THE ASSOCIATION BETWEEN CHILDHOOD MALTREATMENT, SUBSTANCE USE FREQUENCY, AND PHYSICAL INTIMATE PARTNER VIOLENCE: A GENE-ENVIRONMENT STUDY

by

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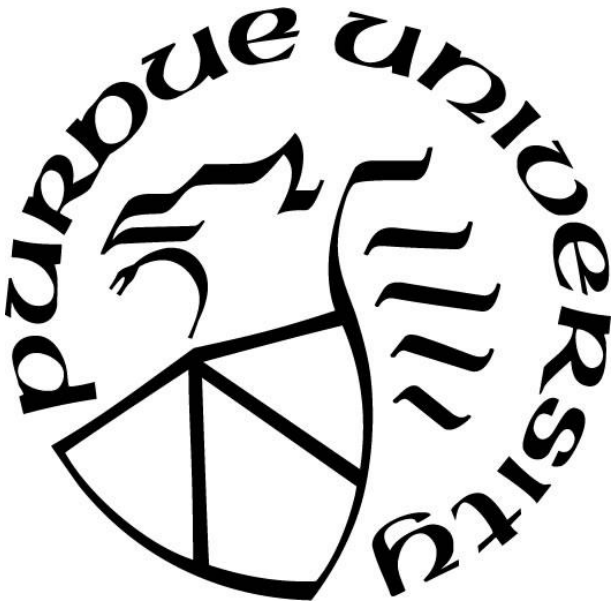

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For my twin pillars of support: Mummy and Papa

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ABSTRACT

This dissertation evaluated the complex inter-relatedness between co-occurring childhood maltreatment exposures, physical intimate partner violence (perpetration and victimization), substance use frequency, and molecular genetics for substance use, utilizing appropriate developmental models and theoretical approaches. Three studies were proposed within this dissertation. Data for the three studies come from a national longitudinal panel study: The National Longitudinal Study of Adolescent to Adult Health (Add Health; Harris, 2013). Across studies, latent profile analysis was used to evaluate co-occurring childhood maltreatment exposures based on type and severity of exposures, which resulted in three homogenous sub-groups. The first sub-group was composed of individuals that had high levels of physical abuse exposure and moderate levels of childhood neglect and emotional abuse exposures (high physical abuse sub-group). The second sub-group (high sexual abuse sub-group) included individuals with high severity of sexual abuse exposure and moderate severity of all other childhood maltreatment types (i.e., physical abuse, emotional abuse, and neglect). This second sub-group was, therefore, the most vulnerable in terms of their childhood maltreatment exposure. A final normative sub-group was also found that included a majority of individuals with low severity of childhood maltreatment exposure across types. Additionally, across all three studies, a probabilistic multifaceted genetic risk score (i.e., polygenic risk score) was created to evaluate substance use related genetic risk. The first study evaluated the role of co-occurring childhood maltreatment exposure on substance use development from adolescence to young adulthood while evaluating substance use related genetic moderation. Generalized estimating equations were used to test the proposed model in study 1. Findings suggest that the high physical abuse sub-group was more susceptible to genetic risk and had increases in substance use frequency only at high levels of genetic risk. In contrast, for the high sexual abuse sub-group, childhood maltreatment and environmental exposures were more ubiquitous for substance use development from adolescence to young adulthood. To elaborate, the high sexual abuse sub-group demonstrated increases in substance use from adolescence to young adulthood irrespective of genetic risk. In study 2, substance use frequency in young adulthood was tested as a mechanism between childhood maltreatment sub-groups and subsequent physical intimate partner violence perpetration in adulthood. Once again, genetic moderation for the direct association between childhood maltreatment sub-groups and substance use frequency in young

adulthood was tested within the larger mediation model. In study 3, physical partner violence victimization in young adulthood was tested as a mediator of the association between childhood maltreatment sub-groups and substance use frequency in adulthood. In study 3, in addition to the above-mentioned genetic risk score, an additional substance use related dopamine polygenic risk score was also tested. Specifically, in study 3, genetic moderation by both genetic risk scores was tested on 1) the direct pathway from childhood maltreatment sub-groups to substance use frequency in adulthood, and 2) the direct pathway from physical intimate partner violence victimization in young adulthood to substance use frequency in adulthood. In both studies 2 and 3, product of co-efficient method was used to estimate mediation hypothesis, and moderated-mediation models were used to test for genetic moderation within the mediation model. Research aims for studies 2 and 3 were largely not supported. However, supplementary models indicate that substance use frequency may not be a causal mechanism but may be a contextual factor exacerbating the association between childhood maltreatment exposures and physical intimate partner violence perpetration. Implications for findings are discussed in detail.

Keywords: Co-occurring childhood maltreatment exposure, substance use frequency, physical intimate partner violence, polygenic risk score, Add Health

CHAPTER 1: INTRODUCTION

Child Maltreatment

This dissertation examines genetic and childhood environmental influences (i.e., co-occurring childhood maltreatment exposure) on substance use and physical intimate partner violence among adolescents and young adults. In 2017, over 3.5 million reports were made to child protective services for alleged child abuse and neglect, and over 674,000 children had substantiated child maltreatment exposure (U.S. Department of Health & Human Services & Administration on Children, Youth and Families, 2017). The cost of child maltreatment in the U.S. is estimated at $124 billion, and the lifetime cost for children who survive child maltreatment is estimated to be around $210,000 per child; higher than the average lifetime costs associated with chronic illnesses such as stroke or type-2 diabetes (Center for Disease Control, 2012), making it a critical public health concern. Childhood maltreatment exposure is negatively associated with many domains of well-being both during childhood and over the life-course, including substance use frequency, physical intimate partner violence, depression, post-traumatic stress, and risky sexual behaviors (Banny, Cicchetti, Rogosch, Oshri, & Crick, 2013; Chaffin, 1996; Famularo, Kinscherff, & Fenton, 1992; Hussey, Chang, & Kotch, 2006; Kaufman, 1991; Kessler et al., 2010; Moran, Vuchinich, & Hall, 2004; Mullen, Martin, Anderson, Romans, & Herbison, 1996; Myers & Prescott, 2000; Shackman & Pollak, 2014; Shonkoff et al., 2012; Tapert, Aarons, Sedlar, & Brown, 2001). According to recent findings, a large portion of children experiencing maltreatment at home were incarcerated as young adults (Berger, Cancian, Cuesta, & Noyes, 2016). Taken together these findings demonstrate the negative sequelae of child maltreatment.

Child maltreatment is broadly comprised two domains: abuse and neglect. Child neglect comprises of emotional neglect and physical neglect and is defined as caregivers' omission of care that is required to meet the child's basic needs (Sedlak et al., 2010). Child abuse consists of sexual, physical, and emotional abuse types and is defined as the commission of an act by a parent or caregiver that jeopardizes the well-being of the child (Sedlak et al., 2010). The Fourth National Incidence Study of Child Abuse and Neglect (NIS-4) detailed that neglect was the most prevalent form of child maltreatment where 53% of all the neglected children were physically neglected (physical and supervisory neglect) and 52% were emotionally neglected.

Accumulating evidence suggests that child maltreatment types often co-occur (i.e., the same individual may experience physical abuse, neglect, sexual abuse; Finkelhor, Turner, Shattuck, & Hamby, 2013; Higgins & McCabe, 2001). However, an evaluation of *co-occurring or multi-type* childhood maltreatment exposures on subsequent negative outcomes such as substance use frequency and physical intimate partner violence is generally lacking in the literature. Such an evaluation can provide empirical evidence for the differential effects of divergent combinations of co-occurring childhood maltreatment exposures on specific negative outcomes, which could ultimately lead to more tailored prevention strategies.

Consequences of Child Maltreatment

Child maltreatment is associated with poor outcomes across domains such as depressive symptoms, anxiety, eating disorder, substance use frequency, poor attachment, relationships and poor educational attainment to name a few (Lansford, et. al., 2002). Given the hostile environment in which maltreated children grow up, they are likely to develop pathological and disorganized attachment, which can then negatively affect their developmental pathways and result in psychopathology (Azar, 2002; Barnett, Ganiban, & Cicchetti, 1999; Ciccheti, Rogosch, & Toth, 2006). There is also evidence that secure attachment can turn into insecure attachment over time in maltreated children (Cicchetti & Barnett, 1991). Moreover, the deleterious effects of child maltreatment are long lasting and have been observed throughout adulthood, including but not limited to depressive symptoms, substance use frequency, sleep problems, relationship difficulties such as intimate partner violence, poverty and poor educational attainment (Banny, Cicchetti, Rogosch, Oshri, & Crick, 2013; Chaffin, 1996; Famularo, Kinscherff, & Fenton, 1992; Hussey, Chang, & Kotch, 2006; Kaufman, 1991; Kessler et al., 2010; Moran, Vuchinich, & Hall, 2004; Mullen, Martin, Anderson, Romans, & Herbison, 1996; Myers & Prescott, 2000; Shackman & Pollak, 2014; Shonkoff et al., 2012; Tapert, Aarons, Sedlar, & Brown, 2001) and a majority of maltreated children end up with a diagnosis of some psychiatric disorder as young adults (Silverman, Reinherz, & Giaconia, 1996).

Of specific interest to this dissertation are physical intimate partner violence perpetration in adulthood and physical intimate partner violence victimization in young adulthood and substance use frequency during adolescence and into adulthood that are associated with childhood maltreatment exposure. Child maltreatment is implicated in the "cycle of violence" (Tunstall &

Gover, 2017). Social learning and operant conditioning due to exposure to child maltreatment can make adult victims of childhood maltreatment accept violence as a normative part of personal relationships and, therefore, be more at risk for perpetrating as well as being victims of physical intimate partner violence during adulthood (Bandura, 1986). Additionally, childhood abuse and neglect are associated with elevated stress among adolescents, which in turn results in coping behaviors such as substance use during adolescence and adulthood (Tanaka, Wekerle, Schmuck, & Paglia-Boak, 2011).

Childhood Maltreatment and Association with Physical Intimate Partner Violence and Substance Use

Despite the known risks conferred by specific forms of child maltreatment for substance use frequency during adolescence and young adulthood (Garner, Hunter, Smith, Smith, & Godley, 2014; Harrison, Fulkerson, & Beebe, 1997; Herrenkohl, Hong, Klika, Herrenkohl, & Russo, 2013; Jones et al., 2013; Narendorf & McMillen, 2010; Trickett, Negriff, Ji, & Peckins, 2011), and strong genetic influences for substance use frequency (Bierut, 2011; Iacono, Carlson, Taylor, Elkins, & McGue, 1999; Neiderhiser, Marceau, & Reiss, 2013; Rende & Slomkowski, 2008), less is known about the direct and interactive effects of co-occurring (based on different types and severity) childhood maltreatment exposures and genetic influences (i.e., polygenic risk for substance use frequency[1]) on substance use frequency development from adolescence to adulthood.

Furthermore, substance use frequency and a history of child maltreatment are both linked to physical intimate partner violence perpetration in adulthood (Desai, Arias, Thompson, & Basile, 2002; Lang, Stein, Kennedy, & Foy, 2004; Richards, Tillyer, & Wright, 2017). Moreover, trauma-induced substance use due to child maltreatment exposure has been implicated in physical intimate partner violence perpetration in adulthood (Faulkner, Goldstein, & Wekerle, 2014). Therefore, it is likely that substance use frequency particularly in young adulthood – a critical period for substance use frequency persistence (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2016; Park-Lee & Tice, 2017) – may be a mediator between multiple co-occurring childhood maltreatment exposures and physical intimate partner violence perpetration in adulthood (Faulkner et al., 2014; Madruga, Viana, Abdalla, Caetano, & Laranjeira, 2017). And, these associations may

[1] Recent developments also demonstrate that SU-problems are associated with several genes of small effects (i.e., polygenic risk; Salvatore et al., 2014).

be further influenced by genetic risk for substance use, such that greater genetic risk would result in higher substance use frequency in young adulthood and higher physical intimate partner violence in adulthood.

Similarly, research also suggests that both child maltreatment and physical intimate partner violence in young adulthood are associated with higher substance use frequency in adulthood as a trauma-related coping mechanism (Desai et al., 2002; Lang et al., 2004; Richards et al., 2017). Therefore, it is also likely that physical intimate partner violence victimization is a mediator between multiple co-occurring childhood maltreatment exposures and substance use frequency in adulthood. That is, an individual who is exposed to maltreatment in childhood is more likely to experience subsequent physical intimate partner violence victimization in young adulthood (Desai et al., 2002; Lang et al., 2004; Richards et al., 2017), which can subsequently lead to higher substance use frequency later in adulthood. It is equally likely that both child maltreatment and physical intimate partner violence victimization (Buller, Devries, Howard, & Bacchus, 2014; Gilbert, El-Bassel, Chang, Wu, & Roy, 2012) would contribute to a double-dose of traumatic interpersonal experiences (i.e., combined effect of both) and this double-dose of trauma can make an individual more likely to choose avoidant coping strategies (i.e., substance use) in order to mentally escape their situation.

In addition, it is probable that polygenic risk for substance use frequency can exacerbate the association of 1) physical intimate partner violence victimization and substance use frequency, and 2) childhood maltreatment and substance use frequency. High genetic risk for substance use frequency in the presence of high severity of child maltreatment exposure and physical intimate partner violence victimization may show higher levels of substance use frequency over time (Ingram & Luxton, 2005) because genetic risk for substance use frequency will likely propel individuals to indulge in substance use as a coping strategy when faced with life stressors such as childhood maltreatment exposure and physical intimate partner violence victimization.

Taken together, these findings point at the necessity to evaluate:

1) the association between co-occurring childhood maltreatment exposures and substance use progression from adolescence to young adulthood (11-26);
2) substance use frequency in young adulthood (ages 18-26) as a mediator between co-occurring childhood maltreatment exposures (prior to age 18) and physical intimate partner violence perpetration (ages 27-32) in adulthood;

3) physical intimate partner violence victimization in young adulthood (ages 18-26) as a mediator between co-occurring childhood maltreatment exposures (prior to age 18) and substance use frequency in adulthood (ages 27-32);
4) genetic risk for substance use on the associations mentioned in 1-3.

Such an evaluation will allow me to disentangle the association between co-occurring childhood maltreatment, substance use frequency, and physical intimate partner violence as well as consider biological pathways for substance use frequency that may be critical for these associations.

Physical Intimate Partner Violence

Intimate partner violence can manifest in multiple forms, the most common of these is physical intimate partner violence that affects both men and women at similar rates (Renner & Whitney, 2010; Smith et al., 2017). Physical intimate partner violence is defined as violent acts perpetrated by one partner towards another in a romantic relationship and includes behaviors such as hitting, shoving, slapping, throwing things, stabbing, or choking (Breiding et al., 2014). Specifically, several large-scale studies show symmetry of physical intimate partner violence (i.e., similar rates of exposure among men and women; Archer, 2000; Medeiros & Straus, 2006), including studies using the sample used in this research that demonstrated symmetry of exposure among men and women (Renner & Whitney, 2010). Nonetheless, I have included biological sex across all the papers in this dissertation and present results for the proposed associations after controlling for biological sex differences.

Consequences of Physical Intimate Partner Violence

Physical intimate partner violence is associated with a plethora of physical health, mental health, and social problems. Particularly, physical intimate partner violence victimization is associated with higher levels of PTSD, depression, fear, sleep problems, and substance use frequency (Beydoun, Beydoun, Kaufman, Lo, & Zonderman, 2012; Breiding et al., 2014). Similarly, physical intimate partner violence can increase physical health problems such as asthma, reproductive problems, gastrointestinal problems, and cardiovascular issues (Breiding et al., 2014;

Breiding, Black, & Ryan, 2008). Social problems consequent of physical intimate partner violence victimization include loss of productivity (i.e., missed work or school), medical costs due to sustained injuries, higher unemployment rates, and unstable housing or homelessness (Adams, Greeson, Kennedy, & Tolman, 2013; Bonomi, Anderson, Rivara, & Thompson, 2009; Breiding et al., 2014). The consequences of physical intimate partner violence victimization are not limited to the victims alone and can also affect other family members, particularly children who witness the physical intimate partner violence. Witnessing physical intimate partner violence can impair multiple domains of functioning among children and result in trauma symptoms (Mishra, Christ, Schwab-Reese, & Nair, 2018; Roberts, Gilman, Fitzmaurice, Decker, & Koenen, 2010; Van der Kolk, 2017). Moreover, several mental health factors are associated with physical intimate partner violence perpetration and unmet mental health needs can lead to a greater incidence of physical intimate partner violence perpetration (DeWall, Anderson, & Bushman, 2011). Furthermore, financial and employment stress (Schwab-Reese, Parker, & Peek-Asa, 2017; Staggs & Riger, 2005) can also be contributing factors for the prevalence rates of this public health problem (i.e., physical intimate partner violence perpetration). Additionally, it is likely that childhood maltreatment exposure can lead to greater levels of substance use frequency in adulthood that may result in higher levels of physical intimate partner violence perpetration (Faulkner et al., 2014; Madruga et al., 2017) and there is also a likelihood that maltreatment may result in higher levels of physical intimate partner violence victimization in young adulthood, which may then lead to high levels of substance use frequency in adulthood (Buller et al., 2014; Gilbert et al., 2012; Goldstein, 1985; Kaysen et al., 2007; Kilpatrick et al., 2000). Therefore, in this dissertation, I try to disentangle the pathways by which substance use frequency influences physical intimate partner violence perpetration and how substance use prevalence is linked to childhood maltreatment and physical intimate partner violence victimization.

Substance Use Frequency

Substance use is a public health concern that affects millions of adolescents and adults per year (Center for Behavioral Health Statistics and Quality, 2015; Johnston et al., 2016). Although prolonged use of substances can lead to higher levels of social, psychological, interpersonal and legal problems (Substance Abuse and Mental Health Services Administration, 2015), during adolescence all substance use frequency is problematic, illegal, and has negative developmental

and health impacts (Fishbein, Rose, Darcey, Belcher, & VanMeter, 2016; Schulte & Hser, 2013). Moreover, during adulthood regular substance use (as evidenced by greater frequency of monthly use) may not be considered problematic in terms of substance addiction, but it can still have detrimental impacts on health, relationships, and overall well-being (Brook, Brook, Zhang, Cohen, & Whiteman, 2002; Crane, Oberleitner, Devine, & Easton, 2014; Schulte & Hser, 2013). In this dissertation, I evaluate substance use frequency by the average frequency of 30-days use for alcohol, marijuana, and illicit drugs at each wave of assessment as done in previous research that used normative samples similar to the one used in this dissertation (Litwiller & Brausch, 2013; Park-Lee & Tice, 2017). However, I also acknowledge across the subsequent chapters that due to the normative nature of the sample used in this research, it will be critical to understand these effects in samples that may have substance addiction or more problematic substance use.

A key consequence of substance use is the alteration of brain circuitry, which persists beyond substance use cessation (American Psychiatric Association, 2013; Moffitt et al., 2011). Moreover, these neurological changes can result from more frequent and increased use over time because substance use behaviors are maintained through the activation of neurobiological reward systems – wherein substance use behaviors are maintained due to feelings associated with such behaviors (American Psychiatric Association, 2013; Moffitt et al., 2011). Substances used not only include illicit drugs such as cocaine, stimulants, meth, inhalants, sedatives, but also include the use of several legal substances such as alcohol. Illicit drug use, alcohol use, and marijuana use are all linked to interpersonal and social problems such as physical intimate partner violence perpetration (Crane, Oberleitner, Devine, & Easton, 2014). Even though alcohol is legal in all states, and marijuana is legal in a few states in the U.S., these substances are still illicit substances for adolescents (Center for Behavioral Health Statistics and Quality, 2015; Johnston et al., 2016) and are the most widely used substances among youth under age 30 (Center for Behavioral Health Statistics and Quality, 2015; Johnston et al., 2016). Furthermore, epidemiological data suggest that there has been an increase in the prevalence of these two substances since 1990 (Center for Behavioral Health Statistics and Quality, 2015; Johnston et al., 2016). Therefore, in addition to understanding the effects of average substance use for the main three articles of this dissertation, substance specific differences are also tested for each paper and presented as post-hoc models across papers.

Consequences of Substance Use Frequency

Much like child maltreatment exposure, several lifelong consequences are resultant from substance use frequency. The most important of these consequences is involvement with the criminal justice system (Brady & Sinha, 2005). A majority of incarcerations are related to possession, distribution, or use of illicit substances and over 60% of incarcerated youth have high substance use frequency (Brady & Sinha, 2005). High substance use frequency is also linked to increased levels of subsequent mental health and behavioral problems such as aggressive behaviors (Crane, et al., 2014) and depression (Brook et al., 2002) and physical health problems such as cardiovascular disease and cancer (Schulte & Hser, 2013). Moreover, in addition to environmental influences such as childhood maltreatment exposure, there is a strong genetic basis for substance use frequency.

Social and Behavior Genetics

Genetic influences together with environmental factors are major contributors for human behaviors and socio-emotional phenotypic attributes. Genetic variance is the proportion of variance in a phenotype in a population that is attributable to genes and represents the relative contribution of genetics vis-à-vis other factors (Knopik, Neiderhiser, DeFries, & Plomin, 2016). Behavior genetics comprises of two broad domains, namely quantitative genetics and molecular genetics. Quantitative genetic research is based on laws of heredity and theoretical assumptions regarding genetic variance, similarity, and inheritance of traits among family members (Knopik et al., 2016). Such quantitative approaches include twin models, sibling designs and adoption studies to name a few. Molecular genetics, on the other hand, involves the measurement of actual DNA data (e.g., candidate gene studies and genome-wide association studies). For this dissertation, a molecular genetic approach will be used to understand genetic influences on substance use frequency during adolescence and adulthood (Bühler et al., 2015). Specifically, this approach has become rapidly popular in the field as it helps understand the role of specific genes that may contribute to certain phenotypes and is able to better isolate the impacts of biological or genetic risk from learning processes that may occur within families.

Molecular Genetics

Molecular genetics typically involves the examination of specific genes or a set of genes within the DNA and their association with phenotypes. The human DNA comprises four base-pairs or single steps (adenine, thymine, guanine, and cytosine) of the DNA double helix. Adenine and Thymine, and Cytosine and Guanine always pair together (Knopik et al., 2016). Whereas some disorders such as Huntington's disease are single gene disorders (i.e., variation in only a single gene contributes to the disorder), many gene variants or multiple polymorphisms of small effects contribute to the genetic basis of many complex behavioral outcomes including substance use frequency and this combined effect of multiple genes is referred to as polygenic risk (Bühler et al., 2015; Knopik et al., 2016). Polymorphisms are alterations in the DNA sequence that produce a different form of a specific allele or gene and the most common among these polymorphisms are single nucleotide polymorphisms (or SNPs; Bühler et al., 2015; Knopik et al., 2016). Typically, SNPs are bi-allelic and the commonly occurring nucleotide base (or ancestral nucleotide) is carried by one allele and is replaced by another different nucleotide base for the other allele (e.g., when an adenine base is replaced by a guanine base at a specific location). If the variant nucleotide codes for the same amino acid as the ancestral nucleotide, then the SNPs are called synonymous or silent. If they code for a different amino acid, then they are called non-synonymous. These non-synonymous SNPs typically influence phenotypic outcomes such as substance use (Knopik et al., 2016).

As mentioned previously, the two most commonly used methods in molecular genetics are candidate gene studies and genome-wide association studies. Candidate gene studies as the name suggests involves the analysis of a single polymorphism in a gene and its association with phenotypic attributes. Candidate gene studies are based on *a priori* hypothesis about specific biological systems and specific genes within these systems that may influence phenotypes such as substance use frequency (Bühler et al., 2015; Knopik et al., 2016). Genome-wide association studies on the other hand do not include any *a priori* hypothesis and all SNPs are freely allowed to correlate with the phenotype in question. SNPs correlated with an outcome must be statistically significant at a genome-wide level (i.e., correcting for all multiple tests) of $p < 10^{-8}$ (Bühler et al., 2015; Knopik et al., 2016). I use a genome-wide association approach to create a polygenic risk score for substance use frequency by including genes that are implicated for substance use frequency across a variety of studies at the genome-wide significance level. Specifically, the score

is created by multiplying the effect allele for the SNP with the effect size estimate from the genome-wide association studies and then combined to create a composite score as done in previous research (Braudt & Harris, 2018; Carey et al., 2016; Meyers et al., 2013). The final SNP list was determined after appropriate quality control methods are undertaken and is discussed in each paper (Marees et al., 2018). This approach is utilized over a candidate gene approach because, in genetic studies of associations, to be sufficiently powered to detect significant effects, it is imperative to have large effect sizes and candidate genes studies are typically underpowered because they examine only one specific gene of small effect using relatively small samples (i.e., not corrected to genome-wide significance level; Munafo, 2006). Moreover, it is also suggested for this data and in previous research to conduct genetic analysis separately by ethnicity due to differences in allelic inheritance (Braudt & Harris, 2018; Rogers & Weiss, 2017). In this dissertation, I therefore, restrict the sample to include those with European ancestry.

Genetic Influences on Substance Use

Substance use is a problem behavior that is susceptible to genetic vulnerabilities (Bühler et al., 2015) and previous research demonstrates that half the variance in substance use frequency are genetic or familial in nature (Duaux, Krebs, Loo, & Poirier, 2000), indicating substance use behaviors may run in families. Moreover, candidate gene studies have demonstrated the link between specific genes within a candidate system and substance use frequency. For instance, effect alleles for certain SNPs for dopamine related genes that code for DRD2, DRD3, DRD4 and COMT have been associated with increased alcohol dependence, opioid addiction, cocaine addiction and overall substance use behaviors (Brody et al., 2012; Le Foll, Gallo, Strat, Lu, & Gorwood, 2009; Volkow, Wang, Maynard, et al., 2002; Volkow, Wang, Fowler, et al., 2002). However, these candidate genes carry very small effects and typically include small sample sizes that are underpowered to detect genetic effects of a single gene. Therefore, the associations found by several candidate gene studies have not been replicated in subsequent research (Gorwood et al., 2012; Knopik et al., 2016). More recently, genome-wide-association studies have demonstrated that multiple genes contribute to the presence of substance use frequency such as alcohol use, cannabis use, opioid and substance use frequency in general (Agrawal et al., 2011; Bierut et al., 2010; Li & Burmeister, 2009; Treutlein & Rietschel, 2011; Verweij et al., 2013; Wetherill et al., 2015). These studies demonstrate the need to evaluate multiple genes that influence substance use

frequency and have greater statistical power to detect significant genetic effects – an approach that is utilized in this dissertation.

Gene-Environment Interactions for Substance Use

Moreover, environmental and genetic influences for substance use interact (G X E) to influence substance use phenotypes such as negative parenting (Creemers et al., 2011), trauma exposure (Brody et al., 2012; Meyers et al., 2013), which interact with genetic risk for substance use to influence substance use frequency. However, a majority of these G X E studies either use quantitative genetic approaches (i.e., twin/family models) or candidate genes. A study evaluating polygenic risk score (PRS) for substance use frequency demonstrated that polygenic risk for substance use frequency increased substance use frequency directly and strengthened the association (i.e., moderated) between peer deviance and low parental knowledge and increased substance use behaviors (Salvatore et al., 2014). Furthermore, no study has evaluated G X E interactions for 1) childhood maltreatment exposure and polygenic risk for substance use, and 2) physical intimate partner violence victimization and polygenic risk for substance use - a gap that is addressed in the current research.

Gaps in the Literature

Even with notable advances made in the field of childhood maltreatment research, several gaps still remain. First, few studies evaluate sub-groups of individuals with multiple co-occurring childhood maltreatment exposure based on both severity and type of childhood maltreatment (Debowska, Willmott, Boduszek, & Jones, 2017). Second, less is known about the association of sub-groups with differing childhood maltreatment exposure (based on severity and type) with trajectories of substance use frequency from adolescence into young adulthood (i.e., at critical developmental periods for substance use; Park-Lee & Tice, 2017). Third, a key gap in current knowledge is that no previous study has evaluated substance use frequency in young adulthood as a mediator between sub-groups with differing childhood maltreatment exposure and physical intimate partner violence perpetration in adulthood. Fourth, no study has tested physical intimate partner violence victimization as a mediator between sub-groups with differing childhood

maltreatment exposures and substance use frequency in adulthood. Finally, evaluation of genetic risk for substance use on these associations are generally lacking.

The inter-relatedness of childhood maltreatment, substance use frequency, and physical intimate partner violence requires the identification of pathways through which these factors influence one another. Moreover, the life-long negative impacts of substance use frequency, childhood maltreatment, and physical intimate partner violence on multiple domains of health and well-being make it necessary to understand how and which factors to intervene upon to reduce the burdens of these public health problems and on the development of secondary problems (e.g. substance use frequency or physical intimate partner violence resulting from childhood maltreatment exposure).

The subsequent sections of this chapter explore theories utilized for understanding the main constructs (i.e., childhood maltreatment, substance use frequency, and physical intimate partner violence) evaluated in this dissertation and the applicability of these theoretical approaches to the models proposed in this dissertation.

Study 1

Analytic Model Study 1

The first model is presented in Figure 1.1, and guides study 1 of the dissertation. In the first model, genetic risk for substance use frequency will be tested as a moderator of the association between sub-groups with differing childhood maltreatment exposure severity and types and substance use frequency development from adolescence to adulthood (Figure 1.1).

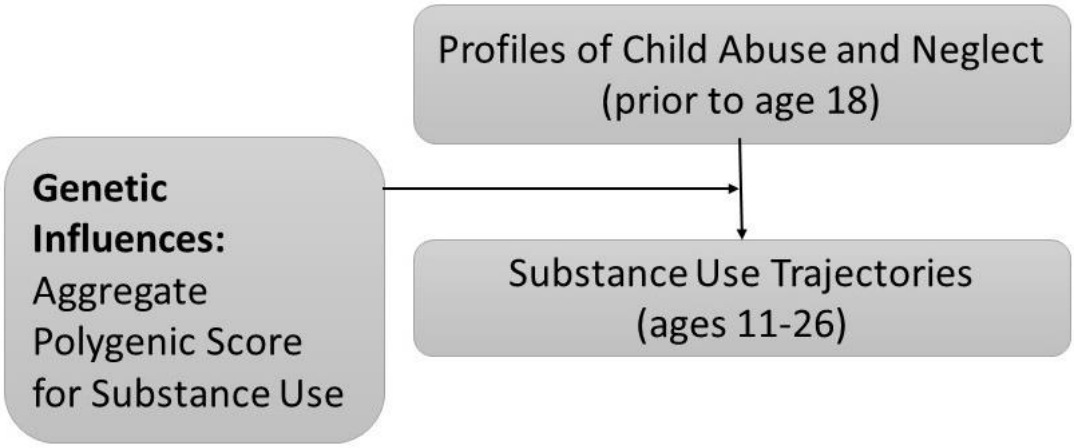

Figure 1.1 Analytic model 1 (study 1) for the association of childhood maltreatment exposure with substance use frequency change from adolescence to young adulthood

The aims of this study include:

A1. Childhood maltreatment influences on trajectories of substance use frequency. Discover multi-type childhood maltreatment sub-groups with differing childhood maltreatment exposures (determined by type and severity of exposure) and assess the impact of childhood maltreatment sub-group membership on developmental trajectories (i.e., change over time) for substance use frequency from adolescence into young adulthood.

A2. Gene-Environment interaction on the development of substance use frequency over time. Test genetic (polygenic risk for substance use related genes; see Table 1.1 for a full initial list of studies and SNPs used to create this score) X environmental (childhood maltreatment sub-group) influences on trajectories of substance use frequency from adolescence into young adulthood.

Table 1.1 Full gene list for substance use polygenic risk score

Gene	Descriptive Name	SNP	Effect Allele	Study
AUTS2	activator of transcription and developmental regulator AUTS2	rs6943555	A	Genome-wide association and genetic functional studies identify autism susceptibility candidate 2 gene (AUTS2) in the regulation of alcohol consumption.
KLB	klotho beta	rs11940694	A	KLB is associated with alcohol drinking, and its gene product β-Klotho is necessary for FGF21 regulation of alcohol preference.
ARID4A	AT-rich interaction domain 4A	rs8012947	A	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
CADM2	cell adhesion molecule 2	rs13078384	A	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
CADM2	cell adhesion molecule 2	rs9841829	G	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
ADH1C	alcohol dehydrogenase 1C (class I), gamma polypeptide	rs2298755	G	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
CADM2	cell adhesion molecule 2	rs67028245	A	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
CTNNA2	catenin alpha 2	rs140089781	A	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
ADH5	alcohol dehydrogenase 5 (class III), chi polypeptide	rs29001570	C	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
ADH5	alcohol dehydrogenase 5 (class III), chi polypeptide	rs29001570	C	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).

Table 1.1 continued

ADH5	alcohol dehydrogenase 5 (class III), chi polypeptide	rs29001570	C	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
CADM2	cell adhesion molecule 2	rs1376935	A	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
KLB	klotho beta	rs11940694	A	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
KLB	klotho beta	rs11940694	A	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
KLB	klotho beta	rs11940694	A	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
GCKR	glucokinase regulator	rs1260326	T	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
ADH5	alcohol dehydrogenase 5 (class III), chi polypeptide	rs29001570	C	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
KLB	klotho beta	rs28712821	A	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
GCKR	glucokinase regulator	rs1260326	G	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
AC114811.1, AC114811.2	translocase of outer mitochondrial membrane 7 homolog (yeast) (TOMM7) pseudogene, novel transcript, antisense TSPAN5	rs193099203	T	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).

Table 1.1 continued

ADH1B, ADH1C	alcohol dehydrogenase 1B (class I), beta polypeptide; alcohol dehydrogenase 1C (class I), gamma polypeptide	rs145452708	C	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
AC114811.1 ,AC114811. 2	translocase of outer mitochondrial membrane 7 homolog (yeast) (TOMM7) pseudogene, novel transcript, antisense TSPAN5	rs193099203	T	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
TSPAN5	tetraspanin 5	rs114026228	C	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
EIF4E,BTF3 P13	eukaryotic translation initiation factor 4E; basic transcription factor 3 pseudogene 13	rs144198753	T	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
ADH1B; ADH1C	alcohol dehydrogenase 1B (class I), beta polypeptide; alcohol dehydrogenase 1C (class I), gamma polypeptide	rs145452708	C	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
ADH1B; ADH1C	alcohol dehydrogenase 1B (class I), beta polypeptide; alcohol dehydrogenase 1C (class I), gamma polypeptide	rs145452708	C	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).

Table 1.1 continued

GCKR	glucokinase regulator	rs11127048	G	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
ADH1B; ADH1C	alcohol dehydrogenase 1B (class I), beta polypeptide; alcohol dehydrogenase 1C (class I), gamma polypeptide	rs145452708	C	Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117).
CDH13	cadherin 13	rs12599112	A	KLB is associated with alcohol drinking, and its gene product β-Klotho is necessary for FGF21 regulation of alcohol preference.
PGM1	phosphoglucomutase 1	rs2749097	G	Genome-wide association study identifies two loci strongly affecting transferrin glycosylation.
SRPRB	SRP receptor subunit beta	rs1534166	A	Genome-wide association study identifies two loci strongly affecting transferrin glycosylation.
TF	transferrin	rs1049296	T	Genome-wide association study identifies two loci strongly affecting transferrin glycosylation.
TF	transferrin	rs3811647	A	Genome-wide association study identifies two loci strongly affecting transferrin glycosylation.
TF	transferrin	rs1799899	A	Genome-wide association study identifies two loci strongly affecting transferrin glycosylation.
RGMA	repulsive guidance molecule BMP co-receptor a	rs12442183	T	Genome-wide Association Study Identifies a Regulatory Variant of RGMA Associated With Opioid Dependence in European Americans.
HFE	homeostatic iron regulator	rs1800562	A	Genome-wide association study identifies two loci strongly affecting transferrin glycosylation.
MIR583HG; AC104123.1	MIR583 host gene; novel transcript, antisense to PCSK1	rs142324060	G	Heritability, SNP- and Gene-Based Analyses of Cannabis Use Initiation and Age at Onset.
OPRM1	opioid receptor mu 1	rs73568641	C	A genome-wide association study of behavioral disinhibition.

Table 1.1 continued

NKAIN1; SNRNP40; ZCCHC17; FABP3; SERINC2	sodium/potassium transporting ATPase interacting 1; small nuclear ribonucleoprotein U5 subunit 40; zinc finger CCHC-type containing 17; fatty acid binding protein 3; serine incorporator 2	rs4478858	G	NKAIN1-SERINC2 is a functional, replicable and genome-wide significant risk gene region specific for alcohol dependence in subjects of European descent.
PECR	peroxisomal trans-2-enoyl-CoA reductase	rs7590720	G	Genome-wide association study of alcohol dependence.
UTP20	UTP20 small subunit processome component	rs57083693	C	Genome-wide survival analysis of age at onset of alcohol dependence in extended high-risk COGA families.
ARL15	ADP ribosylation factor like GTPase 15	rs35951	G	Genome-wide survival analysis of age at onset of alcohol dependence in extended high-risk COGA families.
LINC01324; SI	long intergenic non-protein coding RNA 1324; sucrase-isomaltase	rs2168784	T	Genome-wide survival analysis of age at onset of alcohol dependence in extended high-risk COGA families.
ADH1C; ADH1B	alcohol dehydrogenase 1B (class I), beta polypeptide; alcohol dehydrogenase 1C (class I), gamma polypeptide	rs1789891	A	Genome-wide significant association between alcohol dependence and a variant in the ADH gene cluster.

Table 1.1 continued

ADH1B; ADH1C	alcohol dehydrogenase 1B (class I), beta polypeptide; alcohol dehydrogenase 1C (class I), gamma polypeptide	rs1789891	A	Genetic Contribution to Alcohol Dependence: Investigation of a Heterogeneous German Sample of Individuals with Alcohol Dependence, Chronic Alcoholic Pancreatitis, and Alcohol-Related Cirrhosis.
CNIH3	cornichon family AMPA receptor auxiliary protein 3	rs10799590	G	Evidence of CNIH3 involvement in opioid dependence.
NUP62CL	nucleoporin 62 C-terminal like;	rs12688091	A	Genome-wide association study identifies inversion in the CTRB1-CTRB2 locus to modify risk for alcoholic and non-alcoholic chronic pancreatitis.
AL451142.2 ;RPSAP49	mitofusin 1 (MFN1) pseudogene; ribosomal protein SA pseudogene 49	rs7031417	C	Genome-wide Meta-Analysis of Longitudinal Alcohol Consumption Across Youth and Early Adulthood.
CRYGS	crystallin gamma S	rs1868152	A	A genome-wide association study of behavioral disinhibition.
NCK2	NCK adaptor protein 2	rs2377339	G	Genome-wide association study of therapeutic opioid dosing identifies a novel locus upstream of OPRM1.
ADH1B	alcohol dehydrogenase 1B (class I), beta polypeptide;	rs1229984	T	A meta-analysis of two genome-wide association studies to identify novel loci for maximum number of alcoholic drinks.
AC093001.1	novel transcript	rs143244591	G	Genome-wide Association Study of Cannabis Dependence Severity, Novel Risk Variants, and Shared Genetic Risks.
SLC35G1	solute carrier family 35 member G1	rs146091982	A	Genome-wide Association Study of Cannabis Dependence Severity, Novel Risk Variants, and Shared Genetic Risks.
CSMD1	CUB and Sushi multiple domains 1	rs77378271	A	Genome-wide Association Study of Cannabis Dependence Severity, Novel Risk Variants, and Shared Genetic Risks.

Table 1.1 continued

CSMD1	CUB and Sushi multiple domains 1	rs77378271	A	Genome-wide Association Study of Cannabis Dependence Severity, Novel Risk Variants, and Shared Genetic Risks.
PI4K2B	phosphatidylinositol 4-kinase type 2 beta	rs73252553	A	Genome-wide Association Study of Cannabis Dependence Severity, Novel Risk Variants, and Shared Genetic Risks.
DIP2A; S100B	disco interacting protein 2 homolog A; S100 calcium binding protein B	rs186825689	A	Genome-wide Association Study of Cannabis Dependence Severity, Novel Risk Variants, and Shared Genetic Risks.
RGMA	repulsive guidance molecule BMP co-receptor a	rs12442183	T	Genome-wide Association Study Identifies a Regulatory Variant of RGMA Associated With Opioid Dependence in European Americans.

Theoretical Underpinnings of Analytic Model in Figure 1.1

This study draws from the diathesis-stress model (Ingram & Luxton, 2005). For study 1, the diathesis-stress model is relied on to evaluate genetic diathesis or vulnerability for substance use and evaluate the interaction of this vulnerability with stressful environmental factors (i.e., childhood maltreatment exposure) in order to understand increases in substance use frequency over time.

The diathesis-stress model is a biopsychosocial theory that takes into account a person's predisposition and its interaction with environmental factors that ultimately result in mental health and behavioral problems (Ingram & Luxton, 2005). A predisposition or diathesis is a biological factor (e.g. genetic, endocrine). These predispositions must be present for the individual to develop a negative outcome (e.g., substance use). However, the presence of a predisposition alone is not sufficient for developing a negative outcome. The presence of environmental stressors or stressful life events (e.g. childhood maltreatment) is necessary and must interact with the predisposition in order to trigger the effects of the predisposition and ultimately result in the expressed negative outcome (Ingram & Luxton, 2005; Sigelman & Rider, 2009). The primary goal of the model is to evaluate both biological and environmental influences in the development of negative phenotypes

and psychopathology throughout life (Ingram & Luxton, 2005; Sigelman & Rider, 2009). Although two individuals may be exposed to the same stressor, one individual may develop a certain negative outcome due to their biological predisposition and the other may not due to the lack of this biological predisposition. Therefore, according to this theory, the presence of just an environmental stressor or just a biological predisposition will not result in a negative phenotype and both the stressors and biological predispositions are necessary to produce the negative outcome (Ingram & Luxton, 2005). For example, genes coding for neurological systems associated with substance use when present with neglectful parenting, result in the development of substance use behaviors (Creemers et al., 2011).

Those with a high genetic risk for substance use in the presence of high severity of childhood maltreatment exposure will show greater increases in substance use frequency over time compared to those participants with only high genetic risk for substance use frequency or high severity of childhood maltreatment exposure (Belsky & Pluess, 2009; Ingram & Luxton, 2005). In essence, high genetic risk for substance use in the presence of high severity of childhood maltreatment exposures will show the most disadvantageous trajectories. Additionally, differences in trajectory may also be found for different combinations of childhood maltreatment exposure (Belsky & Pluess, 2009; Ingram & Luxton, 2005). Based on existing research evaluating types on childhood maltreatment on substance use frequency, it is likely that exposure to high severity of physical abuse or emotional abuse or neglect or co-occurring emotional and physical abuse (Berzenski & Yates, 2011; Huang et al., 2011; Widom, Czaja, & Dutton, 2014), may interact with high genetic risk for substance use to produce the highest increases in substance use frequency over time.

To test the aims for study 1, using this theory, the following hypothesis are proposed. It is hypothesized that maltreatment sub-groups with more severe physical abuse, emotional abuse, and neglect will have increases over time in substance use frequency from ages 11-26. (Hypothesis 1). It is hypothesized that high polygenic risk for substance use will exacerbate substance use change over time for all maltreatment exposures but will be most critical for sub-groups with more severe exposures to physical abuse, emotional abuse, and neglect (Hypothesis 2).

Study 2

Analytical Model Study 2

Figure 1.2 depicts the model to be tested for Study 2. For this study, I will test physical intimate partner violence perpetration in adulthood as an outcome of sub-groups with differing childhood maltreatment exposure and substance use frequency in young adulthood (Figure 1.2), and test substance use frequency in young adulthood as a mediator between sub-groups with differing childhood maltreatment exposure and physical intimate partner violence perpetration in adulthood while accounting for genetic risk for substance use. I use the above-mentioned diathesis-stress model to understand the joint influence of childhood maltreatment and genetic risk on substance use frequency in young adulthood and use attachment and social learning (Akers, 2017; Bandura & Walters, 1977) theories to explain the association between childhood maltreatment and physical intimate partner violence perpetration in adulthood. Additionally, social cognitive theory is used to explain the substance use frequency and physical partner violence perpetration and the childhood maltreatment and substance use frequency associations.

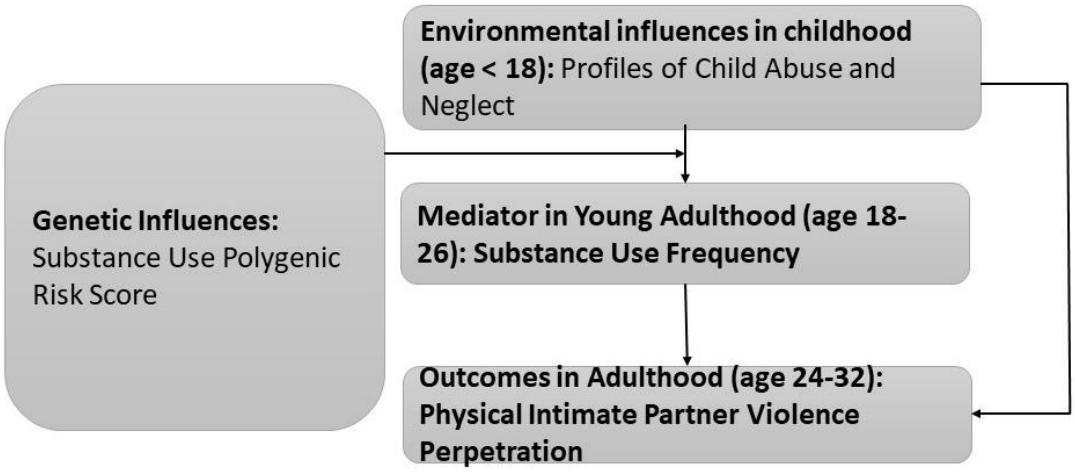

Figure 1.2 Analytic model 2 (study 2) for the association of childhood maltreatment exposure with substance use frequency in young adulthood and subsequent physical intimate partner violence perpetration in adulthood

The aims of this study include:

Aim B1. Evaluate substance use frequency in young adulthood as a mediator between childhood maltreatment sub-groups and physical intimate partner violence perpetration in adulthood.

Aim B2. Test the simultaneous influence of co-occurring childhood maltreatment sub-groups X genetics (indicated by polygenic risk for substance use) on substance use frequency in young adulthood within the overall mediation model in B1 (i.e. moderation of the direct pathway from childhood maltreatment sub-groups to substance use frequency in young adulthood within the mediation model or a moderated-mediation model).

Theoretical Explanation for Study 2

The diathesis-stress model is used to explain the genetic influence on the childhood maltreatment and substance use frequency association in study 2 (same as above in study 1; Ingram & Luxton, 2005). Wherein more severe childhood maltreatment exposure, specifically physical abuse, emotional abuse or neglect or a combination of physical and emotional abuse (Berzenski & Yates, 2011; Huang et al., 2011; Widom et al., 2014), will interact with high genetic risk to produce the most detrimental outcome in substance use frequency and such high levels of substance use frequency in young adulthood will be associated with greater physical intimate partner violence perpetration in adulthood.

The association between childhood maltreatment and physical intimate partner violence perpetration follows the social learning theory and attachment theories. According to the social learning theory, behaviors are a direct result of environmental factors and learning (i.e., modeling and conditioning). Individuals are likely to model behaviors (e.g. physical intimate partner violence perpetration) they witness in their immediate or childhood environments such as exposure to aggression or childhood maltreatment (Bandura, 1986) and accept them as a normative part of social relationships (Bandura & Walters, 1977; Widom & Wilson, 2015). Physical punishment and abuse, in particular, have implications for physical intimate partner violence perpetration. Children who are victims of physical abuse by their caregivers are likely to think of physical violence as a strategy for resolving conflict in inter-personal relationships (Widom & Wilson, 2015).

Attachment theory is an ethological theory rooted in understanding the formation of a strong emotional bond (attachment) between a caregiver and a child and is often used to explain negative outcomes associated with childhood maltreatment. The emotional bonds that are formed by parent-child interactions are dependent on the quality of the caregiver-child relationship. According to this theory, children are instinctively inclined to form attachment relationships because attachment is instrumental in the evolutionary need to survive. These interaction expectations from a caregiver by the child are termed as internal working models or schemas. The child's internal working models or schemas formed due to the interactions with caregiver is a mental model/representation of the self and others, which helps the child: 1) navigate its environment, 2) in social interactions, and 3) in behavioral and personality development (Ainsworth, 1979; Bowlby, 1973).

When infants communicate their needs to their caregiver, the sensitivity of the caregiver's response is instrumental in forming these strong emotional ties (Bowlby, 1973). The sensitivity, quality, and pattern of caregiver response affects the attachment relationship between the parent and child and influences the child's self-worth as well as expectations and interpretations of future relationships with others (Ainsworth et al., 1978; Bowlby, 1973, 1988). Poor attachment can occur when caregivers are abusive or neglectful and may affect the ability of children to develop healthy emotional ties with others.

According to attachment theory, childhood maltreatment would lead to maladaptive internal working models or schemas of relationships. These maladaptive internal working models can then lead to an expression of hostility in ambiguous interpersonal situations and interactions (Ainsworth, 1979; Bowlby, 1973; Widom & Wilson, 2015). According to attachment theory, both neglectful parenting and abusive parenting can lead to poor internal working models (Widom & Wilson, 2015). Therefore, in this dissertation, it is expected that sub-groups of individuals with high severity of childhood maltreatment will be associated with more physical intimate partner violence perpetration in adulthood.

The association between childhood maltreatment exposure and substance use frequency and physical intimate partner violence can be explained with social cognitive theory (Akers, 2017; Bandura, 1986). In the mature form of social learning theory, (i.e., social cognitive theory), coping skills, cognitive processes, and environmental factors triangulate in a reciprocal manner to result in behavioral outcomes such as substance use frequency. Moreover, behavioral outcomes such as

substance use frequency and physical intimate partner violence are also based on perceptions of normative behaviors (Akers, 2017; Bandura & Walters, 1977). Additionally, due to potential expectation of outcomes (i.e., stress reduction, feeling of euphoria) associated with certain behaviors such as substance use frequency, these behaviors are maintained over time and are used to cope with stressful life situations such as childhood maltreatment exposure (Akers, 2017; Bandura, 1986). Such coping behaviors (i.e., substance use frequency) can lead to pleasurable or gratifying outcomes and may be maintained to continually receive these gratifying results. However, discontinuation of these same behaviors (i.e., substance use frequency) can lead to undesirable outcomes such as withdrawal, and these behaviors then are further maintained in order to avoid the negative consequences associated with discontinuation. Under this theory, disavowal and rationalization are two prominent cognitive concepts that are often used to explain problem behaviors (Akers, 2017; Bandura, 1986). Of specific importance to the present dissertation is the concept of rationalization. Rationalization is related to cognitive processing wherein the individual learns social and cultural expectancies and uses a certain behavior such as substance use to justify their other less socially acceptable behaviors (i.e., physical intimate partner violence perpetration).

Based on this theory, an individual may indulge in coping behaviors such as substance use frequency and then continue the use of substance use frequency to maintain the gratifying feeling and to avoid negative outcomes such as withdrawal symptoms. Moreover, in study 2 it is likely that rationalization (Akers, 2017; Bandura, 1986) is a factor influencing the substance use frequency to physical intimate partner violence association. Though not directly tested, based on normative acceptance of substance use frequency in physical intimate partner violence, the perpetrator of physical intimate partner violence may accept substance use frequency as a rational explanation for their aggressive behavior (Akers, 2017; Bandura, 1986).

