taylor, 2004). Though CM remains an important correlate of psychopathology, it is important to understand the complexity of the relationship between CM and mental illness and to gain a better understanding of the genetic mechanisms at play.

While preventing CM is important in its own right, it may be less important in the sense of preventing psychopathology. Providing caregivers with strategies to address behavioral or mood issues in childhood may reduce the incidence of CM, address early signs of psychopathology, and diminish the long-term impact of untreated mental illness. Shifting the clinical framework from regarding mental illness as the outcome of traumatic events, and appreciating the true complexity of these interactions may lead to better clinical outcomes. By more clearly identifying patterns in behavior or characteristics that may leave individuals at risk for or vulnerable to trauma, clinical science can direct efforts to modifying behavioral strategies prevent re-victimization throughout the life-course.

#### **4.5. Limitations**

The current studies had a number of limitations including the use of DSM-III-R diagnostic criteria, and only two types of CM. As with most maltreatment studies, the current data were reported retrospectively during interview or self-report and may be an underestimate by the participants' reluctance to disclose a history of maltreatment. Though self-report is considered a reliable and valid form of assessment, it should not be assumed to be flawless. The current study used combined measures of maltreatment from different inventories and time points, at the same time, this method introduced multiple opportunities for participants to report maltreatment, and introduced convergent validity for the measure of CM. Furthermore, despite the powerful model presented by the counterfactual methodology, MZ twins do not provide a perfect counterfactual pair due to non-shared environmental effects that make them psychologically unique. Because the data collected reflected only psychopathology before the age of 29, future

Despite these limitations, the current work has employed a number of powerful methods to explore the relationship between CM and psychopathology. The results are significant and suggest a future line of research to explore the complicated relationship trauma and psychopathology, as well as the genetic and environmental factors that contribute to the etiology of both in the hope of reducing their prevalence and impact.

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