In study 2, it is hypothesized that more severe co-occurring childhood maltreatment sub-groups will have a direct association with higher levels of physical intimate partner violence perpetration in adulthood and more substance use frequency in young adulthood (Hypothesis 1). It is also hypothesized that substance use frequency in young adulthood will mediate the association between childhood maltreatment sub-group, such that more severe, co-occurring types of childhood maltreatment exposures will be associated with higher frequency of substance use and high frequency of substance use in young adulthood will then be associated with greater (or higher levels) physical intimate partner violence perpetration in adulthood (Hypothesis 2). Finally,

it is hypothesized that genetic risk for substance use will exacerbate the influence of certain childhood maltreatment sub-groups on substance use frequency in young adulthood (Hypothesis 3) within the mediation model in Hypothesis 2.

Study 3

Analytic Model Study 3

The third model evaluates physical intimate partner violence victimization in young adulthood due to childhood maltreatment exposure as a mediator between childhood maltreatment and substance use frequency in adulthood (Figure 1.3). In this final model, overall genetic risk for substance use and substance use related dopamine genetic risk (see Table 1.2 below for a full list of SNPs and corresponding studies) will be evaluated as a moderator of the association between 1) childhood maltreatment and substance use frequency, and 2) physical intimate partner violence victimization and substance use frequency.

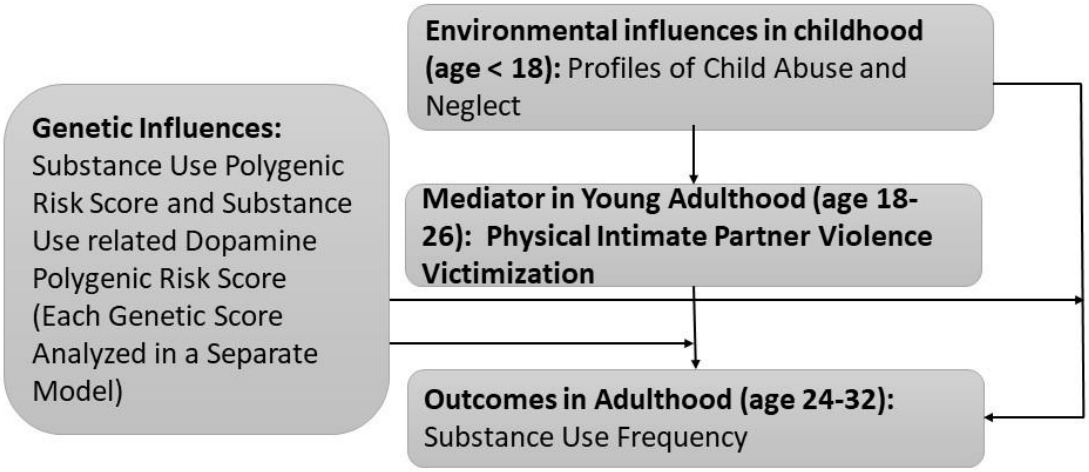

Figure 1.3. Analytic model study 3: Physical intimate partner violence victimization in young adulthood as a mechanism of the association between childhood maltreatment and substance use frequency, while evaluating genetic risk for substance use frequency on these associations

The aims for this model include:

C1. Assess the direct impact of childhood maltreatment sub-group membership on physical intimate partner violence victimization during young adulthood and substance use frequency in adulthood.

C2. Evaluate physical intimate partner violence victimization in young adulthood as a mechanism of the association between sub-groups of childhood maltreatment and substance use frequency in adulthood.

C3. Gene-environment interaction on substance use frequency. Test genetic (polygenic risk for substance use related genes and polygenic risk for dopamine genes for substance use) X environmental (physical intimate partner violence victimization and co-occurring childhood maltreatment exposure) influences on the likelihood for substance use frequency in adulthood.

Table 1.2 Full gene list for substance use related dopamine polygenic risk score

Gene	Descriptive Name	SNP	Effect Allele	Studies
SLC6A3	solute carrier family 6 member 3	rs10052016	G	Limited associations of dopamine system genes with alcohol dependence and related traits in the Irish Affected Sib Pair Study of Alcohol Dependence (IASPSAD).
DRD2	dopamine receptor D2	rs1076560	A	Intronic polymorphisms affecting alternative splicing of human dopamine D2 receptor are associated with cocaine abuse.
DRD2	dopamine receptor D2	rs1079597	T	Using an Event-History with Risk-Free Model to Study the Genetics of Alcoholism.
DRD2	dopamine receptor D2	rs1079727	T	Genetic influences on craving for alcohol. *Addictive behaviors*, *38*(2), 1501-1508.

Table 1.2 continued

DRD2	dopamine receptor D2	rs1125394	C	Intronic polymorphisms affecting alternative splicing of human dopamine D2 receptor are associated with cocaine abuse.
DRD4	dopamine receptor D4	rs12280580	G	Limited associations of dopamine system genes with alcohol dependence and related traits in the Irish Affected Sib Pair Study of Alcohol Dependence (IASPSAD).
COMT	catechol-O-methyltransferase	rs165774	G	A novel SNP in COMT is associated with alcohol dependence but not opiate or nicotine dependence: a case control study.
DRD2	dopamine receptor D2	rs1799978	C	Genetic variants altering dopamine D2 receptor expression or function modulate the risk of opiate addiction and the dosage requirements of methadone substitution.
ANKK1	ankyrin repeat and kinase domain containing 1	rs1800497	A	Association between DRD2/ANKK1 TaqIA polymorphism and common illicit drug dependence: evidence from a meta-analysis.
DRD3	dopamine receptor D3	rs2134655	A	Using an Event-History with Risk-Free Model to Study the Genetics of Alcoholism.
DRD2	dopamine receptor D2	rs2283265	A	Intronic polymorphisms affecting alternative splicing of human dopamine D2 receptor are associated with cocaine abuse.
COMT	catechol-O-methyltransferase	rs4680	G	A novel SNP in COMT is associated with alcohol dependence but not opiate or nicotine dependence: a case control study.

Table 1.2 continued

ANKK1	ankyrin repeat and kinase domain containing 1	rs4938012	G	Family-based association analyses of alcohol dependence phenotypes across DRD2 and neighboring gene ANKK1.
DAT1	Dopamine transporter	rs6350	G	Association between harmful alcohol consumption behavior and dopamine transporter (DAT1) gene polymorphisms in a male Finnish population.
DRD1	dopamine receptor D1	rs686	T	A haplotype of the DRD1 gene is associated with alcohol dependence.
ANKK1	ankyrin repeat and kinase domain containing 1	rs877138	G	Influence of Dopaminergic System Genetic Variation and Lifestyle Factors on Excessive Alcohol Consumption.

Theoretical Explanation for Model 3 (study 3)

Model 3 is built on diathesis-stress model (see above for detailed description; Ingram & Luxton, 2005; Sigelman & Rider, 2009). Based on this theory, high genetic risk and high environmental stress (both childhood maltreatment and physical intimate partner violence victimization stressors) will likely influence negative substance use frequency outcomes in adulthood. Moreover, childhood maltreatment X genetics and physical intimate partner violence victimization x genetics will have independent and combined effects on substance use frequency in adulthood.

Within this model dopamine related genetic risk for substance use frequency will also be tested. Following the neurobiological framework, dopamine systems are implicated in reward pathways (Hyman, et al., 2006; Sinha, 2008). The neurobiological framework is often used to understand the effects of stress or stress allostasis (i.e., changes to the bodies set point as a consequence of long-term stress exposure) and desensitization that leads to specific mechanisms such as reward pathways that are then implicated in psychopathology (Hyman, Garcia, & Sinha, 2006; Sinha, 2008). Of importance to the present dissertation is the reward and learning pathways within the neurobiological framework.

Exposure to stress can reduce prefrontal cortex functioning and promote lower inhibitory behaviors and cognitive functioning. Within the social-cognitive theory (like in model 2), stress can induce cognitive dysregulation that leads to coping behaviors such as substance use (Akers, 2017; Bandura, 1986). Such dysregulated cognitive processes are directly linked to the reward and learning pathways that are used to explain substance use behaviors in particular (Hyman et al., 2006; Sinha, 2008). For example, due to the alteration of learning and reward neurological pathways, an individual is likely to continue an addictive behavior or substance use frequency despite known adverse consequences. These pathways can also be used to explain the cravings and increases in levels of substance use frequency over time (Hyman et al., 2006; Sinha, 2008). To illustrate, substance use can activate neurological reward systems (i.e., dopaminergic system) by increasing the transmission of dopamine, this activation leads to the feeling of high or euphoria when the person uses a substance. Substance use frequency can lead to dysregulated reward pathways, which can result in activation of these pathways even when the substance is not used (e.g., cravings at a specific time when the drug is typically taken), such activation, can lead to substance craving behaviors that may not be manageable by the person. Substance craving can lead to the maintenance of substance use behaviors and may lead to increases in substance use frequency over time to continually increase the activation of the reward pathway so that the individual can get the same feelings of high (Sinha, 2008).

Extant empirical and theoretical evidence demonstrates that substance use behaviors are maintained due to the dysregulation of dopamine systems that control motivation and self-control processes. Moreover, a dysregulated dopamine system increases motivation for substance use frequency and results in the need for gratification of rewarding feelings (e.g., the feeling derived from using the substance) associated with substance use frequency (Hyman, et al., 2006; Sinha, 2008). These factors ultimately lead to maintenance of and increases in substance use frequency. Genes coding for dopamine can, therefore, demonstrate whether dopamine system specific risks are promoting substance use frequency (see Gorwood et al., 2012 for a full review on the role of specific genes and their function). Therefore, high dopamine specific genetic vulnerability when present with high exposure to childhood maltreatment and physical intimate partner violence victimization is expected to produce increased substance use frequency in adulthood (Gorwood et al., 2012). Additionally, as mentioned above, individuals with high childhood neglect or emotional abuse or physical abuse or a combination of physical and emotional abuse exposure (Berzenski &

Yates, 2011; Huang et al., 2011; Widom et al., 2014) will show the most substance use frequency as adults when interacting with high dopamine related genetic risk compared to sub-groups with low or no exposure to these childhood maltreatment types.

Social learning (Akers, 2017; Bandura, 1986; Bandura & Walters, 1977) and attachment theory (Ainsworth, 1979; Bowlby, 1973) explain the pathway from childhood maltreatment exposure to physical intimate partner violence victimization. From attachment theory, maladaptive relationship with caregivers in childhood due to childhood maltreatment can create internal working models wherein individuals accept abusive and neglectful patterns in intimate partner relationships and these internal working models are carried forward into their adult relationships with their partners (Ainsworth et al., 1978; Bowlby, 1973, 1988; Cook et al., 2005; Feerick, Haugaard, & Hein, 2002). These children when grown up, accept negative and abusive interpersonal patterns as normative. Such acceptance could lead to greater or continued exposure to and acceptance of physical intimate partner violence victimization because the individual does not seek to leave the relationship as individuals without childhood maltreatment exposures might (Bandura, 1986; Widom & Wilson, 2015). According to social learning theory, individuals may accept aggressive behaviors or substance use frequency as normative within their immediate environment due to conditioning from childhood experiences. To illustrate, an example of conditioning would be when a person is likely to be accepting of their own physical intimate partner violence victimization as an adult because of earlier victimization within their family during childhood (Akers, 2017; Bandura & Walters, 1977). This social learning then makes victims of physical intimate partner violence accept violence as a normative part of all intimate relationships (Bandura, 1986; Widom & Wilson, 2015).

To test the aims of study 3 within these theoretical models, the following hypothesis are proposed. It is hypothesized that exposure to more severe, co-occurring types of childhood maltreatment will have stronger associations with physical intimate partner violence victimization in young adulthood and substance use frequency than exposure to less severe or fewer types of childhood maltreatment (Hypothesis 1). Specifically, sub-groups with childhood neglect, emotional abuse, and physical abuse exposures are likely to be associated with more (Huang et al., 2011) substance use frequency and presence of multiple childhood maltreatment exposures especially emotional and physical abuse together will be associated with greater physical intimate partner violence victimization in young adulthood (Parks et al., 2011). Higher frequency of

physical intimate partner violence victimization will be more strongly predicted by more severe multiple co-occurring types of childhood maltreatment, which will then predict higher substance use frequency later in adulthood (Hypothesis 2). It is hypothesized that more overall genetic risk for substance use and substance use related dopamine genetic risk will exacerbate the influence of certain childhood maltreatment sub-groups on substance use frequency (Hypothesis 3).

In essence, greater genetic risk for substance use (general and dopamine related) when combined with more severe types of co-occurring childhood maltreatment exposures (especially those mentioned above) will produce greater substance use frequency in adulthood. It is also hypothesized that more overall genetic risk for substance use frequency and more substance use frequency related dopamine genetic risk will worsen the influence of greater frequency of physical intimate partner violence victimization on substance use frequency in adulthood (Hypothesis 4).

Conclusion

This introductory chapter introduced the three studies within this dissertation, the analytic models, and theoretical frameworks guiding this work. Also presented in this chapter was a brief overview and extent of the problem for childhood maltreatment, substance use frequency, and physical intimate partner violence, and a brief overview of genetic concepts that are applicable to the present dissertation. In the remainder of this dissertation, Chapter 2-4 present studies 1-3 respectively. Chapter 5 includes an overall summary and recommendations for future research.

CHAPTER 2: STUDY 1

In chapter 1, I provided the theoretical framework as well as the analytic models guiding the proposed dissertation research. In this chapter, I empirically examine the association between childhood maltreatment subgroups (based on similar exposure to types and frequency of maltreatment) and substance use trajectories from adolescence to young adulthood. I also evaluate the role of genetic risk for substance use by creating a polygenic risk score on trajectories over time. Moreover, I examine post-hoc models for substance-specific frequencies (i.e. alcohol use, marijuana use, and other drug use) over time.

Target Journal: PLOS One

Title: Multi-type childhood maltreatment exposure and substance use development from adolescence to young adulthood: A gene-environment interaction study

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Ethical approval: The study uses pre-existing data from The National Longitudinal Study of Adolescent to Adult Health (Add Health) study that was reviewed and deemed as an

expedited category 5 for Human Subjects Research by the Purdue University IRB. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee.

Abstract

Research indicates that individuals with childhood maltreatment exposures tend to experience multiple types of exposures with varying degrees of severity. Moreover, exposure to childhood maltreatment is associated with high substance use frequency during adolescence and young adulthood. Furthermore, there is evidence suggesting that there is a strong genetic basis for substance use and that impoverished environments (e.g., childhood maltreatment) can interact with genetic risk for substance use to influence substance use phenotype. This research, therefore, aimed to identify childhood maltreatment sub-groups based on both type and severity, and their association with substance use change during critical developmental periods (aim 1), while accounting for the moderating influence of genetic risk (aim 2). First, I found three sub-groups with co-occurring or multi-type childhood maltreatment exposures: 1) a sub-group with high severity of sexual abuse exposure with moderate severity of physical abuse, emotional abuse, and neglect exposures (high sexual abuse sub-group), 2) another sub-group with high severity physical abuse exposure with moderate severity of neglect and emotional abuse exposure (high physical abuse sub-group), and 3) a final sub-group with low severity of all maltreatment exposures (normative sub-group). Second, I found that the high sexual abuse sub-group had steady increases in substance use frequency over time, these associations disappeared with the inclusion of covariates and polygenic risk score for substance use. Therefore, aim 1 was largely not supported. However, there was a significant interaction between childhood maltreatment sub-groups and substance use polygenic risk score for both initial substance use frequency and substance use frequency increases over time with age. Specifically, individuals in the high physical abuse sub-group demonstrated slightly lower initial frequency of substance use compared to the normative sub-group but had faster increases over time at high polygenic risk for substance use compared to the other sub-groups. In comparison at high polygenic risk for substance use, the high sexual abuse sub-group had higher initial frequency of substance use and slower progression over time compared to the normative sub-group. However, at low and medium polygenic risk score, the high sexual abuse sub-group had faster increases in substance use frequency over time. Findings suggest the need to include biological and adversity exposures simultaneously for understanding the effects of high physical abuse sub-group membership on trajectories of substance use frequency over time. Moreover, there may be a need for considering additional psychosocial factors that may explain the associations found for the high sexual abuse sub-group.

Childhood maltreatment is associated with increased substance use frequency during adolescence and young adulthood (Traube, James, Zhang, & Landsverk, 2012) – a time when substance use behaviors first emerge and have the highest prevalence (in terms of frequency of use; Feinstein, Richter, & Foster, 2012). Among adolescent victims of childhood maltreatment, substance use frequency is typically higher than adolescents without maltreatment exposures and is linked to subsequent high frequency of substance use in young adulthood (Garner et al., 2014; Traube et al., 2012). However, there is significant inter-individual variability in exposure to childhood maltreatment (Debowska et al., 2017) and these differences in exposure may be differentially related to substance use outcomes. Research suggests that children with maltreatment exposure are likely to experience multiple maltreatment types with varying degrees of severity (Debowska et al., 2017). Therefore, it is important to understand the role of multi-type childhood maltreatment exposures based on differing degrees of severity (i.e. frequency of exposure) on substance use frequency change over time. Such an evaluation is important because different combinations of maltreatment exposures (based on type and severity) may have a differing association with substance use frequency at any given time and over time. In addition to social exposures, research also suggests genetic influences for high substance use frequency (Reiss, Leve, & Neiderhiser, 2013). However, few studies have evaluated genetic risk for substance use measured using molecular genetic techniques on substance use frequency progression over time within the context of childhood maltreatment exposure. The present study will bridge these gaps in current knowledge by evaluating substance use trajectories from ages 11 to 26 for sub-groups of individuals with different severity of co-occurring childhood maltreatment exposure types. Additionally, substance use polygenic risk score (i.e., genetic risk based on a combination of multiple genes) will also be tested as a moderator of the association between 1) childhood maltreatment sub-group membership and initial frequency of substance use and 2) childhood maltreatment sub-group membership and change over time in substance use frequency from ages 11 to 26.

Childhood Maltreatment and Substance Use

Substance use frequency among adolescent survivors of childhood maltreatment is linked to high prevalence of substance use frequency during young adulthood (Garner et al., 2014). To illustrate, among youth exposed to childhood maltreatment, there was a 10% increase in substance

use frequency during the transition from adolescence to adulthood (Narendorf & McMillen, 2010). Severity of maltreatment exposure during childhood can further exacerbate substance use frequency during adolescence and young adulthood (Garner et al., 2014; Narendorf & McMillen, 2010), and it is likely that substance use may be a coping mechanism for alleviating stress following childhood maltreatment exposure (Oshri, Tubman, & Burnette, 2012). Studies of childhood maltreatment effects on trajectories of substance use frequency over time, however, are limited in number and somewhat mixed in their findings. Whereas some studies reveal that childhood maltreatment is associated with increases in substance use frequency during adolescence (Kosty, Seeley, Farmer, Stevens, & Lewinsohn, 2017), others demonstrate that childhood maltreatment is associated with high stable levels of substance use frequency but not increases during adolescence (Wilson, Samuelson, Staudenmeyer, & Widom, 2015).

Even though all maltreatment types have been implicated in higher levels of substance use frequency among youth, emotional abuse, physical abuse, and neglect have consistently emerged as the most impactful for substance use frequency (Huang et al., 2011). Studies evaluating multi-type childhood maltreatment exposure reveal similar results and illustrate that even though all abuse types (physical abuse, emotional abuse, and sexual abuse) impact substance use frequency during adolescence, emotional abuse is particularly salient for increased substance use frequency (Rogers, McKinney, & Asberg, 2018). However, research on the association between multiple co-occurring childhood maltreatment exposures (based on both type and severity of exposure) and trajectories of substance use frequency from adolescence to young adulthood are limited in number.

The few studies on co-occurring childhood maltreatment exposure typically include an evaluation of the types of exposure. Studies examining such co-occurring types of childhood maltreatment exposures concluded that physical abuse, neglect, and emotional abuse types co-occur together and are associated with high substance use frequency later in life (Berzenski & Yates, 2011; Huang et al., 2011). However, there is a critical need to examine both severity and type of childhood maltreatment, since greater severity of exposure may be more detrimental to future outcomes (Debowska et al., 2017). Such an examination will allow us to understand the effects of multiple co-occurring childhood maltreatment on substance use frequency during critical life periods such as adolescence and young adulthood when the risk for substance use frequency is most prevalent (Park-Lee & Tice, 2017).

Substance Use during Adolescence and Young Adulthood

Any substance use during adolescence is classified as a problem behavior that has implications for continued use over time and is detrimental to health outcomes (Fishbein et al., 2016; Schulte & Hser, 2013). Substance use frequency among adolescents typically increases over time, and can persist well into young adulthood (Johnston et al., 2016; Pine, Cohen, Cohen, & Brook, 1999). Particularly, early initiation of substance use can increase the likelihood for continuation of substance use and development of very high substance frequency later in life (Johnston et al., 2016; Pine et al., 1999). And, 90% of adults with substance use problems report first substance use experiences during adolescence (Feinstein et al., 2012). Specifically, high substance use frequency during adolescence is associated with even higher frequency of substance use during young adulthood (Johnston et al., 2016) and epidemiological studies reveal that, in fact, substance use frequency is highest among adolescents and young adults (i.e. people under the age of 27; Park-Lee & Tice, 2017). High frequency of substance use can have life-long detrimental effects on overall health and well-being such as heart disease, cancer, bipolar disorder, anxiety, depression, vehicular accidents (Schulte & Hser, 2013) as well as impact adolescent and young adult brain development (Fishbein et al., 2016).

Given the significance of substance use in adolescence for continuation of these behaviors in young adulthood, it is important to evaluate the development of substance use frequency over time from adolescence to young adulthood. Moreover, childhood maltreatment experiences can be consequential for substance use as a stress coping mechanism (Hall, 2016; McKinney & Renk, 2011; Paus, Keshavan, & Giedd, 2010). Taken together, it is likely that certain combinations of childhood maltreatment can result in greater stress and a higher likelihood that substance use increases over time from adolescence to young adulthood. Understanding these associations could lead to more targeted prevention and intervention efforts for sub-groups with specific constellations of childhood maltreatment exposures that are at greater risk for high substance use frequency or persistent substance use over time during these critical developmental periods.

Genetic Risk for Substance Use

In addition to social environment exposures, research also suggests genetic influences for substance use frequency (Bierut, 2011; Iacono et al., 1999; Neiderhiser et al., 2013; Rende &

Slomkowski, 2008). Recent advances in molecular genetics and genome-wide association studies have demonstrated that genetic risk for most complex phenotypes such as substance use are polygenic in nature (i.e. combined effect of multiple genes; Maier, Visscher, Robinson, & Wray, 2017). Furthermore, there is evidence suggesting that genetic influences continually interact with environmental factors to predict substance use outcomes (e.g. G x E). Genetic studies pertaining to substance use have demonstrated the moderating effects of genetic risk for substance use on the association between environmental stress and substance use frequency (Creemers et al., 2011; Gorwood et al., 2012; Harden, Hill, Turkheimer, & Emery, 2008; Neiderhiser, Reiss, Hetherington, & Plomin, 1999). Given the litany of problems such as cardiovascular disease, mental health problems, injuries, accidents, and cancers, that are associated with early and frequent substance use (Schulte & Hser, 2013), the role of polygenic risk for substance use in the association between childhood maltreatment exposure and subsequent substance use frequency change over time needs further evaluation. According to the diathesis-stress models (Ingram & Luxton, 2005; Sigelman & Rider, 2009), high biological risk and high environmental stress interact together to result in negative outcomes such as high substance use frequency. For example, negative parenting and genetic risk can interact to produce stronger substance use phenotypes (Creemers et al., 2011). However, this theoretical model also posits that the presence of biological vulnerabilities alone is not sufficient for negative outcomes. It is the interaction of impoverished environments and biological predispositions that results in specific negative outcomes and different environmental adversities interact differently with biological predispositions (Belsky & Pluess, 2009; Ingram & Luxton, 2005). Therefore, in this study, I expect that more severe exposure to certain types of childhood maltreatment exposures (specifically physical abuse, emotional abuse, and neglect as identified by previous research; Huang et al., 2011) will interact with genetic risk for substance use to produce greater initial substance use frequency and increases over time in substance use frequency until young adulthood (i.e. until age 26).

Study Aims

The present study builds on and extends previous research and theory by addressing two primary aims. The first aim is to assess the association of childhood maltreatment sub-group membership - determined by the severity (frequency) of exposure to multiple types of maltreatment - with levels (i.e. initial substance use frequency) and change over time (or trajectory)

in substance use frequency from adolescence into young adulthood (from ages 11 to 26). It is hypothesized that childhood maltreatment sub-groups with more severe physical abuse, emotional abuse, and neglect will have increases over time in substance use frequency from ages 11-26. The second aim is to examine substance use polygenic moderation of the association between childhood maltreatment sub-group membership with change over time in substance use frequency from adolescence into young adulthood (age 11-26). It is hypothesized that high polygenic risk for substance use will exacerbate change over time for all maltreatment exposures but will be most critical for sub-groups with more severe exposures to physical abuse, emotional abuse, and neglect.

Methods

Participants

The data for this study come from The National Longitudinal Study of Adolescent to Adult Health (Add Health; Harris, 2013). Add Health is a longitudinal panel study of adolescents (N = 20,743) who were between 7th and 12th grade at the first wave of data collection (1994-95). Four waves of in-home interviews were conducted - wave 1: 1994-95; wave 2: 1996; wave 3: 2001-2002; wave 4: 2008-2009. Data were collected using paper-based, face-to-face and computer-assisted in-person interviews. The Add Health sampling design is a multiple-stage, school-based (clustered), stratified design with unequal selection probabilities of observations (i.e. certain minority groups were oversampled). Out of the core sample, 12,234 participants agreed to the archival of DNA data (Braudt & Harris, 2018), the present study utilizes a sub-sample of 2,664 unrelated European Americans from the DNA archival data, who also had retrospective childhood maltreatment reports at waves 3 and 4. I restrict a sample to European Americans as prescribed by Add Health researchers and previous genetic studies due to differences in inheritance of allele frequency based on ancestry (Braudt & Harris, 2018; Dudbridge, 2013).

Measures

Child Maltreatment

Retrospective measures assessing child maltreatment exposure: physical abuse, sexual abuse, emotional abuse, and neglect prior to age 18 were administered at waves 3 and 4. Two items

were used to assess neglect (at wave 3), one item assessed sexual abuse (at waves 3 and 4), one item assessed physical abuse (at waves 3 and 4), and one item assessed emotional abuse (at wave 4). Physical abuse items included – "How often had your parents or other adult care-givers slapped, hit, or kicked you?" (wave 3) and "Before your 18th birthday, how often did a parent or adult caregiver hit you with a fist, kick you, or throw you down on the floor, into a wall, or downstairs?" (wave 4). Sexual abuse items included – "How often had one of your parents or other adult care-givers touched you in a sexual way, forced you to touch him or her in a sexual way, or forced you to have sexual relations?" (wave 3) and "Before your 18th birthday, how often did a parent or other adult caregiver touch you in a sexual way, force you to touch him or her in a sexual way, or force you to have sexual relations?" (wave 4). Neglect included the following items at wave 3 "By the time you started 6th grade, how often had your parents or other adult care-givers left you home alone when an adult should have been with you?" and "How often had your parents or other adult care-givers not taken care of your basic needs, such as keeping you clean or providing food or clothing?" and emotional abuse included a single item at wave 4: "Before your 18th birthday, how often did a parent or other adult caregiver say things that really hurt your feelings or made you feel like you were not wanted or loved?". All items were measured with a frequency count (i.e. measure of severity) for each maltreatment type and coded on intervals (e.g., 1 = one time, 2 = two times, 3 = three to five times, 6 = six to ten times, 11 = more than 10 time. Mean scores across items and waves for sexual and physical abuse and across items for neglect were created. These mean scores were subsequently used in a latent profile analysis (outlined below) to create sub-groups of individuals with exposure to similar types and severity of childhood maltreatment.

Substance Use

Self-reported use of marijuana and other drug use (LSD, PCP, ecstasy, mushrooms, speed, ice, heroin, and pills) within the last 30 days was reported at waves 1-3 wherein participants reported the number of times they used these substances. Alcohol use (waves 1-3) was assessed by 12-month use and re-scaled to 30-day use. Responses of 30 or more times were top-coded at 30. Alcohol use (waves 1-3) was originally assessed by 12-month use and were originally coded as: 0 = "never"' 1 = "once or twice"; 2 = "once a month"; 3: "2 to 3 days a month"; 4 = "once or twice a week". 5 = "3 to 5 days a week"; 6 = "nearly every day".

Alcohol items were re-coded as count variables (so that they would be on the same scale as marijuana and illicit drug) to assess monthly use

The revised coding included:

0 = "never"

1 = "once a month",

2 = "2-3 days a month",

4 = "4-8 days a month" (recoded original coding of once or twice a week to approximate number of days in a month);

12 = "12-20 days a month" (recoded 3 to 5 days a week to reflect approximate number of days in a week); and

30 = "30 plus days a month" (recoded all responses of nearly every day).

The alcohol use scale was treated as a continuous variable and conservative values for monthly use were estimated so that alcohol use frequency would be similar to the other two substances (i.e. an estimation of the number of times on average the respondent used alcohol in a month). An average substance use scale was created to assess average monthly substance use at each wave. The creation of this average substance use scale mimicked that from previous research used to evaluate overall substance use (Litwiller & Brausch, 2013; Park-lee & Tice, 2017), with higher frequency of use (assessed by no. of times) indicating more substance use behaviors.

Substance Use Polygenic Risk Score

The Add Health genetic data (genotype platform used: Illumina HumanOmni1-Quad chi and the imputation data are from the HRC r1.1 2016 reference panel) at wave 3 were used in the present research. Single nucleotide polymorphisms (SNPs) for genes related to substance use was used to create a substance use polygenic risk score. Specifically, genome-wide significance levels $p < 5 \times 10\text{-}8$ (from the original genome-wide association studies), were used to identify SNPs for inclusion in the substance use polygenic risk score from multiple genome-wide association studies. SNPs were selected from 18 genome-wide studies of substance use, alcohol use, marijuana use, illicit drug use, and substance use biomarker related phenotypes to create one single genetic risk index for substance use. The initial list consisted of 34 SNPs (full list of genes in chapter 1) and the final list included 15 SNPs from 14 genes (and 5 genome-wide studies) after the below quality control steps were undertaken as prescribed in extant research (Marees et al., 2018). Table 2.1

includes the digitial object identifier for studies from which these SNPs were included and a brief description of the sample for that specific genome-wide association study.

1. Missingness: per individual > 0.1 (i.e. removed individuals with more that 10% missing data; 0 SNPS removed)
2. missingness per marker > 0.1(i.e. removed markers with more that 10% missing data; 0 SNPS removed)
3. Screen allele frequency < 0.01(i.e., included SNPS only with minor allele frequency > 0.01; 0 SNPs removed).
4. Screen for Hardy-Weinberg equilibrium (HWE) p < 0.001 (i.e., excluded markers that deviate from HWE; 13 SNPS removed).
5. Extract only the markers that do not meet the linkage disequilibrium (LD) threshold > 0.3 (removed a SNP within a correlated pair of SNPs if such correlation was greater than 0.3 or medium effects; 1 SNP removed).
6. Five SNPs were dropped because they did not have an effect size estimate.

Table 2.1 Substance use related SNPs retained to create substance use polygenic risk score

Gene	Descriptive Name	SNP	Effect Allele	Cohen's D	GWAS Study	Sample
PGM1	phosphoglucomutase 1	rs2749097	G	0.25	https://doi.org/10.1093/hmg/ddr272	Swiss and Australian samples (European Ancestry) between the ages of 35 and 75
GCKR	glucokinase regulator	rs11127048	G	0.07	https://doi.org/10.1038/mp.2017.153	European Ancestry from United Kingdom; ages 30 to 69
PECR	peroxisomal trans-2-enoyl-CoA reductase	rs7590720	G	0.17	https://doi.org/10.1073/pnas.0911109107	European-American and African-American ancestry; ages 18-77
CADM2	cell adhesion molecule 2	rs9841829	G	0.04	https://doi.org/10.1038/mp.2017.153	European Ancestry from United Kingdom; ages 30 to 69
TF	transferrin	rs1799899	A	0.90	https://doi.org/10.1093/hmg/ddr272	Swiss and Australian samples (European Ancestry) between the ages of 35 and 75
TF	transferrin	rs3811647	A	0.78	https://doi.org/10.1093/hmg/ddr272	Swiss and Australian samples (European Ancestry) between the ages of 35 and 75

Table 2.1 continued

SRPRB	SRP receptor subunit beta	rs1534166	A	0.60	https://doi.org/10.1093/hmg/ddr272	Swiss and Australian samples (European Ancestry) between the ages of 35 and 75
CRYGS	crystallin gamma S	rs1868152	A	1.52	https://doi.org/10.1007/s10519-013-9606-x	Caucasian ancestry; average age: 42.8
KLB	klotho beta	rs28712821	A	0.06	https://doi.org/10.1038/mp.2017.153	European Ancestry from United Kingdom; ages 30 to 69
ADH1B	alcohol dehydrogenase 1B (class I), beta polypeptide	rs145452708	C	0.07	https://doi.org/10.1038/mp.2017.153	European Ancestry from United Kingdom; ages 30 to 69
HFE	homeostatic iron regulator	rs1800562	A	1.72	https://doi.org/10.1093/hmg/ddr272	Swiss and Australian samples (European Ancestry) between the ages of 35 and 75
OPRM1	opioid receptor mu 1	rs73568641	C	1.40	https://doi.org/10.1007/s10519-013-9606-x	Caucasian ancestry; average age: 42.8

Table 2.1 continued

UTP20	UTP20 small subunit processome component	rs57083693	C	0.17	https://doi.org/10.1007/10.1016/j.drugalcdep.2014.05.023	European Descent under the age of 18
ARID4A	AT-rich interaction domain 4A	rs8012947	A	0.03	https://doi.org/10.1038/mp.2017.153	European Ancestry from United Kingdom; ages 30 to 69
RGMA	repulsive guidance molecule BMP co-receptor a	rs12442183	T	1.13	https://doi.org/10.1016/j.biopsych.2017.12.016	European Ancestry; average age 37

Odds Ratio and Beta-weights that were obtained from the literature as effect sizes for the SNPs, were converted to Cohen's D values in order to meaningfully combine the different effect size estimates (Borenstein, Hedges, Higgins, & Rothstein, 2009). The matrix of SNPs coded by the effect alleles (i.e. the allele that when inherited is associated with the risky phenotype or behavior) were multiplied with the corresponding Cohen's D. To illustrate, for the SNP: rs2749097 (Gene: *PGM1*), the effect allele or the allele that is associated with greater substance use frequency is G and the corresponding Cohen's D value is 0.25. If an individual inherited a single G allele then they would get a score of 0.25 (i.e. 0.25*1 copy of the risk allele), if they inherited two G alleles for this SNP, they would get a score of 0.50 (i.e. 0.25*2 copies of the risk allele) for this SNP, and if they inherited no G alleles, then their score for this SNP would be a 0 (i.e. 0.25*0 copies of the risk allele).

The number of alleles for all SNPs that were indicated in the genome-wide association studies as related to higher frequency of substance use (i.e. effect allele) were multiplied with the

corresponding Cohen's D effect size estimates using the same procedure. Subsequently, estimates from all the SNPs were pooled (summed) to obtain a single risk score for substance use for each participant. See Table 2.1 above for a list of genes, SNPs, effect alleles, and corresponding effect size estimates used to create the polygenic risk score.

Covariates

Biological sex and parental education (years of education) were included as covariates. Respondent's highest educational attainment was also included as a covariate. Directed acyclic graphs and previous literature were used to determine covariates (Weng, Hsueh, Messam, & Hertz-Picciotto, 2009).

Analytic Strategy

Step 1: Latent Profile Analysis

Latent profile analysis (Lanza & Cooper, 2016) was used to determine homogenous sub-groups experiencing similar combinations of childhood maltreatment (See Figure 2.2). Respondents were categorized into subgroups based on similar exposures to emotional abuse, neglect, sexual abuse, and physical abuse. These subgroups were used as predictors of the substance use levels and change over time. Three sub-groups emerged from the latent profile analysis, including a normative sub-group with low maltreatment exposure which was the reference sub-group across all subsequent analytic models (described in detail below in the results section). *AIC, BIC, adjusted-BIC,* and *entropy* were used to discern the best class solution as well as replication of models when the number of random starts were increased (i.e., if the models converged on a global solution). Smaller values on relative fit indices such as *AIC, BIC, and adjusted-BIC* are considered better fitting models and entropy closer to1 is indicative of lower error in sub-group membership assignment (e.g., an entropy of 0.95 indicates 5% error in sub-group classification, whereas an entropy of 0.99 indicates a 1% error). Furthermore, the BIC in particular is helpful for discerning best model fit, based on actual and simulated data. Moreover, the large sample size used in this research helps extract smaller relatively stable sub-groups which is typically not possible with smaller data (Nylund-Gibson & Choi, 2018).

Step 2: Substance Use Trajectory

Substance use frequency change was assessed using linear trajectory models and generalized estimating equations to obtain population level trajectories for substance use. An intercept was centered at age 11 and the average annual change in substance use frequency was estimated from ages 11 to 26 (i.e., change in substance per year each year or slope) was (Model 1). Substance use trajectories were then conditioned on the maltreatment sub-groups that emerged from the latent profile analysis to get subpopulation estimates of change over time in substance use for each sub-group.

Step 3: Hypothesis Testing

Next, I estimated the direct association of the childhood maltreatment sub-groups and substance use polygenic risk score, with substance use levels (at age 11) and average annual change over time until age 26 while accounting for the effects of all covariates on both levels and change of substance use over time (Model 2). Next, the substance use polygenic risk score was evaluated as a moderator of the association between sub-groups of childhood maltreatment exposures and substance use levels and trajectory (Model 3) using and interaction between polygenic risk score and maltreatment subgroups. Maltreatment associations with substance use trajectories were probed at different levels of genetic risk: high (+1 *SD* above the mean), low (-1 *SD* below the mean) and medium (mean levels for the sample; Aiken, West, & Reno, 1991). All covariates were included for substance use frequency levels and change over time in Model 3 as well.

SAS statistical software was used for data preparation, Plink v1.9 was used for cleaning and coding genomic data, and Mplus v.7.4 (Muthén & Muthén, 2005) statistical software was used for estimation of analytic models. A maximum likelihood estimator and an integration algorithm was used in Mplus to obtain estimation with robust standard errors in the presence of missing data (Muthén & Muthén, 2005). Add Health created sampling weights were applied to correct for unequal selection bias and a cluster sandwich estimator was used to correct for school-level clustering of individuals (Binder, 1983; Chen & Chantala, 2014). All predictor variables and covariates were grand mean centered prior to analysis (see Figure 2.1) for the analytic model.

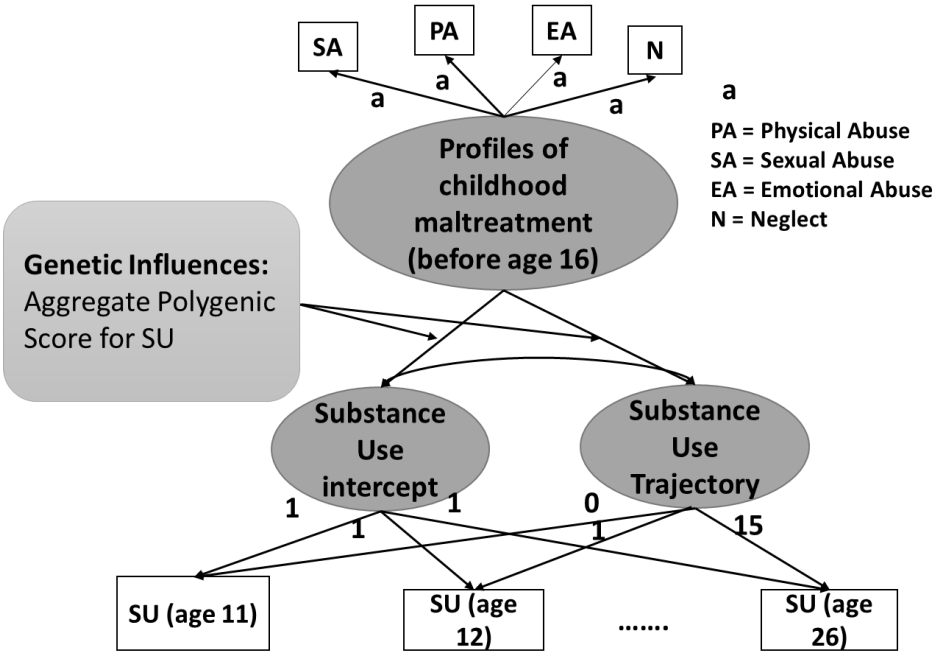

Figure 2.1 Analytic Model

Post-hoc Models

I also tested Model 3 (see above) for substance specific use (i.e. alcohol use frequency, marijuana use frequency, and illicit drug use frequency) at age 11 and over time in a series of post-hoc models

Results

Step 1: Latent Class Analysis

A three sub-group solution was considered optimal for the latent profile analysis. Model fit statistics are summarized in Table 2.2. The three sub-group solution had better overall model fit statistics compared to the two sub-group solution and replicated when random starts were increased. The four sub-group solution did not replicate when random starts were increased. Sub-groups labels were applied for the three sub-group solution and were based on exposure to childhood maltreatment type and frequency - Sub-group 1: Sub-group with high levels of sexual abuse and moderate physical abuse, emotional abuse and neglect (n = 62; high sexual abuse sub-

group); Sub-group 2: Sub-group with high physical abuse and moderate levels of neglect and emotional abuse (*n* = 263; high physical abuse sub-group); and Sub-group 3: Sub-group with low frequency of all maltreatment types (*n* = 2,339; normative sub-group). Figure 2.2 shows the exposure frequency for each maltreatment type for the subgroups and Table 2.3 summarizes the descriptive statistics by each sub-group and for the entire sample. Correlations among study variables are presented in Table 2.4.

Table 2.2 Class enumeration

	AIC	*BIC*	*adj-BIC*	entropy	class distribution
class solution 2-classes	129430.68	129600.54	129524.27	0.99	2%; 98%
class solution 3-classes	113754.88	113924.74	113848.48	1.00	2%; 8%; 90%
class solution 4-classes[1]	110138.05	110343.30	110251.14	0.97	10% ; 86%; 2%; 2%

Note: [1]class solutions beyond 3 classes did not replicate (i.e. the solution was local vs. a global maxima); 3 class solution selected as optimal

Table 2. 3 Descriptive statistics

	Full Sample (n = 2,664)		Sub-group 1: High Sexual Abuse Sub-group (*n* = 62)		Sub-group 2: High Physical Abuse Sub-group (*n* = 263)		Sub-group 3: Normative Sub-group (*n* = 2,339)	
Key Variables	*Mean*	*Std. Dev*	*Mean*	*Std. Dev*	*Mean*	*Std. Dev*	*Mean*	*Std. Dev*
Sexual abuse	0.31	1.56	9.82	2.08	0.18	0.60	0.07	0.36
Physical abuse	1.47	3.13	5.26	4.81	9.71	2.09	0.44	0.99
Emotional abuse	2.22	3.61	5.73	4.89	5.83	4.83	1.69	3.05
Neglect	1.83	3.70	5.20	7.11	4.26	5.74	1.46	3.05
Age Time 1	16.10	1.69	16.05	1.69	16.07	1.56	16.10	1.70
Age Time 2	16.16	1.60	16.04	1.56	16.20	1.48	16.16	1.61
Age Time 3	21.93	1.75	21.82	1.77	21.99	1.61	21.93	1.77
Substance Use Polygenic Risk Score	0.13	0.05	0.12	0.05	0.13	0.05	0.13	0.05
Substance Use Frequency Time 1	4.29	9.27	2.84	4.13	4.54	10.88	4.29	9.13
Substance Use Frequency Time 2	5.30	10.31	2.58	4.96	6.02	10.93	5.28	10.33
Substance Use Frequency Time 3	6.96	10.58	5.08	6.93	8.37	11.83	6.82	10.47
Parent Education (in years)	13.28	2.33	13.35	2.19	13.05	2.27	13.30	2.34
Respondent's Education (in years)	14.27	2.10	13.46	2.28	14.04	1.95	14.32	2.11
Percentages	*Mean*	*Std. Dev*	*Mean*	*Std. Dev*	*Mean*	*Std. Dev*	*Mean*	*Std. Dev*
Gender: Male	47.22%	0.49	11%	0.32	50%	0.50	48%	0.50

Table 2.4 Correlation among study variables

	Substance Use Time 1	Substance Use Time 2	Substance Use Time 3	Parent Education (in years)	Biological Sex	Respondent's Education (in years)	Age Time 1	Age Time 2	Age Time 3	Substance Use Polygenic Risk Score	High Sexual Abuse Sub-group	High Physical Abuse Sub-group
Substance Use Time 1	1	0.43*	0.20*	-0.00	0.07*	-0.09*	0.08*	0.08*	0.06*	-0.03	-0.02	0.01
Substance Use Time 2	-	1	0.25*	-0.01	0.12*	-0.12*	0.15*	0.16*	0.14*	-0.03	-0.04	0.03
Substance Use Time 3	-	-	1	0.08*	0.21*	-0.07*	-0.08*	-0.07*	-0.08*	-0.01	-0.03	0.05
Parent Education (in years)	-	-	-	1	0.02	0.38*	-0.06*	-0.10*	-0.06*	-0.01	0.00	-0.03
Biological Sex	-	-	-	-	1	-0.12*	0.05*	0.08*	0.06*	0.05*	-0.11*	0.02
Respondent's Education (in years)	-	-	-	-	-	1	-0.01	-0.00*	-0.02	-0.04*	-0.06*	-0.04
Age Time 1	-	-	-	-	-	-	1	0.97*	0.98*	0.02	0.00	-0.01
Age Time 2	-	-	-	-	-	-	-	1	0.95*	0.00	-0.01	0.01
Age Time 3	-	-	-	-	-	-	-	-	1	0.016	-0.01	0.01

Table 2.4 Continued

Substance Use Polygenic Risk Score	-	-	-	-	-	-	-	-	-	1	-0.01	0.00
High Sexual Abuse Sub-group	-	-	-	-	-	-	-	-	-	-	1	-0.05
High Physical Abuse Sub-group	-	-	-	-	-	-	-	-	-	-	-	1

*$p < 0.05$

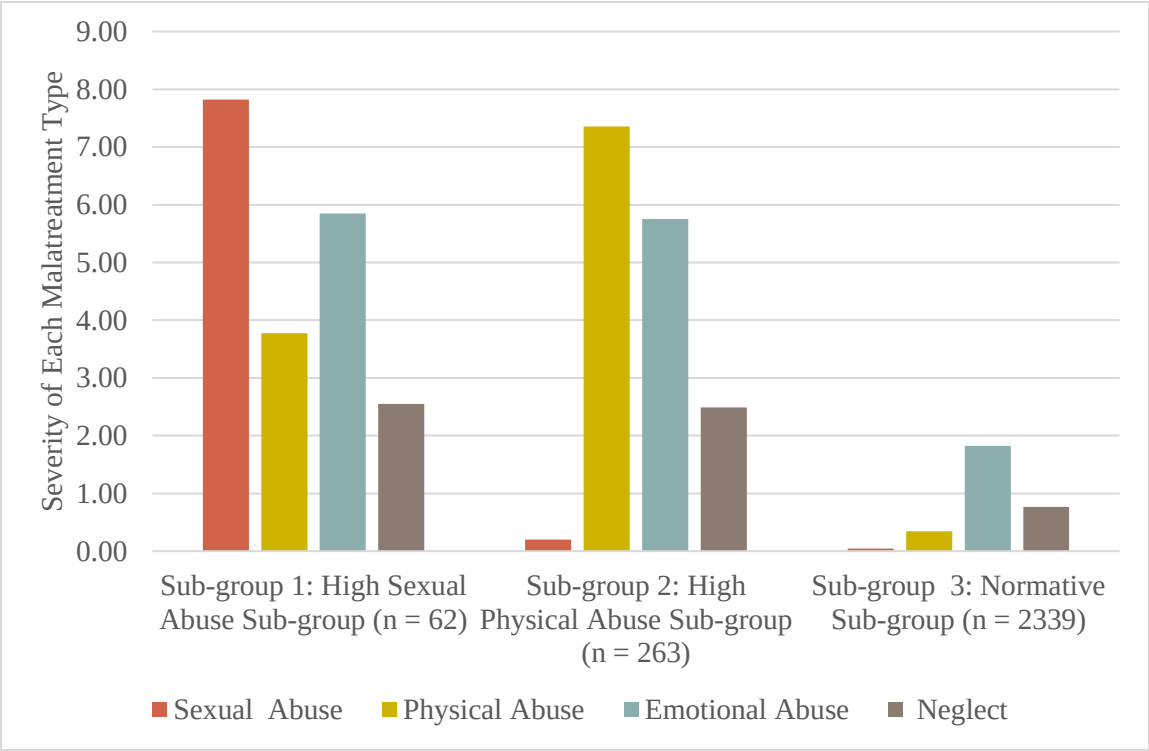

Figure 2.2 Subgroups of childhood maltreatment based on types and severity of exposure

I also tested if exposure to different types of maltreatment frequencies differed across the three sub-groups. The results from this analysis are summarized in Table 2.5. The high sexual abuse sub-group and the high physical abuse sub-group had significantly higher frequency of all maltreatment types compared to the normative sub-group. The high sexual abuse sub-group had significantly higher frequency of childhood sexual abuse exposure and significantly lower frequency of childhood physical abuse exposure compared to the high physical abuse sub-group, but both these sub-groups had similar levels of childhood emotional abuse and neglect exposures.

Table 2.5 Comparison of maltreatment type means by sub-groups

	High Sexual Abuse Sub-group vs. Normative Sub-group				High Physical Abuse Sub-group vs. Normative Sub-group				High Sexual Abuse Sub-group vs High Physical Abuse Sub-group			
	Mean difference	*t*	*df*	*p*	*Mean difference*	*t*	*df*	*p*	*Mean difference*	*t*	*df*	*p*
Physical Abuse	3.53	6.42	55.10	<.001	7.02	44.34	235.55	<.001	-3.49	-6.10	64.30	<.001
Sexual Abuse	7.80	22.63	56.02	<.001	0.13	3.40	238.13	<.001	7.67	22.10	57.45	<.001
Emotional Abuse	4.01	5.72	49.92	<.001	3.99	13.16	227.18	<.001	0.02	0.03	73.59	0.98
Neglect	1.77	3.17	42.34	<.001	1.56	7.23	210.27	<.001	0.21	0.35	54.91	0.73

Step 2: Substance Use Trajectory

Frequency of substance use trajectory for the entire sample is presented in Figure 2.3. On average, adolescents (i.e., the entire sample) reported using substances about 0.25 times ($p < 0.001$) with 0.21 yearly increases in the rate of substance use frequency from age 11 to 26 ($p = < 0.001$). Based on this trajectory, at age 26 respondents were using substances 2.5 times on average. There were maltreatment sub-group specific differences in frequency of substance use trajectories over time. Substance use frequency trajectories by each sub-group is also presented in Figure 2.3.

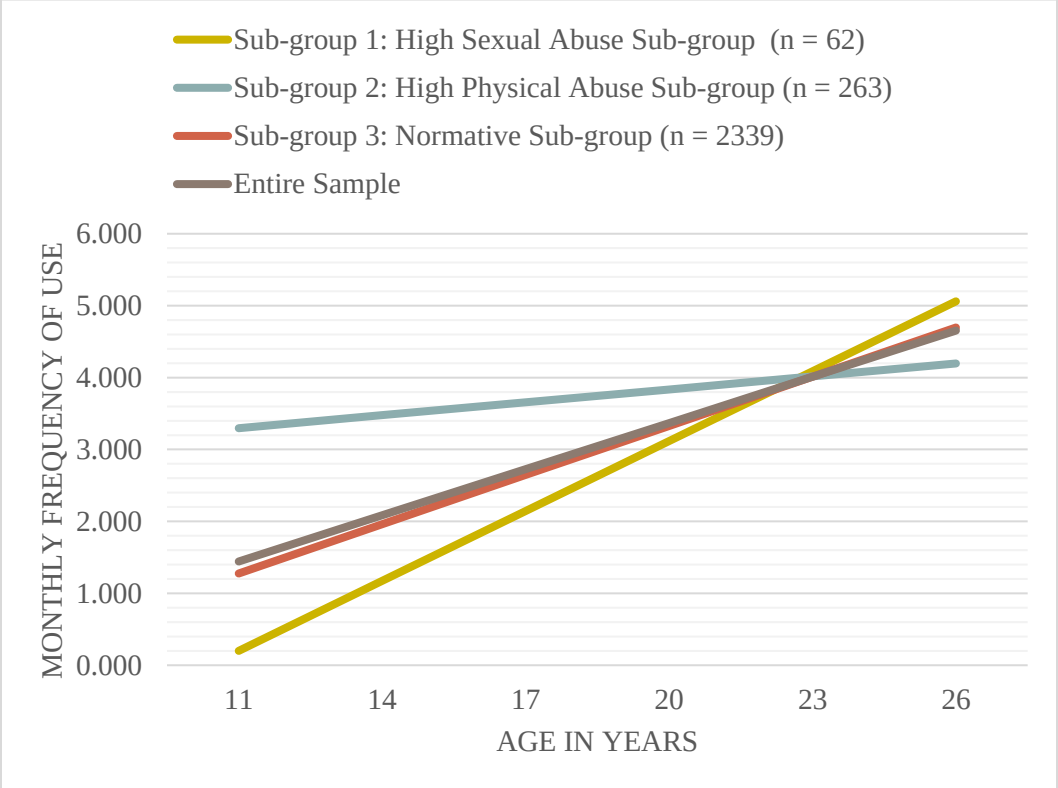

Figure 2.3 Average substance use frequency change over time by maltreatment sub-groups based on severity of four types of maltreatment

The normative sub-group (β = 0.28; $p < 0.001$) had initial frequency of substance use that was different than 0 on average. On average, the normative sub-group also had increases over time in substance use frequency each year from adolescence to young adulthood (β = 0.16; $p < 0.001$). The high sexual abuse sub-group did not have an intercept different from 0 for initial substance use frequency (β = 0.06, $p = 0.88$) but had change over time in substance use frequency (β = 0.29, $p = 0.06$)[2]. In contrast, on average, the high physical abuse sub-group report initial substance use frequency different than 0 (β = 0.59, $p < 0.001$) but no change in substance use frequency over time either (β = 0.03, $p = 0.65$). There was notable variance in substance use frequency change over time (or slopes) for the normative sub-group (σ = 20.74, $p < 0.001$), high sexual abuse sub-group (σ = 10.64, $p = 0.001$), and high physical abuse sub-group (σ = 30.71, $p < 0.001$).

Step 3: Hypothesis Testing

Results from Models 2 and 3 for substance use frequency are summarized in Table 2.6. Neither maltreatment sub-group experienced different levels or change over time in substance use frequency compared to the normative sub-group after controlling on substance use polygenic risk score and other covariates. Average substance use polygenic risk score was associated with slightly lower initial levels of substance use after controlling on maltreatment sub-groups and covariates but did not associate with changes over time in substance use frequency.

Table 2.6 Association of maltreatment sub-groups and genetic risk with initial frequency change in frequency of substance use over time

Initial Substance Use Frequency						
	Model 2			Model 3		
	β	*s.e.*	*p*	β	*s.e.*	*p*
High Sexual Abuse Sub-group	-0.04	0.04	0.23	-0.19	0.03	0.45
High Physical Abuse Sub-group	0.10	0.07	0.15	0.12	0.07	0.11

[2] Please note that marginal *p* values between 0.05 and 0.10 are considered marginally significant for the high sexual abuse sub-group due to the small size of this sub-group in comparison to the normative sub-group.

Table 2.6 continued

Substance Use Polygenic Risk Score	-0.09	0.04	0.03	-0.05	0.05	0.26
Respondent's Education (in years)	-0.12	0.07	0.08	-0.13	0.07	0.05
Parent Education (in years)	-0.01	0.07	0.91	0.03	0.07	0.64
Biological Sex	-0.07	0.05	0.19	-0.07	0.05	0.14
High Sexual Abuse Sub-group *Substance Use Polygenic Risk Score	-	-	-	0.06	0.01	0.00
High Physical Abuse Sub-group *Substance Use Polygenic Risk Score	-	-	-	-0.15	0.01	0.01
Substance Use Frequency Change Over time	β	*s.e.*	*p*	β	*s.e.*	*p*
High Sexual Abuse Sub-group	0.05	0.04	0.22	0.03	0.03	0.34
High Physical Abuse Sub-group	-0.06	0.06	0.30	-0.07	0.06	0.24
Substance Use Polygenic Risk Score	0.05	0.04	0.23	0.01	0.04	0.90
Respondent's Education (in years)	0.05	0.06	0.45	0.06	0.06	0.33
Parent Education (in years)	0.21	0.04	0.00	0.23	0.04	0.00
Biological Sex	0.03	0.06	0.64	0.00	0.05	0.97
High Sexual Abuse Sub-group *Substance Use Polygenic Risk Score	-	-	-	-0.03	0.06	0.02
High Physical Abuse Sub-group *Substance Use Polygenic Risk Score	-	-	-	0.11	0.05	0.02

However, in Model 3, there was an interaction between substance use polygenic risk score and high physical abuse sub-group as well as an interaction between substance use polygenic risk score and high sexual abuse sub-group for average substance use frequency trajectories and initial levels of use.

Specifically, at low (β = 0.09, p = 0.23), medium (β = 0.20, p = 0.89), and high (β = 0.31, p = 0.31) polygenic risk for substance use, members of the high sexual abuse sub-group did not have an initial substance use frequency different than 0. However, at low (β = 0.55, p = 0.01; see Figure 2.4) and medium (β = 0.35, p = 0.02; see Figure 2.5) but not high (β = 0.15, p = 0.73; see Figure 2.5) polygenic risk, the high physical abuse sub-group had an initial substance use level that was different from 0. The significant effects were medium in size.

At low (β = 0.21, p < 0.01; Figure 2.4), medium (β = 0.19, p = 0.01; Figure 2.5) and high levels (β = 0.17, p = 0.08 Figure 2.6) of polygenic risk for substance use, there was an association (albeit a marginal association at high levels) between membership in the high sexual abuse sub-group and substance use frequency change over time. Additionally, at high levels of substance use polygenic risk score, there was an association between the high physical abuse sub-group members (β = 0.21, p < 0.01; Figure 2.6) and substance use frequency change over time.

To elaborate, at high, medium and low levels of polygenic risk score, the high sexual abuse sub-group reported increases in average monthly substance use frequency over time and these yearly increases had a medium effect size. The high sexual abuse sub-group had the highest increases in average monthly substance use frequency at low levels of polygenic risk with an approximate 0.61 increase in average monthly use per year. In comparison, the high sexual abuse sub-group had slower increases in average monthly substance use frequency at high levels of polygenic risk score with approximately 0.25 increase in average monthly substance use frequency per year. At medium polygenic risk for substance use, the high sexual abuse sub-group had a 0.43 average monthly increase per year. Moreover, rate of change over time for the high sexual abuse sub-group were higher than the normative sub-group at low and medium levels of polygenic risk. In contrast, at high polygenic risk the normative sub-group had a greater rate of change in substance use over time such that by the end of the study period the normative sub-group and the high sexual abuse sub-group had similar levels of substance use (i.e., the normative sub-group members caught up with the high sexual abuse sub-group in their levels of substance use frequency by the end of the study when genetic risk was high).

The high physical abuse sub-group demonstrated increases in substance use frequency only at high polygenic risk for substance use. The yearly increase in average monthly substance use frequency was 0.38. The high physical abuse sub-group had the strongest/highest increases in substance use frequency at high polygenic risk score compared to the other two sub-groups at high genetic risk. The effect size estimate for average monthly substance use frequency increases per year was small to medium for the high sexual abuse sub-group and medium for the high physical abuse sub-group.

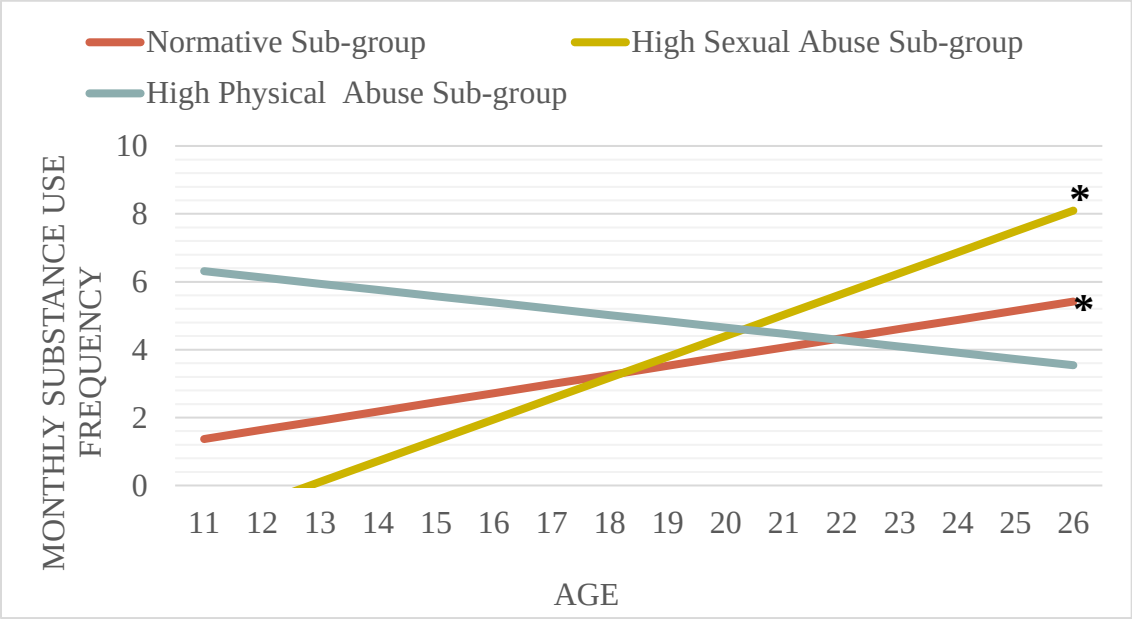

Figure 2.4 Initial levels and change over time in substance use frequency for the three maltreatment sub-groups at low levels of substance use polygenic risk score (i.e., -1 SD). Note: trajectories at $\alpha <= 0.05$ are denoted by *

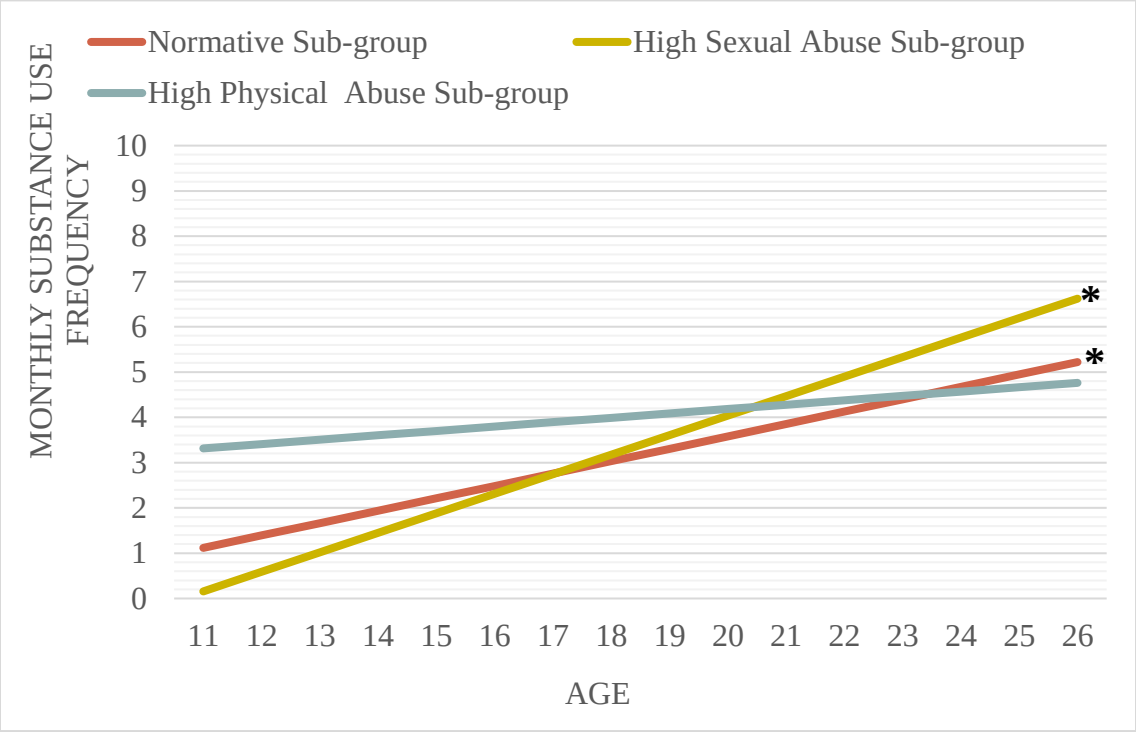

Figure 2.5 Change over time in substance use frequency for the three maltreatment sub-groups at medium levels of substance use polygenic risk score (i.e., mean). Note: trajectories at $\alpha <= 0.05$ are denoted by *

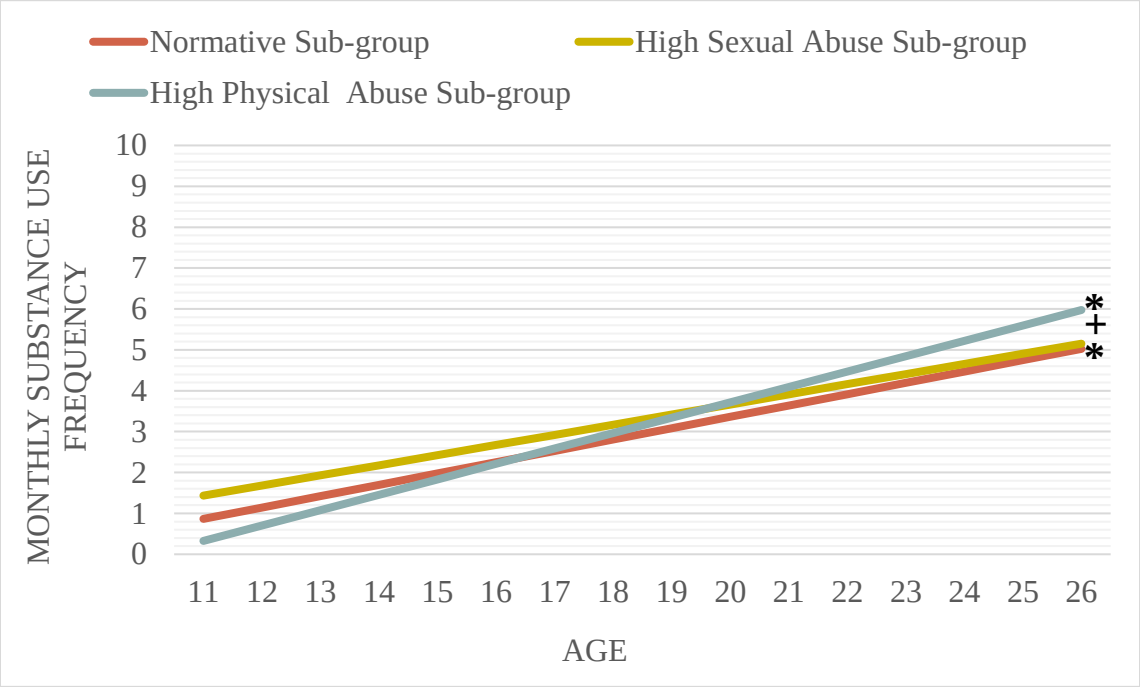

Figure 2.6 Change over time in substance use frequency for the three maltreatment sub-groups at high levels of substance use polygenic risk score (i.e., + 1 SD). Note: trajectories at α = 0.05 are denoted by * and trajectories between α 0.05 and 0.10 are denoted by +

Post-hoc Models

Results from Model 3 for frequency of specific substance (i.e. alcohol, marijuana, and illicit drugs) use are summarized below.

Alcohol Use (Table 2.7)

There was a significant interaction between high sexual abuse sub-group membership and substance use polygenic risk score. Substance use polygenic risk was significantly associated with initial frequency of alcohol use at medium ($\beta = 0.10$, $p = 0.04$), and low ($\beta = 0.14$, $p = 0.02$) but not high ($\beta = 0.06$, $p = 0.13$) levels for the high sexual abuse sub-group. At low and medium levels, the sexual abuse sub-group had frequency of initial levels of alcohol use frequency different than 0 and these effects were small in size.

At low ($\beta = 0.18$, $p < 0.001$; Figure 2.7), medium ($\beta = 0.23$, $p < 0.001$; Figure 2.8), and high ($\beta = 0.28$, $p < 0.001$; Figure 2.9) levels of substance use polygenic risk score, the high sexual abuse sub-group demonstrated increases in average monthly alcohol use frequency and these yearly increases had a medium effect size. The high physical abuse sub-group did not interact with substance use polygenic risk score to associate with alcohol use levels or trajectory.

The high sexual abuse sub-group had increases in alcohol use frequency at low levels of polygenic risk with an approximate 0.52 increase in average monthly use per year. In comparison, the high sexual abuse sub-group had slower increases in average monthly alcohol use frequency at high levels of polygenic risk with approximately 0.08 increases in alcohol use frequency per year. Moreover, increases over time and rate of change over time for the high sexual abuse sub-group were higher at low and medium levels of polygenic risk but not at high levels of polygenic risk. The effects for alcohol use trajectories in the high sexual abuse sub-group were medium in size across levels of polygenic risk score and were similar to the overall findings for substance use for this sub-group.

Table 2.7 Association of maltreatment sub-groups and genetic risk with initial frequency and change in frequency of alcohol use over time

Initial Alcohol Use Frequency			
	β	*s.e.*	*p*
High Sexual Abuse Sub-group	-0.05	0.02	0.00
High Physical Abuse Sub-group	0.08	0.05	0.13
Substance Use Polygenic Risk Score	-0.05	0.05	0.37
Respondent's Education (in years)	-0.11	0.05	0.02
Parent Education (in years)	0.05	0.05	0.37
Biological Sex	-0.09	0.04	0.05
High Sexual Abuse Sub-group *Substance Use Polygenic Risk Score	0.02	0.00	0.00
High Physical Abuse Sub-group *Substance Use Polygenic Risk Score	-0.04	0.05	0.36
Alcohol Use Frequency Change Over time	β	*s.e.*	*p*
High Sexual Abuse Sub-group	0.04	0.02	0.03
High Physical Abuse Sub-group	-0.09	0.05	0.07
Substance Use Polygenic Risk Score	0.06	0.05	0.24
Respondent's Education (in years)	0.11	0.05	0.03
Parent Education (in years)	0.23	0.05	0.00
Biological Sex	0.02	0.06	0.76
High Sexual Abuse Sub-group *Substance Use Polygenic Risk Score	-0.01	0.01	0.06
High Physical Abuse Sub-group *Substance Use Polygenic Risk Score	0.00	0.04	0.98

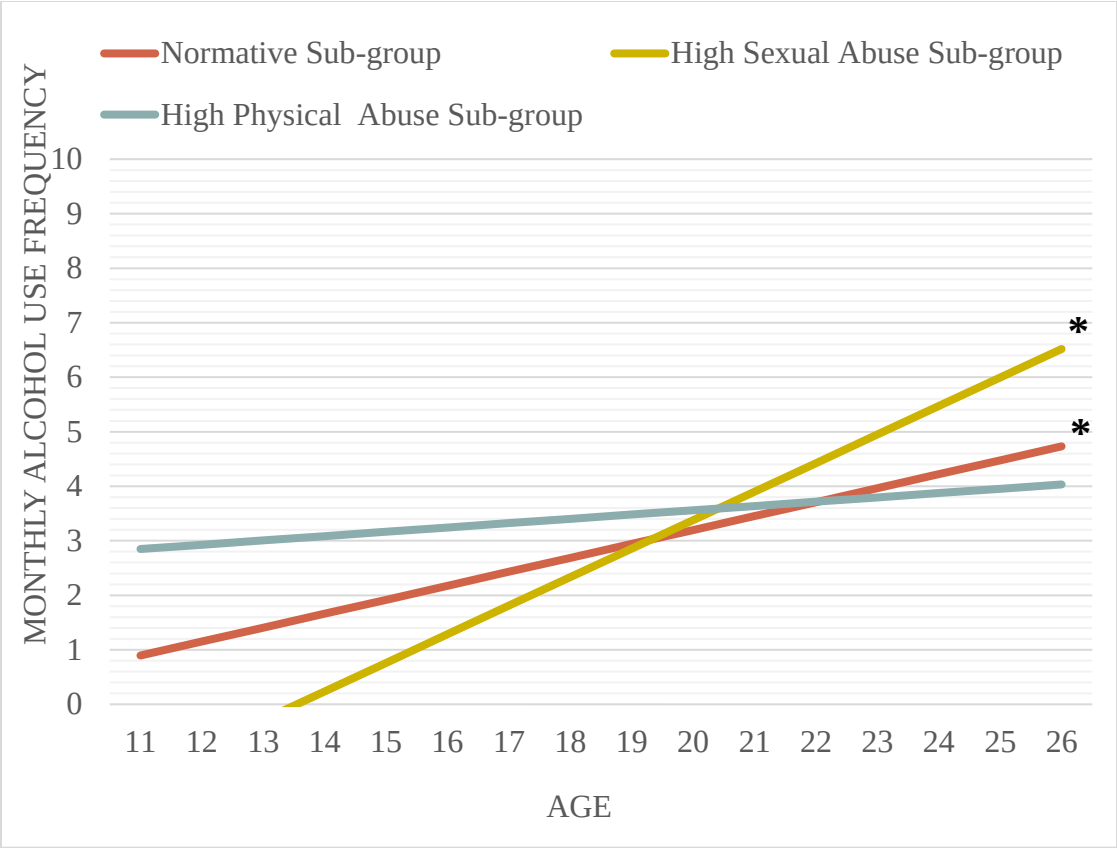

Figure 2.7 Change over time in alcohol use frequency for the three maltreatment sub-groups at low levels of substance use polygenic risk score (i.e., -1 SD). Note: trajectories at $\alpha <= 0.05$ are denoted by *

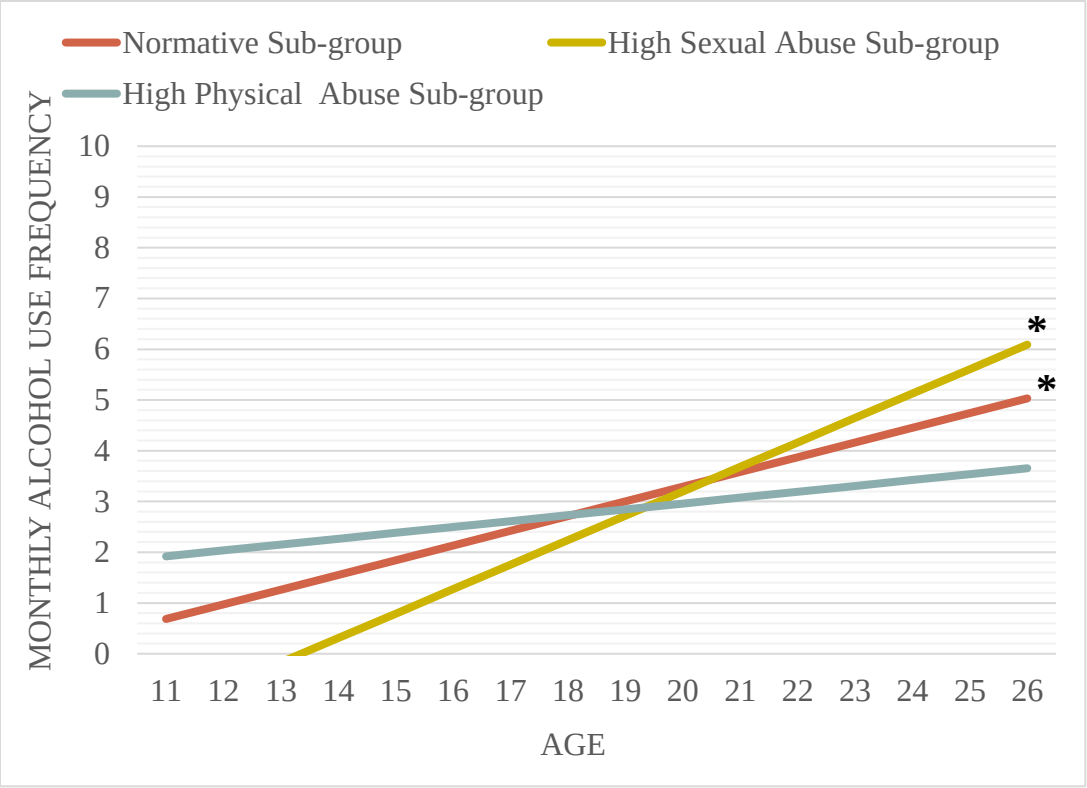

Figure 2.8 Change over time in alcohol use frequency for the three maltreatment sub-groups at mean levels of substance use polygenic risk score (i.e., mean). Note: trajectories at $\alpha <= 0.05$ are denoted by *

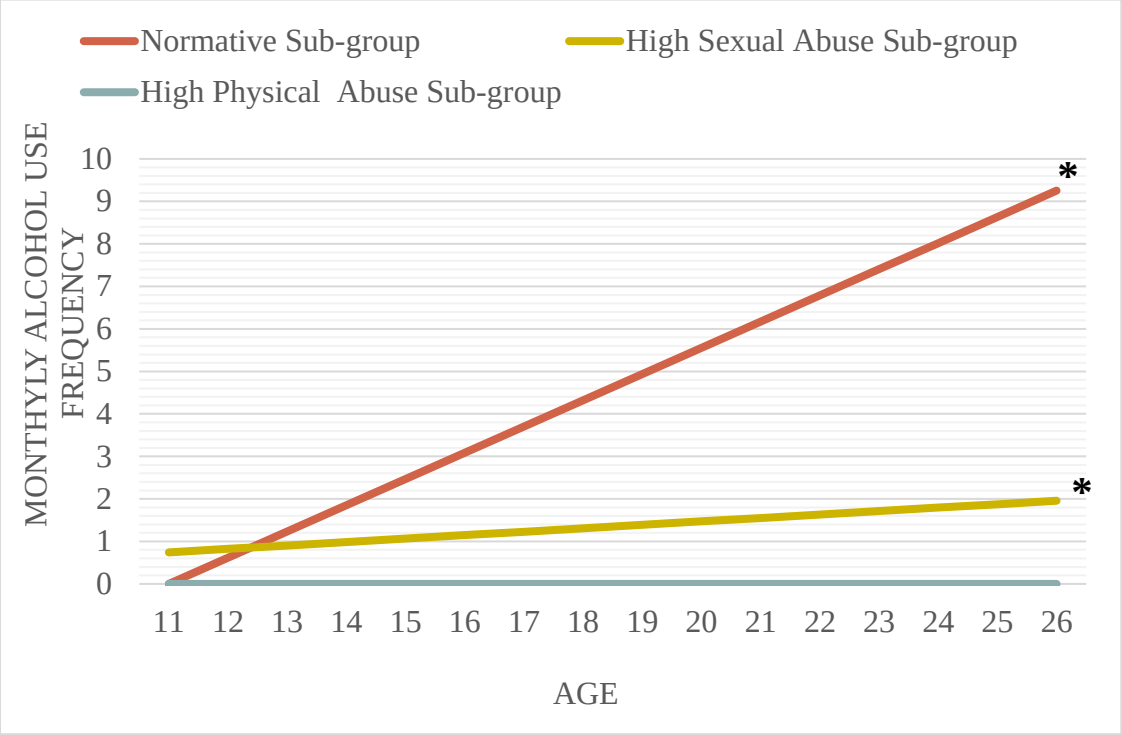

Figure 2.9 Change over time in alcohol use frequency for the three maltreatment sub-groups at high levels of substance use polygenic risk score (i.e.,+1 SD). Note: trajectories at $\alpha <= 0.05$ are denoted by *

Marijuana Use (Table 2.8)

At high substance use polygenic risk, the high sexual abuse sub-group had initial levels of marijuana use frequency (β = 0.36, $p < 0.01$; see Figure 2.10) that was different than 0. The high sexual abuse sub-group did not have initial levels of marijuana use different than 0 at low (β = 0.24, $p = 0.86$) and medium (β = 0.30, $p = 0.11$) levels of substance use polygenic risk. The high physical sub-group did not have an initial level of marijuana use that was different than 0 at high levels (β = 0.08, $p = 0.65$) but did have an initial frequency of marijuana use different than 0 at low (β = 0.62, $p = 0.01$; see Figure 2.11) and medium (β = 0.35, $p = 0.05$; see Figure 2.11) levels of substance use polygenic risk score.

There was a significant interaction between substance use polygenic risk and both maltreatment sub-groups for marijuana use over time (Table 2.8). A high (β = 0.00, $p = 0.04$; see Figure 2.10) substance use polygenic risk, membership in the high sexual abuse sub-group was associated with an average monthly decrease of 0.77 in marijuana use frequency per year. In comparison, the other two sub-groups had increases over time at high polygenic risk score. At high (β = 0.26, $p = 0.01$; see Figure 2.10) substance use polygenic risk, the high physical abuse sub-group had an average monthly increase of 1.14 in marijuana use frequency per year and these increases were higher than the other two sub-groups. Significant effects were medium in size.

Table 2.8 Association of maltreatment sub-groups and genetic risk with initial frequency and change in frequency of marijuana use over time

Initial Marijuana Use Frequency			
	β	*s.e.*	*p*
High Sexual Abuse Sub-group	0.04	0.05	0.37
High Physical Abuse Sub-group	0.10	0.09	0.27
Substance Use Polygenic Risk Score	-0.06	0.07	0.42
Respondent's Education (in years)	-0.09	0.14	0.51
Parent Education (in years)	0.06	0.12	0.62
Biological Sex	-0.03	0.09	0.76
High Sexual Abuse Sub-group *Substance Use Polygenic Risk Score	0.09	0.01	0.00
High Physical Abuse Sub-group*Substance Use Polygenic Risk Score	-0.05	0.02	0.01
Marijuana Use Frequency Change Over time	β	*s.e.*	*p*
High Sexual Abuse Sub-group	-0.04	0.04	0.33
High Physical Abuse Sub-group	-0.02	0.09	0.85
Substance Use Polygenic Risk Score	-0.03	0.08	0.68
Respondent's Education (in years)	-0.03	0.13	0.82
Parent Education (in years)	0.19	0.09	0.04
Biological Sex	-0.03	0.12	0.80
High Sexual Abuse Sub-group *Substance Use Polygenic Risk Score	-0.22	0.08	0.01
High Physical Abuse Sub-group*Substance Use Polygenic Risk Score	0.17	0.07	0.02

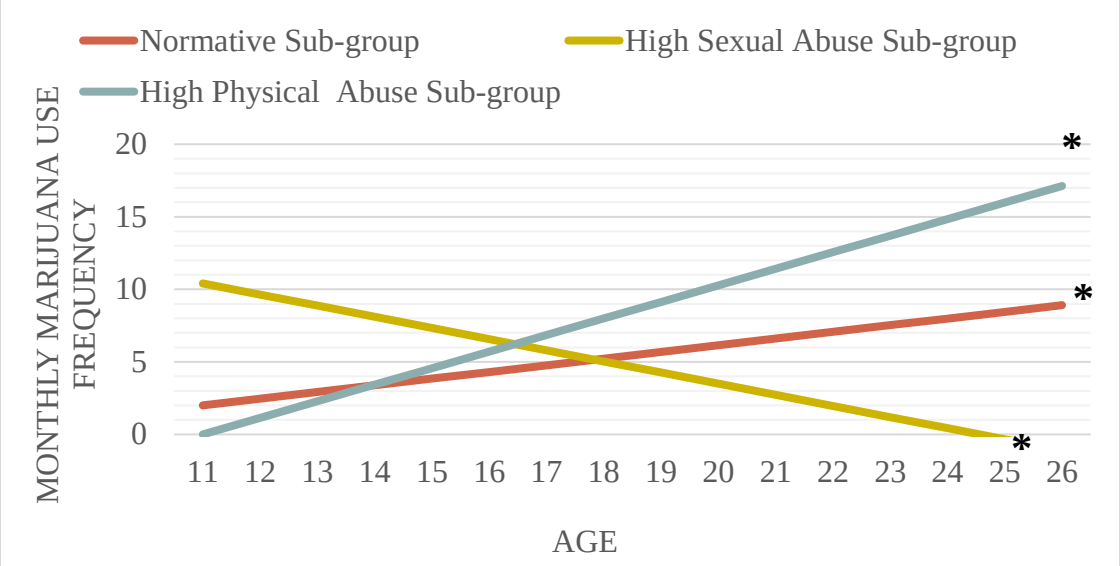

Figure 2.10 Change over time in marijuana use frequency for the three maltreatment sub-groups at high levels of substance use polygenic risk score (i.e.,+1 SD). Note: trajectories at $\alpha <= 0.05$ are denoted by *

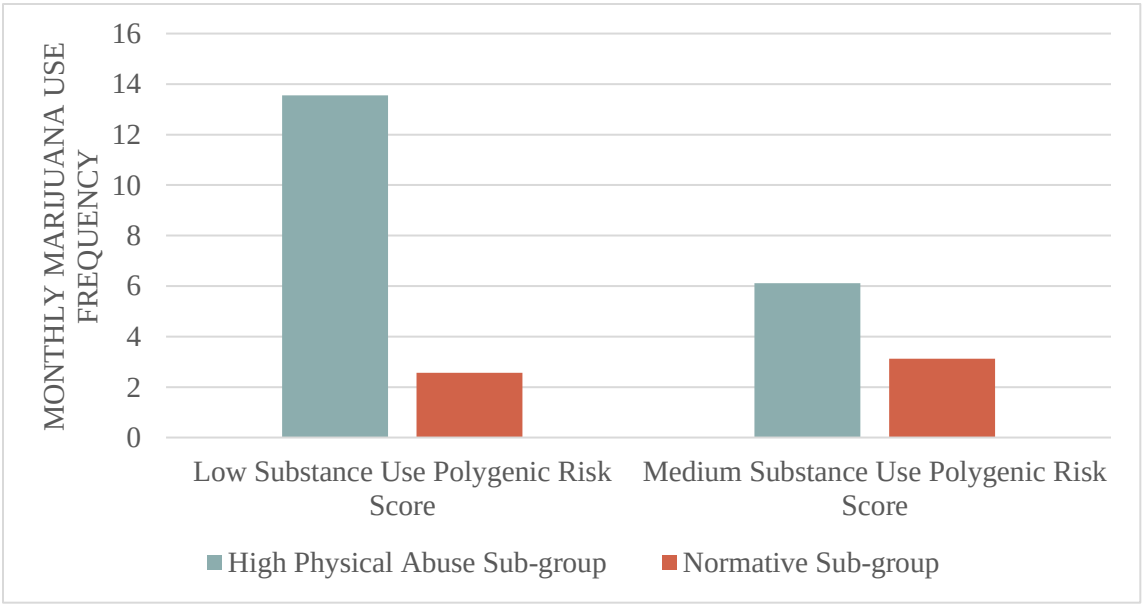

Figure 2.11 Initial marijuana use frequency for significant sub-groups at low and medium levels of substance use polygenic risk score (i.e.,-1 SD and mean)

Illicit Drug Use (Table 2.9)

There was a significant interaction between substance use polygenic risk score and both maltreatment sub-groups (high physical abuse and high sexual abuse) and initial frequency of substance use and change over time in substance use. At low levels of polygenic risk for substance use, the high sexual abuse sub-group had lower initial levels of illicit drug use frequency ($\beta = 0.05$, $p < 0.01$; see Figure 2.11) but saw increases over time in illicit drug use frequency ($\beta = 0.81$, $p < 0.01$; see Figure 2.11). The high sexual abuse sub-group on average had a monthly illicit drug use frequency of 2 times and an increase in average monthly use by 2.25 per year. The effects were small for initial levels but large for change over time.

Additionally, the high sexual abuse sub-group had high initial levels of illicit drug use frequency ($\beta = 1.01$, $p < 0.001$; see Figure 2.12) at high polygenic risk for substance use but had gradual declines in illicit drug use frequency over time ($\beta = -0.57$, $p < 0.01$; see Figure 2.12). The high sexual abuse sub-group had an initial illicit drug use frequency of 22 times and had declines by a factor of 3 in monthly use per year. These effects were large in size.

In contrast, at low polygenic risk for substance use, the high physical abuse sub-group had high initial frequency of illicit drug use ($\beta = 1.13$, $p < 0.01$; see Figure 2.11) and then gradual declines in frequency of use with increases in age ($\beta = -0.45$, $p = 0.01$; see Figure 2.11). At low substance use polygenic risk, the high physical abuse sub-group started out at 18 times of illicit drug use on average but had an approximate decline of 1.45 in average monthly use each year. The effect size for both estimates for the high physical abuse sub-group were medium to large.

Table 2.9 Association of maltreatment sub-groups and genetic risk with initial frequency and change in frequency of illicit drug use over time

Initial Illicit Drug Use Frequency			
	β	*s.e.*	*p*
High Sexual Abuse Sub-group	0.05	0.06	0.43
High Physical Abuse Sub-group	0.19	0.19	0.30
Substance Use Polygenic Risk Score	0.05	0.10	0.64
Respondent's Education (in years)	0.01	0.21	0.97
Parent Education (in years)	-0.28	0.22	0.21
Biological Sex	0.08	0.13	0.54
High Sexual Abuse Sub-group *Substance Use Polygenic Risk Score	0.43	0.04	0.00
High Physical Abuse Sub-group*Substance Use Polygenic Risk Score	-0.50	0.12	0.00
Illicit Drug Use Frequency Change Over time	β	*s.e.*	*p*
High Sexual Abuse Sub-group	-0.08	0.07	0.24
High Physical Abuse Sub-group	-0.11	0.18	0.56
Substance Use Polygenic Risk Score	-0.12	0.14	0.41
Respondent's Education (in years)	-0.13	0.19	0.50
Parent Education (in years)	0.01	0.12	0.95
Biological Sex	0.19	0.18	0.29
High Sexual Abuse Sub-group *Substance Use Polygenic Risk Score	-0.32	0.03	0.00
High Physical Abuse Sub-group*Substance Use Polygenic Risk Score	0.42	0.08	0.00

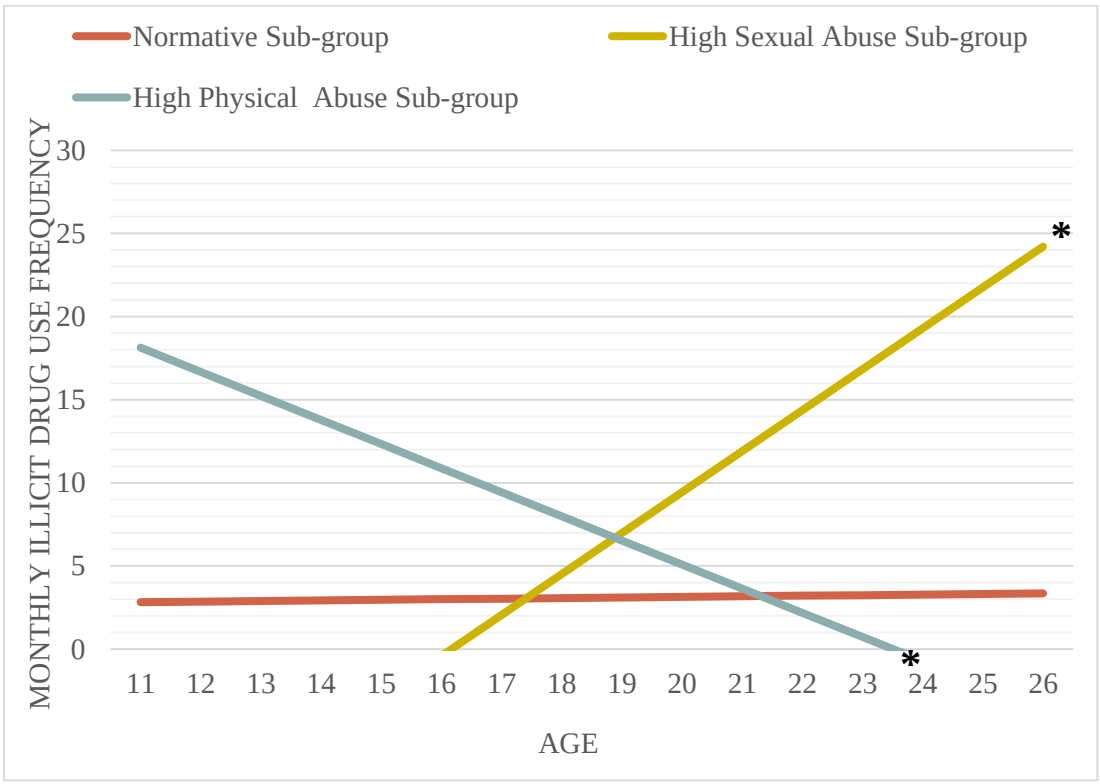

Figure 2.12 Change over time in illicit drug use frequency for the three maltreatment sub-groups at low levels of substance use polygenic risk score (i.e., -1 SD). Note: trajectories at α <= 0.05 are denoted by *

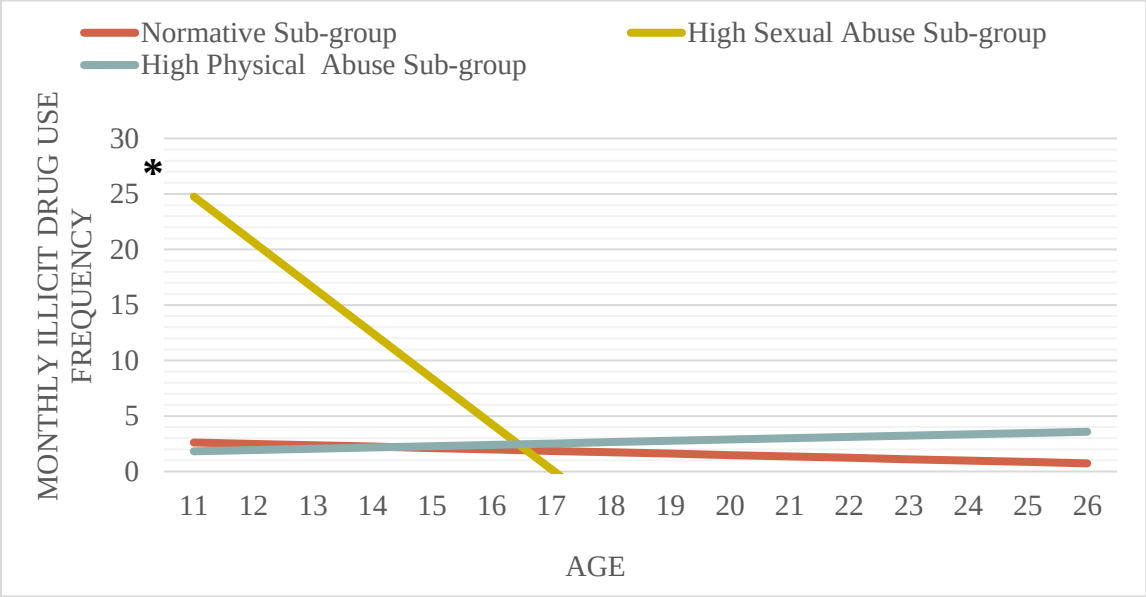

Figure 2.13 Change over time in illicit drug use frequency for the three maltreatment sub-groups at high levels of substance use polygenic risk score (i.e.,+1 SD). Note: trajectories at $\alpha <= 0.05$ are denoted by *

Summary

In summary, the main results from this study include:

1) at high, medium and low levels of polygenic risk, the high sexual abuse sub-group reported increases in substance use frequency over time and these increases were highest at low levels of polygenic risk score for substance use;

2) at high polygenic risk for substance use, members of the high physical abuse sub-group demonstrated faster increases over time in substance use frequency compared to the other two sub-groups;

3) at all levels of polygenic risk, members of the high sexual abuse sub-group demonstrated increases in alcohol use frequency with higher increases at low and medium levels of polygenic risk for substance use;

4) at low substance use polygenic risk, the high physical abuse sub-group demonstrated higher increases in marijuana use frequency over time and in comparison, the high sexual abuse sub-group demonstrated declines in marijuana use frequency at the same (high) level of polygenic risk;

5) at high polygenic risk for substance use, the high sexual abuse sub-group had decreases in illicit drug use frequency over time and the same sub-group had increases in illicit drug use frequency for low polygenic risk;

Discussion

This study pursued two main aims. The first aim was to understand how childhood maltreatment sub-groups determined by multiple types and severity of exposure were associated with change over time in substance use frequency from adolescence into young adulthood. Specifically, it was hypothesized that childhood maltreatment sub-groups with more severe physical abuse, emotional abuse, and neglect would have increases over time in substance use frequency (Hypothesis 1).

The second aim of this study was to determine if substance use polygenic risk score moderated the association of childhood maltreatment sub-groups on change over time in substance use frequency from adolescence into young adulthood (age 11-26). Under this aim, I hypothesized that high substance use polygenic risk score – indicating greater risk for substance use phenotype – would exacerbate substance use change over time for all maltreatment exposures but would be

most critical for sub-groups with more severe exposures to physical abuse, emotional abuse, and neglect (Hypothesis 2).

Childhood Maltreatment Sub-groups

I identified three sub-groups of co-occurring multi-type childhood maltreatment and these findings map onto previous research with a different national sample of middle-aged adults that examined retrospective childhood maltreatment exposure based on both type and severity of exposure (Mishra, Friedman, Mihalec-Adkins, et al., 2019; Mishra & Marceau, 2019). In this study, I replicate these sub-groups of co-occurring childhood maltreatment exposures in a national sample of young adults. Furthermore, the sample in this study recalled maltreatment from more recent exposures compared to the other studies that included a sample of middle-aged adults.

Specifically, based on the findings of this and previous research using large epidemiological samples, it is likely that childhood maltreatment exposures may co-occur in specific clusters in the larger European American population. The first sub-group included individuals that had high severity of physical abuse exposures and moderate severity of childhood neglect and emotional abuse exposures. Moreover, a second sub-group was identified that comprised a small proportion of individuals who were most vulnerable to childhood maltreatment exposures and had high severity of sexual abuse exposures with moderate severity of neglect, emotional abuse, and physical abuse exposures in childhood. The final sub-group was composed of a majority of individuals that reported low childhood maltreatment exposures.

The proportion of individuals in the high physical abuse sub-group (11%) and the high sexual abuse sub-group (3%) map onto child protective services (CPS) data for physical abuse and sexual abuse exposures respectively (Olson & Stroud, 2012). However, CPS data seldom examines childhood maltreatment exposures that may co-occur, and CPS data reveals an increasing trend in childhood neglect exposure over time (Olson & Stroud, 2012). In this epidemiological sample, I did not find a high prevalence of neglect exposures and instead find that it co-occurs with either high rates of physical abuse or sexual abuse exposures. Recently researchers have recommended using large survey data (Christ & Schwab-Reese, 2019) to capture the complex phenomenological dimensions of childhood maltreatment exposures. Based on the findings of this research, I also suggest evaluating overall patterns of correlated childhood maltreatment types along with large

survey-based data to understand the complex nature of childhood maltreatment exposures and to then associate it with outcomes of interest.

Additionally, the maltreatment sub-groups identified indicate that certain co-occurring maltreatment exposures may be recalled more frequently among individuals (irrespective of their age) compared to others and may, therefore, be more detrimental for outcomes throughout life. A large body of literature on trauma-focused research indicates that events that are perceived as more traumatic are often remembered or recalled throughout life and can be more detrimental for life long outcomes such as substance use (Center for Substance Abuse Treatment, 2014). Therefore, it is likely that the recollection of specific co-occurring childhood maltreatment exposures may largely depend on the trauma induced by such experiences and could potentially be more detrimental for negative outcomes – reiterating the need for better survey data to understand the complex experiences of maltreatment exposures as recommended by Christ and Schwab-Reese (2019).

Furthermore, the high prevalence of neglect in CPS data could also be a direct factor of poverty since the items used to evaluate childhood neglect comprise of the parent's inability to provide or monitor the child. Therefore, neglect exposures may not produce lived experiences of trauma such as those experienced by childhood victims of physical, sexual, or emotional abuse. It may be safe to preliminarily presume that low levels of trauma associated with childhood neglect exposure may make recalls of such exposures less likely in adulthood.

Therefore, both researchers and CPS should include an evaluation of multiple co-occurring childhood maltreatment exposures in order to understand the complexity of such exposures. Such an evaluation may lead to a better understanding of which specific combination of maltreatment exposures are detrimental for which outcomes and may help CPS workers develop prevention plans specific to co-occurring maltreatment sub-groups based on empirical findings.

Childhood Maltreatment and Substance Use Trajectory

In line with previous research, I also find overall increases in substance use frequency over time from adolescence to young adulthood in the unconditional model (Johnston et al., 2016; Pine et al., 1999). Specifically, adolescents in the full sample reported a substance use frequency of 1.44 times at age 11 and approximately 4.7 times by age 26. Given that high levels of substance use frequency during adolescence is associated with high levels of substance use frequency in

young adulthood (Johnston et al., 2016; Park-Lee & Tice, 2017; Pine et al., 1999), my findings reiterate the ubiquitous nature of adolescence for substance use development over time.

Unexpectedly, membership in the high physical abuse sub-group was not associated with initial levels or change over time in substance use frequency in the unconditional model (i.e. conditioned only on maltreatment sub-group membership). For the high sexual abuse sub-group, there was a low frequency of substance use at age 11 (almost 0 use) which rapidly grew over time to approximately 5 times use by the end of the study, and this sub-group had the highest frequency of substance use by age 26 among the three sub-groups. Childhood sexual abuse exposures may be associated with more trauma symptoms and psychological problems (discussed in detail below), which may result in a rapid progression of substance use over time.

However, in model 2 the inclusion of substance use polygenic risk score and covariates suggests that neither sub-group had an initial substance use frequency that was different than 0 or a change in substance use frequency over time. Therefore, hypothesis 1 was not supported. Nonetheless, there were significant interaction effects in support of hypothesis 2 which are discussed below.

Interaction between Co-occurring Childhood Maltreatment and Substance Use Polygenic Risk Score

Findings for High Physical Abuse Sub-group

The findings for research hypothesis 2 were supported. Based on results from previous research (Huang et al., 2011), it was anticipated that individuals who had severe exposure to a combination of physical abuse, emotional abuse, and neglect would demonstrate the most detrimental substance use trajectory over time particularly at high genetic risk. I found that members of high physical abuse sub-group who reported high severity of co-occurring physical abuse and moderate severity of emotional abuse and neglect exposures had the most detrimental substance use development over time at high (+1 *SD*) substance use polygenic risk. This finding indicates that combined exposure to physical abuse, emotional abuse, and neglect together with high genetic risk or biological predisposition towards substance use act in an interactive manner to influence substance use development during critical developmental periods (i.e., adolescence to young adulthood).

According to the diathesis-stress model (Belsky & Pluess, 2009; Ingram & Luxton, 2005), it is critical to understand both biological predispositions and environmental risks simultaneously and to understand their synergistic effects for the presence and development of risky outcomes. Within the context of childhood maltreatment, combined environmental stressors such as those experienced by the physical abuse sub-group seem to influence negative outcomes through biological mechanisms, and there is some empirical support for this assumption. In one recent study, that found similar maltreatment exposure sub-groups, the high physical abuse sub-group was associated with mental health problems in adulthood through physiological processes and in contrast, the high sexual abuse sub-group transmitted its influences on adult mental health outcomes through more psychological processes (Mishra & Marceau, 2019).

A closer examination of specific substances used helped further clarify the findings from hypothesis 2 for the high physical abuse sub-group. To illustrate, the high physical abuse sub-group at high genetic risk displayed similar patterns for marijuana use change over time (i.e., similar to the overall substance use trajectory at high genetic risk). Members of the high physical abuse sub-group demonstrated faster increases in marijuana use frequency from ages 11 to 26 at high genetic risk for substance use in comparison to the other sub-groups and marijuana use for this sub-group may be propelling the overall substance use trajectory at high genetic risk.

Drug use, including marijuana use, may require some personal affinity towards seeking out these substances. Even though recreational marijuana use is legal in a few states in the U.S. currently, it remains illegal in a majority of states and at the federal level. Moreover, the three waves of data used in this study come from a time period when the recreational use of marijuana was illegal across all states. Therefore, it can be speculated that seeking out illegal substances may be rooted in a biologically affinity or desire towards using such substances.

There is also some evidence suggesting that deviant peer affiliation during adolescence could be a factor influencing marijuana use among physically maltreated youth (Fergusson, Swain-Campbell, & Horwood, 2002). Whereas the deviant peer hypothesis may be true for the high initial levels of marijuana use in the high physical abuse sub-group at low and medium polygenic risk, such an explanation for change over time in marijuana use at high polygenic risk for the high physical abuse sub-group seems implausible for two reasons. First, if deviant peer affiliation was a contributor of marijuana use development over time for members of the high physical abuse sub-group, then this sub-group would demonstrate higher initial levels of marijuana use frequency at

high genetic risk during adolescence – when such peer influences are more likely. Second, if deviant peer affiliation was a contributor for high marijuana use, then the high physical abuse sub-group would demonstrate increasing trajectories of marijuana use at all levels of genetic risk. Similarly, based on these reasons, other potential ecological factors as contributors of substance and marijuana use progression for the high physical abuse sub-group also seem unlikely.

Therefore, a broader biosocial model of development is critical for understanding how maltreatment exposures such as those experienced by the high physical abuse sub-group transmit their influence on substance use frequency over time.

Findings for High Sexual Abuse Sub-group

Contrary to the findings for the high physical abuse sub-group, the findings for hypothesis 2 for the high sexual abuse sub-group largely point towards a stronger and more ubiquitous influence of the social environment on substance use development. Specifically, the high sexual abuse sub-group had increasing substance use frequency over time across all levels of polygenic risk and the overall substance use trajectories for this sub-group may largely be driven by their alcohol use frequency over time (i.e., the alcohol use trajectories were identical to the substance sue trajectories across levels of polygenic risk). Given, alcohol is more socially acceptable and is available for legal purchase, it may be used more frequently by members of the high sexual abuse sub-group to alleviate the trauma associated with sexual abuse experiences. Furthermore, since the high sexual abuse sub-group demonstrated increases in substance use and alcohol use over time at all levels of genetic risk, their substance use behaviors may not depend on genetic risk. If genetic risk for substance use was more influential for this sub-group compared to environmental (i.e., maltreatment) exposure, then I would have found higher increases in substance use (and alcohol use) change over time at high genetic risk. However, the sexual abuse sub-group had higher increases in overall frequency of substance and alcohol use at low and medium genetic risk compared to high genetic risk. Therefore, maltreatment exposure but not genetics may be largely influencing the trajectories for overall substance use and alcohol use for the high sexual abuse sub-group.

A potential explanation for such maltreatment related substance and alcohol use change over time could be the presence of other psychological mechanisms. It has been well-established in previous literature that childhood sexual abuse is associated with high levels of internalizing

and mental health problems throughout life (Murray, Nguyen, & Cohen, 2014). Additionally, parental alcohol use often co-exists with childhood sexual abuse (Dube, Anda, Felitti, Edwards, & Croft, 2002). Within the social learning theory, victims of childhood sexual abuse may learn from their parents to use alcohol as a coping mechanism to deal with the trauma, distress, and psychological burdens of sexual abuse. The easy availability of alcohol could further add to this problem. Additionally, as members of this sub-group develop a tolerance for alcohol, they may increase their alcohol use frequency over time to get the same feelings of high as before (Sinha, 2008). However, these mechanisms linking the high sexual abuse sub-group to substance use and alcohol use frequency increases over time are merely speculative and will need examination in future research.

Two additional findings for the high sexual abuse sub-group that were contradictory from the general findings for substance and alcohol use over time need to be clarified further. First, at high polygenic risk for substance use, the high sexual abuse sub-group demonstrated high levels of initial marijuana and illicit drug use and gradual declines in both substances over time.

The trauma induced by sexual abuse is generally considered much more severe than those inflicted by other forms of childhood maltreatment (Murray, Nguyen, & Cohen, 2014). Moreover, the high sexual abuse sub-group had the most disadvantaged exposure to childhood maltreatment in this study - as indicated by high levels of sexual abuse combined with moderated levels of all other childhood maltreatment types. Therefore, it is likely that this sub-group experienced higher levels of trauma compared to the other two sub-groups, which when combined with a high genetic risk for substance use was associated with higher initial levels of drug use (marijuana and illicit drug use).

As indicated earlier, that drug-seeking behaviors may be more strongly linked to a personal (or biological) affinity due to these substances being less socially acceptable, illegal, and harder to obtain compared to alcohol. Further, within the adverse childhood experiences literature, there is growing evidence for other family dysfunctions such as parental drug use may co-exist with childhood sexual abuse exposures (Dube, Anda, Felitti, Edwards, & Croft, 2002). Particularly, parental substance use may provide easier access to marijuana or other illicit substances during adolescence, which may lead to early experimentation with these substances among members of the high sexual abuse sub-group and particularly among those with a high genetic risk for substance use. This early experimentation could largely be driven by the high levels of trauma

induced by sexual abuse exposure compared to high physical abuse exposure. Similarly, sexually maltreated youth tend to report higher levels of deviant peer affiliation (Fergusson & Horwood, 1999), which together with the trauma induced by sexual abuse could also lead to earlier experimentation with marijuana and illicit drugs (compared to the high physical abuse sub-group) for genetically vulnerable adolescents.

Taken together, these environmental factors along with high genetic risk may lead to initially higher illicit and marijuana use frequencies. However, due to the initial high levels of marijuana and illicit drug use, it may be equally likely that individuals in this sub-group may experience interventions such as removal from home by Child Protective Services (CPS) or other intervention by family members or school personnel (e.g., grandparents or teachers) to address these problematic (as indicated by a high frequency of use) levels of drug use in adolescence. Such interventions may be protective for future substance use and could explain declines in marijuana and illicit drug use over time for this sub-group even when genetic susceptibility towards substance use remains high. In comparison, the high physical abuse sub-group may demonstrate low levels of initial substance and marijuana use at high genetic risk because this sub-group may experience lower trauma than the high sexual abuse sub-group, which may not be linked to early experimentation and initiation. However, given the genetic vulnerability and in the absence of other early interventions, the high physical abuse sub-group may demonstrate gradual increases over time in marijuana and substance use. Once again, the assumptions made about sub-group differences are speculative and will need to be clarified in future research.

The second finding that needs attention is the low initial levels of illicit drug use for the high sexual abuse sub-group at low genetic risk, which gradually increases over time. As indicated before, sexual abuse exposures in childhood are linked to higher deviant peer affiliations and the presence of parental drug use problems (Dube, Anda, Felitti, Edwards, & Croft, 2002; Fergusson & Horwood, 1999). Since individuals with low genetic risk for substance use may not have a biological predisposition towards drug use, their later initiation to these substances may be due to social learning and not due to combination of trauma and high genetic risk. According to the social learning theory (Bandura & Walters, 1977), children may also mimic their parents' or peers' behavior which could be another potential factor explaining the progression of illicit drug and marijuana use in the high sexual abuse sub-group with low genetic risk. Another alternative explanation could be that members of the high sexual abuse sub-group are at a greater risk for

intimate partner violence in adolescence and young adulthood (Murray et al., 2014) which could lead to a double-dose of trauma, eventually leading to the use of illicit substances as a means to cope with and to deal with the distress associated with such trauma (Murray et al., 2014). Moreover, there is some evidence suggesting a 1) link between physical intimate partner violence victimization and illicit drug use and 2) an association between physical intimate partner violence perpetration and illicit drug use (Buller et al., 2014; Faulkner et al., 2014; Gilbert et al., 2012; Goldstein, 1985; Kaysen et al., 2007; Kilpatrick et al., 2000; Madruga et al., 2017). Together these findings are suggestive of higher use of illicit drug among victims of physical intimate partner violence with a history of childhood sexual abuse and greater availability of such illicit drugs to victims of physical intimate partner violence due to their violence perpetrating partner's use of illicit drug.

Additionally, as highlighted above, mental health problems may be a potential mechanism for increases in subsequent drug use over time. Moreover, the substance use polygenic risk score which was created as a global index for overall genetic risk for substance use, may not provide sufficient coverage for marijuana, alcohol, and illicit drug use and findings in the opposite direction than those captured by the polygenic risk score is typically an indication of low power (Dudbridge, 2013). A final and perhaps most plausible explanation for the irregular findings for illicit drug use is the overall low endorsement of illicit drug use in this sample. On average at each time point, only 211 individuals reported the use of illicit drugs and this number is even smaller for the high sexual abuse sub-group ($n \sim 10$ at each time point). Therefore, the findings for illicit drugs may not be trustworthy and may just be a chance finding for the high sexual abuse sub-group. Replication of these findings with larger samples of illicit drug users will be necessary.

It will also be imperative for future research to examine additional pathways to better understand the association between high sexual abuse sub-group membership and substance use (and use of specific substances) while accounting for genetic risk. Findings from previous research have shown that high sexual abuse sub-group membership may be associated with depressive symptoms in adulthood via psycho-social pathways and in comparison, the high physical abuse sub-group was associated with depressive symptoms through biological pathways (Mishra & Marceau, 2019). In fact, I do find that biological (i.e., genetic) pathways were particularly salient for the high physical abuse sub-group and were associated with increases in substance use

frequency over time. Similarly, it is likely that psychosocial factors may explain the associations between high sexual abuse sub-group membership and substance use frequency over time.

In summary, mitigation efforts for the high sexual abuse sub-group can be focused on prevention of substance use, alcohol use, and illicit drug use and can be implemented uniformly for all individuals (Torkamani, Wineinger, & Topol, 2018) who report similar maltreatment exposures since increases over time for substance use in this sub-group are most likely linked to environmental risks. However, for the high physical abuse sub-group future prevention efforts should increase the dosage of intervention for individuals who have high genetic risk (Torkamani et al., 2018) for substance use since this sub-group of individuals experience a double dose of risk (i.e. maltreatment x high genetic risk).

Limitations

The findings of this research are informed by several limitations. First, this study is restricted to those with European American ancestry. Although the large sample size of this study and the use of survey methods (weight and clustering) used to correct for selection bias allow us to generalize findings for substance use patterns from adolescence to young adulthood among European Americans. However, replication of findings will be necessary with other ancestries using polygenic risk score that are representative of substance use genetic risk for that ancestry. A common way to use polygenic risk score in analyzing sub-groups with different ancestries is to create ancestry specific polygenic risk score and to evaluate associations and moderations for these sub-groups separately (Braudt & Harris, 2018; Dudbridge, 2013). This approach has been recommended particularly for the Add Health sample (Braudt & Harris, 2018). Several genome-wide association studies are currently being conducted to understand genes that may carry a risk for substance use in different ancestral sub-groups and should be utilized in future research. Second, I use SNPs from multiple genome-wide association studies to capture substance use genetic risk. It is still likely that the substance use polygenic risk score does not encompass genetic risk for substance use entirely (i.e. lack of coverage for substance use phenotype and may be underpowered). Therefore, replication of these findings with the same gene set in different samples and using extended gene sets is imperative. Third, I use retrospective childhood maltreatment data, which may suffer from under-reporting and does not indicate substantiated childhood maltreatment exposure. However, previous research has shown a strong link between retrospective maltreatment

reports and health outcomes throughout life (Suglia, Clark, Boynton-Jarrett, Kressin, & Koenen, 2014). Moreover, there is also a moderate association between prospective and retrospective reports of childhood maltreatment (Tajima, Herrenkohl, Huang, & Whitney, 2004), with retrospective reports typically downwardly biased (i.e. under-reported; Ferraro, Schafer, & Wilkinson, 2016). However, future studies should use prospective childhood maltreatment exposure data and compare their findings to those of the present research. Finally, the use of secondary data does not allow for understanding more problematic substance use such as substance use disorders or addictions. Future research should evaluate the aims of the present study with clinical samples of adolescents of more problematic substance use behaviors.

Conclusion

Even with these limitations, the present study has several merits. To my knowledge, no other study has examined the differential impacts of multi-type childhood maltreatment exposures while accounting for severity of exposure on substance use change over time during critical developmental periods - adolescence to young adulthood. I also evaluate the potential exacerbating role of genetic risk for substance use. This study, therefore, provides a first understanding of 1) which combination of childhood maltreatment exposures interact with genetic risk for substance use to influence the progression of substance use frequency over time, and 2) which combination of childhood maltreatment exposures by themselves may be detrimental for substance use over time even when genetic risk is low.

Existing research has demonstrated that high severity of physical abuse, emotional abuse, and neglect can associate with higher frequency of substance use (Huang et al., 2011), but these findings have not been extended to the evaluation of co-occurring childhood maltreatment exposures and substance use trajectories while simultaneously understanding genetic influences. The findings of this research are, therefore, unique and establish that individuals with high severity of physical abuse and moderate severity of emotional abuse and neglect types of maltreatment, are susceptible to increased substance use frequency over time (as well as increased marijuana use frequency over time) but only when they have a high genetic predisposition for substance use.

In contrast, individuals with high severity of sexual abuse exposure and moderate severity of emotional abuse, physical abuse, and neglect exposures are not only most vulnerable in terms of their childhood maltreatment exposures but also exhibit greater increases in substance use and

alcohol use at all levels of genetic risk. This second sub-group of individuals also has increases in illicit drug use at low genetic risk. The findings for this high sexual abuse sub-group illustrate a more pervasive influence of environmental factors over genetics.

With polygenic risk scores becoming more commonly used to predict susceptibility to specific negative phenotypes including substance use frequency (Torkamani et al., 2018), the inclusion of such a probabilistic model based on genetic susceptibility can be particularly critical for understanding the influence of adversity on changes in outcomes over time. Particularly, research has demonstrated that understanding for which individuals' high genetic risk can be more detrimental can lead to more precise clinical efforts to mitigate those problems (Torkamani et al., 2018).

CHAPTER 3: STUDY 2

In chapter 2, I presented results on how maltreatment sub-groups based on both type and severity of exposure were associated with substance use change from adolescence to young adulthood. In this chapter, I empirically examined the association between maltreatment sub-groups (based on similar exposure to types and frequency of maltreatment) and substance use in young adulthood and subsequent physical intimate partner violence perpetration in adulthood. Once again, I brought to these analyses genetic risk for substance use as a moderator of these associations. I also evaluated substance specific (i.e. alcohol use, marijuana use, and illicit drug use) mediation in post-hoc models in this chapter. Additional supplementary models for the interaction between childhood maltreatment sub-groups and substance use frequency in young adulthood and moderated-moderation by genetic predisposition on physical intimate partner violence perpetration were also tested.

Target Journal: Child Maltreatment

Title: Association of childhood maltreatment exposure with physical intimate partner violence perpetration through substance use: Testing moderation by genetic risk

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Abstract

In this study, the mediating role of substance use frequency during young adulthood in the association between co-occurring childhood maltreatment exposure and physical intimate partner violence perpetration in adulthood was tested. Genetic risk for substance use was also tested for the direct pathway from childhood maltreatment exposure to substance use frequency within the mediation model. Data for this study came from The National Longitudinal Study of Adolescent to Adult Health (Add Health; n = 2,664). Latent profile analysis was used to estimate childhood maltreatment sub-groups, product of coefficient method was used to test the mediation model and moderated-mediation model was used to test genetic moderation. There was a lack of direct association between the maltreatment sub-groups and substance use frequency in young adulthood, and maltreatment sub-groups and physical intimate partner violence perpetration in adulthood. Moreover, results indicated that substance use frequency in young adulthood did not act as a mediator between maltreatment exposure in childhood and physical intimate partner violence perpetration in adulthood. Moreover, genetic risk as measured by a multifaceted genetic risk score did not moderate the association between childhood maltreatment sub-groups and substance use within the mediation model.

The negative impacts of childhood maltreatment are not only prevalent during childhood but can manifest well into adulthood and include problems such as higher substance use frequency and more physical intimate partner violence perpetration (Banny, Cicchetti, Rogosch, Oshri, & Crick, 2013; Chaffin, 1996; Famularo, Kinscherff, & Fenton, 1992; Hussey, Chang, & Kotch, 2006; Kaufman, 1991; Kessler et al., 2010; Moran, Vuchinich, & Hall, 2004; Mullen, Martin, Anderson, Romans, & Herbison, 1996; Myers & Prescott, 2000; Shackman & Pollak, 2014; Shonkoff et al., 2012; Tapert, Aarons, Sedlar, & Brown, 2001). Moreover, greater substance use frequency has also been linked to more aggressive behaviors such as physical intimate partner violence perpetration in adulthood (Madruga et al., 2011). In addition to the influence of environmental exposures such as childhood maltreatment, there is evidence suggesting a genetic basis for substance use behaviors (Bühler et al., 2015). However, several critical gaps remain in our knowledge regarding the inter-relatedness of childhood maltreatment, substance use, and physical intimate partner violence perpetration and the role of substance use genetics on these associations. Therefore, in the present study, I disentangle: 1) how childhood maltreatment (before age 18) may influence substance use frequency during young adulthood (ages 18-26) and physical intimate partner violence perpetration later in adulthood (ages 24-32); 2) how substance use frequency during young adulthood (ages 18-26) explains the association between childhood maltreatment exposure (before age 18) and physical intimate partner violence perpetration later in adulthood (ages 24-32); and 3) how genetic predisposition for substance use could be a potential modifying factor of the direct effects of childhood maltreatment exposure (before age 18) on substance use frequency in young adulthood (ages 18-26) within the mediation model.

Child Maltreatment and Physical Intimate Partner Violence Perpetration

Childhood maltreatment is implicated in the "cycle of violence" or intergenerational transmission of violence (Tunstall & Gover, 2017). Victims of childhood maltreatment are almost three times more likely to be arrested for violent crimes and have a greater likelihood of being perpetrators of physical intimate partner violence as adults compared to their non-maltreated peers (Whitfield, Anda, Dube, & Felitti, 2003; Widom & Wilson, 2015). In particular, physical abuse, sexual abuse, and exposure to more than one childhood maltreatment type have been linked to a greater likelihood of physical intimate partner violence perpetration (Whitfield et al., 2003). Moreover, in the sample used for this research, there were no sex differences in physical intimate

partner violence perpetration (Renner & Whitney, 2010). Both men and women in this sample perpetrated physical intimate partner violence at the same rates (Renner & Whitney, 2010).

According to social learning and social cognitive theories, violence perpetration including physical intimate partner violence is resultant of learned behaviors during childhood such as exposure to childhood maltreatment (Bandura, 1986; Bandura & Walters, 1977). Children exposed to maltreatment may accept violence as a normative part of close relationships and may model these behaviors due to social learning and conditioning (Bandura, 1986; Widom & Wilson, 2015). Within social cognitive and social learning theories, children learn maladaptive relationship patterns from their parents, and it is believed that maltreated children learn to accept aggression and violence as a normative part of social interactions and intimate relationships (Akers, 2017; Bandura, 1986; Bandura & Walters, 1977). Through learning, modeling, and conditioning, individuals with childhood maltreatment exposure may display aggressive behaviors within their intimate partner relationships as adults (Akers, 2017; Bandura, 1986; Bandura & Walters, 1977). According to attachment theory, childhood maltreatment may lead to maladaptive internal working models of relationships, which can then lead to the expression of hostility in ambiguous interpersonal interactions (Ainsworth, Blehar, Waters, & Wall, 1978; Bowlby, 1973, 1988; Widom & Wilson, 2015) which may include perpetration of physical intimate partner violence (Widom & Wilson, 2015).

Links between Child Maltreatment to Substance Use

Young adulthood is considered an important period for substance use and in a recent epidemiological study, there was a 39% prevalence of substance use among young adults under the age of 29 (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2016). Substance use frequency is more widespread among young adults with exposure to childhood maltreatment compared to those without such exposures (Narendorf & McMillen, 2010). Among maltreated youth, substance use is seen as a coping mechanism to deal with the strain of childhood maltreatment exposure (Oshri, Tubman, & Burnette, 2012). Specifically, the social cognitive theory has been used to explain the links between childhood maltreatment exposure and substance use frequency in young adulthood. According to this theory, childhood maltreatment exposure can lead to feelings of stress, and to alleviate this stress, coping mechanisms such as substance use behaviors develop. Furthermore, substance use behaviors are maintained not only due to their

effectiveness in alleviating stress but also to prevent the negative effects (e.g., withdrawal) resulting from the discontinuation of such behaviors and prolonged use can often lead to higher frequency of use to get the same level of satisfaction (Akers, 2017; Bandura, 1986; Bandura & Walters, 1977).

In a nationally representative sample, 47.7% of youth with childhood maltreatment exposure reported using substances (Traube, James, Zhang, & Landsverk, 2012), a number that is much larger than national averages of 39% (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2016). The association of both specific childhood maltreatment types (physical abuse, emotional abuse, and sexual abuse; Moran et al., 2004; Rodgers et al., 2004) and multiple childhood maltreatment exposures (i.e. presence of more than one childhood maltreatment) with higher substance use frequency have been found in previous research (Moran et al., 2004; Rogers, McKinney, & Asberg, 2018). Specifically, emotional abuse, physical abuse, neglect, multiple forms of childhood maltreatment, and the co-occurrence of emotional and physical abuse have been associated with higher substance use frequency in adulthood (Berzenski & Yates, 2011; Finkelhor, Turner, Shattuck, & Hamby, 2013; Moran et al., 2004; Rogers et al., 2018). However, no study has examined the extent to which co-occurring childhood maltreatment types based on severity of exposures influence substance use in young adulthood. Such an evaluation is important since certain combinations of maltreatment exposures such as exposures to high severity of physical abuse, neglect, and emotional abuse combined may be more detrimental for substance use frequency (Huang et al., 2011) compared to other multitype or co-occurring maltreatment exposures that do not include physical or emotional abuse exposures (or low severity of exposure for these two types). This study focuses on the joint impact of co-occurring childhood maltreatment exposures based on severity and type and its association with substance use frequency in young adulthood and subsequent physical intimate partner violence perpetration.

Links between Substance Use Frequency to Physical Intimate Partner Violence Perpetration

Substance use frequency plays a significant role in the higher perpetration of physical intimate partner violence among young adults (i.e. higher frequency of use has been linked to greater intimate partner violence perpetration; Madruga, Viana, Abdalla, Caetano, & Laranjeira, 2017). Particularly, for individuals with a history of childhood maltreatment exposure, substance

use frequency is associated with physical intimate partner violence perpetration (Faulkner et al., 2014). Even with these well-established associations, less is known about the role of substance use frequency in young adulthood on the association between co-occurring childhood maltreatment types and severity and physical intimate partner violence perpetration. Within the social cognitive theory, substance use frequency may act as a trauma-related coping strategy for adult victims of childhood maltreatment (Akers, 2017; Bandura, 1986; Bandura & Walters, 1977). And, within this same theory individuals may attribute (rationalize) their aggressive behaviors to substance use (Akers, 2017; Bandura, 1986; Bandura & Walters, 1977). The social cognitive theory also theorizes the interconnectedness of social experiences (e.g., childhood maltreatment), coping skills (e.g., substance use), and cognitive processes (e.g., rationalizing physical intimate partner violence perpetration). Therefore, based on research evidence and the social cognitive theory, substance use frequency in young adulthood may explain the association between co-occurring childhood maltreatment exposure and physical intimate partner violence perpetration.

Genetic Influence on Substance Use and Gene-Environment Interactions

Even though exposure to environmental factors such as childhood maltreatment exposure has been studied extensively to determine their effects on substance use frequency, no previous study (with exception to the studies evaluated in this dissertation) has evaluated genetic risk for substance use as a moderator of the maltreatment-substance use association. Substance use is a health behavior problem that is susceptible to genetic vulnerabilities (Bühler et al., 2015), and twin and adoption studies demonstrate that nearly 50% of variance in substance use is attributable to genetic influences (Duaux, Krebs, Loo, & Poirier, 2000). Recent developments in molecular genetic research have demonstrated that single nucleotide polymorphisms or SNPs - the most commonly occurring genetic variants - are major contributors of substance use inheritance. In single nucleotide polymorphisms, a specific allele (or effect allele) which when inherited is associated with increased risk for a disease or phenotype (e.g. substance use), replaces the ancestral allele that does not result in the phenotype of interest (Bühler et al., 2015). This effect allele typically contributes to phenotypic risk such as substance use problems (Bühler et al., 2015). Moreover, substance use like other complex phenotypes is attributed to the presence of multiple genes of small effects that span over a large genomic area (i.e. polygenic risk; Salvatore et al., 2014). Given the high heritability of substance use, it becomes necessary to understand how

genetic risk for substance use interacts with childhood maltreatment exposure to influence substance use frequency during young adulthood.

Accumulating evidence demonstrates that environmental and genetic influences for substance use are not transmitted in isolation and these factors of influence interact (G x E) with one another to exert their influence on substance use behaviors (Knopik et al., 2016). To illustrate, negative parenting (Creemers et al., 2011), poor parental supervision (Enoch, 2012), and exposures to traumatic life events and stress (Brody et al., 2012; Meyers et al., 2013), each interact with genetic influences for substance use to influence substance use phenotypes. These findings fit well within the diathesis-stress model (Ingram & Luxton, 2005).

Specifically, within a diathesis-stress framework, genetic risk can exacerbate the influence of childhood maltreatment exposure on substance use frequency (Ingram & Luxton, 2005). To illustrate, individuals with the most vulnerable profile of childhood maltreatment (based on severity and type) who also have high genetic risk for substance use, will display higher frequency of substance use in young adulthood compared to individuals with low genetic risk for substance use (Ingram & Luxton, 2005). Such moderation by substance use genetic risk also has implications for the maltreatment-physical intimate partner violence cycle. To elaborate, higher substance use frequency due to the interaction of specific combinations of childhood maltreatment exposures and high genetic risk for substance use will likely increase physical intimate partner violence perpetration by increasing frequency of substance use in young adulthood. In contrast, the interaction of low genetic risk with the same combination of maltreatment exposure will likely produce lower substance use frequency, which may then associate with lower levels of physical intimate partner violence perpetration. Therefore, even when the environmental risk is the same, different levels of genetic risk will interact differently with this environmental risk to influence substance use frequency in young adulthood which could then potentially explain the levels of physical intimate partner violence perpetration in adulthood.

Present Study

To address the gaps in present knowledge, the aims of this study are as follows (see Figure 3.1):

Aim 1. Evaluate substance use frequency in young adulthood (ages 18-26) as a mediator between childhood maltreatment (prior to age 18) sub-groups identified by types and frequency of exposure and physical intimate partner violence perpetration later in adulthood (ages 24-32).

Aim 2. Test the simultaneous influence of childhood maltreatment sub-groups X genetics (indicated by polygenic risk score for substance use) on substance use frequency in young adulthood (ages 18-26) and its association with subsequent likelihood of physical intimate partner violence perpetration (ages 24-32; i.e. moderation by substance use polygenic risk score of the direct pathway from childhood maltreatment sub-groups to substance use frequency in young adulthood within the mediation model).

Individuals will be classified into sub-groups based on their similar co-occurring types and severity of childhood maltreatment. Based on previous research, it is expected that one sub-group will have high levels of sexual abuse exposure along with relatively high levels of other childhood maltreatment exposures (Petrenko, Friend, Garrido, Taussig, & Culhane, 2012). It is also likely that one sub-group will have high levels of all childhood maltreatment exposures except sexual abuse and another sub-group will have only high levels of sexual abuse exposure (Higgins & McCabe, 2001). The direct effects of the sub-groups will be estimated on physical intimate partner violence perpetration and moderation between polygenic risk for substance use and sub-groups of childhood maltreatment will be used to estimate substance use frequency in young adulthood. Finally, substance use frequency in young adulthood will be tested as a mediator between childhood maltreatment sub-groups and physical intimate partner violence perpetration while accounting for genetic moderation for substance use on the direct pathway from each sub-group to substance use frequency within a single moderated-mediation model.

It is hypothesized that more severe co-occurring childhood maltreatment sub-groups will have a direct association with higher levels of physical intimate partner violence perpetration in adulthood and more substance use frequency in young adulthood (Hypothesis 1). It is also hypothesized that substance use frequency in young adulthood will mediate the association between childhood maltreatment sub-group, such that more severe, co-occurring types of childhood maltreatment exposures will be associated with higher frequency of substance use and

high frequency of substance use in young adulthood will then be associated with greater (or higher levels) physical intimate partner violence perpetration in adulthood (Hypothesis 2). Finally, it is hypothesized that genetic risk for substance use will exacerbate the influence of certain childhood maltreatment sub-groups on substance use frequency in young adulthood (Hypothesis 3) within the mediation model in Hypothesis 2.

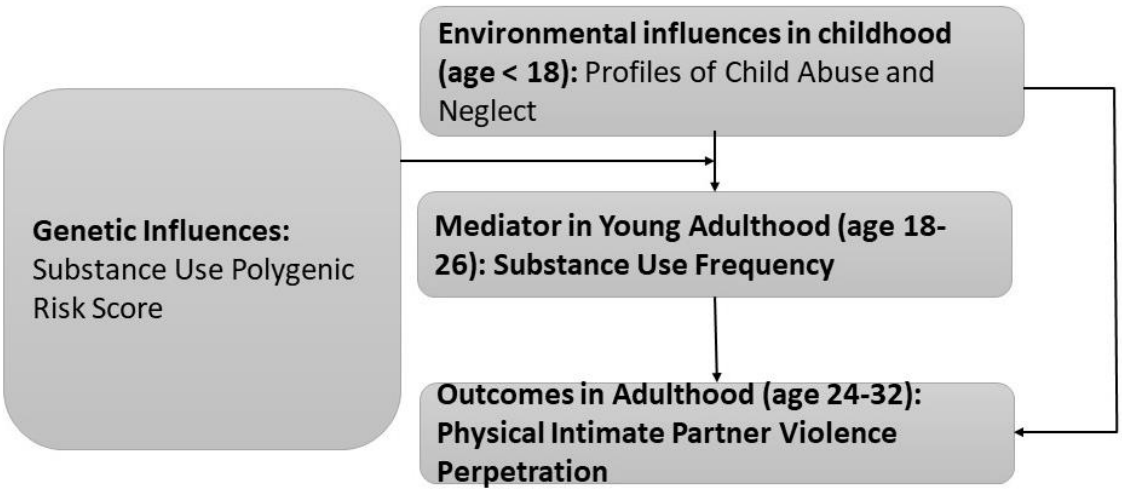

Figure 3.1 Analytic model

Methods

The National Longitudinal Study of Adolescent to Adult Health (Add Health; Harris, 2013) was used to test hypothesized pathways. Add Health sample comprises of a cohort of adolescents (N = 20,743) who were between 7th and 12th grade at the beginning of the study 1994-95 and had a sampling design that was clustered (i.e. students recruited from same schools) with unequal selection. Four waves of data were collected between 1994 and 2008. Face-to-face interviews and computer-assisted in-person interviews were used to collect data at waves 1-4, DNA archival data was extracted from those that consented (n = 12,234). The present study utilizes a sub-sample of 2,664 European Americans from the DNA archival data (n = 6,822 European Americans in the main sample) with retrospective childhood maltreatment reports. Specifically European Americans were included in the sample because of differences by ancestry in allele inheritance and following recommendations from previous research and by the directors of the data used in this research (Braudt & Harris, 2018; Dudbridge, 2013).

Measures

Child Maltreatment

Childhood maltreatment prior to age 18 was measured retrospectively at waves 3 and 4. Four types of childhood maltreatment were assessed: physical abuse, sexual abuse, emotional abuse, and neglect. Responses were coded as frequency of exposure (e.g. 1 = one time, 2 = two times, 3 = three to five times, 6 = six to ten times, 11 = more than 10 times) at each wave. Since physical abuse, sexual abuse, and neglect consisted of the same item assessed at both waves 3 and 4, an average frequency of exposure across the two waves was used for these childhood maltreatment types. The emotional abuse domain consisted of only one item that was assessed at wave 4. Overall exposure to each type of childhood maltreatment was used to estimate latent profiles of sub-groups with similar maltreatment exposure as outlined below.

Substance Use Frequency

Marijuana and illicit drug use (LSD, PCP, ecstasy, mushrooms, speed, ice, heroin, or pills) frequency within the last 30 days (i.e. no. of times used) was assessed at wave 3, when the

respondents were between the ages of 18 and 26 or young adults and were self-reported by respondents. Alcohol use frequency was assessed for last year use and was re-coded to monthly use to mimic the other two substance use scales. The alcohol use scale was treated as a continuous variable and conservative values for monthly use frequency were created (e.g. if a respondent reported drinking 2-3 times a month, these values were coded at the conservative estimate of 2 times a month). Average substance use was assessed by creating an average score across all items at wave 3. The re-coding of this scale mimicked that from previous research used to evaluate substance use (Litwiller & Brausch, 2013; Park-Lee & Tice, 2017), with higher frequency of use indicating higher levels of substance use behavior.

Physical Intimate Partner Violence Perpetration

Self-reported items originated in the Add Health study (Harris, 2013) were used to assess physical intimate partner violence perpetration in the last 12 months at wave 4 when the respondents were adults between the ages of 24 and 32. Three items were used to assess physical intimate partner violence perpetration and included: how often the respondent's has done the following to their partner in the past 12 months: 1. caused physical injury, 2. thrown things or threatened violence and 3. hit, slap or kicked. Items were scored from 0 (never) to 6 (more than 20 times). A sum score was created to index total physical intimate partner violence perpetration ($\alpha = 0.75$).

Substance Use Polygenic Risk Score

A genotype platform of Illumina HumanOmni1-Quad chi and the imputation data are from the HRC r1.1 2016 reference panel was conducted by Add Health researchers at wave 3. Substance use related genes were obtained from multiple previous genome-wide studies (a total of 18 genome-wide studies were used to get substance use related genes; see chapter 1 for this full list) and were used to create a substance use polygenic risk score. This approach was used to get a larger genomic area coverage for substance use, instead of use more traditional methods of gene selection such as just using a single genome-wide association study. The genome-wide studies included in this study were those that conducted genome-wide associations for overall substance use, as well as for alcohol use, marijuana use, illicit drug use and substance use biomarkers.

Specifically, single nucleotide polymorphisms or SNPs of specific genes were used to create the substance use polygenic risk score. I only included single nucleotide polymorphisms that were significant at the genome-wide significance levels ($p < 5 \times 10^{-8}$) in the genome-wide studies. The initial list comprised 34 SNPs.

Appropriate quality control measures were applied to the original list of SNPs as previously recommended and included: 0 SNPs were dropped after test of missingness at the individual level (threshold >.01), 0 SNPs were dropped for test of missingness at the each marker (threshold >.01), 0 SNPs were dropped after test of minor allele frequency (threshold <.01), 13 SNPs were dropped after the test of Hardy-Weinberg exact test, 1 SNP was dropped after the test of linkage disequilibrium (threshold >.3), and 5 SNPs were removed that did not have an effect size estimate (Marees et al., 2018).

Following quality control measures, the final polygenic risk score consisted of SNPs located in or close to the following 14 genes from 5 genome-wide studies (see Table 3.1 for the final list of SNPs included). The effect allele (i.e. is the allele which when inherited is considered to influence the risk phenotype) was multiplied with the corresponding effect size estimates obtained from the different genome-wide studies for each SNP from which the genes were obtained and then summed across all the genes/SNPs to create a single composite substance use polygenic risk score (Borenstein, Hedges, Higgins, & Rothstein, 2009). Since the effect size estimates from the genome-wide association studies included both beta weights and odds ratios, I used previous recommendations to convert these beta weights and odds ratio to a Cohen's D score in order to combine these effect size estimates in a meaningful way and to have a common overall effect size (Borenstein et al., 2009).

Table 3.1 Gene list for substance use polygenic risk score

Gene	Descriptive Name	SNP	Effect Allele	Cohen's D	GWAS Study	Sample
PGM1	phosphoglucomutase 1	rs2749097	G	0.25	https://doi.org/10.1093/hmg/ddr272	Swiss and Australian samples (European Ancestry) between the ages of 35 and 75
GCKR	glucokinase regulator	rs11127048	G	0.07	https://doi.org/10.1038/mp.2017.153	European Ancestry from United Kingdom; ages 30 to 69
PECR	peroxisomal trans-2-enoyl-CoA reductase	rs7590720	G	0.17	https://doi.org/10.1073/pnas.0911109107	European-American and African-American ancestry; ages 18-77
CADM2	cell adhesion molecule 2	rs9841829	G	0.04	https://doi.org/10.1038/mp.2017.153	European Ancestry from United Kingdom; ages 30 to 69
TF	transferrin	rs1799899	A	0.90	https://doi.org/10.1093/hmg/ddr272	Swiss and Australian samples (European Ancestry) between the ages of 35 and 75
TF	transferrin	rs3811647	A	0.78	https://doi.org/10.1093/hmg/ddr272	Swiss and Australian samples (European Ancestry) between the ages of 35 and 75
SRPRB	SRP receptor subunit beta	rs1534166	A	0.60	https://doi.org/10.1093/hmg/ddr272	Swiss and Australian samples (European Ancestry) between the ages of 35 and 75
CRYGS	crystallin gamma S	rs1868152	A	1.52	https://doi.org/10.1007/s10519-013-9606-x	Caucasian ancestry; average age: 42.8

Table 3.1 continued

KLB	klotho beta	rs28712821	A	0.06	https://doi.org/10.1038/mp.2017.153	European ancestry from United Kingdom; ages 30 to 69
ADH1B	alcohol dehydrogenase 1B (class I), beta polypeptide	rs145452708	C	0.07	https://doi.org/10.1038/mp.2017.153	European ancestry from United Kingdom; ages 30 to 69
HFE	homeostatic iron regulator	rs1800562	A	1.72	https://doi.org/10.1093/hmg/ddr272	Swiss and Australian samples (European Ancestry) between the ages of 35 and 75
OPRM1	opioid receptor mu 1	rs73568641	C	1.40	https://doi.org/10.1007/s10519-013-9606-x	Caucasian ancestry; average age: 42.8
UTP20	UTP20 small subunit processome component	rs57083693	C	0.17	https://doi.org/10.1007/10.1016/j.drugalcdep.2014.05.023	European descent under the age of 18
ARID4A	AT-rich interaction domain 4A	rs8012947	A	0.03	https://doi.org/10.1038/mp.2017.153	European Ancestry from United Kingdom; ages 30 to 69
RGMA	repulsive guidance molecule BMP co-receptor a	rs12442183	T	1.13	https://doi.org/10.1016/j.biopsych.2017.12.016	European Ancestry; average age 37

GWAS - Genome-wide association study;

Covariates

Biological sex, parental education (years of education), and respondent's highest educational attainment were included as covariates and age of the respondent was included as a time-varying covariate. Covariate selections were based on previous research and directed acyclic graphs (Weng, Hsueh, Messam, & Hertz-Picciotto, 2009).

Analytic Strategy

Latent Profile Analysis

Latent profile analysis was conducted to estimate sub-groups with similar childhood maltreatment exposure based on type of exposure and frequency of exposure for each type of maltreatment. Probability of class membership based on joint exposures and frequency was used to classify individuals into specific classes. A 3-class solution was optimal with the normative sub-group with low maltreatment exposure across all types was used as the reference sub-group in subsequent analysis (details provided in the results section). I used the AIC, BIC, adjusted-BIC and entropy as fit indices to discern optimal class solution as well as theoretical reasons to guide my final model choice (i.e. a combination of patterns found in previous research and model fit indices; Nylund-Gibson & Choi, 2018). The BIC especially has repeatedly emerged as one the most stable indicators of model fit both in simulation studies and in real world examples (Nylund-Gibson & Choi, 2018). Specifically, AIC, BIC, and adjusted BIC that are lower are indicative of better model fit as is an entropy closer to 1. Probability of class membership based on joint exposures and frequency was used to classify individuals into specific classes.

Direct and Indirect Effects

Models were estimated wherein maltreatment sub-groups stemming from the latent profile analysis directly associated with substance use frequency in young adulthood and physical intimate partner violence in adulthood. Direct association of substance use frequency and covariates with physical intimate partner violence perpetration were also estimated. In addition to maltreatment sub-group membership and covariates, the association between polygenic risk score for substance use and substance use frequency was evaluated. Moreover, the interaction between polygenic risk score for substance use and maltreatment sub-groups was also assessed for substance use frequency in young adulthood (see Figures 3.2 to 3.4). Indirect association of maltreatment sub-groups (Figure 3.5) with physical intimate partner violence perpetration via substance use frequency in young adulthood was estimated next using a product of coefficient method (MacKinnon, Fairchild, & Fritz, 2007). Covariates were included for the outcome (i.e. physical intimate partner violence perpetration) and the mediator (i.e. substance use frequency).

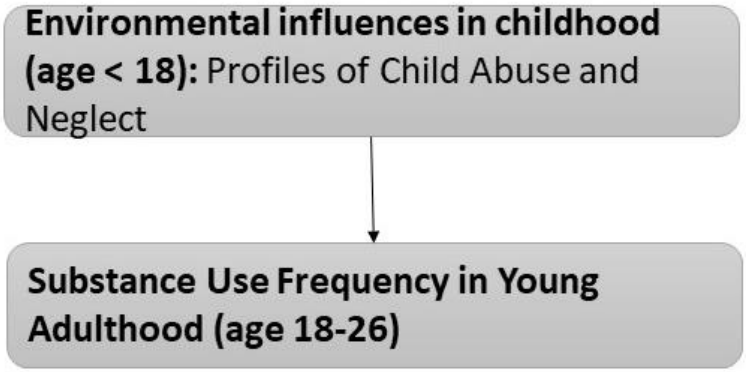

Figure 3.2 Direct association between maltreatment sub-groups and substance use frequency in young adulthood

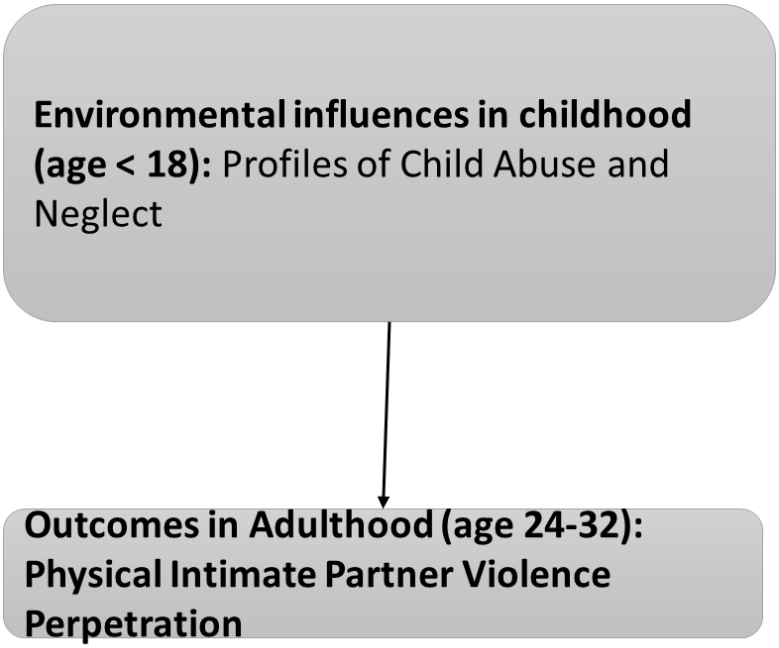

Figure 3.3 Direct association between maltreatment sub-groups and physical intimate partner violence perpetration in adulthood

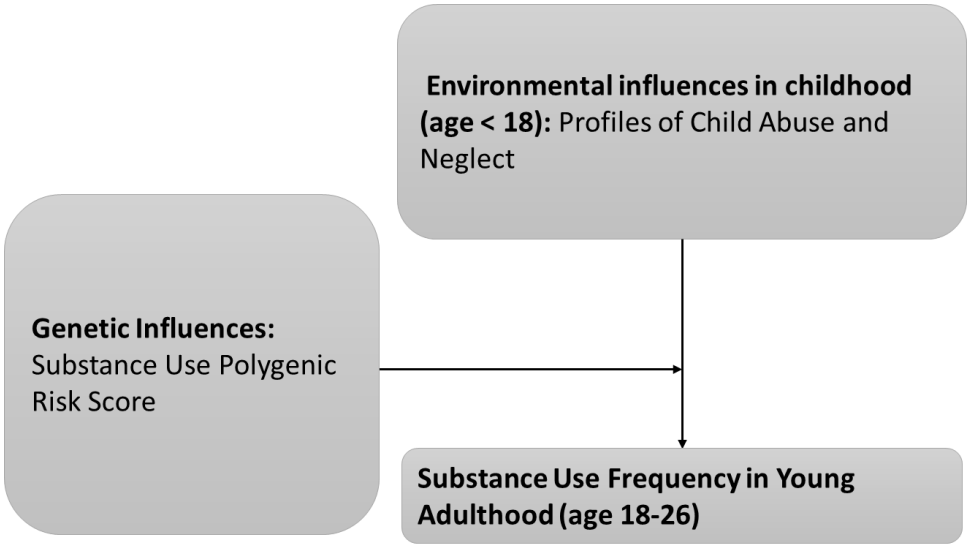

Figure 3.4 Moderation by substance use polygenic risk score on the association between maltreatment sub-groups and substance use frequency in young adulthood

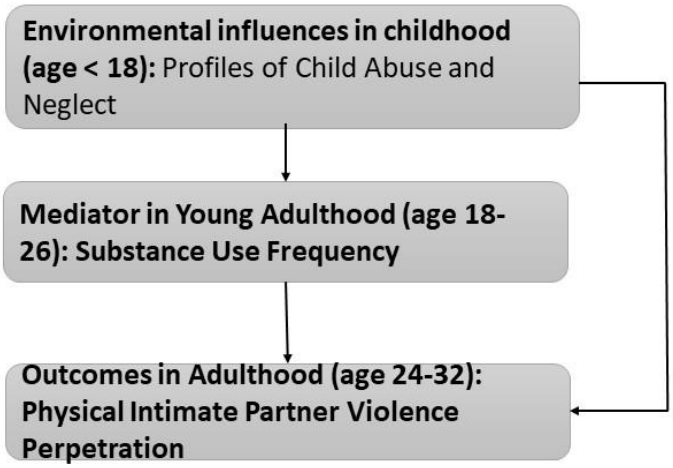

Figure 3.5 Mediation by substance use frequency in young adulthood on the association between childhood maltreatment sub-groups and physical intimate partner violence perpetration in adulthood

Moderated-Mediation (see Figure 3.1)

Moderation by substance use polygenic risk score on the pathway from childhood maltreatment exposure to substance use frequency was evaluated within the mediation model using model constraints and procedures outlined by Stride and colleagues (see model 15 in Stride, Gardner, Catley, & Thomas, 2015). Specifically, model constraints were used on the pathway from maltreatment sub-groups to substance use frequency wherein interaction terms between maltreatment sub-groups and substance use polygenic risk (which were simultaneously probed at medium, low, and high levels) were tested on the indirect pathway from maltreatment sub-groups to substance use frequency.

Maximum likelihood estimation with numerical integration was used for model estimation. Full information likelihood was used to deal with missing data and to reduce biased estimates due to data attrition (Acock, 2012). Bootstrapping (10,000 bootstraps) was used to obtain empirical standard errors. Probability weights were used to correct for unequal selection probability and between cluster sandwich estimator (Binder, 1983) were used to correct for nesting of individuals within clusters (i.e., school-level nesting).

All descriptive statistics were estimated using *SAS 9.4* software and analytic models were estimated using *Mplus 7.4* (Muthén & Muthén, 2020) software.

Post-hoc Models

Post-hoc direct, indirect, and moderated-mediation models were estimated for specific substances - alcohol, marijuana, and illicit drug use frequencies.

Results

Latent profile analysis yielded a 3-class solution. The 3-class solution had overall better model fit (AIC =129430.68; BIC = 129600.54; adjusted-BIC =129524.27; entropy =0.99) compared to the model fit of the 2-class solution (AIC =129430.68; BIC = 129600.54; adjusted-BIC = 129524.27; entropy = 0.99). Class solutions higher than three never converged on a global solution. Sub-group labels were assigned for the 3-class solution. Sub-group 1: High sexual abuse sub-groups with high levels of all other maltreatment exposure (high sexual abuse sub-group); Sub-group 2: High physical abuse sub-group with exposure to emotional abuse and neglect (high

physical abuse sub-group); and Sub-group 3: Low exposure to all maltreatment types or normative sub-group. Figure 3.6 shows average maltreatment frequency by each maltreatment types for each sub-group. Descriptive statistics for each maltreatment sub-group and the entire sample is presented in Table 3.1 and correlation for study variables are summarized in Table 3.2.

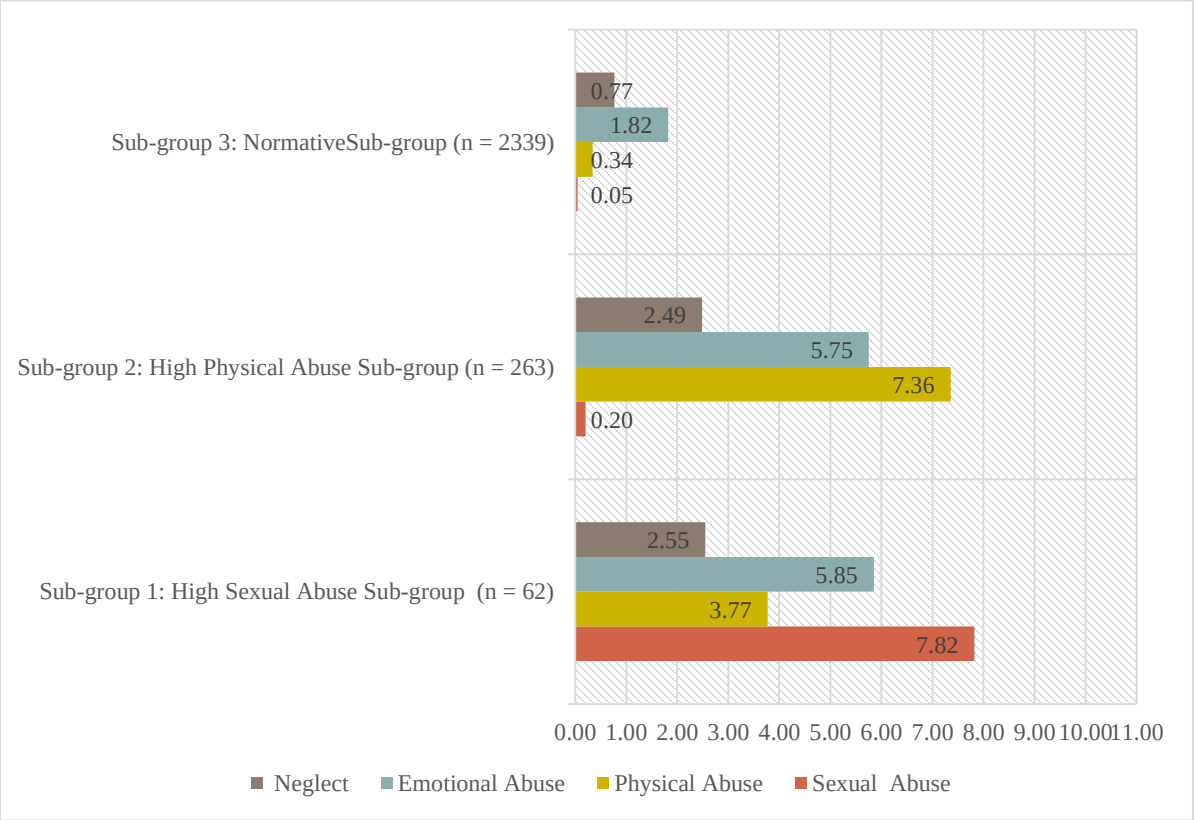

Figure 3.6 3-class solution for childhood maltreatment sub-groups based on type and severity of exposure

Table 3.2 Descriptive statistics by each sub-group

	Complete Sample (n = 2,664)		Sub-group 1: High Sexual Abuse Sub-group (*n* = 53)		Sub-group 2: High Physical Abuse Sub-group (*n* = 207)		Sub-group 3: Normative Sub-group (*n* = 2,404)	
Key Variables	*Mean*	*Std. Dev*	*Mean*	*Std. Dev*	*Mean*	*Std. Dev*	*Mean*	*Std. Dev*
Physical Intimate Partner Violence Perpetration	0.30	2.05	0.94	2.80	0.28	0.92	0.28	2.10
Sexual Abuse	0.21	1.19	7.82	2.59	0.20	0.63	0.05	0.27
Physical Abuse	0.96	2.24	3.77	4.09	7.36	2.39	0.34	0.78
Emotional Abuse	2.22	3.61	5.85	4.96	5.75	4.89	1.82	3.20
Neglect	0.93	1.89	2.55	3.75	2.49	3.09	0.77	1.60
Age Time 3	21.93	1.75	21.98	1.85	21.91	1.61	21.93	1.76
Age Time 4	28.67	1.76	28.69	1.83	28.59	1.63	28.67	1.77
Substance Use Polygenic Risk Score	0.13	0.05	0.12	0.05	0.13	0.05	0.13	0.05
Substance use Time 3	3.90	4.98	3.28	3.75	4.36	5.60	3.87	4.94
Parent Education (in years)	13.28	2.33	13.27	2.14	13.06	2.23	13.30	2.34
Respondent's Education (in years)	14.27	2.10	13.40	2.25	13.89	1.95	14.32	2.11
Percentage	*Mean*	*Std. Dev*	*Mean*	*Std. Dev*	*Mean*	*Std. Dev*	*Mean*	*Std. Dev*
Gender: Male	47.22%	0.50	7.55%	0.27	52.17%	0.50	47.67%	0.50

Note: 1. Categorical variables are presented as proportion of the sample;

Table 3.3 Correlation among study variables

	Physical Intimate Partner Violence Perpetration	Parent Education (in years)	Biological Sex	Respondent Education (in years)	Substance Use Polygenic Risk Score	High Sexual Abuse Sub-group	High Physical Abuse Sub-group	Age at Wave 3	Age at Wave 4	Substance Use Frequency Wave 3
Physical Intimate Partner Violence Perpetration	1	-0.03	-0.05*	-0.034	-0.02	0.05*	-0.000	-0.03	-0.03	0.05
Parent Education (in years)	-	1	0.02	0.38*	-0.01	0.00	-0.03	-0.06*	-0.05*	0.06*
Biological Sex	-	-	1	-0.12*	0.05*	-0.11*	0.03	0.07*	0.07	0.23*
Respondent Education (in years)	-	-	-	1	-0.04*	-0.06*	-0.05*	-0.02	-0.01	-0.07*
Substance Use Polygenic Risk Score	-	-	-	-	1	-0.01	0.01	0.02	-0.00	-0.01
High Sexual Abuse Sub-group	-	-	-	-	-	1	-0.04	0.00	0.00	-0.02
High Physical Abuse Sub-group	-	-	-	-	-	-	1	-0.00	-0.01	0.03
Age at Wave 3	-	-	-	-	-	-	-	1	0.99*	-0.04*
Age at Wave 4	-	-	-	-	-	-	-	-	1	-0.06*
Substance Use Frequency Wave 3	-	-	-	-	-	-	-	-	-	1

* $p < 0.05$

Direct and Indirect Effects

Model direct effects are summarized in Table 3.3 and model indirect effects are summarized in Table 3.4. Substance use frequency in young adulthood was not associated with subsequent self-reports of increased physical intimate partner violence perpetration later in adulthood ($\beta = 0.06$; $p = 0.06$). Membership in the high sexual abuse sub-group ($\beta = 0.04$; $p = 0.37$) or the high physical abuse sub-group ($\beta = 0.00$; $p = 0.78$) was not associated with physical intimate partner violence in adulthood. Moreover, membership in the high sexual abuse sub-group ($\beta = 0.00$; $p = 0.98$) or the high physical abuse sub-group ($\beta = 0.00$; $p = 0.90$) was not associated with substance use frequency in young adulthood. Furthermore, substance use frequency in young adulthood did not mediate the associations between 1) high sexual abuse sub-group and physical intimate partner violence perpetration in adulthood ($\beta = 0.00$; $p = 0.98$) and 2) high physical abuse sub-group and physical intimate partner violence perpetration in adulthood ($\beta = 0.00$; $p = 0.90$).

Table 3.4 Direction association with physical intimate partner violence perpetration in adulthood and substance use in young adulthood

Physical Intimate Partner Violence Perpetration			
	β	*s.e.*	*p*
Substance use	0.06	0.03	0.06
High Sexual Abuse Sub-group	0.04	0.05	0.37
High Physical Abuse Sub-group	0.00	0.02	0.78
Respondent's education level	-0.04	0.03	0.12
Parent's Education Level	-0.03	0.02	0.13
Respondent's Age at Wave 3	-0.05	0.11	0.68
Respondent's Age at Wave 4	0.00	0.09	0.97
Biological Sex	-0.05	0.02	0.03
Substance Use			
	β	*s.e.*	*p*
High Sexual Abuse Sub-group	0.00	0.02	0.98
High Physical Abuse Sub-group	0.00	0.03	0.90
Substance use Polygenic Risk Score	-0.04	0.03	0.21
Substance use Polygenic Risk Score* High Sexual Abuse Sub-group	-0.03	0.04	0.36
Substance use Polygenic Risk Score* High Physical Abuse Sub-group	0.00	0.03	0.99
Respondent's Education Level	-0.04	0.04	0.23
Parent's Education Level	0.04	0.04	0.34
Respondent's Age at Wave 3	-0.04	0.14	0.77
Respondent's Age at Wave 4	-0.03	0.14	0.84
Biological Sex	0.23	0.02	0.00

Table 3.5 Estimating indirect effects for physical intimate partner violence perpetration via substance use

Substance Use						
	High Sexual Abuse Sub-group			High Physical Abuse Sub-group		
	β	*s.e.*	*p*	β	*s.e.*	*p*
Physical Intimate Partner Violence Perpetration	0.00	0.00	0.98	0.00	0.00	0.90

Note: Models were conditioned on all covariates for both the outcome and mediator

Moderated-Mediation

The direct pathway from high sexual abuse sub-group to substance use frequency within the mediation model was not moderated by polygenic risk for substance use (β = -0.02; p = 0.61). Similarly, the direct pathway from high physical abuse sub-group to substance use frequency within the mediation model was also not moderated by polygenic risk for substance use (β = 0.00; p = 0.90).

Post-hoc Models

Direct Effects

Direct effects for specific substances – alcohol use, marijuana use, and illicit drugs use are summarized in Table 3.5. Membership in the high physical abuse sub-group was associated with lower alcohol use frequency (β = -0.05; p = 0.02) but higher marijuana use frequency (β = 0.09; p = 0.00) in young adulthood. Membership in the high sexual abuse sub-group was associated with lower marijuana use frequency (β = -0.10; p = 0.02). The effect size estimates for all significant effects were small.

Additionally, substance use polygenic risk score moderated the association between the high physical abuse sub-group and alcohol use frequency (β = -0.05; p = 0.00), such that at high (β = -0.06; p = 0.00) and low polygenic risk score (β = -0.05; p = 0.00), the physical abuse sub-group had lower alcohol use frequency in comparison to the normative sub-group (Figure 3.7). These effect sizes are, however, small.

Table 3.6 Direction association with physical intimate partner violence perpetration in adulthood and specific substances in young adulthood

Physical Intimate Partner Violence Perpetration									
	Alcohol Use			Marijuana Use			Illicit Drug Use		
	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*
Substance Use[1]	0.09	0.05	0.06	0.01	0.03	0.84	0.05	0.09	0.57
High Sexual Abuse Sub-group	0.05	0.05	0.36	0.05	0.05	0.38	0.04	0.05	0.38
High Physical Abuse Sub-group	0.00	0.02	0.97	0.00	0.02	0.79	-0.01	0.02	0.72
Respondent's Education Level	-0.05	0.03	0.06	-0.04	0.03	0.10	-0.03	0.04	0.37
Parent's Education Level	-0.03	0.02	0.08	-0.03	0.02	0.16	-0.03	0.02	0.18
Respondent's Age at Wave 3	-0.06	0.11	0.60	-0.05	0.11	0.68	-0.05	0.11	0.62
Respondent's Age at Wave 4	0.01	0.09	0.95	-0.01	0.09	0.94	0.01	0.10	0.93
Biological Sex	-0.05	0.02	0.03	-0.03	0.02	0.09	-0.04	0.02	0.06
Substance Use[1] Outcome									
	Alcohol Use			Marijuana Use			Illicit Drug Use		
	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*
High Sexual Abuse Sub-group	-0.01	0.01	0.57	0.10	0.04	0.04	0.00	0.05	0.99
High Physical Abuse Sub-group	-0.05	0.02	0.02	-0.01	0.04	0.24	0.06	0.06	0.36
Substance use Polygenic Risk Score	0.04	0.03	0.18	-0.12	0.04	0.01	-0.14	0.13	0.28

Table 3.6 continued

Substance use Polygenic Risk Score* High Sexual Abuse Sub-group	-0.01	0.02	0.49	0.00	0.05	0.98	-0.05	0.11	0.67
Substance use Polygenic Risk Score* High Physical Abuse Sub-group	-0.05	0.02	0.01	-0.01	0.04	0.66	0.04	0.04	0.33
Respondent's Education Level	0.05	0.03	0.10	-0.11	0.07	0.09	-0.18	0.07	0.01
Parent’s Education Level	0.06	0.03	0.07	0.02	0.07	0.82	0.00	0.07	0.95
Respondent's Age at Wave 3	0.12	0.12	0.31	-0.32	0.22	0.16	0.12	0.40	0.77
Respondent's Age at Wave 4	-0.15	0.12	0.23	0.23	0.22	0.30	-0.26	0.42	0.54
Biological Sex	0.20	0.03	0.00	0.17	0.05	0.00	0.10	0.07	0.15

Note: [1]Please note that substance use in this case is based on the phenotype assessed – alcohol, marijuana, illicit drug use

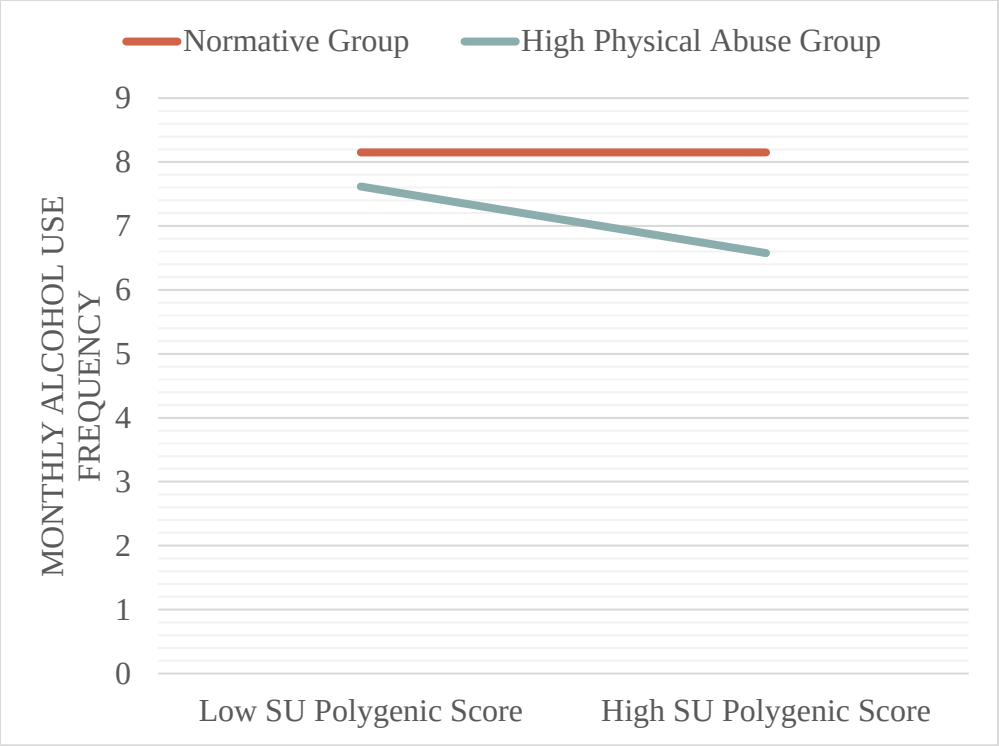

Figure 3.7 Genetic moderation of maltreatment sub-group by substance use polygenic risk score predicting alcohol use in young adulthood

Indirect Effects

Indirect effects of specific substances mediating the association between childhood maltreatment sub-groups and physical intimate partner violence are presented in Table 3.6. Alcohol use frequency in young adulthood did not mediate the associations between 1) high sexual abuse sub-group and physical intimate partner violence perpetration in adulthood (β = 0.00; p = 0.99) and 2) high physical abuse sub-group and physical intimate partner violence perpetration in adulthood (β = 0.00; p = 0.14). Similarly, frequency of marijuana use in young adulthood did not mediate the associations between 1) high sexual abuse sub-group and physical intimate partner violence perpetration in adulthood (β = 0.00; p = 0.84) and 2) high physical abuse sub-group and physical intimate partner violence perpetration in adulthood (β = 0.00; p = 0.84). And, illicit drug use frequency also did not mediate the associations between 1) high sexual abuse sub-group and physical intimate partner violence perpetration in adulthood (β = 0.00; p = 0.98) and 2) high

physical abuse sub-group and physical intimate partner violence perpetration in adulthood (β = 0.00; $p = 0.70$).

Table 3.7 Estimating indirect effects for physical intimate partner violence perpetration via substance use

Alcohol Use						
	High Sexual Abuse Sub-group			High Physical Abuse Sub-group		
	β	*s.e.*	*p*	β	*s.e.*	*p*
Physical Intimate Partner Violence Perpetration	0.00	0.00	0.99	0.00	0.00	0.14
Marijuana Use						
	High Sexual Abuse Sub-group			High Physical Abuse Sub-group		
	β	*s.e.*	*p*	β	*s.e.*	*p*
Physical Intimate Partner Violence Perpetration	0.00	0.00	0.84	0.00	0.00	0.84
Illicit Drug Use						
	High Sexual Abuse Sub-group			High Physical Abuse Sub-group		
	β	*s.e.*	*p*	β	*s.e.*	*p*
Physical Intimate Partner Violence Perpetration	0.00	0.00	0.98	0.00	0.01	0.70

Note: Indirect effects were estimated above and beyond all covariates and interaction between substance use genetic risk

Moderated-Mediation

Substance use polygenic risk score did not moderate the direct pathway from high sexual abuse sub-group membership to alcohol use frequency (β = -0.02; p = 0.67), marijuana use frequency (β = -0.02; p = 0.84) or illicit drug use frequency (β = -0.03; p = 0.76) within the mediating model from high sexual abuse sub-group to physical intimate partner violence perpetration.

Substance use polygenic risk also did not moderate the direct pathway from high physical abuse sub-group membership to alcohol use frequency (β = -0.05; p = 0.28), marijuana use frequency (β = 0.00; p = 0.85) or illicit drug use frequency (β = 0.01; p = 0.56) within the mediating model from high physical abuse sub-group to physical intimate partner violence perpetration.

Discussion

The first aim of this study was to understand substance use frequency in young adulthood as a mediating mechanism between childhood maltreatment sub-group membership and subsequent physical intimate partner violence in adulthood. For this aim, I tested two hypotheses. First, I tested if more severe co-occurring childhood maltreatment sub-groups had a direct association with higher levels of physical intimate partner violence perpetration in adulthood and more substance use frequency in young adulthood. Second, I evaluated if substance use frequency in young adulthood mediated the association between childhood maltreatment sub-groups and physical intimate partner violence perpetration, such that more severe, co-occurring types of childhood maltreatment exposure was associated with higher frequency of substance use and high frequency of substance use in young adulthood was then be associated with greater (or higher levels of) physical intimate partner violence perpetration in adulthood.

Child Maltreatment Association with Substance Use Frequency and Physical Intimate Partner Violence Perpetration

Specifically, I did not find a direct association linking childhood maltreatment sub-groups to physical intimate partner violence perpetration in adulthood and substance use frequency in young adulthood. Although childhood maltreatment has been linked to the "cycle of violence" or intergenerational transmission of violence (Widom & Wilson, 2015), I did not find evidence for

such as association in this large national sample of European Americans. There was also no association between childhood maltreatment sub-groups and substance use frequency in young adulthood, even though there is evidence suggesting that childhood maltreatment and more severe exposure to childhood maltreatment are linked to high frequency of substance use in adulthood (Berzenski & Yates, 2011; Finkelhor, Turner, Shattuck, & Hamby, 2013; Moran et al., 2004; Rogers et al., 2018). Therefore, hypothesis one, that more severe co-occurring childhood maltreatment sub-groups will have a direct association with higher levels of physical intimate partner violence perpetration in adulthood and more substance use frequency in young adulthood was not supported. Below I outline reasons for these null findings.

Measurement Related Consideration

Several measurement issues may explain the null findings for hypothesis one. Self-reporting may not be the most reliable means to test these associations (Widom & Wilson, 2015) as individuals tend to under-report their intimate partner violence perpetration in adulthood due to response bias. I do find evidence for likely under-reporting in this sample as evidenced by the low endorsement rates for physical intimate violence perpetration. Self-reports of violence exposure and substance use frequency may result in lower estimates of actual prevalence (Latkin, Edwards, Davey-Rothwell, & Tobin, 2017; Widom & Wilson, 2015), ultimately resulting in the lack of association among these constructs. Multiple reporter measures may provide a more accurate prevalence of the constructs evaluated. Additionally, this study uses retrospective maltreatment reports, which also tend to be downwardly biased (Schafer & Ferraro, 2012), making it even more difficult to ascertain the proposed associations (i.e., estimates of associations are weaker).

Sample Related Consideration

The large survey sample used in this research allows us to examine associatons in populations of European Americans. The sample size of this research is powered at 93% to detect effect sizes of 0.05 at $\alpha = 0.05$. Given the large sample, there is a strong possibility that the associations proposed in hypothesis one are actually not supported in larger populations of European American adults and may only exist in at-risk sub-populations such as those in contact with child protective services.

Specifically, a majority of studies demonstrating the links between childhood maltreatment and substance use in young adulthood tend to use samples of individuals with substantiated cases of childhood maltreatment exposures wherein the child was removed from home due to high levels of exposure to childhood maltreatment or at a minimum had some involvement with child protective services (Narendorf & McMillen, 2010; Oshri et al., 2012). Similarly, individuals with childhood maltreatment exposures that also report higher levels of physical intimate partner violence perpetration in adulthood, usually have more severe exposures to childhood maltreatment (Widom & Wilson, 2015). Therefore, the population based sample used in this research may be charecteristically different than those used in previous research and that these associations hold true only when evaluating extreme exposure to childhood maltreatment (as evidenced by removal from home or contact with child protective services due to alleged maltreatment). It may be necessary to test the hypothesized model with samples of individuals that have more severe maltreatment exposure to understand if proposed associations, are in fact, true for more risky samples.

Substance Use Frequency as a Mediator between Childhood Maltreatment and Physical Intimate Partner Violence Perpetration

The second hypothesis for this research was also not supported and I did not find any evidence for the mediating influence of substance use frequency on the association between childhood maltreatment sub-groups and physical intimate partner violence perpetration.

There may be three other potential explanations for the null findings for hypothesis two. First, by restricting the sample of the present research to unrelated European Americans, I may be eliminating variance in the outcome, mediator, and/or predictor that may exist in the general population. Although evidence for this mediation hypothesis is lacking in the Add Health data using this full nationally representative sample (See Appendix A and chapter 5). Nonetheless, future research could consider the proposed aims of this study in large diverse populations. Second, it is also likely that the association between childhood maltreatment and physical intimate partner violence in adulthood is transmitted via substance use only in combination with other mental health and behavioral problems such as anxiety and aggression. Previous research suggests a strong correlation between mental health and substance use problems (Faulkner et al., 2014; Madruga et al., 2017). These additional mental health factors that may be comorbid with substance use

frequency, will need further evaluation and may be critical in the intergenerational transmission of violence.

The third explanatory factor could be that substance use may not be the causal link in the "cycle of violence". There is some evidence suggesting that substance use may be proximally linked to physical intimate partner violence perpetration and may, therefore, be the causal link between childhood maltreatment and physical intimate partner violence perpetration (Leonard, 2001; Leonard, 2005). Similarly, the social cognitive theory also supports the notion that substance use frequency may be a mechanism between childhood maltreatment exposure and subsequent physical intimate partner violence perpetration. According to this theory, substance use may stem from childhood maltreatment exposures as a coping behavior which may then lead to subsequent physical intimate partner violence perpetration. Under this theory, individuals may attribute their aggressive behaviors to the inebriated state (Akers, 2017; Bandura, 1986). However, these proposed theoretical models were not supported by the data used in this research.

It is likely though that instead of being a proximal process, substance use frequency may be a contextual factor within the ecological model of human development (Bronfenbrenner, 2009), that exacerbates the likelihood of physical intimate partner violence perpetration in adulthood among victims of childhood maltreatment. Support for substance use as a contextual factor can also be found in the existing literature. Specifically, there is evidence suggesting such a contextual influence of substance use frequency on the association between adversity exposure and subsequent outcomes including physical intimate partner violence perpetration (Lang & Stover, 2008). Therefore, it might be necessary to test substance use as a moderator instead of a mediator of the association between childhood maltreatment and physical intimate partner violence perpetration. I test this new model (see supplementary results below for the new proposed model and results from this model) with the data used in this research.

The findings from the revised model demonstrated that marijuana and illicit drug use alter the association between certain subgroups of individuals experiencing high frequency of sexual abuse and moderate frequency of emotional abuse and neglect in childhood and physical intimate partner violence perpetration. Even though, there is evidence suggesting higher levels of violence perpetration among drug users (Crane, et al., 2014), these findings demonstrate that marijuana and illicit drug use may not by itself be related to higher frequency of violence perpetration - as evidenced by the lack of influence of both substances on physical intimate partner violence

perpetration in the normative sub-group. However, among individuals with high childhood sexual abuse exposures in particular, high frequency of marijuana and illicit drug use can particularly be salient for greater physical intimate partner violence perpetration in adulthood. This finding adds to previous literature demonstrating the long-term impact of sexual abuse on interpersonal relationships and well-being in adulthood (Archer, Pereira, & Power, 2017; Davis & Petretic-Jackson, 2000; Trickett & McBride-Chang, 1995; Trickett, Noll, & Putnam, 2011).

Furthermore, this study extends previous research by demonstrating that substance use frequency, alcohol use frequency, and drug use frequency are not causal in the childhood maltreatment and physical intimate partner violence association. In the sample used in this researcher, marijuana and illicit drug use frequency phenotypes are contextual factors, that increase physical intimate partner violence perpetration among victims of high sexual childhood maltreatment (with co-occurring neglect and emotional abuse). Intervening on drug use (marijuana and illicit drug use) frequency among victims of childhood sexual abuse is likely a potential target for future prevention efforts. Such prevention efforts could include motivational interviewing or cognitive behavioral therapy targeting marijuana and illicit drug use (Carroll & Kiluk, 2017; Saitz et al., 2020) among individuals with high severity of sexual abuse that co-occurs with emotional abuse and neglect in order to prevent physical intimate partner violence perpetration in adulthood. Additionally, these findings also have implications for research at a theoretical level. Specifically, multiple theories are proposed on how childhood maltreatment may be linked to physical intimate partner violence perpetration via substance use frequency, such a multi-theoretical approach (i.e. using multiple theories such as social learning and social cognitive theory, ecological model) will be necessary to disentangle associations in different populations. Using multiple theories, future research should evaluate both the contextual and mechanistic effects of substance use on the association between childhood maltreatment and physical intimate partner violence perpetration, in order to understand the nature and role of substance use in the cycle of violence in different populations.

The findings from this research provide an initial step in understanding intergenerational transmission of violence and should be extended to other violence phenotypes that may be associated with childhood maltreatment exposures. Results should also be replicated in individuals with more severe co-occurring childhood maltreatment exposures as well as for individuals with more severe levels of physical intimate partner violence perpetration and substance use behaviors.

Substance Use Polygenic Risk Score as a Moderator

The second aim of this research was to understand the moderating effect of substance use polygenic risk score on the indirect path from childhood maltreatment sub-group membership to substance use frequency in young adulthood. For this aim, I tested the hypothesis that higher genetic risk for substance use would exacerbate the influence of certain childhood maltreatment sub-groups on substance use frequency in young adulthood (Hypothesis 3) within the mediation model in Hypothesis 2.

I also did not find genetic moderation of the indirect pathways from childhood maltreatment sub-groups to substance use in young adulthood. Previous studies have demonstrated that single genes may be underpowered to detect significant effects for phenotypes under observation (Duncan, Ostacher, & Ballon, 2019). However, polygenic risk scores may have several inherent problems including that they too may be underpowered to detect significant effects if the SNPs included do not encompass a large enough genomic area that might be associated with the specific phenotype (i.e. adequate coverge for the phenotype; Dudbridge, 2013). Even though a majority of studies using polygenic risk scores tend to use one genome-wide study for the phenotype to create their score (Krapohl et al., 2018; Musliner et al., 2015), I used multiple studies to get a larger coverage of the phenotype assessed (i.e. substance use) but it is still likely that the polygenic risk score is underpowered and does not provide adequate coverage of substance use phenotype. Another problem with polygenic risk scores is that creating polygenic risk scores from SNP heritability may not be the most effective way to understand genetic effects or overall heritability of complex behavioral phenotypes due to the phenomena of "missing heritability" (i.e. SNPs do not account for all the genetic variability that are found in family based studies; Dudbridge, 2013). A final limitation of polygenic risk scores is that I only evaluate additive genetic effects and fail to account for interactive genetic effects that may result in a myriad of combinations of how genetic traits are inherited (Dudbridge, 2013).

However, in study 1 of this dissertation, I do find genetic moderation (despite the above-mentioned shortcomings) for the association between maltreatment sub-groups and substance use change over time. Together, the moderation results from study 1 and the lack of association in this study, provide support for the lack of power in this study to detect significant genetic findings. To elaborate, in chapter 1, the repeated measures design and long-form of data (i.e., each repeated measure getting its own record), can greatly improve statistical power (Guo, Logan, Glueck, &

Muller, 2013). Therefore, study 1 may be sufficiently powered to detect substance genetic moderation due to the structure of the data and the dynamic change over time model used. In comparison, this study is likely underpowered to detect genetic moderation since I am evaluating static associations using wide form data.

In addition to the overall model, I also tested substance specific (alcohol, marijuana, and illicit drugs) sub-models to discern if there were specific substances that were influential in the association between childhood maltreatment and physical intimate partner violence. Although, the findings from these sub-models largely replicate the findings from the overall model for substance use. One specific finding needs to be highlighted. The finding for lower alcohol use frequency at high polygenic risk among member of the high physical abuse sub-group compared to the normative sub-group. The findings indicate that the substance use polygenic risk may be protective for alcohol use frequency for members of the high physical abuse sub-group. However, the effect size difference ($\beta = 0.01$) between the two sub-groups is very small and though statistically significant, may not be a meaningful difference. These findings may have also emerged because the substance use polygenic risk score was not created for substance specific phenotypes and only included five SNPS for alcohol use, and so it is very likely that the polygenic risk score is underpowered to detect meaningful variation in alcohol use frequency. In fact simulation studies have demonstrated that opposite findings from anticipated direction in genetic research stem from a lack of statistical power (Dudbridge, 2013). Nonetheless, replication with the same substance use polygenic risk score and alcohol use specific polygenic risk score utilizing larger samples of maltreated children will be necessary to determine if similar or different associations emerge when better measures of genetic risk are utilized compared to the current substance use genetic score.

Future Directions

Two divergent perspectives exist when considering the life-long impacts of childhood maltreatment exposures. The first perspective is a risk model similar to one evaluated in this research. This risk model explores the mechanisms through which adversity may be linked to subsequent negative outcome. The second perspective is a resilience model that explores the potential for resources or protective factors that may buffer against the negative impacts of adversity exposure and promote positive adaptation despite adversity. In fact, a majority of individuals with adversity exposure such as childhood maltreatment do not actually develop the

risk of subsequent violence or negative outcomes (Feder, Nestler, & Charney, 2009; Liu, Zhang, Ji, & Yang, 2018; Widom & Wilson, 2015). Both the risk and resilience models take a biopsychological perspective for explaining pathways by which adversity exposure may influence outcomes throughout life and have several common threads. Below I explore some common threads across the risk and resilience models that may be applicable for the analytic model evaluated in this research and may need evaluation in future research. Specifically, I explore the dopaminergic system, cognitive factors, psychosocial factors, and stress processes that are most commonly explored by the risk and resilience models for externalizing problems such as violence, aggression, and substance use (i.e., outcomes similar to those evaluated in this study) and to adversity and childhood maltreatment exposures.

Dopamine System

The dopaminergic system has been critical specifically for explaining substance use behaviors due to its role in modulating impulse control and sensation-seeking (Le Foll, Gallo, Strat, et al., 2009). Specifically, dysregulation of dopamine metabolism, encoding of dopamine enzymes, and increases in dopamine levels in specific regions of the brain can increase the need for instant gratification of substance use and lower substance use related impulse control (Hyman et al., 2006; Sinha, 2009). Therefore, dopamine related dysregulation may be an additional risk factor through which biological risk can influence substance use behaviors.

Stress Processes

Another potential mechanism through which stress such as childhood maltreatment may have an indirect effect on violence perpetration is by the alteration of stress-related systems such as the HPA axis, catecholamine systems, and the sympathetic nervous system (Widom & Wilson, 2015). Specifically, biological stress responses are activated when individuals are exposed to stressful situations and when these stressors become chronic (e.g. severe childhood maltreatment exposures), such stress processes may result in allostatic overload or the deregulation of the body's ability to adapt to such stressors (Miller, Chen, & Zhou, 2007). Such biological stress dysregulation has been associated with childhood maltreatment exposure (Doom, Cicchetti, & Rogosch, 2014; Tarullo & Gunnar, 2006) as well as childhood maltreatment related externalizing

problems (e.g. antisocial behavior, attention problems, aggressive behaviors; Isaksson, Nilsson, & Lindblad, 2013; White et al., 2017).

However, few studies have examined the role of these stress processes on the associations between co-occurring childhood maltreatment exposures and externalizing outcomes in adulthood. Stress related indirect effects from co-occurring childhood maltreatment exposures to substance use frequency in young adulthood and physical intimate partner violence perpetration in adulthood could be examined in future research, as it may be a critical indirect pathway via which childhood maltreatment may exert its influence on externalizing problems in adulthood.

Furthermore, there is some evidence suggesting that high levels of DHEA (dehydroepiandrosterone; a hormone released in stressful situations), can be protective for trauma (Morgan et al., 2004). The role of DHEA could also be considered as an additional protective factor within the proposed model of this study.

Psychological Factors

Some research has demonstrated that in addition to biological stress, psychological stress or the perceptions of stress may mediate the association between co-occurring childhood maltreatment exposures and negative outcomes in adulthood (Mishra & Marceau, 2019). Particularly, perceived stress can be negatively attributed to both physical intimate partner violence and substance use in adulthood (Capaldi, Knoble, Shortt, & Kim, 2012; Sacco, Bucholz, & Harrington, 2014; Tavolacci et al., 2013).

In contrast, optimism and adaptive coping mechanism may be potential protective psychosocial factors that promote resilient functioning among individuals when faced with stressors, adversity, or trauma (Hauser, Allen, & Golden, 2009; Ong, Bergeman, Bisconti, & Wallace, 2006; Tugade & Fredrickson, 2004). However, these factors will need an in-depth examination within the context of the proposed model of this research. Specifically, perceived stress may be an indirect pathway by which childhood maltreatment exposures may associate with subsequent substance use frequency or physical intimate partner violence perpetration. Similarly, it is equally likely that optimism and adaptive coping strategies may buffer against the negative effects of childhood maltreatment exposures on adult externalizing outcomes.

Cognitive Factors

In addition to biological and psychological stress, cognitive factors such as self-regulation have been studied extensively for their negative association with childhood maltreatment exposure, substance use frequency, and violence outcomes. Specifically, researchers have demonstrated impulsivity (i.e. reactive or bottoms up self-regulation) is instrumental for higher substance use frequency and violence outcomes such as aggression and physical intimate partner violence perpetration (Holmes, Hollinshead, Roffman, Smoller, & Buckner, 2016; Shorey, Brasfield, Febres, & Stuart, 2011). There is also evidence suggesting that childhood maltreatment may lead to poorer inhibitory control and impulsivity, and that poor inhibitory control and impulsivity may exacerbate the association between childhood maltreatment and negative outcomes such as more interpersonal violence, depression, and self-injurious behaviors (Blair, 2010; Evans & Kim, 2013; Finkenauer et al., 2015; McMahon et al., 2018). Therefore, inhibitory control and impulsivity may be indirect mechanisms that are associated with greater physical intimate partner violence perpetration and substance use frequency during different developmental stages among victims of co-occurring childhood maltreatment exposures.

Similarly, top-down or deliberate self-regulation processes such as effortful control and ego-resiliency which are indicative of cognitive flexibility (Nigg, 2017), have shown to promote resilient functioning for a wide variety of outcomes in vulnerable samples (Taylor, Evich, Marceau, Nair, & Jones, 2019; Taylor, Ruiz, & Nair, 2019) and may be particularly protective for externalizing problems (Brady & Sinha, 2005; Causadias, Salvatore, & Sroufe, 2012; Hofer, Eisenberg, & Reiser, 2010; Olson, Sameroff, Kerr, Lopez, & Wellman, 2005). Ego-resiliency involves the implementation of various cognitive strategies and the ability to regulate self-control and behavior adaptation (Block & Block, 2014; Nigg, 2017). Similarly, effortful control allows individuals to modulate emotions and behaviors as well as the expression of behaviors based on situational demands (Nigg, 2017). Therefore, these protective self-regulatory factors that promote resilience, could be additional factors for researchers to consider in future work for the proposed direct associations hypothesized in this study. The evaluation of these protective cognitive factors is generally lacking in adults with childhood maltreatment and adversity exposures.

Therefore, the biopsychosocial factors suggested above should be evaluated in future research as both potential mechanisms and buffers influencing the direct association between childhood maltreatment exposure and subsequent violence and substance use outcomes throughout

life. Findings from such future research could be critical for prevention trials and intervention efforts.

Conclusion

Even with the null findings and limitations that inform this research, there are several strengths of this research. The lack of associations with the large sample size that makes use to appropriate sampling weights to deal with unequal probability of selection and corrects for clustering of data, highlights that there may, in fact, be no meaningful association between specific joint childhood maltreatment exposures and physical intimate partner violence perpetration in adulthood or substance use frequency in young adulthood in the larger population of European Americans (please see chapter 5 and Appendix A for mediation results with the full nationally representative sample from Add Health). Additionally, this study demonstrates the need for better measurement for childhood maltreatment and genetic risk in future research. Nonetheless, drug use frequency may exacerbate the association of sexual abuse exposure with physical intimate partner violence perpetration in adulthood. Motivational interviewing and cognitive behavioral therapy strategies for sexual abuse victims with a high frequency of drug use in young adulthood could be beneficial to reduce the incidence of physical intimate partner violence at the population level (Carroll & Kiluk, 2017; Saitz et al., 2020). Additionally, it may be important to use different theoretical perspectives to understand the role of substance use frequency in the association between childhood maltreatment exposure and physical intimate partner violence. Several additional pathways such as psychological, cognitive, and physiological are proposed that may further help disentangle the association of co-occurring childhood maltreatment exposures with externalizing problems in adulthood.

Supplementary Models

A new conceptual model was proposed to understand the interaction of childhood maltreatment sub-groups and substance use frequency (and alcohol, marijuana, and illicit drug use frequencies) influences (see Figure S3.1). In addition to proposing this conceptual model, I also tested this model in the present sample (n = 2,664) of unrelated European Americans. Findings are summarized in Table S3.1 for the moderating influences of overall substance use frequency, alcohol use frequency, marijuana use frequency, and illicit drug use frequency on the association between childhood maltreatment sub-groups and physical intimate partner violence perpetration.

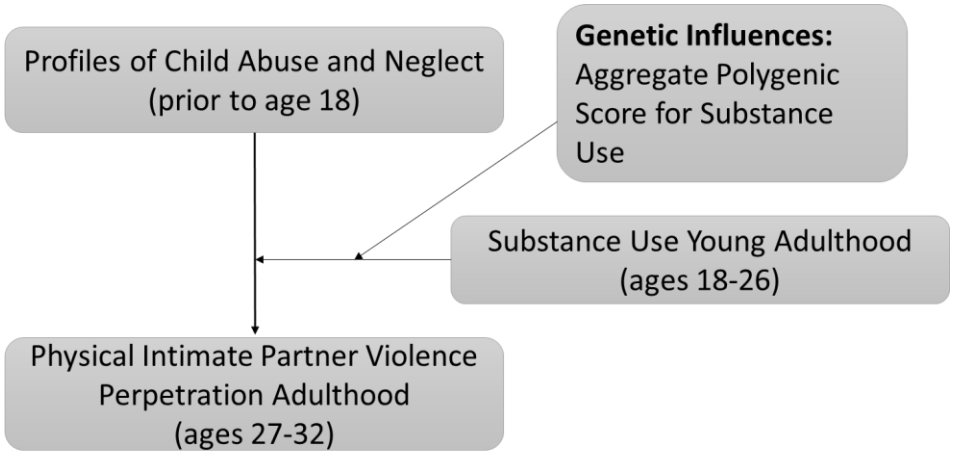

Figure S3.1 Revised conceptual model where substance use (and alcohol, marijuana, and illicit drug use) frequency moderates the association between sub-groups of childhood maltreatment exposure and physical intimate partner violence perpetration in adulthood and genetic moderation of the moderated pathway

Table S3.1 Interaction between childhood maltreatment sub-groups and substance use frequency on physical intimate partner violence perpetration

	Substance Use			Alcohol Use			Marijuana Use			Illicit Drugs Use		
	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*
High Sexual Abuse Sub-group	-0.02	1.38	0.99	0.10	1.45	0.94	-0.06	2.58	0.98	0.06	1.77	0.97
High Physical Abuse Sub-group	-0.02	0.15	0.91	0.02	0.17	0.90	-0.12	0.21	0.57	-0.02	0.24	0.95
Substance Use[1]	0.03	0.02	0.27	0.05	0.04	0.23	0.00	0.01	0.81	-0.01	0.02	0.38
Substance Use*High Sexual Abuse Sub-group	0.56	0.58	0.33	0.35	0.38	0.36	0.95	0.23	0.00	1.11	0.14	0.00
Substance Use*High Physical Abuse Sub-group	0.00	0.03	0.92	-0.03	0.04	0.51	0.01	0.02	0.80	0.00	0.02	0.97

Note: 1 - based on the substance evaluated in the model; models include covariates

I found that marijuana use, and illicit drug use frequencies moderated the association between high sexual abuse sub-group and physical intimate partner violence perpetration in adulthood. These interactions were probed at low, medium, and high frequencies of use and are presented in Figures S3.2 and S3.3. Specifically, the high sexual abuse sub-group at medium (β = 0.36, $p = 0.00$), and high (β = -0.12, $p = 0.00$) frequency of marijuana use but not low (β = -0.03, $p = 0.40$) had greater physical intimate partner violence perpetration in adulthood compared to the normative sub-group. Similarly, members of the high sexual abuse sub-group at high (β = 0.65, $p = 0.00$) but not at low (β = -0.04, $p = 0.17$) or medium (β = 0.01, $p = 0.13$) frequency of illicit drug use had greater physical intimate partner violence perpetration in adulthood compared to the normative sub-group.

Genetic risk, however, did not moderate the moderating influence (i.e. moderated moderation) of substance use frequency (β = 0.03, $p = 0.91$), alcohol use frequency (β = -0.10, $p = 0.50$), marijuana use frequency (β = 1.11, $p = 0.16$), and illicit drug use frequency (β = -1.58, $p = 0.33$) on the association between high sexual abuse sub-group and physical intimate partner violence perpetration. Genetic risk also did not moderate the moderating influence of substance use frequency (β = -0.02, *s.e.* = 0.02, $p = 0.42$), alcohol use frequency (β = 0.01, *s.e.* = 0.02, $p = 0.60$), marijuana use frequency (β = -0.03, $p = 0.32$), and illicit drug use frequency (β = -0.03, *s.e.* = 1.34¸ $p = 0.72$) on association between high physical abuse sub-group and physical intimate partner violence perpetration. Therefore, the substance specific influences of marijuana and illicit drug use were not dependent on specific genetic risks and interventions efforts that are highlighted above can be uniform irrespective of genetic risk for substance use.

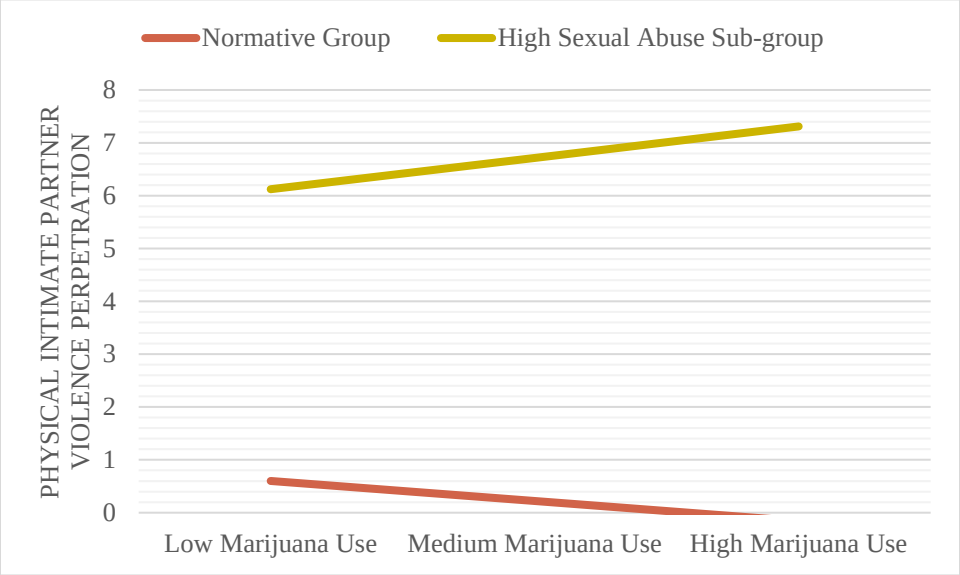

Figure S3.2 Marijuana use frequency moderating the association between sub-groups of co-occurring childhood maltreatment exposures and physical intimate partner violence perpetration

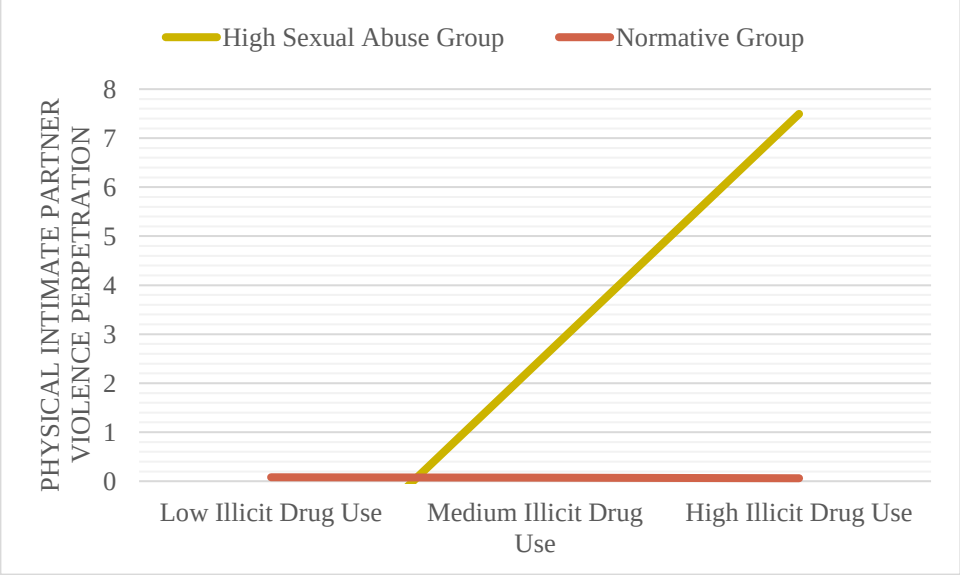

Figure S3.3 Illicit drug use frequency moderating the association between sub-groups of co-occurring childhood maltreatment exposures and physical intimate partner violence perpetration

CHAPTER 4: STUDY 3

In chapter 3, I presented results on how substance use in young adulthood mediates the association between co-occurring childhood maltreatment exposure and physical intimate partner violence perpetration in adulthood. I also tested genetic risk for substance use as moderator of the indirect pathway from childhood maltreatment sub-group membership to substance use within the mediating model. In this chapter, I empirically examine the association between childhood maltreatment sub-groups (based on similar exposure to types and frequency of maltreatment) and physical intimate partner violence victimization in young adulthood and subsequent substance use in adulthood. Once again, I bring to these analyses genetic risk for substance use as a moderator of the associations between maltreatment and physical intimate partner violence victimization with substance use and I also test an additional polygenic risk score for substance use related dopamine genes. Like in Study 2, I provide results for substance specific (i.e. alcohol use, marijuana use, and illicit drug use) outcomes in post-hoc models.

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Ethical approval: The study uses pre-existing data from The National Longitudinal Study of Adolescent to Adult Health (Add Health) study that was reviewed and deemed as an expedited category 5 for Human Subjects Research by the Purdue University IRB. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee.

Abstract

Childhood maltreatment is associated with higher rates of physical intimate partner violence victimization and substance use in adulthood. Similarly, physical intimate partner violence and genetic risk and substance use related dopamine genetic risk are associated with higher levels of substance use. To understand the role of childhood maltreatment, physical intimate partner violence victimization, and genetic risk, on substance use in adulthood, I test three aims. First, I tested the direct association of childhood maltreatment sub-groups defined by similar levels of exposure to distinct maltreatment types on substance use in adulthood. Second, I evaluated physical intimate partner violence in young adulthood as a mediator of the association between childhood maltreatment sub-groups and substance use in adulthood. Finally, I assessed 1) substance use specific genetic risk and 2) substance use related dopamine genetic score on the direct association between childhood maltreatment sub-groups and substance use, as well as on the direct pathway from physical intimate partner violence victimization in young adulthood to substance use in adulthood within the mediation model. Data came from the National Longitudinal Study of Adolescent to Adult Health. Models were evaluated using product of coefficient methods and moderated mediation models. Research aims were largely not supported. Suggestions and implications for future research are discussed in detail.

Research across disciplines has linked childhood maltreatment exposure to several social and behavioral problems in adulthood including physical intimate partner violence victimization and higher substance use frequency (Oshri et al., 2012; Widom & Wilson, 2015). There is also a large body of research supporting the association of specific childhood maltreatment types with physical intimate partner violence victimization and adult substance use frequency (Barnes, Noll, Putnam, & Trickett, 2009; Berzenski & Yates, 2011; Desai et al., 2002; Vaughn, Salas-Wright, Underwood, & Gochez-Kerr, 2015). A few studies have also demonstrated a link between physical intimate partner violence victimization and subsequent substance use wherein physical intimate partner violence victimization increased substance use frequency (Gilbert et al., 2012). However, studies evaluating the influence of co-occurring childhood maltreatment exposures based on both type and severity (evaluated by frequency) on physical intimate partner violence victimization and adult substance use frequency are generally lacking. Moreover, evidence for biological mechanisms for substance use frequency in adulthood within the context of childhood maltreatment and physical intimate partner violence victimization exposures are rare, even though the heritability of substance use has been well established (Nugent et al., 2014). To address gaps in current knowledge, the present study utilizes a developmental model to evaluate physical intimate partner violence victimization in young adulthood and substance use frequency in adulthood among sub-groups of individuals experiencing similar childhood maltreatment types and severity. I also bring to these analyses a test of physical intimate partner violence victimization in young adulthood as a mediator of the association between childhood maltreatment sub-groups and substance use frequency during adulthood. Moreover, I examine the moderating influence of overall genetic risk for substance use and substance use related dopamine genetic risk on the direct pathways linking 1) childhood maltreatment sub-groups to substance use frequency in adulthood and 2) physical intimate partner violence victimization in young adulthood to substance use frequency in adulthood.

Child Maltreatment and Physical Intimate Partner Violence Victimization

Over 10 million individuals in the United States are likely to be victims of physical intimate partner violence during their lifetime (Black, Basile, Smith, Walters, Merrick, Chen, & Stevens, 2010; Cafferky, Mendez, Anderson, & Stith, 2016). Results from epidemiological studies (including data used in this research), demonstrate symmetry of physical intimate partner violence

victimization exposure among men and women (i.e. men and women experiences physical intimate partner violence victimization at similar rates; Renner & Whitney, 2010). Further, there is strong evidence suggesting that a majority of physical intimate partner violence victimization occur in young adulthood (prior to age 30), making it a critical time for understanding both factors leading to increased prevalence of such exposures as well as the long term consequences of such exposures (Breiding et al., 2014; Ennis, 2018). The links between childhood maltreatment exposure and physical intimate partner violence victimization are documented by previous research (Renner & Slack, 2006) and exposure to childhood violence has been linked to 3 times the likelihood of physical intimate partner violence victimization in adulthood for both men and women (Whitfield, Anda, Dube, & Felitti, 2003).

Social learning (Akers, 2017; Bandura, 1986; Bandura & Walters, 1977) and attachment theories (Ainsworth et al., 1978; Bowlby, 1973, 1988) are used extensively to explain the association between childhood maltreatment exposure and physical intimate partner violence victimization. According to attachment theory, maladaptive relationship with caregivers during childhood due to experiences such as childhood maltreatment can create internal working models wherein individuals accept abusive and neglectful patterns in intimate partner relationships and these internal working models are carried forward into their adult relationships with their partners (Ainsworth et al., 1978; Bowlby, 1973, 1988). Similarly, children exposed to childhood maltreatment may accept violence as a normative part of close relationships and may accept their partner's violent behaviors as adults due to social learning and conditioning to such patterns of behaviors during childhood (Bandura, 1986; Widom & Wilson, 2015).

All types of childhood maltreatment exposures carry the risk for physical intimate partner violence victimization (Abajobir, Kisely, Williams, Clavarino, & Najman, 2017; Barnes et al., 2009; Desai et al., 2002; Parks et al., 2011; Widom et al., 2014). To illustrate, physical abuse and sexual abuse types of childhood maltreatment, in particular, exert independent and joint influences on physical intimate partner violence victimization in adulthood (Barnes et al., 2009; Desai et al., 2002). Another study demonstrates that both physical abuse and neglect domains of childhood maltreatment are associated with the greater likelihood of physical intimate partner violence victimization, however, physical abuse exposure in childhood is associated with the highest likelihood of physical intimate partner violence victimization (Widom et al., 2014). In another study, victims of neglect and emotional abuse exposure during childhood report 5 times greater

likelihood of physical intimate partner violence victimization in adulthood compared to those without such exposures (Abajobir et al., 2017). Taken together, these findings illustrate that many types of childhood maltreatment exposures are associated with an increased risk for physical intimate partner violence victimization (Parks et al., 2011). Moreover, experiencing more severe and more than one type of childhood maltreatment can increase the risk for physical intimate partner violence victimization compared to experiencing only one type of childhood maltreatment (Parks et al., 2011). Therefore, it is imperative to evaluate multiple childhood maltreatment exposures based on a combination of type and severity of exposures on physical intimate partner violence victimization, since multi-type exposure is fairly characteristic of the maltreatment phenomenology (Debowska et al., 2017). However, such evaluation of co-occurring types of childhood maltreatment exposures based on severity of exposure on subsequent violence victimization are lacking in the existing literature and it is likely that specific combinations of childhood maltreatment exposures could be more detrimental for subsequent victimization (e.g., physical intimate partner violence victimization) in young adulthood.

Child Maltreatment and Physical Intimate Partner Violence Victimization Effects on Substance Use

Childhood maltreatment exposure is not only associated with an increased likelihood of physical intimate partner violence victimization but is also associated with increased substance use (Edalati & Krank, 2016). According to social learning and cognitive theories, the association between childhood maltreatment and substance use frequency is explained as a coping strategy to deal with the trauma experienced due to childhood maltreatment (Akers, 2017; Bandura, 1986; Bandura & Walters, 1977).

Victims of childhood maltreatment show a propensity for early initiation to substance use (Dube et al., 2006; Enoch, 2011) and indulge in higher frequency of substance use as adults (Ducci et al., 2009; Klanecky, McChargue, & Bruggeman, 2012). Although all abuse forms of childhood maltreatment (i.e. physical, sexual, and emotional) are associated with an increased risk for using multiple substances such as opioids, alcohol, hallucinogens, cannabis, amphetamines and other drug use, among adult survivors, childhood neglect has not been linked to substance use (Afifi, Henriksen, Asmundson, & Sareen, 2012). Studies on the association of multiple co-occurring maltreatment types on adult substance use demonstrate that the co-occurrence of emotional and

physical abuse types together, and the co-occurrence of physical abuse and neglect together are associated with greater substance use frequency in adulthood (Berzenski & Yates, 2011; Vaughn et al., 2015). However, these studies do not consider the severity of multiple childhood maltreatment types on substance use problems, and severity of multiple exposures may be differently associated with substance use in adulthood.

Another key contributor of greater substance use problems is physical intimate partner violence victimization (World Health Organization, 2013). Much like childhood maltreatment exposures, it is hypothesized that victims of physical intimate partner violence may use substances as a coping mechanism to deal with the trauma resulting from physical intimate partner violence victimization (Goldstein, 1985; Kaysen et al., 2007; Kilpatrick et al., 2000). Indeed physical intimate partner violence victimization is associated with a greater substance use frequency throughout adulthood (Gilbert et al., 2012). Moreover, since childhood maltreatment is associated with physical intimate partner violence victimization and substance use problems, and physical intimate partner violence victimization is associated with substance use problems, it is equally likely that physical intimate partner violence victimization in young adulthood is a mediator between co-occurring childhood maltreatment and subsequent substance use problems in adulthood. Such a developmental model needs further examination as is the need to further examine the genetic basis for substance use within this developmental model in order to disentangle different factors that may result in greater frequency of substance use in adulthood.

Genetic Risk for Substance Use

Substance use is a familial problem (i.e. runs in families; Nugent et al., 2014) and is moderately heritable. Genome-wide association studies have found several genes that are associated with higher frequency for specific substances such as alcohol, cocaine, cannabis, and substance use in general (Bühler et al., 2015; Gorwood et al., 2012; Jensen, 2016) and have demonstrated the polygenicity (multiple genes of small effects influencing a phenotype) of substance use behaviors (Knopik et al., 2016).

Additionally, the dopaminergic system has been studied extensively by candidate genes studies as a potential mechanism linked to substance use frequency. The dopaminergic system regulates the function of the neurotransmitter dopamine, which has been implicated in numerous inhibition related problem behaviors including substance use behaviors (Gorwood et al., 2012).

Substance use is linked to compulsive behaviors and distress alleviation, which are also linked to the dopaminergic system (Gorwood et al., 2012; Wise, 2004). A majority of studies have demonstrated that features of the dopaminergic system are associated with temperamental attributes such as sensation seeking (Duaux et al., 1998) and compulsiveness (Limosin et al., 2003), which could lead to substance use. However, other studies have demonstrated that dopamine receptors also play a role in learned or conditioned behaviors (Schultz, 2002) that results in high frequency of substance use. Dysregulation of the dopamine system (i.e. dysregulation in encoding of enzymes or dopamine related metabolism, increases in dopaminergic reward processes, modulation of dopamine levels in the cortical or limbic region, see Gorwood et al., 2012 for a full review) can reduce self-control and, therefore, increased substance use frequency (Hyman, et al., 2006; Sinha, 2008). Moreover, a dysregulated dopamine system can also increase instant gratification of rewarding feelings associated with substance use (Hyman, et al., 2006; Sinha, 2008). These factors could ultimately lead to the continuance of substance use behaviors. There is also some evidence suggesting a genetic basis for dopamine system functions (Cubells et al., 1997; Gorwood et al., 2012; Le Foll, Gallo, Le Strat, Lu, & Gorwood, 2009; Skrinskaya, Nikulina, & Popova, 1992). Single nucleotide polymorphism (SNPs) occurring in genes for SLC6A3 which codes for dopamine reuptake transporter, is associated with increased alcohol use (Le Strat et al., 2008). Similarly, an allele variation in DRD2 dopamine receptor genes (Taq1A polymorphism), has been studied extensively for substance use such as alcohol (Le Foll, Gallo, Strat, et al., 2009; Volkow, Wang, Maynard, et al., 2002; Volkow, Wang, Fowler, et al., 2002), cocaine (Moyer et al., 2011), and opioid (Doehring et al., 2009) use. Genes coding for the enzyme Catechol-*O*-methyltransferase (COMT) that metabolizes dopamine have also been implicated in more substance use (Tunbridge et al., 2012). Therefore, it is likely that genes coding for dopamine system-specific inherited risks could be associated with increased substance use frequency. In addition to testing overall substance use polygenic risk, the treatment of genetic influences in the current study includes the dopaminergic biological system specific genetic mechanism. Such an evaluation of a specific biological system is important as it could lead to implementation of effective treatments. For instance, if dopamine related risk is found to be a modifier of environmental (i.e., childhood maltreatment sub-groups and physical intimate partner violence victimization) influences for substance use frequency, then future trials could target this system to reduce substance use behaviors.

However, several of the dopamine gene association studies have not been subsequently replicated (Gorwood et al., 2012; Le Foll, Gallo, Strat, Lu, & Gorwood, 2009; Le Strat, Ramoz, & Gorwood, 2016). These null findings could be due to the small effect sizes for the associations found for dopamine specific genes (Gorwood et al., 2012), and computing a polygenic risk score which would aggregate across the multiple genes and their corresponding effect sizes could potentially deal with this small effect size problem. Therefore, in this study two risk scores or polygenic risk scores will be computed by combining multiple SNPs (i.e., the most commonly occurring genetic variants). The first polygenic risk score will include all SNPs that were significant from genome-wide association studies to assess overall substance use related genetic risk, and the second polygenic risk score will include significant dopamine related genes from single gene/candidate gene studies for substance use. Inclusion of SNPs and methods for calculation of polygenic risk scores are discussed in detail below.

Gene-Environment Interaction for Substance Use

Accumulating research demonstrates the role of gene-environment interactions in shaping phenotypes including substance use (Larsson, Viding, Rijsdijk, & Plomin, 2008; Legrand, Keyes, McGue, Iacono, & Krueger, 2008; Neiderhiser et al., 1999). Research has demonstrated that environmental and genetic influences are especially salient for the development of substance use problems (Hostinar, Lachman, Mroczek, Seeman, & Miller, 2015). Genetic influences and their interaction with adverse environments such as prenatal exposure to smoking (Bidwell et al., 2017), negative parenting (Creemers et al., 2011; Neiderhiser et al., 1999), traumatic life-events (Meyers et al., 2013), lack of parental monitoring (Enoch, 2012), and stress (Brody et al., 2012) can be associated with substance use behaviors. Some evidence also exists specifically for the effects of negative environments (e.g. life stress, adverse childhood experiences, chronic adversity, and trauma exposure) and dopamine specific genes (e.g. SLC6A3, COMT, DRD2) on substance use frequency (Brody et al., 2012; Schellekens et al., 2013; Sinha, 2009). However, the moderating influence of substance use polygenic risk score and substance use related dopamine polygenic risk score for the association of co-occurring childhood maltreatment sub-groups and substance use in adulthood and the association of physical intimate partner violence victimization and substance use in adulthood needs explicit examination to understand specific environmental paths that may influence substance use in adulthood (see Figure 4.1 for the proposed analytic model). According

to the diathesis-stress model (Ingram & Luxton, 2005; Sigelman & Rider, 2009), both environmental stressors (i.e., childhood maltreatment and physical intimate partner violence victimization in young adulthood) will individually interact with each genetic risk to influence substance use outcomes in adulthood within the hypothesized mediation model.

Present Study

To address the key gaps identified above, the present address the following aims:

Aim 1: Assess the direct impact of childhood maltreatment sub-group membership on physical intimate partner violence victimization during early adulthood and substance use frequency in adulthood.

Aim 2: Evaluate physical intimate partner violence victimization as a mediator of the association between sub-groups with similar childhood maltreatment exposures and substance use in adulthood.

Aim 3: Test genetic (polygenic risk score for substance use related genes and polygenic risk for substance use related dopamine genes) X environmental (physical intimate partner violence victimization and co-occurring childhood maltreatment exposure) influences on the likelihood for substance use (i.e. a moderated mediation model with moderation effects for both polygenic risk scores on the indirect and direct pathways; see Figure 4.1).

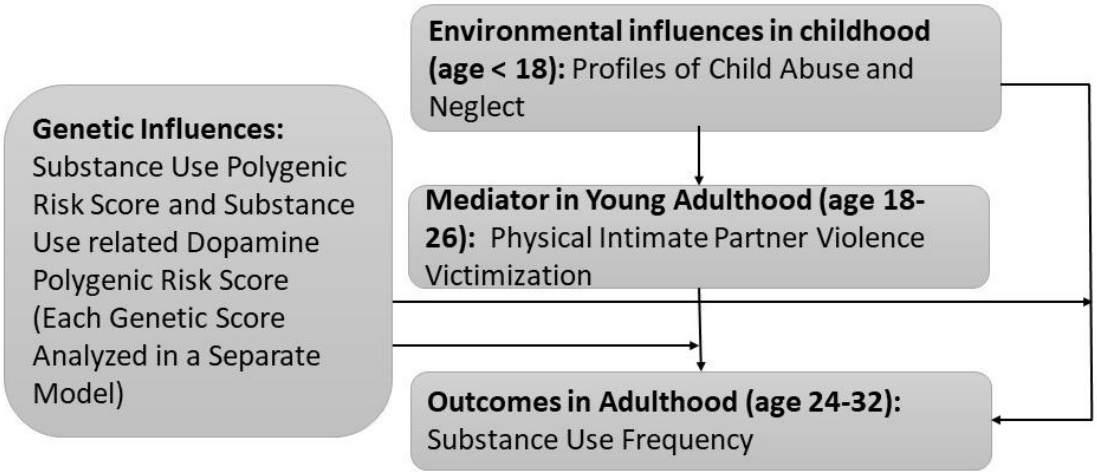

Figure 4.1 Analytic model for proposed aims of the study; separate models were estimated for each genetic risk score (substance use polygenic risk score and substance use related dopamine polygenic risk score)

Methods

Data

The data for the present study come from the National Longitudinal Study of Adolescent to Adult Health (Add Health; Harris, 2013) which includes a national cohort of adolescents followed over a 15-year period (N = 20,743) who were between the 7th and 11th grade at the first wave of data collection in 1994-95. Add Health used a clustered (i.e. students recruited from same schools) study design and oversampled for minority sub-groups. Data have already been collected at four waves from 1995 to 20008 (wave 1: 1994-95; wave 2:1996; wave 3: 2001-02; wave 4: 2008-09) via face-to-face and computer-assisted in-person interviews, and consist of a wide range of measures to assess different domains of well-being and health outcomes as well as neighborhood and environmental level data. At wave 3, a sub-section of the main sample consented to the extraction and archiving of DNA data (n = 12,234). The present study utilizes a sub-sample of 2,664 unrelated European Americans from the DNA archival data (n = 6,822 European Americans in the main sample) with retrospective childhood maltreatment reports. I restrict the sample to European Americans as prescribed by Add Health researchers and previous

genetic studies based on ancestral differences in inheritance of allelic frequencies (Braudt & Harris, 2018; Dudbridge, 2013).

Measures

Child Maltreatment

Childhood maltreatment prior to age 18 was assessed via retrospective measures that were administered at waves 3 and 4. At wave 3 and 4 two questions were used to assess: physical abuse (wave 3: "How often had your parents or other adult care-givers slapped, hit, or kicked you?"; "Before your 18th birthday, how often did a parent or adult caregiver hit you with a fist, kick you, or throw you down on the floor, into a wall, or down stairs?"), sexual abuse (wave 3: "How often had one of your parents or other adult care-givers touched you in a sexual way, forced you to touch him or her in a sexual way, or forced you to have sexual relations?"; wave 4: How often did a parent or other adult caregiver touch you in a sexual way, force you to touch him or her in a sexual way, or force you to have sexual relations?), and neglect (wave 3: "By the time you started 6th grade, how often had your parents or other adult care-givers left you home alone when an adult should have been with you?"; "How often had your parents or other adult care-givers not taken care of your basic needs, such as keeping you clean or providing food or clothing?"). Responses on these items assessed how many times the individual experienced each type of maltreatment and ranged from 1-11 (i.e. one time to more than 10 times). Mean scores across items was used to get average exposure levels for physical abuse, sexual abuse, and neglect. Emotional abuse was assessed by a single item at wave 4 ("Before your 18th birthday, how often did a parent or other adult caregiver say things that really hurt your feelings or made you feel like you were not wanted or loved?") and responses were recorded on the same scale as the other maltreatment items. Latent profile analysis of the four childhood maltreatment types (physical abuse, sexual abuse, emotional abuse, and neglect) was used to determine sub-groups with similar maltreatment exposure based on both type and frequency of exposure.

Physical Intimate Partner Violence Victimization

Self-reported items on Add-health created questions (Harris, 2013) were used to assess physical intimate partner violence victimization in the last 12 months at wave 3 when the

respondents were young adults or between the ages of 18 to 26 (α = .75). Three items were used to assess physical intimate partner violence victimization and included: how often the respondent's partner has done the following to the respondent in the past 12 months: 1. caused physical injury, 2. thrown things or threatened violence, and 3. hit, slap or kicked. Items were scored from 0 (never), 1 for once, 2 for twice, 3 for 3 to 5 times, 6 for 6 to 10 items, 11 for 11 to 20 time and 21 (more than 20 times). Items were coded at the lower end of the interval to get conservative estimates of overall physical intimate partner violence victimization exposure. A sum score across items was used to assess overall physical intimate partner violence victimization.

Substance Use Frequency

Participants reported on their marijuana, alcohol, and illicit drug use (LSD, PCP, ecstasy, mushrooms, speed, ice, heroin, or pills) in the last 30 days at waves 4, when the respondents were between the ages of 24 and 32. Alcohol use was assessed by number of days the participants used alcohol. Since the marijuana and illicit drug use were measured by no. of times individuals used these substances in the last 30 days, the marijuana and illicit drug use scales were capped at 30 for individuals who reported using these drugs 30 or more times in the last 30 days. This was done to get an approximation on the average no. of days marijuana was used (nonetheless, substance specific models were also estimated as outlined below). Average substance use was assessed as done in previous research (see Litwiller & Brausch, 2013; Park-Lee & Tice, 2017) by creating an average score across all substance use types at wave 4.

Substance Use Polygenic Risk Score

Substance use related genes were obtained from multiple previous genome-wide studies (included genome-wide association for substance use, alcohol use, marijuana use, and illicit drug use) to create a substance use polygenic risk score. Single nucleotide polymorphisms or SNPs for these genes were used to create the substance use polygenic risk score. I only included single nucleotide polymorphisms that were significant at the genome-wide significance levels ($p < 5 \times 10^{-8}$). The initial list comprised 34 SNPs (18 genome-wide studies, see chapter 1 for a full list of all studies included to create the initial list of 34 SNPs) and the final list was pared down to 15

SNPs (from 5 total genome-wide studies; see Table 4.1) following the below mentioned quality control steps.

Quality control measures included: test of missingness at the individual level (threshold >.01; dropped = 0 SNPs), test of missingness at the each marker (threshold >.01; dropped = 0 SNPs), test of minor allele frequency (threshold <.01; dropped = 0), test of Hardy-Weinberg exact test (dropped = 13 SNPs), test of linkage disequilibrium (threshold >.3; dropped = 1 SNP) and removal of any SNPS that did not have an effect size estimate (dropped = 5 SNPs) as prescribed for creating substance use polygenic risk scores (Marees et al., 2018). The final 15 substance use SNPs that were retained are included in Table 4.1.

The effect size estimates for these SNPs from the genome-wide studies included both Beta weights and Odds Ratios which were converted in Cohen Ds to get a single effect size estimate (Borenstein et al., 2009). Then, the effect allele for each SNP was multiplied with the corresponding Cohen's D and then summed across all the SNPs to create a substance use polygenic risk score for each individual (see Table 4.1).

Substance Use Related Dopamine Polygenic Risk Score

A second substance use related dopamine polygenic risk score was created using similar steps as the substance use polygenic risk score. In the absence of a genome-wide association study for dopamine genes, the SNPs for the substance use related dopamine polygenic risk score were obtained from 11 candidate gene studies (see chapter 1 for the full list of studies, genes and SNPs) that link specific dopaminergic genes to substance use, alcohol use, marijuana use, and illicit drug use. These SNPs are summarized in Table 4.1. Quality control steps for this score were identical to those for the substance use polygenic risk score outlined above. 19 SNPs were included at the outset of the study which were reduced to a total 6 SNPs after quality control steps (dropped 10 SNPs after Hardy-Weinberg exact test, dropped SNPs 2 after test of linkage disequilibrium, and dropped 1 SNP that did not have an effect size estimate). Since all the studies for dopamine SNPs used odds ratios as their effect size estimate, a probability value was created as an effect size estimate, and multiple odds ratios for a specific SNP (n = 1) were averaged prior to converting them into probability values. The effect allele for each SNP was then multiplied with the

corresponding probability values and values across SNPs were summed to create a single composite index of substance use related dopamine polygenic risk score.

Table 4.1 Gene list for substance use polygenic risk score and substance use related dopamine polygenic risk score

Substance Use Related SNPs Retained to Create Substance Use Polygenic Risk Score

Gene	Descriptive Name	SNP	Effect Allele	Cohen's D	GWAS Study	Sample
PGM1	phosphoglucomutase 1	rs2749097	G	0.25	https://doi.org/10.1093/hmg/ddr272	Swiss and Australian samples (European Ancestry) between the ages of 35 and 75
GCKR	glucokinase regulator	rs11127048	G	0.07	https://doi.org/10.1038/mp.2017.153	European Ancestry from United Kingdom; ages 30 to 69
PECR	peroxisomal trans-2-enoyl-CoA reductase	rs7590720	G	0.17	https://doi.org/10.1073/pnas.0911109107	European-American and African-American ancestry; ages 18-77
CADM2	cell adhesion molecule 2	rs9841829	G	0.04	https://doi.org/10.1038/mp.2017.153	European Ancestry from United Kingdom; ages 30 to 69
TF	transferrin	rs1799899	A	0.90	https://doi.org/10.1093/hmg/ddr272	Swiss and Australian samples (European Ancestry) between the ages of 35 and 75
TF	transferrin	rs3811647	A	0.78	https://doi.org/10.1093/hmg/ddr272	Swiss and Australian samples (European Ancestry) between the ages of 35 and 75
SRPRB	SRP receptor subunit beta	rs1534166	A	0.60	https://doi.org/10.1093/hmg/ddr272	Swiss and Australian samples (European Ancestry) between the ages of 35 and 75
CRYGS	crystallin gamma S	rs1868152	A	1.52	https://doi.org/10.1007/s10519-013-9606-x	Caucasian ancestry; average age: 42.8
KLB	klotho beta	rs28712821	A	0.06	https://doi.org/10.1038/mp.2017.153	European ancestry from United Kingdom; ages 30 to 69

Table 4.1 continued

ADH1B	alcohol dehydrogenase 1B (class I), beta polypeptide	rs145452708	C	0.07	https://doi.org/10.1038/mp.2017.153	European ancestry from United Kingdom; ages 30 to 69
HFE	homeostatic iron regulator	rs1800562	A	1.72	https://doi.org/10.1093/hmg/ddr272	Swiss and Australian samples (European Ancestry) between the ages of 35 and 75
OPRM1	opioid receptor mu 1	rs73568641	C	1.40	https://doi.org/10.1007/s10519-013-9606-x	Caucasian ancestry; average age: 42.8
UTP20	UTP20 small subunit processome component	rs57083693	C	0.17	https://doi.org/10.1007/10.1016/j.drugalcdep.2014.05.023	European descent under the age of 18
ARID4A	AT-rich interaction domain 4A	rs8012947	A	0.03	https://doi.org/10.1038/mp.2017.153	European Ancestry from United Kingdom; ages 30 to 69
RGMA	repulsive guidance molecule BMP co-receptor a	rs12442183	T	1.13	https://doi.org/10.1016/j.biopsych.2017.12.016	European Ancestry; average age 37

Dopamine Related Substance Use SNPs Retained to Create Substance Use Related Dopamine Genes Polygenic Risk Score

Gene	Descriptive Name	SNP	Minor/Effect Allele	Probability	CGS Study https://DOI:10.1111/j.1530-0277.2010.01353.x https://doi:10.1097/YPG.0b013e32832a4f7b https://doi.org/10.1093/alcalc/agv114	Sample
SLC6A3	solute carrier family 6 member 3	rs10052016	G	0.57		European ancestry from Ireland
SLC6A3	solute carrier family 6 member 3	rs6350	G	0.74		European ancestry between the ages of 21 and 75
DRD2	dopamine receptor D2	rs877138	G	0.60		European ancestry from Spain, median age ranging from 46-51

DRD2	dopamine receptor D2	rs1800497	A	0.58	https://doi.org/10.1093/alcalc/agv114	European and Asian adults
DRD2	dopamine receptor D2	rs1799978	C	0.69	https://10.1097/FPC.0b013e328320a3fd	European; ages 22-58
COMT	catechol-O-methyltransferase	rs165774	G	0.66	https://doi.org/10.1186/1744-9081-7-51	Caucasian; average age 36.8

GWAS - Genome-wide association study; CGS - Candidate gene study

Covariates

Biological sex, parental education (years of education), and respondent's highest educational attainment were included as covariates and age of the respondent was included as a time-varying covariate. Direct acyclic graphs were along with prior research was used for covariate selection (Weng, Hsueh, Messam, & Hertz-Picciotto, 2009).

Analytic Strategy

Latent Profile Analysis

Childhood maltreatment exposure based on type and frequency of exposure for each maltreatment type was used to estimate latent profiles with homogenous sub-groups experiencing similar type and levels of exposure. Four statistical model fit criteria (AIC, BIC, adjusted-BIC and entropy) as well as findings from previous research were used to determine the best fitting model. The AIC, BIC, and adjusted-BIC are relative model fit indices with lower numbers indicating better model fit. The entropy is indicative of error in classification and ranges from 0-1 with values closer to 1 indicating better sub-group classification. Additionally, the large sample size in this research allows us to extrapolate more classes that are relatively stable even when the proportion of individuals in each class may be small. Class membership probability was used to classify individuals into specific classes (Nylund-Gibson & Choi, 2018). Class solutions were tested for class 1-4 and the 3-class solution emerged as the optimal class (explained in detail in the results section).

Direct Effects

A direct effect model was estimated where I tested the direct effects of maltreatment sub-groups on physical intimate partner violence victimization (model 1; Figure 4.2). The direct effects of covariates were included for physical intimate partner violence victimization in all models.

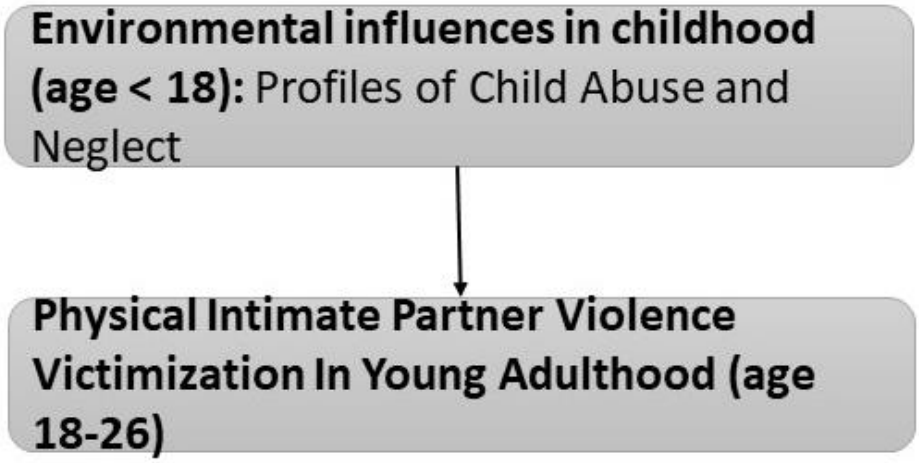

Figure 4.2 Association between childhood maltreatment sub-groups and physical intimate partner violence victimization

Two additional direct effect models were estimated, one model where I tested the direct effects of substance use polygenic risk score, maltreatment sub-groups, physical intimate partner violence victimization, and covariates on substance use (model 2; Figure 4.3) and another where I used the substance use related dopamine polygenic risk score in place of the general substance use polygenic risk score (model 3; Figure 4.4). In model 2, the interaction between polygenic risk for substance use and maltreatment sub-groups and the interaction between polygenic risk for substance use and physical intimate partner violence victimization was also assessed for substance use. Similarly, in model 3, the interaction between dopamine polygenic risk for substance use related and maltreatment sub-groups and the interaction between substance use related dopamine polygenic risk and physical intimate partner violence victimization was assessed for substance use.

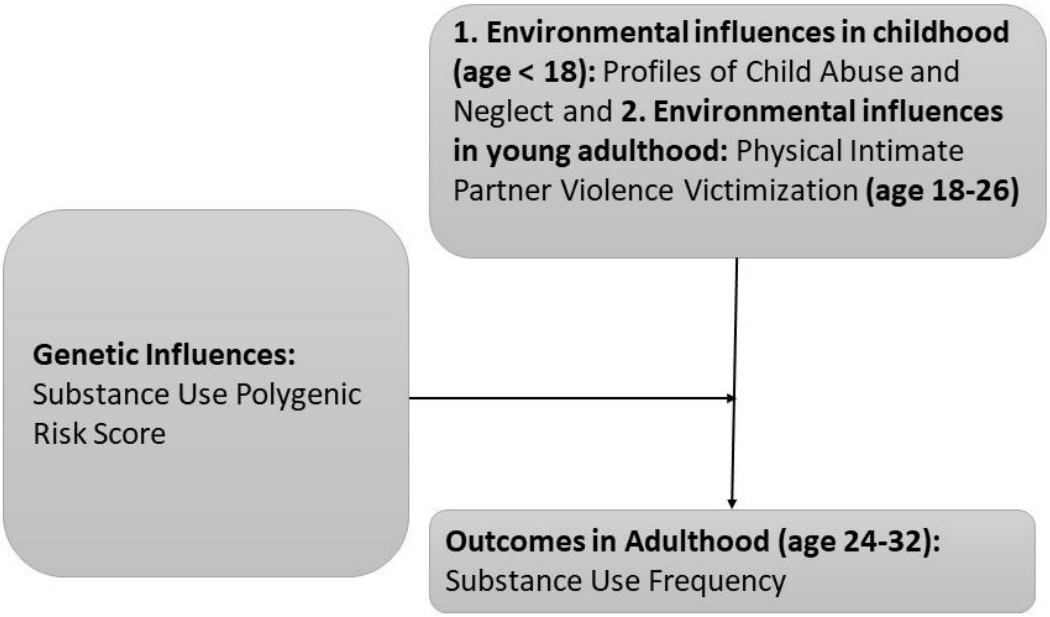

Figure 4.3 Genetic moderation by substance use polygenic risk score for the association between each environmental factor (i.e., childhood maltreatment sub-groups and physical intimate partner violence victimization) and substance use frequency in adulthood

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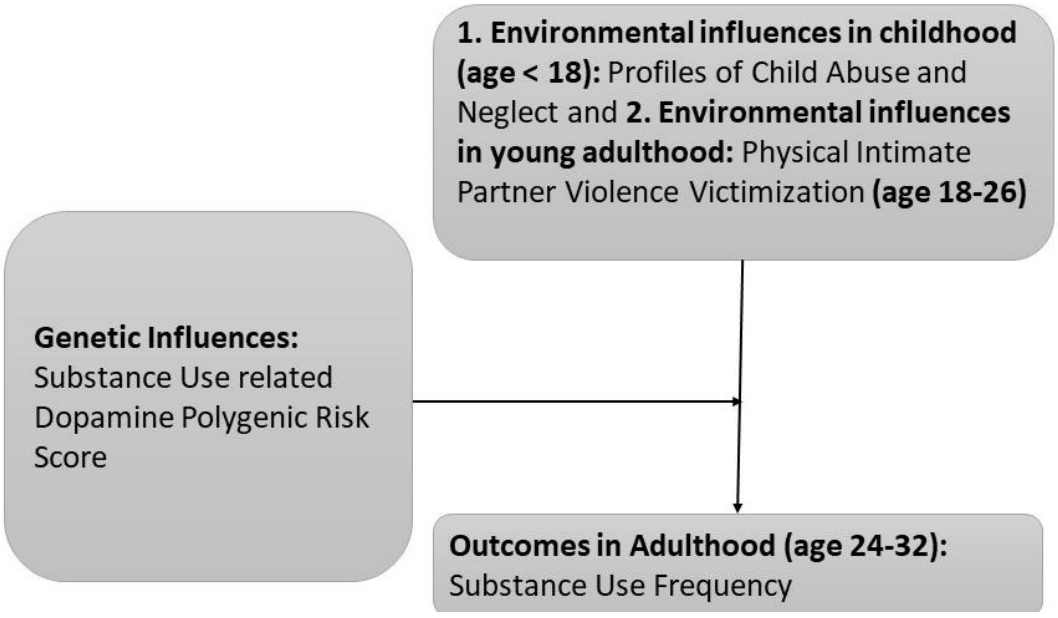

Figure 4.4 Genetic moderation by substance use related dopamine polygenic risk score for the association between the two environmental factors (i.e., childhood maltreatment sub-groups and physical intimate partner violence victimization) and substance use frequency in adulthood

Indirect Effects

Two mediation (indirect effect) models were estimated next (models 4 and 5; Figure 4.5). In these models, the indirect association of maltreatment sub-groups via physical intimate partner violence victimization on substance use was estimated using product of coefficient methods (MacKinnon et al., 2007). Two separate mediation models were estimated, one for each polygenic risk score.

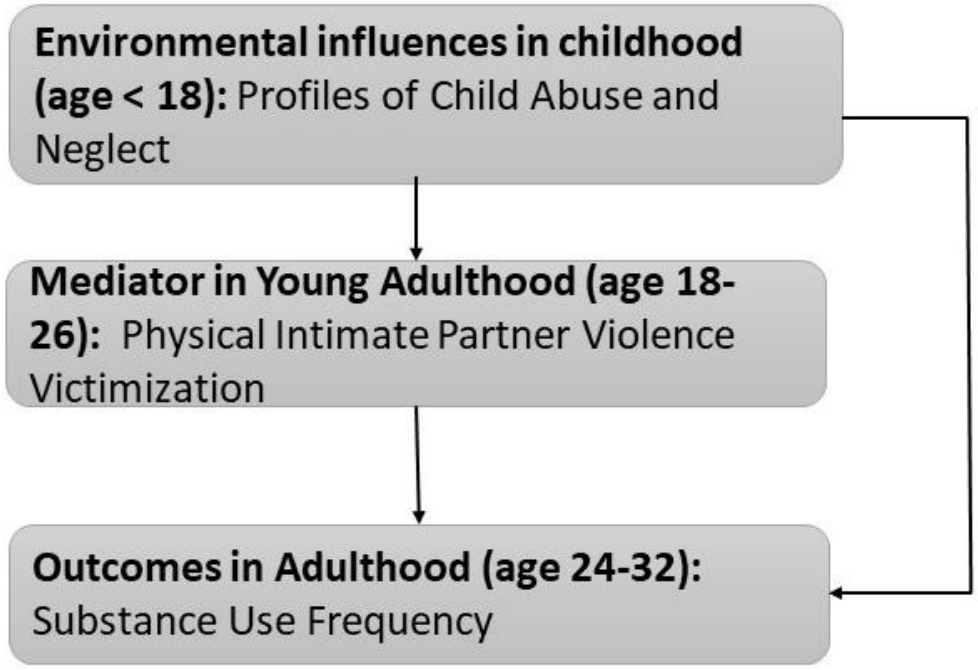

Figure 4.5 Mediation or indirect effects model from childhood maltreatment sub-groups to substance use frequency in adulthood via physical intimate partner violence in young adulthood

Moderated-Mediation

Moderation of substance use polygenic risk score (model 6; Figure 4.1) was tested on two pathways: 1) the direct pathway from childhood maltreatment exposure to substance use, and 2) the direct pathway from physical intimate partner violence victimization to substance use and was evaluated for each of the mediation models separately (i.e., moderated-mediation) using model constraints following procedures outlined by Stride and colleagues (see model 15 in Stride, Gardner, Catley, & Thomas, 2015). The syntax outlined by Stride and colleagues, is an adapted version of the moderated-mediation models by Hayes and colleagues (Hayes, 2017). Specifically, model constraints were used to probe effects at medium (mean), high (+1 *SD*) and low levels (-1 *SD*) of substance use polygenic risk score on the 1) direct pathway from childhood maltreatment exposure to substance use and 2) the direct pathway from physical intimate partner violence victimization to substance use for each mediation model, wherein the interaction terms between substance use polygenic risk and maltreatment sub-groups and the interaction terms between substance use and physical intimate partner violence victimization were probed at low, medium, and high levels of substance use polygenic risk score. Another model (model 7; Figure 4.1) was estimated that is identical to model 6, except the substance use related dopamine polygenic risk score was used in place of the general substance use polygenic risk score.

Covariates were included for the outcome (i.e. substance use) and the mediator (i.e. physical intimate partner violence victimization) across all models 1-7. All descriptive statistics were estimated using *SAS 9.4* software and analytic models were estimated using *Mplus 7.4* (L. Muthén & Muthén, 2020) software. Full information maximum likelihood was used to handle item missing data as this procedure improves precisions of estimates by including all available data and reduces bias due to missing data (Acock, 2012). Models were corrected for complex sampling features of the Add Health data by the use of probability weights and correction of clustering of data. Bootstrap procedures (10,000 bootstraps) and numerical integration were used to estimate both moderated-mediation models.

Post-hoc Models

Post-hoc direct, indirect and moderated-mediation models were estimated for specific substances – alcohol, marijuana, and illicit drug use – for both polygenic risk scores.

Results

For the latent profile analysis, I tested a 2-class, 3-class and 4-class solutions. The model fit for the 2-class solution was AIC =129430.68; BIC = 129600.54; adjusted-BIC = 129524.27; entropy = 0.99; for the 3-class solution the model fit was AIC =129430.68; BIC = 129600.54; adjusted-BIC =129524.27; entropy =0.99; and the fit for the four class solution was AIC =110138.05; BIC = 110343.30; adjusted-BIC = 110251.14; entropy =0.97. Based on these model fit statistics, the 4-class solution had the best fit, however, this model did not replicate when random starts were increased indicating the model obtained did not reach a global solution (i.e. the log likelihood from the maximum likelihood estimator did not converge at a single value when a certain number of iterations were performed). Therefore, the 3-class solution was selected as optimal because it had better model fit than the 2-class solution and mapped on theoretically to classes derived in previous research (explained below in the discussion section). Descriptive labels were assigned for the 3-class solution and included Sub-group 1: High sexual abuse sub-groups with high levels of all other maltreatment exposure (high sexual abuse sub-group); Sub-group 2: High physical abuse sub-group with exposure to emotional abuse and neglect (high physical abuse sub-group); and Sub-group 3: Low exposure to all maltreatment types or normative sub-group. Figure 4.6 maltreatment exposure by type and frequency for each maltreatment sub-group.

Descriptive statistics for each maltreatment sub-sub-group and the entire sample are presented in Table 4.2 and bivariate correlations are presented in Table 4.3.

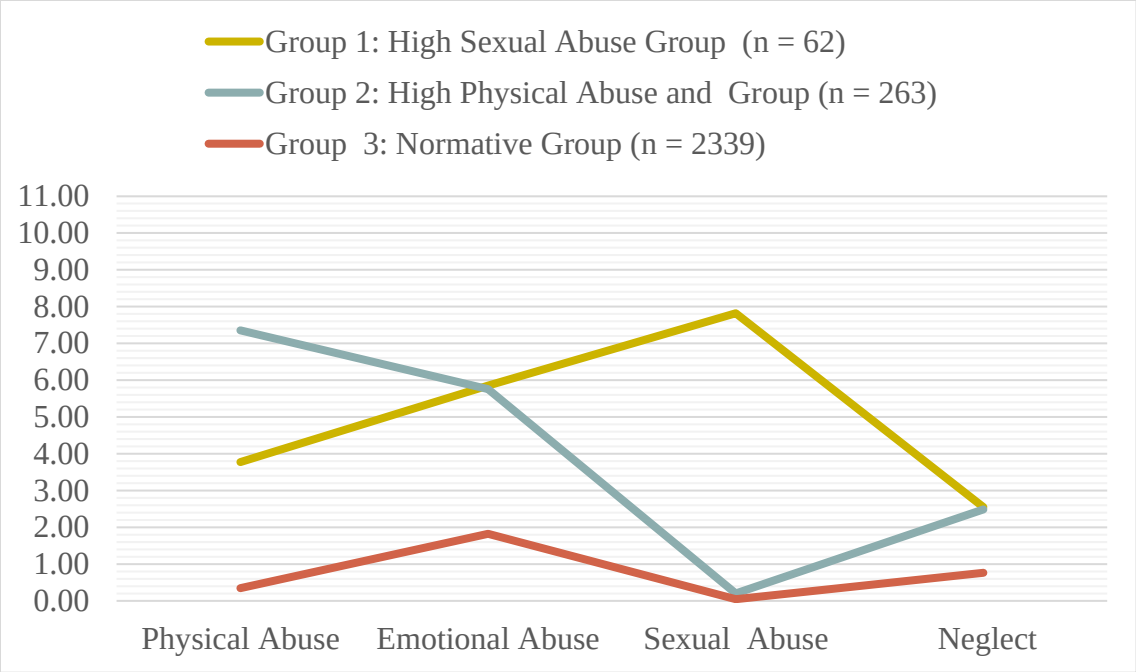

Figure 4.6 Maltreatment sub-groups based on latent profile analysis for childhood maltreatment exposures prior to age 18 based on both types of exposure and maltreatment severity

Table 4.2 Descriptive statistics by each sub-group and for the entire sample

	Complete Sample (n = 2,664)		Sub-group 1: High Sexual Abuse Sub-group (*n* = 53)		Sub-group 2: High Physical Abuse Sub-group (*n* = 207)		Sub-group 3: Normative Sub-group (*n* = 2,404)	
Key Variables	*Mean*	*Std. Dev*	*Mean*	*Std. Dev*	*Mean*	*Std. Dev*	*Mean*	*Std. Dev*
Sexual Abuse	0.21	1.19	7.82	2.59	0.20	0.63	0.05	0.27
Physical Abuse	0.96	2.24	3.77	4.09	7.36	2.39	0.34	0.78
Emotional Abuse	2.22	3.61	5.85	4.96	5.75	4.89	1.82	3.20
Neglect	0.93	1.89	2.55	3.75	2.49	3.09	0.77	1.60
Age Wave 3	21.93	1.75	21.98	1.85	21.91	1.61	21.93	1.76
Age Wave 4	28.67	1.76	28.69	1.83	28.59	1.63	28.67	1.77
Substance Use Polygenic Risk Score	0.13	0.05	0.12	0.05	0.13	0.05	0.13	0.05
Substance use Frequency	3.52	5.07	2.83	10.97	4.08	5.56	3.52	5.07
Physical Intimate Partner Violence Victimization	1.67	5.85	4.87	10.97	2.44	6.94	1.67	5.85
Parent Education (in years)	13.28	2.33	13.27	2.14	13.06	2.23	13.30	2.34
Respondent's Education (in years)	14.27	2.10	13.40	2.25	13.89	1.95	14.32	2.11
Percentage	*Mean*	*Std. Dev*	*Mean*	*Std. Dev*	*Mean*	*Std. Dev*	*Mean*	*Std. Dev*
Gender: Male	47.22%	0.50	7.55%	0.27	52.17%	0.50	47.67%	0.50

Table 4. 3 Bi-variate correlation among study variables

	Physical Intimate Partner Violence Victimization	Substance Use Frequency	Sexual Abuse	Physical Abuse	Emotional Abuse	Neglect	Substance Use Polygenic Risk Score	Substance Use Related Dopamine Polygenic Risk Score	Age at Wave 3	Age at Wave 4	Parent Education	Biological Sex	Respondent's Education Level
Physical Intimate Partner Violence Victimization	1	0.02	0.08*	0.08*	0.13*	0.03	-0.04*	-0.01	0.02	0.01	-0.03	-0.10*	-0.06*
Substance Use Frequency	-	1	0.01	0.03	-0.03	0.03	0.02	-0.01	-0.04	-0.04	0.058*	0.23*	-0.09*
Sexual Abuse	-	-	1	0.23*	0.17*	0.16*	0.00	-0.00	0.00	-0.00	-0.01	-0.12*	-0.08*
Physical Abuse	-	-	-	1	0.43*	0.32*	0.01	-0.04*	0.01	0.00	-0.05*	0.00	-0.08*
Emotional Abuse	-	-	-	-	1	0.22*	-0.02	-0.01	0.00	-0.01	0.01	-0.11*	-0.05*
Neglect	-	-	-	-	-	1	-0.01	-0.01	-0.06*	-0.06*	-0.06*	0.03	-0.06*
Substance Use Polygenic Risk Score	-	-	-	-	-	-	1	0.01	0.01	-0.00	-0.01	0.05	-0.04*
Substance Use Related Dopamine Polygenic Risk Score	-	-	-	-	-	-	-	1	-0.03	-0.03)	-0.02	-0.02	-0.02

Table 4.3 continued

Age at Wave 3	-	-	-	-	-	-	-	-	1	0.97*	-0.06*	0.06*	-0.02
Age at Wave 4	-	-	-	-	-	-	-	-	-	1	-0.05*	0.07*	-0.01
Parent Education	-	-	-	-	-	-	-	-	-	-	1	0.02	0.38*
Biological Sex	-	-	-	-	-	-	-	-	-	-	-	1	-0.12*
Respondent's Education Level	-	-	-	-	-	-	-	-	-	-	-	-	1

$p < 0.0$

Direct Effects for Physical Intimate Partner Violence Victimization (Model 1; Figure 4.2)

Membership in the high sexual abuse sub-group (β = 0.05; p = 0.23) or the high physical abuse sub-group (β = 0.03; p = 0.34) was not associated with physical intimate partner violence victimization (see Table 4.4).

Direct and Indirect Effects of the Substance Use Polygenic Risk Score Model (Model 2 and Model 4)

Model 2 direct effects (Figure 4.3) are summarized in Table 4.4 and model 4 (Figure 4.5) indirect effects are summarized in Table 4.5. Physical intimate partner violence victimization in young adulthood was not associated with subsequent self-reports of substance use frequency in adulthood (β = 0.01; p = 0.81). Membership in the high sexual abuse sub-group (β = -0.01; p = 0.74) or the high physical abuse sub-group (β = 0.04; p = 0.14) were also not associated with substance use frequency in adulthood.

The interaction between substance use polygenic risk score and high sexual abuse sub-group (β = 0.00; p = 0.90), the interaction between substance use polygenic risk score and high physical abuse sub-group (β = -0.03; p = 0.23), and the interaction between substance use polygenic risk score and physical intimate partner violence victimization (β = 0.01p = 0.76) in young adulthood were not associated with substance use frequency in adulthood.

Furthermore, in Model 4 (Figure 4.5), physical intimate partner violence victimization in young adulthood did not mediate the associations between 1) high sexual abuse sub-group and substance use frequency in adulthood (β = 0.00; p = 0.81) and 2) high physical abuse sub-group and physical substance use frequency in adulthood (β = 0.00; p = 0.82).

Table 4.4 Direct association with physical intimate partner violence victimization in young adulthood and substance use frequency in adulthood (substance use polygenic risk score model)

Substance Use Frequency			
	β	*s.e.*	*p*
Physical Intimate Partner Violence Victimization	0.01	0.03	0.81
High Sexual Abuse Sub-group	-0.01	0.02	0.74
High Physical Abuse Sub-group	0.04	0.03	0.14
Substance Use Polygenic Risk Score	-0.02	0.03	0.45
Substance Use Polygenic Risk Score*High Sexual Abuse Sub-group	0.00	0.02	0.90
Substance Use Polygenic Risk Score*High Physical Abuse Sub-group	-0.03	0.03	0.23
Substance Use Polygenic Risk Score*Physical Intimate Partner Violence Victimization	0.01	0.03	0.76
Respondent's Education Level	-0.05	0.04	0.19
Parent’s Education Level	0.09	0.03	0.01
Respondent's Age at Wave 3	-0.26	0.12	0.03
Respondent's Age at Wave 4	0.18	0.12	0.14
Biological Sex	0.25	0.03	0.00
Physical Intimate Partner Violence Victimization			
	β	*s.e.*	*p*
High Sexual Abuse Sub-group	0.05	0.05	0.23
High Physical Abuse Sub-group	0.03	0.03	0.34
Respondent's Education Level	-0.05	0.03	0.12
Parent’s Education Level	0.03	0.03	0.41
Respondent's Age at Wave 3	-0.01	0.11	0.92
Respondent's Age at Wave 4	0.03	0.11	0.79
Biological Sex	-0.12	0.02	0.00

Table 4.5 Indirect effects from childhood maltreatment sub-groups to substance use in adulthood via physical intimate partner violence victimization in young adulthood (substance use polygenic risk score model)

Substance Use Frequency						
	High Sexual Abuse Sub-group			High Physical Abuse Sub-group		
	β	*s.e.*	*p*	β	*s.e.*	*p*
Physical Intimate Partner Violence Victimization	0.00	0.00	0.81	0.00	0.00	0.82

Note: Models were conditioned on all covariates for both the outcome and mediator

Direct and Indirect Effects of the Substance Use Related Dopamine Polygenic Risk Score Model (Model 3 and Model 5)

Model 3 (Figure 4.4) direct effects are summarized in Table 4.6 and model 5 (Figure 4.5) indirect effects are summarized in Table 4.7. Physical intimate partner violence victimization in young adulthood was not associated with subsequent self-reports of substance use frequency in adulthood (β = 0.01; p = 0.81). Membership in the high sexual abuse sub-group (β = -0.01; p = 0.74) or the high physical abuse sub-group (β = 0.04; p = 0.14) were also not associated with substance use frequency in adulthood.

The interaction between substance use related dopamine polygenic risk score and high sexual abuse sub-group (β = 0.00; p = 0.83), the interaction between substance use related dopamine polygenic risk score and high physical abuse sub-group (β = -0.02; p = 0.45), and the interaction between substance use related dopamine polygenic risk score and physical intimate partner violence victimization (β = 0.01; p = 0.80) in young adulthood were not associated with substance use frequency in adulthood.

Furthermore, in Model 5 (Figure 4.5), physical intimate partner violence victimization in young adulthood did not mediate the associations between 1) high sexual abuse sub-group and substance use frequency in adulthood (β = 0.00; p = 0.81) and 2) high physical abuse sub-group and physical substance use frequency in adulthood (β = 0.00; p = 0.83).

Table 4.6 Direct association with physical intimate partner violence victimization in young adulthood and substance use in adulthood (substance use related dopamine polygenic risk model)

Substance Use Frequency			
	β	*s.e.*	*p*
Physical Intimate Partner Violence Victimization	0.01	0.03	0.81
High Sexual Abuse Sub-group	-0.01	0.02	0.76
High Physical Abuse Sub-group	0.04	0.03	0.14
Substance Use Polygenic Risk Score	-0.04	0.04	0.33
Substance Use Polygenic Risk Score*High Sexual Abuse Sub-group	0.00	0.02	0.83
Substance Use Polygenic Risk Score*High Physical Abuse Sub-group	-0.02	0.03	0.45
Substance Use Polygenic Risk Score*Physical Intimate Partner Violence Victimization	0.01	0.03	0.80
Respondent's education level	-0.05	0.04	0.19
Parent’s Education Level	0.09	0.03	0.01
Respondent's Age at Wave 3	-0.25	0.12	0.04
Respondent's Age at Wave 4	0.17	0.12	0.17
Biological Sex	0.24	0.03	0.00

Table 4.7 Indirect effects from childhood maltreatment sub-groups to substance use in adulthood via physical intimate partner violence victimization in young adulthood (substance use related dopamine polygenic risk score model)

Substance Use Frequency						
	High Sexual Abuse Sub-group			High Physical Abuse Sub-Group		
	β	*s.e.*	*p*	β	*s.e.*	*p*
Physical Intimate Partner Violence Victimization	0.00	0.00	0.81	0.00	0.00	0.83

Note: Indirect effects were estimated above and beyond all covariates and interaction between substance use genetic risk

Moderated-Mediation Substance Use Polygenic Risk Score Model (Model 6; Figure 4.1)

The indirect pathway (within the mediation model) from physical intimate partner violence victimization in young adulthood to substance use frequency was not moderated by polygenic risk for substance use (β = 0.00; p = 0.80). Similarly, the pathway from physical intimate partner violence victimization in young adulthood to substance use frequency in adulthood was not moderated by polygenic risk for substance use (β = 0.00; p = 0.82).

The direct pathway from high sexual abuse sub-group to substance use frequency in adulthood was not moderated by polygenic risk for substance use (β = 0.00; p = 0.65). Similarly, the direct pathway from high physical abuse sub-group to substance use frequency in adulthood was not moderated by polygenic risk for substance use (β = 0.05; p = 0.30).

Moderated-Mediation of the Substance Use Related Dopamine Polygenic Risk Score Model (Model 7)

The indirect pathway within the mediation model from physical intimate partner violence victimization to substance use frequency in young adulthood was not moderated by substance use related dopamine polygenic risk score (β = 0.00; p = 0.85) within the mediation model. The direct pathway from high sexual abuse sub-group to substance use in adulthood was not moderated by

substance use related dopamine polygenic risk score (β = -0.01; p = 0.85). Similarly, the direct pathway from high physical abuse sub-group to substance use in adulthood was not moderated by substance use related dopamine polygenic risk score (β = 0.03; p = 0.85).

Post-hoc Models for Specific Substance Use

Direct Effects of Substance Use Polygenic Risk Score Model

Direct effects for specific substances – alcohol use, marijuana use, and illicit drug use are summarized in Table 4.8. Physical intimate partner violence victimization in young adulthood was not associated with alcohol (β = 0.01; p = 0.72), marijuana (β = 0.04; p = 0.29) or illicit drug (β = -0.02; p = 0.61) use frequencies in adulthood. Membership in the high sexual abuse sub-group was associated with lower illicit drug use frequency (β = -0.05; p = 0.00) but not with marijuana use frequency (β = -0.01; p = 0.80) or alcohol use frequency (β = 0.00; p = 0.98) in adulthood. Membership in the high physical abuse sub-group was associated with higher marijuana use frequency (β = 0.09; p = 0.02) but was not associated with alcohol use frequency (β = 0.00; p = 0.92) or illicit drug use frequency (β = 0.00; p = 0.98) in adulthood. For both statistically significant associations, the effect size estimates were small.

Additionally, there was a small association between substance use polygenic risk score and lower illicit drug use frequency (β = -0.10; p = 0.04) but there was no association between substance use polygenic risk score and alcohol use frequency (β = -0.02; p = 0.55) or marijuana use frequency (β = -0.01; p = 0.85) in adulthood. Substance use polygenic risk score did not moderate the association between the high sexual abuse sub-group membership and marijuana use frequency (β = -0.01; p = 0.64), alcohol use frequency (β = 0.01; p = 0.30), or illicit drug use frequency (β = 0.00; p = 0.74). There was also no interaction between high physical abuse sub-group and substance use polygenic risk score for marijuana use frequency (β = -0.02; p = 0.58), alcohol use frequency (β = -0.03; p = 0.25) or illicit drug use frequency (β = -0.04; p = 0.14). Finally, interaction between physical intimate partner violence victimization and substance use polygenic risk score for alcohol use frequency (β = -0.01; p = 0.58), marijuana use frequency (β = 0.00; p = 0.98) or illicit drug use frequency (β = 0.01; p = 0.72) were also not different than zero.

Table 4.8 Direction association with physical intimate partner violence victimization in young adulthood and substance specific use in adulthood (substance use polygenic risk score model)

Substance Use Frequency									
	Alcohol Use Frequency			Marijuana Use Frequency			Illicit Drug Use Frequency		
	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*
Physical Intimate Partner Violence Victimization	0.01	0.03	0.72	0.04	0.03	0.29	-0.02	0.03	0.61
High Sexual Abuse Sub-group	0.00	0.02	0.98	-0.01	0.03	0.80	-0.05	0.01	0.00
High Physical Abuse Sub-group	0.00	0.03	0.92	0.09	0.04	0.02	0.00	0.05	0.98
Substance Use Polygenic Risk Score	-0.02	0.03	0.55	-0.01	0.04	0.85	-0.10	0.05	0.04
Substance Use Polygenic Risk Score*High Sexual Abuse Sub-group	0.01	0.01	0.30	-0.01	0.03	0.64	0.00	0.01	0.75
Substance Use Polygenic Risk Score*High Physical Abuse Sub-group	-0.03	0.02	0.25	-0.02	0.04	0.58	-0.04	0.03	0.14
Substance Use Polygenic Risk Score*Physical Intimate Partner Violence Victimization	-0.01	0.02	0.58	0.00	0.04	0.98	0.01	0.03	0.72
Respondent's Education Level	0.05	0.04	0.20	-0.17	0.05	0.00	-0.07	0.07	0.31
Parent’s Education Level	0.14	0.03	0.00	-0.01	0.05	0.77	-0.02	0.07	0.72
Respondent's Age at Wave 3	-0.32	0.12	0.01	-0.08	0.17	0.65	-0.26	0.24	0.28
Respondent's Age at Wave 4	0.27	0.12	0.02	0.00	0.18	0.98	0.24	0.24	0.32
Biological Sex	0.22	0.04	0.00	0.19	0.04	0.00	-0.04	0.05	0.48

Table 4.8 continued

Physical Intimate Partner Violence Victimization									
	β	*s.e.*	*p*						
High Sexual Abuse Sub-group	0.05	0.05	0.23	-	-	-	-	-	-
High Physical Abuse Sub-group	0.03	0.03	0.34	-	-	-	-	-	-
Respondent's Education Level	-0.05	0.03	0.12	-	-	-	-	-	-
Parent’s Education Level	0.03	0.03	0.43	-	-	-	-	-	-
Respondent's Age at Wave 3	-0.01	0.11	0.92	-	-	-	-	-	-
Respondent's Age at Wave 4	0.03	0.11	0.79	-	-	-	-	-	-
Biological Sex	-0.12	0.02	0.00	-	-	-	-	-	-

Indirect Effects from the Substance Use Polygenic Risk Score Model

Overall, there were no indirect effects of childhood maltreatment sub-groups on specific substance use (alcohol, marijuana, and illicit drug use frequencies) in adulthood via physical intimate partner violence victimization in young adulthood (see Table 4.9). Physical intimate partner violence victimization in young adulthood did not mediate the associations between 1) high sexual abuse sub-group and alcohol use frequency in adulthood ($\beta = 0.00$; $p = 0.72$) and 2) high physical abuse sub-group and alcohol use frequency in adulthood ($\beta = 0.00$; $p = 0.73$). Similarly, physical intimate partner violence victimization in young adulthood did not mediate the associations between 1) high sexual abuse sub-group and marijuana use frequency in adulthood ($\beta = 0.00$; $p = 0.45$) or 2) high physical abuse sub-group and marijuana use frequency in adulthood ($\beta = 0.00$; $p = 0.51$) and physical intimate partner violence victimization also did not mediate the associations between 1) high sexual abuse sub-group and illicit drug use frequency in adulthood ($\beta = 0.00$; $p = 0.62$) or 2) high physical abuse sub-group and illicit drug use frequency in adulthood ($\beta = 0.00$; $p = 0.63$).

Table 4.9 Indirect effects from childhood maltreatment sub-groups to specific substances in adulthood via physical intimate partner violence victimization in young adulthood (substance use polygenic risk score model)

Alcohol Use Frequency						
	High Sexual Abuse Sub-group			High Physical Abuse Sub-group		
	β	*s.e.*	*p*	β	*s.e.*	*p*
Physical Intimate Partner Violence Victimization	0.00	0.00	0.72	0.00	0.00	0.73
Marijuana Use Frequency						
	High Sexual Abuse Sub-group			High Physical Abuse Sub-group		
	β	*s.e.*	*p*	β	*s.e.*	*p*
Physical Intimate Partner Violence Victimization	0.01	0.00	0.45	0.00	0.00	0.51
Illicit Drug Use Frequency						
	High Sexual Abuse Sub-group			High Physical Abuse Sub-group		
	β	*s.e.*	*p*	β	*s.e.*	*p*
Physical Intimate Partner Violence Victimization	0.00	0.00	0.62	0.00	0.01	0.63

Note: Standardized estimates presented in table; Indirect effects were estimated above and beyond all covariates and interaction between substance use genetic risk

Moderated-Mediation Substance Use Polygenic Risk Score Model

Substance use polygenic risk score did not moderate the direct pathway from sexual abuse sub-group membership to alcohol use frequency (β = 0.02; p = 0.22), marijuana use frequency (β = -0.04; p = 0.13) or illicit drug use frequency (β = -0.04; p = 0.71) in adulthood within the mediation models. Similarly, substance use polygenic risk score did not moderate the direct from physical abuse sub-group membership to alcohol use frequency (β = 0.00; p = 0.94) or illicit drug use frequency (β = -0.04; p = 0.30) in adulthood.

Within the moderated-meditation model, substance use polygenic risk score did moderate the direct pathway from physical abuse sub-group membership to marijuana use frequency at low (β = 0.09; p = 0.02), medium (β = 0.10; p = 0.03), and high (β = 0.10; p = 0.04) levels but the simple slopes were not different than zero for the normative sub-group at low (β = 0.00; p = 0.54), medium (β = 0.00; p = 0.58) and high (β = 0.01; p = 0.61) levels of substance use polygenic risk score for marijuana use frequency (see Figure 4.7).

Also, substance use polygenic risk score did not moderate the indirect pathway from physical intimate partner violence perpetration in young adulthood to alcohol use frequency (β = 0.00; p = 0.59), marijuana use frequency (β = 0.24; p = 0.52) or illicit drug use frequency (β = 0.00; p = 0.71) in adulthood within the mediation models.

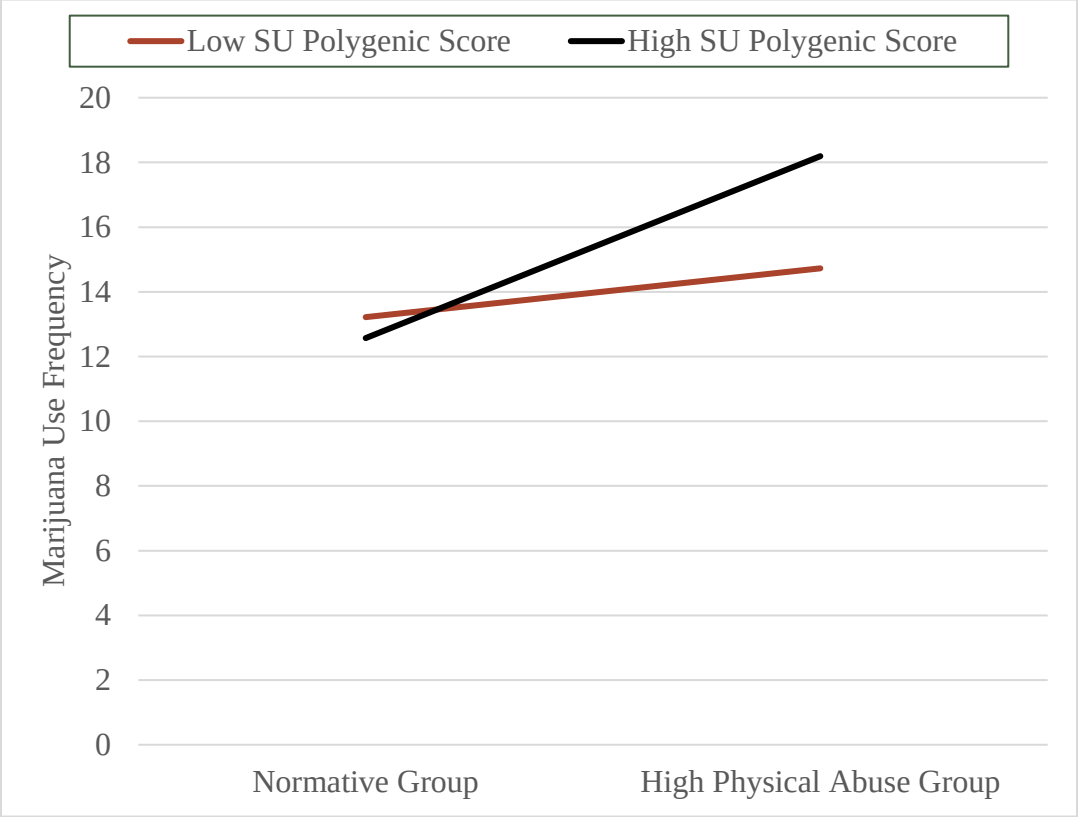

Figure 4.7 Moderation by substance use polygenic risk score for the association between high physical abuse sub-group (compared to the normative sub-group) and marijuana use frequency in adulthood

Direct Effects from the Substance Use Related Dopamine Polygenic Risk Score Model

Direct effect estimates for specific substances – alcohol use, marijuana use, and illicit drug use frequencies – for this model are summarized in Table 4.10. Similar to the previous model with substance use polygenic risk score, physical intimate partner violence victimization in young adulthood was not associated with alcohol (β = 0.01; p = 0.71), marijuana (β = 0.06; p = 0.29) or illicit drug (β = -0.01; p = 0.72) use frequencies in adulthood. Membership in the high sexual abuse sub-group was associated with lower illicit drug use frequency (β = -0.04; p = 0.00) but not with marijuana use frequency (β = -0.61; p = 0.81) or alcohol use frequency (β = 0.00; p = 0.99) in adulthood. Membership in the high physical abuse sub-group was associated with higher marijuana use frequency (β = 0.09; p = 0.02) but was not associated with alcohol use frequency (β = 0.00; p = 0.92) of illicit drug use frequency (β = 0.00; p = 0.98) in adulthood. The effect size estimate for associations found were small. Additionally, substance use related dopamine polygenic risk score was not associated with illicit drug use frequency (β = -0.0; p = 0.18), alcohol use frequency (β = -0.01; p = 0.66) or marijuana use frequency (β = -0.01; p = 0.80) in this model as well.

Substance use related dopamine polygenic risk score did not moderated the association between the high sexual abuse sub-group membership and marijuana use frequency (β = -0.01; p = 0.70), alcohol use frequency (β = 0.02; p = 0.26), or illicit drug use frequency (β = 0.01; p = 0.49). There was also no significant interaction between high physical abuse sub-group and substance use related dopamine polygenic risk score for marijuana use frequency (β = -0.02; p = 0.65), alcohol use frequency (β = -0.01; p = 0.35) or illicit drug use frequency (β = -0.03; p = 0.41). Finally, interactions between physical intimate partner violence victimization and substance use related dopamine polygenic risk score for alcohol (β = -0.01; p = 0.55), marijuana (β = 0.00; p = 0.97) or illicit drug (β = 0.01; p = 0.72) use frequencies were also not different than zero.

Table 4.10 Direct association with physical intimate partner violence victimization in young adulthood and substance use frequency (substance use related dopamine polygenic risk score model)

Substance Use Frequency									
	Model: Alcohol Use Frequency			Model: Marijuana Use Frequency			Model: Illicit Drug Use Frequency		
	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*
Physical Intimate Partner Violence Victimization	0.01	0.03	0.71	0.04	0.03	0.29	-0.01	0.03	0.72
High Sexual Abuse Sub-group	0.00	0.02	0.99	-0.01	0.03	0.81	-0.04	0.01	0.00
High Physical Abuse Sub-group	0.00	0.03	0.92	0.09	0.04	0.02	0.00	0.05	0.98
Substance use Polygenic Risk Score	-0.01	0.03	0.66	-0.01	0.05	0.80	-0.08	0.06	0.18
Substance use Polygenic Risk Score*High Sexual Abuse Sub-group	0.02	0.01	0.26	-0.01	0.03	0.70	0.01	0.01	0.49
Substance use Polygenic Risk Score*High Physical Abuse Sub-group	-0.02	0.02	0.35	-0.02	0.04	0.65	-0.03	0.03	0.41
Substance use Polygenic Risk Score*Physical Intimate Partner Violence Victimization	-0.01	0.02	0.55	0.00	0.04	0.97	0.01	0.03	0.72
Respondent's Education Level	0.05	0.04	0.19	-0.17	0.05	0.00	-0.06	0.07	0.43
Parent’s Education Level	0.13	0.03	0.00	-0.01	0.05	0.78	-0.04	0.07	0.56
Respondent's Age at Wave 3	-0.31	0.12	0.01	-0.07	0.17	0.66	-0.24	0.24	0.32
Respondent's Age at Wave 4	0.26	0.12	0.02	-0.01	0.18	0.97	0.22	0.24	0.36
Biological Sex	0.22	0.04	0.00	0.18	0.04	0.00	-0.04	0.05	0.40

Indirect Effects from the Substance Use Related Dopamine Polygenic Risk Score Model

Physical intimate partner violence victimization in young adulthood did not mediate the association between childhood maltreatment sub-groups and specific substance use (alcohol, marijuana, and illicit drug use frequencies) in adulthood (see Table 4.11). Physical intimate partner violence victimization in young adulthood did not mediate the associations between 1) high sexual abuse sub-group and alcohol use frequency in adulthood (β = 0.00; p = 0.63) and 2) high physical abuse sub-group and alcohol use frequency in adulthood (β = 0.00; p = 0.66). Similarly, physical intimate partner violence victimization in young adulthood did not mediate the associations between 1) high sexual abuse sub-group and marijuana use frequency in adulthood (β = 0.00; p = 0.45) and 2) high physical abuse sub-group and marijuana use frequency in adulthood (β = 0.00; p = 0.50). Physical intimate partner violence victimization use also did not mediate the associations between 1) high sexual abuse sub-group and illicit drug use frequency in adulthood (β = 0.00; p = 0.72) and 2) high physical abuse sub-group and illicit drug use frequency in adulthood (β = 0.00; p = 0.73).

Table 4.11 Indirect effects from childhood maltreatment sub-groups to substance use in adulthood via physical intimate partner violence victimization in young adulthood (substance use related dopamine polygenic risk score model)

Alcohol Use Frequency						
	High Sexual Abuse Sub-group			High Physical Abuse Sub-group		
	β	*s.e.*	*p*	β	*s.e.*	*p*
Physical Intimate Partner Violence Victimization	0.00	0.00	0.63	0.00	0.00	0.66
Marijuana Use Frequency						
	High Sexual Abuse Sub-group			High Physical Abuse Sub-group		
	β	*s.e.*	*p*	β	*s.e.*	*p*
Physical Intimate Partner Violence Victimization	0.00	0.01	0.45	0.00	0.01	0.50
Illicit Drug Use Frequency						
	High Sexual Abuse Sub-group			High Physical Abuse Sub-group		
	β	*s.e.*	*p*	β	*s.e.*	*p*
Physical Intimate Partner Violence Victimization	-0.02	0.02	0.72	0.02	0.03	0.73

Note: Indirect effects were estimated above and beyond all covariates and interaction between genetic risk

Moderated-Mediation from the Substance Use Related Dopamine Polygenic Risk Score Model

Substance use related dopamine polygenic risk score did not moderate the direct pathway from sexual abuse sub-group membership to alcohol use frequency (β = 0.00; p = 0.36), marijuana use frequency (β = -0.01 to 0.00; p = 0.62) or illicit drug use frequency (β = -0.01 to -0.06; p = 0.76) in adulthood within the mediation models. Similarly, substance use related dopamine polygenic risk score did not moderate the direct pathway from physical abuse sub-group membership to alcohol use frequency (β = 0.00; p = 0.31), marijuana use frequency (β = 0.08 to 0.09; p = 0.68) or illicit drug use frequency (β = 0.00; p = 0.30) in adulthood. Also, substance use related dopamine polygenic risk score did not moderate the indirect pathway within the mediation models from physical intimate partner violence perpetration in young adulthood to alcohol use frequency (β 0.00; p = 0.68), marijuana use frequency (β = 0.00; p = 0.88) or illicit drug use frequency (β = 0.00; p = 0.96) in adulthood.

Discussion

Previous research suggests a link between childhood maltreatment exposure and subsequent physical intimate partner violence victimization (Widom & Wilson, 2015). There is also some evidence suggesting that exposure to both childhood maltreatment and physical intimate partner violence victimization are associated with substance use frequency in adulthood, and that there is a strong genetic risk for substance use frequency which when combined with impoverished environments may result in high levels of substance use frequency (Abajobir et al., 2017; Barnes et al., 2009; Bühler et al., 2015; Desai et al., 2002; Gilbert et al., 2012; Gorwood et al., 2012; Jensen, 2016; Nugent et al., 2014; Oshri et al., 2012; Parks et al., 2011; Widom & Wilson, 2015). This research tries to bridge gaps in current knowledge by testing three study aims that have not been previously tested. The first aim was to assess the direct impact of childhood maltreatment sub-group membership on physical intimate partner violence victimization during early adulthood and substance use in adulthood. The second aim was to evaluate physical intimate partner violence victimization as a mediator of the association between sub-groups with similar childhood maltreatment exposures and substance use in adulthood. The final aim was to test genetic (polygenic risk score for substance use related genes and polygenic risk for substance use related dopamine genes) X environmental (physical intimate partner violence victimization and co-

occurring childhood maltreatment exposure) influences on the likelihood for substance use (i.e. a moderated mediation model with moderation effects for both polygenic risk scores on the direct pathways).

Co-occurring Childhood Maltreatment Exposures Based on Type and Severity of Exposures

Prior to testing aim 1, I discovered multi-type childhood maltreatment subgroups with differing exposures determined by type and severity of exposure. For this analysis, I replicated findings for the maltreatment sub-groups from previous research utilizing a different national sample of middle-aged adults reporting on their retrospective maltreatment exposures (Mishra, Friedman, Mihalec-Adkins, et al., 2019; Mishra & Marceau, 2019). Remarkably, the sample size for the specific sub-groups identified in this research also maps onto to those found in previous research. I not only replicate the sub-groups with co-occurring maltreatment types and severity but have a similar number of individuals in each of these sub-groups (Mishra, et al., 2019; Mishra & Marceau, 2019). The results from the sub-group analyses demonstrated that in national samples of European Americans, individuals seem to experience specific clusters of co-occurring childhood maltreatment. Specifically, physical abuse, neglect and emotional abuse types of maltreatment exposures seemed to cluster together, and another smaller segment of the population seemed to experience sexual abuse along with emotional abuse, physical abuse, and neglect simultaneously and was at the greatest risk for overall maltreatment exposures and severity. Such findings in large national samples of European Americans provides insight into the patterns of childhood maltreatment exposures in this population.

It would also be interesting to observe how these sub-groups with differing exposures change over time and map onto Child Protective Services (CPS) data. For instance, CPS data from 1990-2000 (when the sample in this research was still younger than 18 years of age) indicates a decline in sexual and physical abuse and an increase in neglect exposures (Olson & Stroud, 2012), but in this population-based survey sample, I found a higher prevalence of sexual and physical abuse that co-occurs with moderate levels of neglect. Researchers have argued for comprehensive population-level survey research methods (Christ & Schwab-Reese, 2019) to capture the complex phenomenological dimensions of childhood maltreatment exposures to disrupt the incidence of childhood maltreatment in the population. Such large-scale survey measures along with the

evaluation of multi-type maltreatment will be needed to understand the full extent and complexity of childhood maltreatment in the population.

Childhood Maltreatment Exposure and Physical Intimate Partner Violence Victimization and Substance Use Frequency

Next, I assessed the direct impact of the childhood maltreatment sub-group membership on physical intimate partner violence victimization during early adulthood and substance use frequency in adulthood. I did not find a direct association between these childhood maltreatment sub-groups and adult substance use frequency or physical intimate partner violence victimization, although previous research has shown a link between childhood maltreatment and more physical intimate partner violence victimization and greater substance use frequency (Abajobir et al., 2017; Barnes et al., 2009; Desai et al., 2002; Oshri et al., 2012; Parks et al., 2011; Widom et al., 2014; Widom & Wilson, 2015). Several possible explanations could explain these null findings for the direct effects of childhood maltreatment on physical intimate partner violence victimization in young adulthood and substance use frequency in adulthood.

Additional Adversity Exposure

Firstly, there may be a need to shift focus from childhood maltreatment exposures alone to include additional adversity exposures that are correlated to multi-type or co-occurring childhood maltreatment. In recent years, there has been an increased focus on broader measures of childhood adversity exposures. In scoping the literature, I found that other adversities such as parental incarceration, parental mental health, parental substance use problems, and witnessing interparental violence in the home can co-occur with childhood maltreatment exposures (Scott, Burke, Weems, Hellman, & Carrión, 2013; Turney & Wildeman, 2017). These adversities may be more problematic for both social, as well as internalizing and externalizing problems above and beyond childhood maltreatment exposures. Future research should consider, identifying additional childhood adversities experienced by sub-groups with co-occurring childhood exposures.

Assessing Indirect Mechanisms

Secondly, the association between childhood maltreatment sub-groups and substance use frequency in adulthood may exist indirectly through other mechanisms. These mechanisms may include psychological processes such as mental health problems or low self-esteem, or social factors such as deviant peer affiliation or chronic homelessness that seem to disproportionately affect individuals with childhood maltreatment exposures and have also been linked to higher substance use frequency (Cicchetti & Toth, 2005; Fergusson et al., 2002; Hedtke et al., 2008; Kim & Williams, 2009; Madruga et al., 2011; McVicar, Moschion, & van Ours, 2015; Rosenkranz, Muller, & Henderson, 2014; Shrier, Harris, Sternberg, & Beardslee, 2001; Stein, Leslie, & Nyamathi, 2002). Similarly, mechanisms such as the perception of stress, low educational attainment, lack of strong social relationships, and social isolation during adulthood that seem to be common between childhood maltreatment exposures and physical intimate partner violence victimization need further examination (Berlin, Appleyard, & Dodge, 2011; Capaldi et al., 2012; Lanier & Maume, 2009; Messing, La Flair, Cavanaugh, Kanga, & Campbell, 2012; Patel, Bhaju, Thompson, & Kaslow, 2012), since these factors may also indirectly influence the association between childhood maltreatment and physical intimate partner violence victimization in young adulthood. The evaluation of these additional mechanisms by which the influences of childhood maltreatment may be transmitted for physical intimate partner violence victimization and substance use frequency in adulthood will be critical in future research.

Resilience Factors and Resources

Thirdly, given the large sample size used in this research, there is a strong possibility that childhood maltreatment exposures do not associate with subsequent physical intimate partner violence victimization in young adulthood and substance use frequency in adulthood due to the availability of life-course resources and resilience factors. Specifically, resources and resilience related mechanisms could result in the mitigating of negative influences of childhood maltreatment exposures on subsequent outcomes. These resources are seen to buffer against the negative stress processes consequent of early life adversity exposures and include factors such as social support or healthy social relationships such as friendships and strong neighborhood cohesion, health behaviors such as physical activity and sleep (Mackin, Perlman, Davila, Kotov, & Klein, 2017;

Nurius, Green, Logan-Greene, & Borja, 2015). Additionally, individual levels of factors such as hope for the future, optimism, a desire to overcome adversities and personal agency (Hauser et al., 2009; Thoits, 2010) in childhood and positive affect, life satisfaction and purpose in life in adulthood can result in resilient functioning across a variety of domains (Mishra, et al., 2019; Ryff, 2017; Ryff & Singer, 1998, 2008; Tsenkova, Morozink, Friedman, & Ryff, 2012). Moving forward, there is a need to explicitly examine these above-mentioned resources and resilience factors for physical intimate partner violence victimization and substance use frequency within the context of co-occurring childhood maltreatment and adversity exposures.

Measurement Issues

Finally, there were a few measurement issues that also need acknowledgment. The physical abuse and sexual abuse were measured by a single item assessed at two different waves. Neglect was assessed by two items and emotional abuse by a single item. These items may not be able to adequately and accurately capture the complexity of childhood maltreatment exposures. Additionally, grouping people into categories based on their maltreatment exposure may further result in loss of information and an underestimation of variance in the data. The use of self-reports can also lead to underestimation of actual childhood maltreatment, substance use frequency, and physical intimate partner violence exposures as evidenced by the low endorsement rates in this study. Utilizing a multi-reporter approach such as partner reports, and reports from other family members along with casework, and/or police reports in addition to self-reports may provide a more accurate estimation.

Taken together, these findings point towards the use of large-scale survey data and better measurement for childhood maltreatment, physical intimate partner violence victimization, and substance use frequency in adulthood. It may also be necessary to include additional childhood adversities that may be correlated with co-occurring childhood maltreatment exposures and to test a larger more holistic model of childhood adversity exposures on subsequent outcomes at different developmental stages. However, researchers must be mindful to include an exhaustive list of childhood adversities and assess them on a continuum to capture the variability in exposure types (McLennan, MacMillan, & Afifi, 2020; Watson, 2019). Moreover, inclusion of other mechanisms such as deviant peer affiliation, self-esteem, mental health problems and social isolation, and the simultaneous evaluation of life-course resilience factors and resources would be important. Such

multifactorial examinations can help determine 1) how stress induced by correlated childhood maltreatment and adversity exposures impact negative outcomes, 2) different mechanisms that may link early adversity exposure to subsequent intimate partner violence victimization and substance use, and 3) factors that ameliorate or buffer against the negative effects of stress induced by childhood maltreatment and adversity on subsequent outcomes.

Maltreatment Sub-groups and Drug Use

Although not a primary aim of this research, I found that individuals in the high sexual abuse sub-group reported lower illicit drug use in adulthood compared to the normative sub-group. Similarly, individuals in the high physical abuse sub-group reported more marijuana use frequency in adulthood compared to the normative sub-group. These findings are in line with previous work demonstrating differences by high physical abuse and high sexual abuse sub-groups.

Previous research on the association between types of childhood maltreatment exposure on substance use frequency demonstrates that emotional abuse may be the most impactful type and particularly in combination with neglect and high physical abuse exposures (Berzenski & Yates, 2011; Rogers et al., 2018). By including both severity and type of exposures in this evaluation of co-occurring childhood maltreatment exposures, I was able to establish unique associations between the combination of high severity of physical abuse and moderate emotional abuse and neglect exposures and marijuana use frequency in adulthood. Particularly, this finding lends support to my previous argument for understanding how specific combinations of maltreatment exposures may be more impactful for specific outcomes. Findings also demonstrate that it may be necessary to forestall the links between maltreatment exposures similar to the high physical abuse sub-group and marijuana use frequency in adulthood by implementing effective prevention efforts.

The results for the high sexual abuse sub-group were contrary to what was expected, and a possible examination of previously mentioned life-course resources and resilience factors will be necessary among individuals who have exposures similar to those experienced by this sub-group. However, it must also be noted that although statistically significant, the effect size for this association was very small to be truly meaningful ($\beta = -0.05$).

There has been a long-standing debate on moving beyond statistical significance to meaningful effect sizes in published research (Peeters, 2016) and the precision of those effect sizes (Miller, Schwab, & Starbuck, 2017). Specifically, a small effect size that is statistically significant

may not have practical relevance for prevention efforts (McGough & Faraone, 2009; Peeters, 2016) as the observed small effects post-prevention may not merit the cost associated with the implementation of the prevention trials.

Future research could use the childhood maltreatment exposure patterns identified in this research along with correlated adversities and trauma throughout life to examine if there are varied implications by specific clusters of adversity and identify which specific clusters are detrimental for which outcomes. It will also be important to examine different mechanisms through which these associations are transmitted and the role of potential buffers.

Physical Intimate Partner Violence Victimization as a Mediator

For the second aim, I evaluated physical intimate partner violence victimization as a mediator of the association between sub-groups of childhood maltreatment and substance use frequency in adulthood. Once again, this aim was also not supported. Physical intimate partner violence victimization was also not a mediator between childhood maltreatment sub-group membership and alcohol, marijuana, or illicit drug use frequencies in adulthood. Although, there is evidence linking childhood maltreatment to more substance use frequency and physical intimate partner violence victimization, and physical intimate partner violence victimization to higher substance use frequency, the causal links between maltreatment exposure to substance use frequency via physical intimate partner violence victimization were difficult to establish for a variety of reasons.

A majority of individuals with childhood maltreatment exposure, may not become victims of physical intimate partner violence (Widom & Wilson, 2015). Moreover, physical intimate partner violence victimization may not be causally linked to the association between childhood maltreatment exposure and substance use frequency in adulthood (Hammen, 1991). Instead, divergent theories suggest that there may be a cumulative and/or synergistic effect of adversity and stressors during different developmental periods that may be critical for negative outcomes throughout life (Evans & Kim, 2010; Evans, Li, & Whipple, 2013; Maas, Herrenkohl, & Sousa, 2008). Specifically, based on the cumulative stress model, it is posited that continued exposure to adversity such as poverty (Evans & Kim, 2010; Evans et al., 2013; Pollitt, Rose, & Kaufman, 2005) or even victimization may result in negative outcomes due to their additive or combined effects. In contrast, the synergistic model which is derived from the early-life stress sensitization model

posits that early life adversity would increase the impact of later-life stress on negative outcomes (Hostinar et al., 2015). Based on the early-life stress sensitization model, it is likely that childhood maltreatment may have a combined effect with physical intimate partner violence victimization for substance use frequency in adulthood or may worsen the impact of physical intimate partner violence victimization on substance use frequency in adulthood.

Therefore, in addition to testing the causal model wherein childhood maltreatment leads to greater victimization, adversity, and stressful life-events due to social learning and conditioning (Akers, 2017; Bandura & Walters, 1977), I also used these two other theorized models of cumulative (i.e. additive) stress and synergetic (i.e. interactive) stress to assess if victimization at different life stages (i.e. childhood maltreatment and physical intimate partner violence in young adulthood) have a cumulative or synergistic effects on overall substance use frequency as well as on alcohol, marijuana, and illicit drug use frequencies (see supplemental tables, figures and results below for details). With the exception of lower illicit drug use among members of high sexual abuse sub-group at low and medium levels of intimate partner violence victimization, neither the cumulative stress nor the synergistic stress models were supported by supplementary analysis.

Some previous research has demonstrated an interactive effect between childhood maltreatment exposure and everyday life stress on substance use outcomes (Young-Wolff, Kendler, & Prescott, 2012). Other studies have demonstrated only cumulative effects but not synergistic effects of childhood and adulthood adversities on negative outcomes (Hostinar et al., 2015). To my knowledge, this is the first study that examined physical intimate partner violence victimization as a mechanism of the association between childhood maltreatment exposure and substance use frequency and tested the cumulative and synergetic model using a large population-based survey study.

The inconsistent findings from previous research together with the main and supplementary findings from this research provide additional evidence in support of the above-mentioned discussion on increasing the scope of adversities included in analytic models, and for simultaneous evaluation of life-course resilience factors and resources. In particular, an evaluation of resilience factors and resources may provide insight into the findings that highlight lower illicit drug use among members of the high sexual abuse sub-group and more generally for their buffering effects against specific negative outcomes associated with adversity exposures that are strongly correlated with childhood maltreatment exposures.

Future work should also evaluate each theoretical approach – cumulative stress, social learning and conditioning relating to subsequent stressful life-events, and synergistic stress models – for all possible combinations of childhood adversity exposures in order to determine which specific exposures that co-exist with multi-type childhood maltreatment exposures are most salient for substance use frequency in adulthood. Moreover, it may be important to understand how the mediating (or moderating or additive) influences of physical intimate partner violence victimization on the association between childhood maltreatment sub-groups and substance use in adulthood differ for samples of individuals with 1) severe physical intimate partner violence victimization and 2) substance use disorders. Given, a higher prevalence of substance use disorder among victims of physical intimate partner violence and childhood maltreatment (Afifi, Henriksen, Asmundson, & Sareen, 2012; Rivera et al., 2015), an evaluation of this model presented in this study with clinical samples may be more appropriate.

Gene-Environment Interaction

For the final aim, I tested the genetic (polygenic risk score for substance use frequency related genes and polygenic risk for substance use frequency related dopamine genes) X environmental (physical intimate partner violence victimization and co-occurring childhood maltreatment exposure) influences on the likelihood for substance use frequency in adulthood (i.e. a moderated mediation model with moderation effects for both polygenic risk scores on the direct pathways). I did not find that substance use frequency polygenic risk score or dopamine related substance use frequency polygenic risk score moderated the direct pathway from childhood maltreatment to substance use frequency. I also did not find evidence for genetic moderation by both polygenic risk scores on the indirect pathway between physical intimate partner violence victimization and substance use frequency in the mediated association between childhood maltreatment sub-groups and substance use frequency in adulthood.

A potential reason for the null findings for the substance use frequency polygenic risk score could be limited coverage for substance use frequency because I only included 15 SNPs after quality control. Specifically, LD pruning has been criticized as a quality control method as it randomly selects SNPs from correlated pairs, which may result in the SNP that is most significantly associated with the phenotype being removed from the final list of SNPs included (Chatterjee, Shi, & García-Closas, 2016). Moreover, SNPs extracted from genome-wide

association studies may not be able to capture all the heritability because they do not account for interactive effects between genes and do not account for gene-environment interactions that may explain genetic variation. Therefore, SNP-based heritability may result in biased estimation due to the confounding effects of these factors (Zaitlen & Kraft, 2012). Furthermore, the sample size used in this study may be underpowered to detect significant effects that were detected in chapter 2 or study. Specifically, the repeated measure design of study 1 significantly improved statistical power compared to this study that assessed more static associations over time (Guo, Logan, Glueck, & Muller, 2013).

Interestingly, I find that substance use frequency polygenic risk score does interact with high physical abuse sub-group membership for marijuana use. Although this score was not explicitly created for marijuana use risk, the genetic variants included in the polygenic risk score seem to produce detrimental effects on marijuana use at high genetic risk but only for members of the high physical abuse sub-group. Replication of these findings with larger samples of individuals with maltreatment exposure similar to those of the physical abuse sub-group will be important in future work. Nonetheless, these findings suggest that there may be biologically mediated pathways from exposures to high physical abuse with moderated levels of neglect and emotional abuse to marijuana use frequency in adulthood. Specifically, even though there is a secular trend towards legalization of marijuana in the United States, it is still socially limited in its availability and based on my findings, marijuana use may result from the combined influence of maltreatment exposures such as those experienced by the high physical abuse sub-group and a genetic predisposition towards substances use.

For the null findings for the substance use frequency related dopamine polygenic risk score across all phenotypes (substance use frequency, alcohol use, marijuana use, and other drug use), it must be highlighted that the genes included to create this score were from candidate gene studies that have been confirmed in single studies but never replicated in subsequent studies (Gorwood et al., 2012; Le Foll, Gallo, Strat, et al., 2009; O'Sullivan, Evans, & Lees, 2009). Therefore, it may be likely that the SNPs included in the substance use related dopamine polygenic risk score may not be related to substance use frequency phenotypes.

As discussed later in Chapter 5, the dopaminergic pathways are considered a major neurological system that regulates reward and impulsive behaviors and has emerged as significant systems that may contribute to substance use behaviors (Gorwood et al., 2012; Le Foll, Gallo, Strat,

et al., 2009; O'Sullivan et al., 2009). However, it must be noted that across all genome-wide association studies for substance use phenotypes, no dopamine SNP has ever been significantly associated with substance use outcomes. Nonetheless, it may be important to conduct a genome-wide association study for the entire dopamine system and then utilize all significant genes from said genome-wide association study to create a polygenic risk score to test dopamine specific genetic vulnerabilities for substance use.

Conclusion

This research is important despite the generally null findings because the study was adequately powered in terms of sample size (although not for the genetic moderation hypothesis) to detect all effect size estimates greater than 0.05 (power = 93% at $\alpha = 0.05$). Therefore, the null findings are likely true for this population and I provide several recommendations for future research. First, I recommend the use of broad survey measures and better overall measurement for childhood maltreatment, physical intimate partner violence victimization and substance use frequency. Second, I recommend evaluating both sub-groups experiencing multiple childhood maltreatment types and understanding their cumulative, interactive and causal associations with a wide range of other childhood adversities to fully understand the combinations and pathways by which early adversity, victimization and life stressors are linked to negative outcomes throughout life. Third, I also recommend the inclusion of life-course resources and resilience factors that may forestall or buffer against specific adversity exposures. Specifically, I recommend using a large dynamic, multi-factorial model for understanding victimization and adversity related life-course outcomes. Finally, I recommend more robust measures for genetic risks associated with substance use frequency. I also recommend improving the understanding of substance use related dopamine genetic risk by conducting large scale genome-wide association studies for the dopamine system.

Supplementary Models

First to test cumulative influences (Figure S4.1), I combined (sum score) overall childhood maltreatment exposure and physical intimate partner violence victimization to create a cumulative victimization index and tested its direct effects and interaction with substance use polygenic risk score on substance use frequency in adulthood (see Table S4.1). As evidenced by the results, this additive model was not supported and cumulative influences of childhood maltreatment and physical intimate partner violence victimization did not have a direct effect on substance use frequency or alcohol, marijuana and illicit drug use frequencies. There was also no genetic moderation by polygenic risk for substance use found across models.

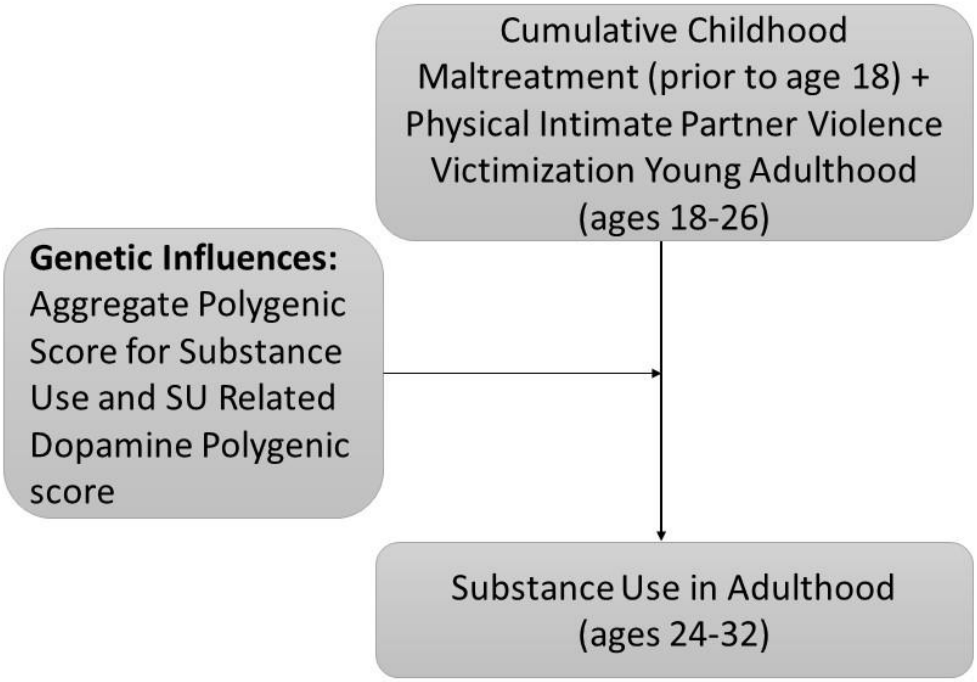

Figure S4.1 Revised conceptual model 3 where cumulative or additive effects of childhood maltreatment exposure and physical intimate partner violence victimization are tested on substance use frequency (and alcohol use, marijuana use, and illicit drug use) and genetic moderation of the direct pathway

Table S4.1 Interaction between cumulative childhood maltreatment and physical intimate partner violence victimization and substance use polygenic risk score on overall substance use and specific substances

	Substance Use			Alcohol Use			Marijuana Use			Illicit Drug Use		
	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	p	β	*s.e.*	*p*
Cumulative Childhood Maltreatment and Physical Intimate Partner Violence Victimization	-0.02	0.03	0.50	0.00	0.03	0.97	0.01	0.04	0.76	-0.03	0.04	0.47
Substance Use Polygenic Risk Score	-0.03	0.04	0.48	-0.02	0.05	0.76	-0.05	0.06	0.35	-0.04	0.08	0.62
Substance Use Polygenic Risk Score*Cumulative Childhood Maltreatment and Physical Intimate Partner Violence Victimization	0.02	0.04	0.69	-0.02	0.06	0.78	0.07	0.05	0.13	-0.06	0.07	0.39

Note: Models include all covariates

Next, I tested the interaction between childhood maltreatment sub-groups and physical intimate partner violence victimization in young adulthood on substance use frequency as well as alcohol use frequency, marijuana use frequency, and illicit drug use frequency in adulthood (Figure S4.2). The results from the interactive model (Figure S4.3) is presented in Table S4.2. High sexual abuse sub-group interacted with physical intimate partner violence victimization to influence illicit drug use frequency in adulthood. Specifically, at low (β = -0.22, *s.e.* = 1.59, $p < 0.001$; Figure S4.3) and at medium (β = -0.11, *s.e.* = 1.12 , $p = 0.01$) but not at high (β = 0.00, *s.e.*= 0.65, $p = 0.70$) levels of physical intimate partner violence victimization, members of the high sexual abuse sub-group had lower frequency of illicit drug use in adulthood compared to the normative sub-group.

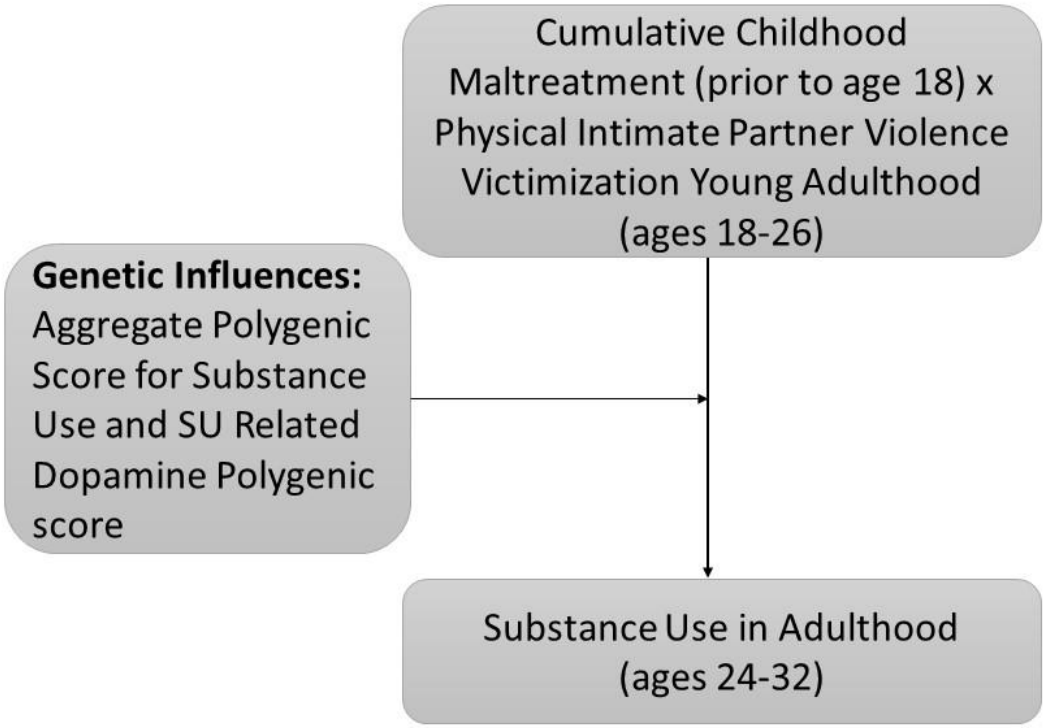

Figure S4.2 Revised conceptual model 3 where synergistic effects of childhood maltreatment exposure and physical intimate partner violence victimization are tested on substance use frequency (and alcohol use, marijuana use, and illicit drug use) and genetic moderation of the direct pathway

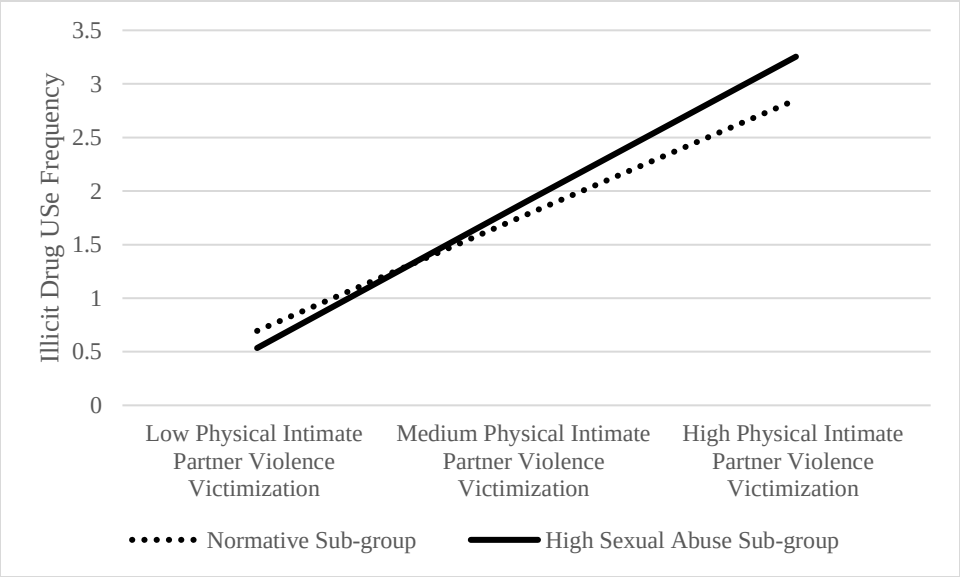

Figure S4.3 Difference between maltreatment sub-groups at levels of intimate partner violence victimization for illicit drug use

Table S4.2 Interaction between childhood maltreatment sub-groups and physical intimate partner violence victimization on overall substance use and specific substances

	Substance Use			Alcohol Use			Marijuana Use			Illicit Drug Use		
	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*
High Sexual Abuse Sub-group	0.27	1.21	0.83	0.02	0.03	0.46	0.00	0.05	1.00	-0.11	0.04	0.00
High Physical Abuse Sub-group	-0.01	0.03	0.70	0.03	0.04	0.45	0.00	0.03	1.00	-0.05	0.03	0.08
Physical Intimate Partner Violence Victimization	-0.05	0.05	0.29	-0.04	0.02	0.10	0.00	0.02	0.95	-0.01	0.02	0.38
Physical Intimate Partner Violence Victimization *High Sexual Abuse Sub-group	0.35	0.56	0.53	0.00	0.03	0.93	0.06	0.05	0.21	1.11	0.14	0.00
Physical Intimate Partner Violence Victimization *High Physical Abuse Sub-group	0.13	0.11	0.27	-0.01	0.03	0.65	0.05	0.04	0.25	0.11	0.05	0.04

Note: Models include covariates

However, these findings may not be meaningful even though they were statistically significant since only 367 individuals reported the use of illicit drug in adulthood and it may be necessary to evaluate these associations in larger samples of illicit drug users and those with more chronic use. However, there was no genetic moderation by substance use polygenic risk score of the moderated models (i.e. moderated-moderation model; see Table S4.3).

Table S4.3 Interaction between childhood maltreatment sub-groups and physical intimate partner violence victimization and polygenic risk for substance use on overall substance use and specific substance

	Substance Use			Alcohol Use			Marijuana Use			Illicit Drug Use		
	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*
High Sexual Abuse Sub-group	0.00	0.03	0.89	0.03	0.04	0.38	-0.03	0.03	0.29	-0.10	0.04	0.01
High Physical Abuse Sub-group	0.02	0.03	0.49	0.00	0.03	0.91	0.07	0.04	0.08	-0.03	0.03	0.44
Physical Intimate Partner Violence Victimization	0.01	0.03	0.84	0.01	0.03	0.68	0.04	0.03	0.22	-0.03	0.03	0.44
Substance Use Polygenic Risk Score	-0.03	0.02	0.29	-0.02	0.03	0.56	-0.01	0.03	0.69	-0.11	0.04	0.00
Physical Intimate Partner Violence Victimization *High Sexual Abuse Sub-group	-0.01	0.14	0.93	-0.03	0.09	0.71	0.03	0.74	0.96	0.13	0.19	0.49
Physical Intimate Partner Violence Victimization *High Physical Abuse Sub-group	0.07	0.04	0.08	0.01	0.03	0.86	0.07	0.04	0.09	0.01	0.05	0.87

Table S4.3 continued

High Sexual Abuse Sub-group *Substance Use Polygenic Risk Score	0.01	0.06	0.86	0.04	0.08	0.63	-0.02	0.07	0.83	0.00	0.05	0.99
High Physical Abuse Sub-group*Substance Use Polygenic Risk Score	0.04	0.03	0.26	0.02	0.04	0.61	0.07	0.05	0.16	0.09	0.09	0.35
Physical Intimate Partner Violence Victimization* Substance Use Polygenic Risk Score	-0.01	0.02	0.71	-0.03	0.04	0.41	0.02	0.03	0.57	0.02	0.02	0.42
Physical Intimate Partner Violence Victimization *High Sexual Abuse Sub-group *Substance Use Polygenic Risk Score	0.01	0.18	0.97	0.00	0.12	0.97	-0.13	0.68	0.85	-0.03	0.18	0.89
Physical Intimate Partner Violence Victimization *High Physical Abuse Sub-group*Substance Use Polygenic Risk Score	-0.06	0.04	0.12	-0.04	0.04	0.38	-0.01	0.04	0.79	-0.12	0.10	0.21

Note: Models include covariates

CHAPTER 5: SUMMARY AND CONCLUSION

This dissertation provides a comprehensive model for understanding intergenerational transmission of violence by evaluating the life-long consequences of co-occurring childhood maltreatment exposures. Specifically, I evaluated the role of co-occurring childhood maltreatment exposures prior to age 18 on substance use frequency trajectory from ages 11 to 26 (chapter 2). Next, I tried to understand substance use frequency in young adulthood as a proximal factor influencing the association between co-occurring childhood maltreatment sub-groups and physical intimate partner violence perpetration in adulthood (chapter 3). Subsequently, I evaluated physical intimate partner violence victimization in young adulthood as a mediator of the association of childhood maltreatment sub-groups and adult substance use frequency (chapter 4). In the analytic models presented in chapters 2-4, I also evaluated the role of substance use related genetic risk (i.e., polygenic risk for substance use frequency).

The three studies presented in chapters 2-4 were evaluated using multiple theories of human development. First, attachment theory and social learning theories (Ainsworth, 1979; Akers, 2017; Bandura, 1986; Bandura & Walters, 1977; Bowlby, 1973) were used to understand the association between childhood maltreatment exposure and physical intimate partner violence. Second, the role of substance use frequency on these associations was evaluated within the social cognitive theory (Akers, 2017; Bandura & Walters, 1977). Finally, the interaction between environmental factors such as childhood maltreatment and genetic risk (including substance use frequency related dopamine genetic risk and overall substance use frequency genetic risk;) and physical intimate partner violence victimization and genetic risk are tested using the diathesis-stress model (Ingram & Luxton, 2005).

The association of childhood maltreatment exposure with substance use frequency during adolescence and adulthood has been previously established. As have the associations between 1) childhood maltreatment and physical intimate partner violence (perpetration and victimization) and 2) substance use frequency and physical intimate partner violence (all associations reviewed in chapters 1-4). There is also evidence for the genetic basis for substance use frequency (reviewed in previous chapters).

Childhood Maltreatment Sub-groups

Across the three studies, I utilized latent profile analysis to identify sub-groups with co-occurring childhood maltreatment exposures based on both type and severity of exposures. I identified three sub-groups that map onto previous research findings of retrospective childhood maltreatment exposures. The first sub-group was composed of individuals who had remarkably high levels of sexual abuse with moderate levels of all other types of childhood maltreatment exposures (high sexual abuse sub-group), the second sub-group included individuals who had very high levels of physical abuse with moderate levels of emotional abuse and neglect (high physical abuse sub-group), and finally, a normative sub-group that comprised majority of the sample who exhibited overall low levels of all maltreatment types. The high physical abuse sub-group and the high sexual abuse sub-group also had moderate but similar levels of childhood neglect and emotional abuse exposures. These findings point to several critical things.

First, given the co-occurrence of specific maltreatment types, it may be important for researchers to consider multiple co-occurring childhood maltreatment exposures on outcomes throughout life and specific mechanisms through which such different combinations of exposures are associated with outcomes differentially. Second, such an evaluation can also lead to more tailored prevention efforts and treatment plans. For example, since the high physical abuse sub-group transmits its influences on substance use frequency through biological mechanism (i.e., high genetic risk for substance use frequency assessed by polygenic risk score for substance use frequency), such mechanism must be considered by future prevention trials when testing new prevention strategies for individuals with exposures that are similar to the high physical abuse sub-group. Finally, instead of using legal definitions to understand childhood maltreatment exposures, use of survey methods could be critical for understanding the complexity of childhood maltreatment experiences (Christ & Schwab-Reese, 2019) and it may be equally important to understand using survey data, trauma induced outcomes of specific clusters of co-occurring exposures.

Analytic Model 1 (Study 1; Chapter 2)

In the first analytic model (see figure 5.1), it was hypothesized that following the diathesis-stress model higher severity of co-occurring childhood maltreatment (particularly physical abuse,

emotional abuse, and neglect) would interact wth high genetic risk to produce the most detrimental trajectories (i.e., high increasing) of substance use frequency from adolescence to young adulthood.

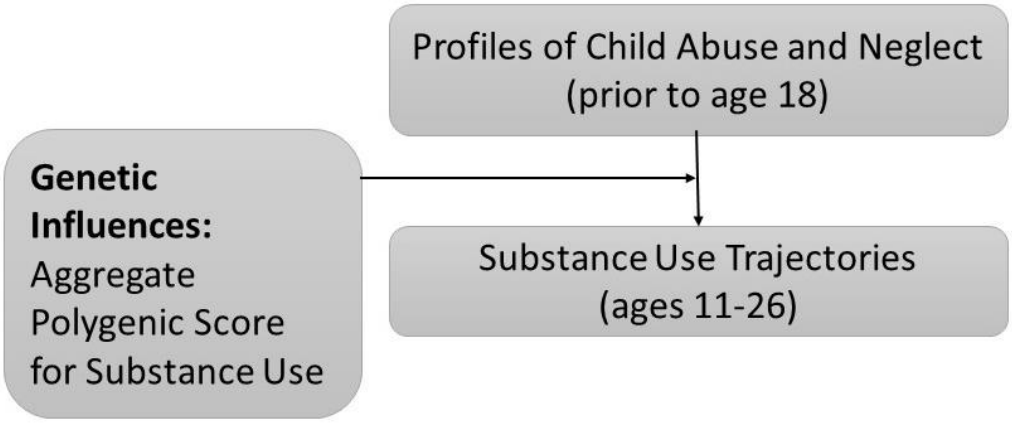

Figure 5.1 Analytic Model 1 (Study 1) for the association between childhood maltreatment exposure and substance use frequency from adolescence to young adulthood

Based on the results from the unconditional models in chapter 2, there was some evidence for increases in substance use frequency over time for the normative and high sexual abuse sub-group. The high sexual abuse sub-group started out with nearly 0 initial substance use frequency and had the highest substance use frequency by age 26. In contrast, the high physical abuse sub-group did not associate with initial levels or change over time in substance use frequency. The findings from this dissertation demonstrated that specific clusters of maltreatment exposures (e.g., those experienced by the high sexual abuse sub-group) may result in increasing substance use frequency over time. Whereas other clusters with exposures such as those experienced by the high physical abuse sub-group may result in no change in substance use frequency over time. However, the direct pathway from childhood maltreatment sub-groups to substance use frequency at age 11 and over time was not supported with the inclusion of substance use frequency polygenic risk score and covariates in the analytic model.

The moderated pathway (i.e., moderation of the direct pathway from childhood maltreatment exposure to substance use frequency over time by substance use frequency polygenic

risk score) was supported. Findings from the moderation analysis suggest that high genetic risk may be critical for substance use and marijuana use progression over time for the high physical abuse sub-group (i.e., supported within a diathesis-stress model such that high environmental risk interacts with high genetic risk to produce the most detrimental outcome). In contrast, exposure to childhood maltreatment irrespective of genetic risk may be more pervasive and detrimental for the high sexual abuse sub-group for overall substance use frequency progression and alcohol use progression. For the high sexual abuse sub-groups there may also be the presence of some protective factors (e.g., early interventions) for marijuana use and illicit drug use over time at high genetic risk.

Findings for the high sexual abuse sub-group demonstrated a greater role of environmental exposures on substance use and alcohol use frequency development over time and are suggestive of other social (e.g., parental use or peer affiliation; Dube, Anda, Felitti, Edwards, & Croft, 2002; Yoon, Yoon, Yoon, & Snyder, 2019) or psychological (e.g., trauma or depressive symptoms; Aspelmeier, Elliott, & Smith, 2007; Hall, Sachs, Rayens, & Lutenbacher, 1993) pathways that may explain how and why the influence of childhood maltreatment exposure for the high sexual abuse sub-group are transmitted or not transmitted onto average substance use frequency and substance specific use frequency (e.g., alcohol use frequency) progression. Therefore, the diathesis-stress model is not supported for the findings from the high sexual abuse sub-group and necessitates the need to examine other theoretical perspectives (e.g., risk/resilience model, or social learning or ecological theory; Bandura & Walters, 1977; Bronfenbrenner, 2009; Masten, 2001). There is also a need to further examine the above-mentioned factors that may explain the nature of the relationship between high sexual abuse exposures and substance use frequency progression from adolescence to adulthood for this sub-group.

Alternative Theoretical Explanation for Study 1/Analytic Model 1

Risk and resilience theoretical frameworks have been used to explain the distinction in why certain children with adversity exposure develop certain negative outcomes and others bounce back despite these adversities (Fergusson & Horwood, 2003; Gutman, 2008; Masten, 2001). Among members of the high sexual abuse sub-group, it is likely, that some form of early interventions may be protective for marijuana and illicit drug use progression even when there is a high biological predisposition for substance use (Hauser et al., 2009; Masten, 2001). Similarly,

parental alcohol or drug use may result in modeling of behavior or easier access to substances such as alcohol (i.e., social learning; Bandura & Walters, 1977; Dube et al., 2002; Yoon et al., 2019) for members of the high sexual abuse sub-group.

From an ecological perspective, person-level psychological factors such as depressive symptoms that emerge from childhood maltreatment exposures (Aspelmeier et al., 2007; Hall et al., 1993) or childhood maltreatment in itself may be the only factors influencing substance use and alcohol use frequency change over time. Within the ecological theory, it is also likely that the interaction of childhood maltreatment with psychological problems or other contextual problems such as parental mental health problems (Dube et al., 2002) or other environmental factors such as socioeconomic status may be factors that are important for substance use (and alcohol use) frequency progression, particularly for the high sexual abuse sub-group. These diverse theoretical perspectives need to be examined further to fully understand the different pathways through which different childhood maltreatment sub-groups influence substance use frequency during adolescence and over time until young adulthood.

In the future, researchers could also explore further and ascertain if some childhood maltreatment exposures are more detrimental across different domains of development and outcomes, even when genetic risk is low for that phenotype. A further exploration of whether exposures such as those experienced by the high physical abuse sub-group are transmitted via more biologically mediated pathways is also required. It will also be necessary to elucidate how biological and social mechanisms may be dependent on the outcome evaluated within the context of childhood maltreatment exposure.

For adult victims of co-occurring childhood maltreatment, behavior modification via cognitive behavioral therapies or motivational interviewing may be useful for improving substance use frequency over time (Cahill, Rothbaum, Resick, & Follette, 2009; Grenard, Ames, Pentz, & Sussman, 2006; Leenarts, Diehle, Doreleijers, Jansma, & Lindauer, 2013). However, the findings from analytic model 1 suggest the need for uniform implementation of prevention efforts of childhood maltreatment related substance use frequency for all individuals with maltreatment exposures similar to the high sexual abuse sub-group. In contrast, taking into consideration genetic risk for those individuals with maltreatment risks similar to the physical abuse sub-group will be necessary for future prevention trials for substance use frequency reduction.

Analytic Model 2 (Study 2)

To understand the second analytic model (Figure 5.2), I utilized multiple theories of human development. The association between childhood maltreatment sub-groups and physical intimate partner violence was tested using attachment theory (Ainsworth et al., 1978; Bowlby, 1973, 1988) and social learning theory (Bandura & Walters, 1977). According to these theories, individuals develop negative schemas of social relationships and accept violence perpetration as a normative part of relationships as a result of childhood maltreatment exposures, which then leads to higher perpetration of physical intimate partner violence. The association between childhood maltreatment and substance use frequency was examined within the social cognitive theory (Akers, 2017; Bandura, 1986) wherein substance use behaviors are used as a coping mechanism to deal with the trauma induced by childhood maltreatment exposures. Similarly, the use of rationalization within the social cognitive theory (Akers, 2017; Bandura, 1986) was proposed as a theoretical reason for the proposed positive association between substance use frequency and physical intimate partner violence perpetration - individuals may blame their violence perpetration or unacceptable behaviors on their inebriated state. Finally, like analytic model 1, a diathesis-stress model was used to explain the role of high genetic risk for substance use on the pathway from childhood maltreatment sub-groups and substance use frequency in young adulthood (i.e., high genetic risk would make this direct pathway stronger within the larger mediation model).

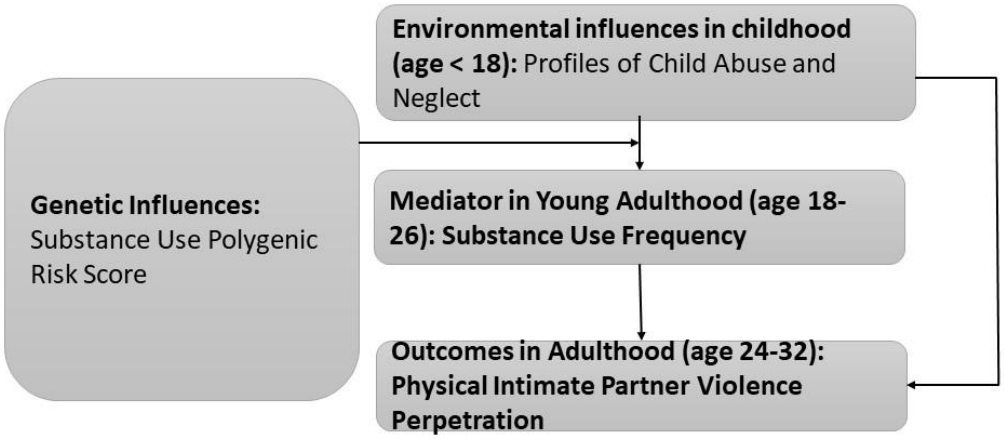

Figure 5.2 Analytic Model 2 (Study 2) for the association between childhood maltreatment exposure with substance use frequency in young adulthood and subsequent physical intimate partner violence perpetration in adulthood

Based on these theoretical frameworks, in the second analytic model (chapter 3), I tested substance use frequency in young adulthood as a mediator of childhood maltreatment sub-groups and physical intimate partner violence perpetration. Within this mediation model, I also tested substance use genetc risk (i.e., substance use polygenic risk score) as a moderator of the pathway from childhood maltreatment sub-groups and substance use frequency in young adulthood.

Unfortunately, the mediation and the moderated-mediation pathways were not supported in this sample. I also tested the mediation model with the entire nationally representative sample (i.e., the full Add Health sample) in order to ensure that the lack of associations was not due to the homogeneity of the sample used in this dissertation (see Appendix A). The mediation model was also not supported in the full sample. I also did not find moderation by levels of genetic risk and therefore, the diathesis-stress model was not supported for this analytic model. In fact, alcohol use frequency was slightly lower for the high physical abuse sub-group at high polygenic risk.

Additionally, the other theoretical approaches were also largely not supported by the findings from this analytic model. Based on the findings from analytic model 2, it is likely that substance use in young adulthood may not be a mechanism linking childhood maltreatment

exposure and physical intimate partner violence perpetration in adulthood and genetic risk for substance use may not play a role in the association between childhood maltreatment sub-groups and substance use frequency in young adulthood. In chapter 3, I propose several factors that may influence these findings within a risk and resilience framework (e.g., stress processes, cognitive factors, and psychosocial domains). These additional pathways will need further examination in future research.

Alternative Theoretical Explanation for Study 2/Analytic Model 2

I also proposed an alternate theory - the ecological model of human development (Bronfenbrenner & Morris, 2006), in chapter 3 (See Figure 5.3). The ecological theory (Bronfenbrenner, 2009; Bronfenbrenner & Morris, 2006) focuses on the context of the individual in explaining their development. Under this theory, substance use could be considered a contextual factor influencing the association between childhood maltreatment and physical intimate partner violence perpetration. A test of substance use as a contextual factor within this theory in chapter 3 demonstrated that in this population, substance use was a contextual factor exacerbating the association between childhood maltreatment exposures and physical intimate partner violence perpetration in adulthood. Specifically, the high sexual abuse sub-group had increased physical intimate partner violence perpetration at medium and high marijuana use and at medium and high illicit drug use. Replication of these findings will be necessary using other diverse samples. Nonetheless, in populations such as those used in this dissertation, substance use could be a tangible contextual factor that can be targeted in future prevention efforts to break the cycle of inter-generational transmission of violence and these efforts may focus particularly on individuals with maltreatment exposures similar to the high sexual abuse sub-group and on those individuals within this sub-group that have moderate to high levels of marijuana and illicit drug use.

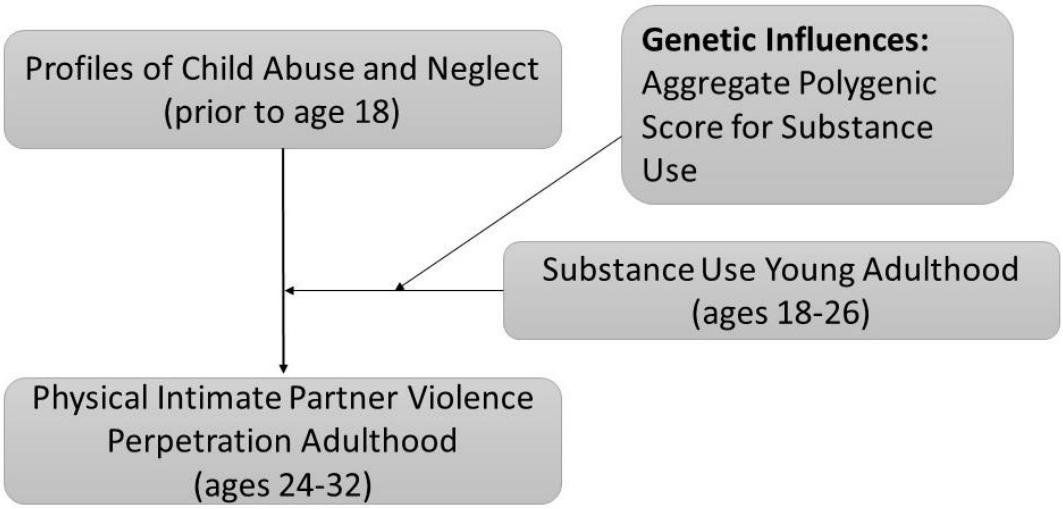

Figure 5.3 Revised conceptual model: moderation by substance use frequency of the association between sub-groups of childhood maltreatment exposure and physical intimate partner violence perpetration in adulthood and genetic moderation of the moderated pathway

Analytic Model 3 (Study 3)

Finally, in chapter 4, I tested analytic model 3 (Figure 5.4). Much like the previous conceptual model, the association between childhood maltreatment sub-groups and physical intimate partner violence victimization was tested using attachment theory (Ainsworth et al., 1978; Bowlby, 1973, 1988) and social learning theory (Bandura & Walters, 1977). Again, like in analytic model 2, the association between childhood maltreatment and substance use frequency was evaluated within the social cognitive theory (Akers, 2017; Bandura, 1986) and genetic moderation was tested within a diathesis-stress model. Additionally, the direct association between physical intimate partner violence victimization and substance use frequency was also examined within the social cognitive theory (Akers, 2017; Bandura, 1986).

With the exception of lower illicit drug use frequency among members of the high sexual abuse sub-group and high frequency of marijuana use among members of the high physical abuse sub-group, a majority of other direct and indirect hypothesized pathways were not supported in this study. Genetic moderation by substance use polygenic risk of the direct pathway from childhood maltreatment sub-groups to substance use frequency in adulthood and from the direct

pathway from physical intimate partner violence victimization in young adulthood to substance use frequency in adulthood within the overall mediation model was also not supported for overall substance use frequency, alcohol use, marijuana use, and illicit drug use.

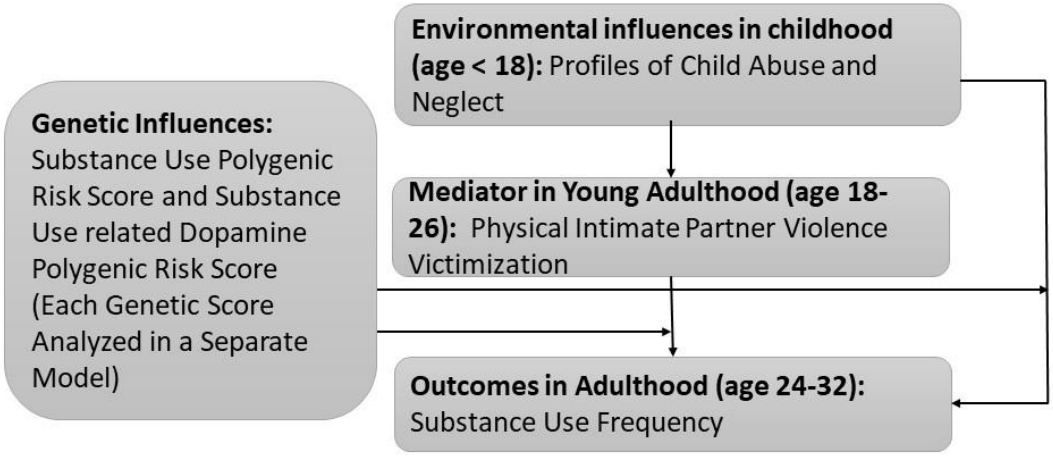

Figure 5.4 Analytic model study 3: Physical intimate partner violence victimization in young adulthood as a mediator of the association between childhood maltreatment and substance use frequency, and testing moderation by substance use and substance use related dopamine genetic risk

Similarly, genetic moderation by substance use related dopamine polygenic risk of the direct pathway from childhood maltreatment sub-groups to substance use frequency in adulthood and from the direct pathway from physical intimate partner violence victimization in young adulthood to substance use frequency in adulthood within the overall mediation model was also not supported for overall substance use frequency, alcohol use, marijuana use, and illicit drug use.

The Dopamine Hypothesis

I also tested the substance use related dopamine polygenic risk score for analytic models 1 and 2 (see Appendix A) due to the hypothesized role of the dopamine system in substance use behaviors (motivation for use, feelings of gratification, etc. - reviewed in chapter 1 and 4).

Dopamine polygenic risk score was not a significant moderator across all analytic models. Like a majority of replication studies using dopamine genes, I was unable to replicate previous findings for dopamine genes being implicated in higher frequency of substance use frequency or higher frequencies of alcohol, marijuana, or illicit drug use. In the era of candidate gene studies, the dopamine hypothesis was proposed as a notable model for understanding genetic risk or susceptibility for substance use. However, a majority of these dopamine gene studies have not been replicated, and no dopamine gene has emerged as a significant predictor of substance use frequency phenotype in subsequent genome-wide association studies (Gorwood et al., 2012; Le Foll, Gallo, Le Strat, et al., 2009). Therefore, it is likely that dopamine genes may not be implicated in increased risk for substance use frequency like previously thought.

Although, the shape and size of dopamine receptors and the metabolism of dopamine may be inherited (Cubells et al., 1997; Gorwood et al., 2012; Le Foll, Gallo, Le Strat, et al., 2009; Skrinskaya et al., 1992), it is likely that the genes and SNPs included in this dissertation to understand dopamine related risks may not provide complete coverage of the entire dopamine neurological system. It is equally likely that the risk for dopamine is passed on through specific mediated pathways such as inhibition or impulse control, increased number of dopamine receptors, and metabolism of dopamine. Finally, genetic research has shifted focus from polygenic risk models of complex phenotypes onto epigenetic changes and gene expression. It is, therefore, likely that substance use frequency and prolonged substance use frequency may result in epigenetic changes of the dopamine system that result in the continuation of these behaviors. Such epigenetic changes need further examination in future work.

Alternative Theoretical Explanation for Study 3/Analytic Model 3

From a life-course and cumulative adversity and stress perspective, developmental outcomes in adulthood are a culmination of or an interaction between events that happen over the duration of development (Kuh, Ben-Shlomo, Lynch, Hallqvist, & Power, 2003; Lifshitz, Ifrah, Markovitz, & Shmotkin, 2019; Maas, Herrenkohl, & Sousa, 2008). Based on this theoretical approach, childhood maltreatment and physical intimate partner violence experiences may have cumulative (i.e. additive) or interactive effects (Lifshitz, Ifrah, Markovitz, & Shmotkin, 2019; Maas, Herrenkohl, & Sousa, 2008) that could explain the association between victimization and

substance use frequency in adulthood. I tested both these alternative models in chapter 4 (see Figures 5.5 and 5.6).

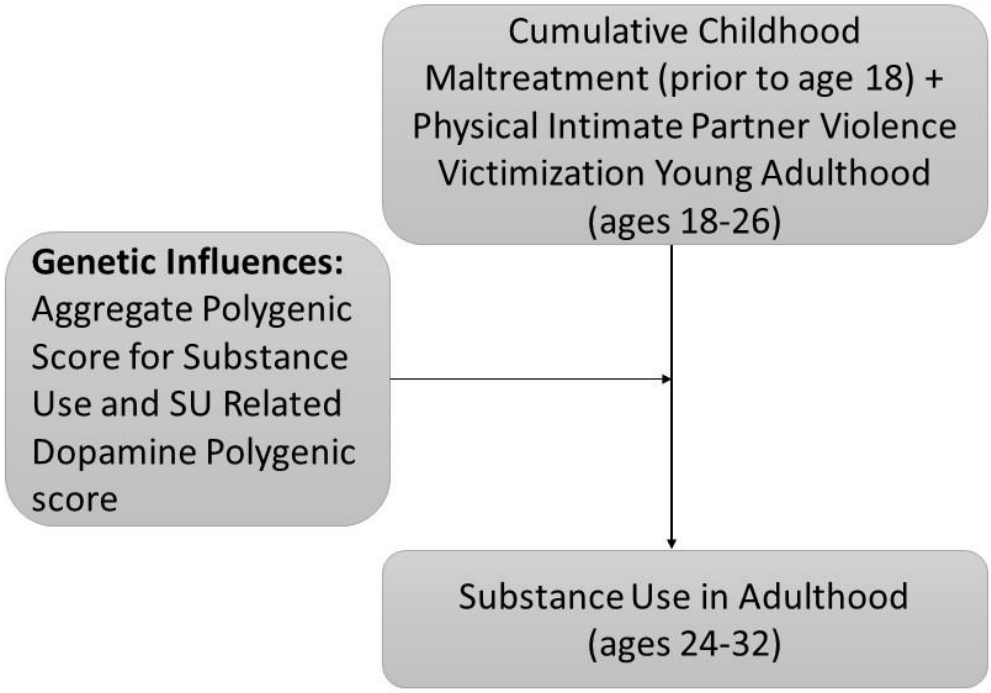

Figure 5.5 Revised conceptual model 3 where cumulative or additive effects of childhood maltreatment exposure and physical intimate partner violence victimization are tested on substance use frequency and genetic moderation of the direct pathway

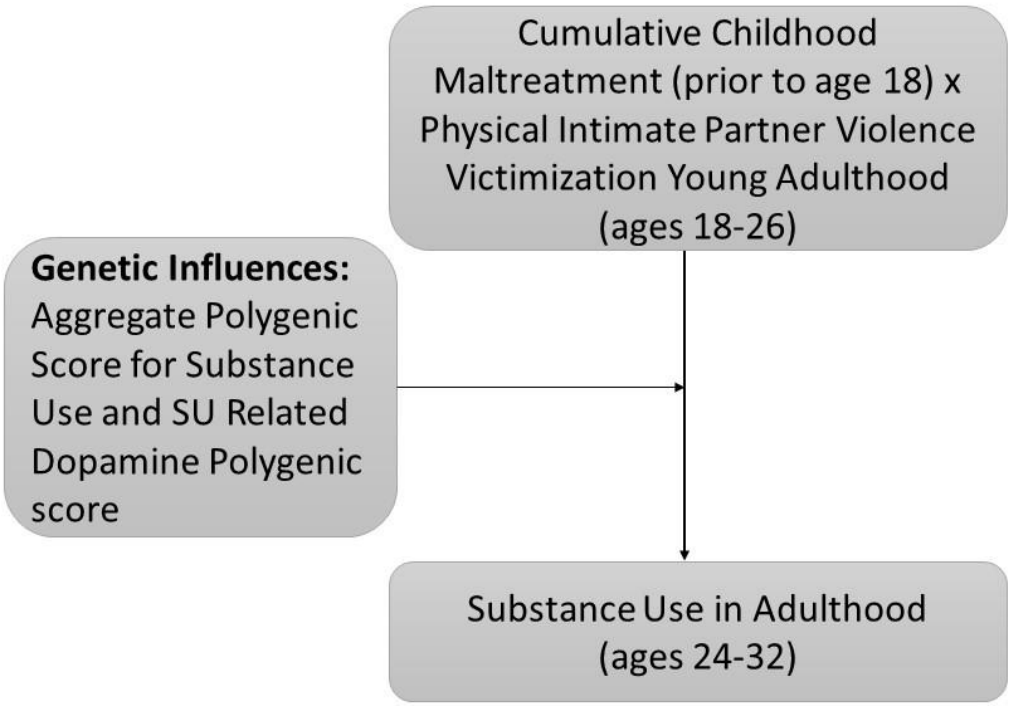

Figure 5.6 Revised conceptual model 3 where interactive effects of childhood maltreatment exposure and physical intimate partner violence victimization are tested on substance use frequency and genetic moderation of the moderated pathways

The cumulative influences of childhood maltreatment and physical intimate partner violence victimization on substance use frequency and genetic moderation within this model was not supported. For the interactive or synergistic model, interaction between childhood maltreatment sub-groups and high and medium levels of physical intimate partner violence victimization in young adulthood only associated with lower levels of illicit drug use among members of the high sexual abuse sub-group.

However, an examination of other life-long adversities should be considered along with childhood maltreatment within the framework of social cognitive and life-course theories, including life-course resilience factors (e.g., optimism, life satisfaction) and risk mechanisms (e.g., homelessness, peer affiliation) that may influence substance use frequency in adulthood (discussed in detail in chapter 4). Nonetheless, the large sample size used in this research, the use of sampling weights, and correction of clustering within this sample allow me to generalize the findings from the original and revised models to the larger population of European American young adults.

Null Genetic Findings Across Models

Findings for genetic moderation for substance use frequency polygenic risk score are partially supported. Although, I find no evidence for substance use frequency polygenic risk score moderation in analytic models 2 and 3 or in revised analytic models 2 and 3, there was some evidence for genetic moderation in analytic model 1.

It is reasonable to preliminarily speculate that for the high sexual abuse sub-group that irrespective of biological risks, social and environmental risk (i.e., maltreatment exposures) may be more pervasive for substance use development. In contrast, both environmental and genetic risk are important for substance use change over time for the high physical abuse sub-groups. This finding is important for future prevention trials which should include not only environmental risk factors but also biological risk for certain constellation of childhood maltreatment exposures. Furthermore, the null genetic findings in certain models could be attributable to issues of measurement such as lack of coverage for the phenotype by the SNPs or issues related to pruning of SNPs (Chatterjee et al., 2016) as identified in previous chapters (genetic measurement issues are discussed in detail in chapters 3 and 4). An additional explanation could be that in study 1, the repeated measures design makes it adequately powered to detect significant genetic moderation

but the other two studies that evaluate more static associations are still underpowered to detect significant genetic effects.

Other Considerations

Though outside the scope of the present dissertation, it is also likely that more extreme exposures to childhood maltreatment such as those involving child protective services may change the findings of the models evaluated in this dissertation. Therefore, replication of the proposed models will be necessary for individuals with more severe childhood maltreatment exposures. Additionally, replication of all study models for more severe forms of substance use frequency (addiction or dependence) and more severe physical intimate partner violence (perpetration and victimization) will be necessary in the future. Finally, better measurement of genetic risk scores and all constructs will also be needed in future research to get better coverage for substance use frequency phenotypes and to better capture childhood maltreatment exposures and prevalence of substance use and physical intimate partner violence.

Conclusion

The purpose of this research was to understand the role of substance use frequency and genetic risk for substance use frequency and its role in the intergenerational cycle of violence in a normative epidemiological sample (i.e. a national population based sample comprising a representative population of European Americans) rather than in clinical sub-samples of individuals with risky substance use frequency or violence exposures. The methods used in this dissertation make use of population-based analytic approaches.

Moreover, the models evaluated (including post-hoc models) across chapters provide a first and much needed step towards understanding 1) the association between childhood maltreatment and physical intimate partner violence, 2) the association between childhood maltreatment and substance use frequency throughout life, 3) the genetics of substance use within the context of childhood maltreatment, and 4) the inter-relation between substance use frequency, physical intimate partner violence, and childhood maltreatment exposure, in a large national population of European Americans.

Based on the findings across the three models, the diathesis-stress model is only supported partially for analytic model 1. Similarly, social learning theory and attachment theories for the association between childhood maltreatment and physical intimate partner violence (both victimization and perpetration) was not supported in this sample. Social cognitive theory for the interrelation between physical intimate partner violence and substance use within the context of childhood maltreatment also did not hold up in this sample. Furthermore, null findings with this large sample of individuals provide robust support for the null findings and could reflect two primary things. First, childhood maltreatment may not be instrumental for influencing subsequent substance use frequency or subsequent violence outcomes in populations similar to the one used. Second, the models as initially conceptualized within social learning theory for greater acceptance of violence victimization among survivors of childhood maltreatment which may lead to negative coping behaviors such as substance use frequency may not necessarily be true across normative sub-populations. Similarly, greater childhood maltreatment related substance use frequency may not be associated with subsequent perpetration of violence.

The ecological theory of human development may explain the associations for the high sexual abuse sub-group in analytic model 1 (i.e., environmental factors but not genetic are critical for substance use outcomes) and the association between childhood maltreatment and physical intimate partner violence perpetration with substance use moderation (as outlined above). Additional protective factors throughout the life-course, along with additional risk mechanisms through which co-occurring childhood maltreatment - that may influence substance use frequency during adolescence and adulthood - and violence outcomes in adulthood need further examination. Future research could also examine life-course risk and protective factors for the inter-relatedness between substance use frequency and physical intimate partner violence victimization within the context of childhood maltreatment exposures. It may also be necessary to expand upon and evaluate additional early life adversities such as family dysfunction along with co-occurring childhood maltreatment exposures.

This is the first study to conduct a multi-factorial exploration of pathways via which childhood maltreatment may influence physical intimate partner violence and high frequency of substance use frequency both of which have detrimental influences on health and personal as well as societal well-being. The large national sample, the use of probability weights and correction of school-level clustering, and the multiple pathways explored within a multi-theoretical framework

in this research significantly add to its strengths. Findings suggest that family based primary prevention efforts in childhood and secondary prevention efforts in adulthood such as cognitive behavioral and motivation interviews (Cahill et al., 2009; Carroll & Kiluk, 2017; Grenard et al., 2006; Leenarts et al., 2013; Saitz et al., 2020) may be important to target co-occurring childhood maltreatment exposures and factors such as substance use frequency to break the intergenerational cycles to violence. Additional avenues for consideration are also discussed. In the future, it will be critical to systematically evaluate the associations presented using multiple theoretical approaches and by utilizing a multifactorial life-course model that includes both risk and protective factors, additional childhood and life-long adversities, and other mechanisms in divergent populations (normative and at-risk populations).

With an estimated 650,000 victims of child maltreatment and 3.3 million victims of lifelong violence victimization each year, this research tries to understand the implication of violence victimization on substance use frequency as well as examines substance use frequency and genetic risk for substance use frequency as factors that may help disentangle the association between intergenerational violence. Identifying marijuana and illicit drug use frequencies as contextual and potentially malleable factors between co-occurring childhood maltreatment exposures and physical intimate partner violence perpetration has implications for future work prevention and intervention efforts. Several recommendations are also made throughout this dissertation (e.g., person-level resilience factors, family level risk factors, and contextual factors) and for future research to explore to better understand the inter-relatedness of co-occurring childhood maltreatment exposures, substance use, physical intimate partner violence and genetic risk for substance use. Therefore, the knowledge generated from this research provides a solid foundation for future research endeavors.

APPENDIX A. SUPPLEMENTARY ANALYSIS

Testing Mediation Hypothesis with Full Sample (Model 2; Chapter 3)

To ascertain, if homogeneity of the study sample was an explanatory factor for the null mediation findings, I tested substance use frequency in young adulthood as a mediator of overall childhood maltreatment exposure and physical intimate partner violence perpetration in adulthood (β = 0.00, *s.e.* = 0.00, *p* = 0.14) using the full nationally representative Add Health sample. I also tested to see if specific substances such as alcohol (β = 0.00, *s.e.* = 0.00, *p* = 0.56), marijuana (β = 0.01, *s.e.* = 0.00, *p* = 0.12), and illicit drug use (β = 0.00, *s.e.* = 0.00 , *p* = 0.87) emerged as mediators of the association between childhood maltreatment exposure and physical intimate partner violence perpetration utilizing the full Add Health sample. Once again, no support for the mediation model was found with the entire sample.

Testing Mediation Hypothesis with Full Sample (Model 3; Chapter 4)

Since homogeneity of the study sample could once again be a reason for null findings, I tested physical intimate partner violence victimization in young adulthood as a mediator of overall childhood maltreatment exposure and substance use frequency in adulthood (β = 0.00, *s.e.* = 0.00, *p* = 0.35), utilizing the full nationally representative sample. I also tested to see if physical intimate partner violence victimization emerged as a mediator for alcohol (β =0.00, *s.e.* = 0.00, *p* = 0.48), marijuana (β = 0.00, *s.e.* = 0.01, *p* = 0.53), and illicit drug use (β = 0.00, *s.e.* = 0.00, *p* = 0.44) frequencies. However, the mediation model was not supported in the full sample.

Testing of Dopamine Genetic Risk for Paper 1 (Model 1; Chapter 2) and Paper (Model 2; Chapter3)

Paper 1

I tested the substance use related dopamine polygenic risk score from chapter 4 as a moderator of the association between sub-groups of childhood maltreatment exposures and

substance use levels and trajectory in chapter 2 (i.e. Models 2 and 3). Significant interactions were probed at levels of genetic risk high (+1 *SD* above the mean), low (-1 *SD* below the mean) and medium (mean levels for the sample; Aiken, West, & Reno, 1991). All covariates were included for substance use levels and change over time for Model 3 as well.

Paper 2

Direct effects, indirect effects and moderated-mediation models were tested for average substance use and substance specific use (marijuana use, alcohol use, and other drug use) wherein the genetic moderator was substance use related dopamine polygenic risk score.

Post-hoc Models Results

Paper 1

Results from Model 2 for substance use polygenic risk score are summarized in Table A1 and Model 3 (interaction models) are presented in Table A2. Substance use related dopamine polygenic risk score did not have a direct association with levels or change of substance use (or specific substances used). Substance use related dopamine polygenic risk score also did not moderate the association between maltreatment sub-groups and substance use levels or change.

Appendix Table A1 Association of maltreatment-sub-groups and dopamine genetic risk with levels and change of substance use frequency over time

Substance Use Related Dopamine Polygenic Risk Score on Substance Use[1] Levels	Model 3 (Substance Use)			Model 3 (Alcohol Use)			Model 3 (Marijuana Use)			Model 3 (Illicit Drug Use)		
	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*
High Sexual Abuse Sub-group	-0.03	0.04	0.42	-0.05	0.02	0.00	0.04	0.06	0.54	-0.10	0.13	0.44
High Physical Abuse Sub-group	0.11	0.08	0.16	0.07	0.06	0.19	0.10	0.09	0.30	0.06	0.19	0.74
Substance Use Related Dopamine Polygenic Risk Score	0.02	0.05	0.62	0.04	0.05	0.38	-0.02	0.07	0.76	-0.26	0.14	0.07
Respondent's Education (in years)	-0.12	0.07	0.09	-0.11	0.05	0.02	-0.07	0.15	0.64	-0.12	0.16	0.44

Table A1 Continued

Parent Education (in years)	0.03	0.07	0.68	0.05	0.05	0.35	0.07	0.13	0.60	-0.15	0.18	0.42
Biological Sex	-0.08	0.05	0.14	-0.09	0.04	0.04	-0.03	0.10	0.80	0.41	0.16	0.01
Substance Use Related Dopamine Polygenic Risk Score on Substance Use[1] Change	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*
High Sexual Abuse Sub-group	0.04	0.04	0.33	0.04	0.02	0.05	-0.03	0.07	0.64	0.14	0.19	0.45
High Physical Abuse Sub-group	-0.06	0.06	0.30	-0.08	0.05	0.12	-0.02	0.08	0.86	-0.01	0.21	0.97
Substance Use Related Dopamine Polygenic Risk Score	0.00	0.04	0.97	-0.01	0.05	0.83	0.05	0.07	0.47	0.20	0.14	0.15
Respondent's Education (in years)	0.05	0.06	0.39	0.11	0.05	0.02	-0.04	0.13	0.75	-0.06	0.15	0.68
Parent Education (in years)	0.23	0.04	0.00	0.24	0.05	0.00	0.18	0.08	0.03	-0.26	0.16	0.09
Biological Sex	0.00	0.06	0.96	0.01	0.05	0.80	-0.05	0.12	0.70	0.09	0.17	0.60

1 - depends on overall phenotype or specific substances assessed as outcome

Appendix Table A2 Association of maltreatment-sub-groups and dopamine genetic risk with levels and change of substance use frequency over time

Substance Use Related Dopamine Polygenic Risk Score on Substance Use[1] levels												
	Substance Use			Alcohol Use			Marijuana Use			Illicit Drug Use		
	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*
High Sexual Abuse Sub-group	-0.04	0.04	0.25	-0.05	0.02	0.00	-0.02	0.06	0.79	-0.25	0.11	0.03
High Physical Abuse Sub-group	0.12	0.08	0.14	0.08	0.06	0.16	0.11	0.10	0.28	0.06	0.19	0.75
Substance Use Related Dopamine Polygenic Risk Score	0.01	0.05	0.87	0.04	0.06	0.43	-0.05	0.08	0.54	-0.22	0.14	0.10
Respondent's Education (in years)	-0.12	0.07	0.09	-0.11	0.05	0.02	-0.06	0.15	0.68	-0.13	0.17	0.44
Parent Education (in years)	0.03	0.07	0.68	0.05	0.05	0.34	0.07	0.13	0.61	-0.16	0.19	0.40
Biological Sex	-0.08	0.05	0.13	-0.09	0.04	0.03	-0.02	0.10	0.84	0.38	0.14	0.01

Table A2 Continued

High Sexual Abuse Sub-group*Substance Use Related Dopamine Polygenic Risk Score	-0.01	0.01	0.60	-0.01	0.01	0.20	0.00	0.03	0.95	0.08	0.15	0.58
High Physical Abuse Sub-group *Substance Use Related Dopamine Polygenic Risk Score	-0.01	0.02	0.54	0.02	0.01	0.28	-0.04	0.03	0.25	-0.21	0.15	0.16
Substance Use Related Dopamine Polygenic Risk Score on Substance Use[1] Change	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*
High Sexual Abuse Sub-group	0.05	0.04	0.20	0.04	0.02	0.03	0.03	0.06	0.63	0.35	0.14	0.01
High Physical Abuse Sub-group	-0.07	0.06	0.25	-0.08	0.05	0.10	-0.02	0.09	0.84	-0.02	0.20	0.93
Substance Use Related Dopamine Polygenic Risk Score	0.02	0.05	0.61	-0.01	0.06	0.93	0.09	0.08	0.29	0.21	0.13	0.09
Respondent Education (in years)	0.05	0.06	0.42	0.11	0.05	0.02	-0.05	0.14	0.69	-0.07	0.16	0.67
Parent Education (in years)	0.23	0.04	0.00	0.24	0.05	0.00	0.18	0.09	0.04	-0.24	0.15	0.10
Biological Sex	0.00	0.06	0.96	0.01	0.05	0.82	-0.04	0.12	0.72	0.11	0.17	0.53

Table A2 Continued

High Sexual Abuse Sub-group*Substance Use Related Dopamine Polygenic Risk Score	0.05	0.06	0.35	0.00	0.04	0.94	0.07	0.09	0.42	-0.15	0.20	0.47
High Physical Abuse Sub-group *Substance Use Related Dopamine Polygenic Risk Score	-0.07	0.04	0.11	-0.03	0.03	0.33	-0.07	0.08	0.41	0.06	0.19	0.75

1 - depends on overall phenotype or specific substances assessed as outcome

Paper 2

Direct Effects

Direct effects are summarized in Table A3. Higher levels of dopamine related substance use polygenic risk score were associated with lower marijuana use in young adulthood.

Indirect Effects

Indirect effects from these models are summarized in Table A4. Once again substance use and specific types on substance use did not mediate the association between childhood maltreatment exposure and physical intimate partner violence perpetration.

Moderated-Mediation Dopamine Related Substance Use Polygenic Risk Score

Substance use related dopamine polygenic risk score did not moderate the mediating pathway from no physical abuse sub-group membership to alcohol use (b = -0.01; *s.e.* = 0.02 to 0.03 ; p = 0.62 to 0.74), marijuana use (b = 0.00 to 0.01 ; *s.e.* = 0.02 to 0.14 ; p = 0.96 to 0.97), other drug use (b = 0.00 to 0.02 ; *s.e.* = 0.08 to 0.14 ; p = 0.85 to 0.99) or average substance use frequency (b = -0.02 to -0.01 ; *s.e.* = 0.02; p = 0.32 to 0.78) in young adulthood.

Substance use related dopamine polygenic risk score also did not moderate the mediating pathway (high, medium, or low level) from no sexual abuse sub-group membership to alcohol use (b = -0.04 to -0.01 ; *s.e.* = 0.02 to 0.04 ; p = 0.30 to 0.74), marijuana use (b = -0.00 to 0.01 ; *s.e.* = 0.01 to 0.02; p = 0.62 to 0.83), other drug use (b = 0.00 to 0.01 ; *s.e.* = 0.02 to 0.05 ; p = 0.85 to 0.90) or average substance use frequency (b = -0.01 to 0.01; *s.e.* = 0.01 ; p = 0.35 to 0.70) in young adulthoo

Appendix Table A3 Direct association with physical intimate partner violence perpetration in adulthood and substance u
young adulthood (dopamine related substance use polygenic risk score model)

Physical Intimate Partr Violence Perpetratio	Substance Use			Alcohol Use			Marijuana Use			Illicit Drug Use		
	β	*s.e.*	*p*	β	*s.e*	*p*	β	*s.e*	*p*	β	*s.e*	*p*
Substance Use[1]	0.(	0.0	0.(	0.0	0.0	0.0	-0.(	0.0	0.8	0.0	0.0	0.7
High Sexual Abuse Sub-g	0.(	0.0	0.3	0.0	0.0	0.3	0.0	0.0	0.3	0.0	0.0	0.3
High Physical Abuse Sub-	0.(	0.0	0.7	0.0	0.0	0.9	0.0	0.0	0.8	0.0	0.0	0.7
Respondent's Education	-0.	0.0	0.1	-0.(	0.0	0.0	-0.(	0.0	0.0	-0.(	0.0	0.2
Parent's Education Lev	-0.	0.0	0.1	-0.(	0.0	0.0	-0.(	0.0	0.1	-0.(	0.0	0.1
Respondent's Age at Wa	-0.	0.1	0.6	-0.(	0.1	0.6	-0.(	0.1	0.6	-0.(	0.1	0.6
Respondent's Age at Wa	0.(	0.0	0.9	0.0	0.0	0.9	-0.(	0.0	0.9	0.0	0.1	0.9
Biological Sex	-0.	0.0	0.(	-0.(	0.0	0.0	-0.(	0.0	0.1	-0.(	0.0	0.0

Table A3 continued

Substance Use

	Substance Use			Alcohol Use			Marijuana Use			Illicit Drug Use		
	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*	β	*s.e.*	*p*
High Sexual Abuse Sub-group	0.01	0.03	0.56	0.00	0.01	0.87	0.06	0.05	0.20	0.06	0.06	0.29
High Physical Abuse Sub-group	0.00	0.03	0.91	-0.05	0.02	0.03	0.10	0.04	0.02	0.04	0.06	0.53
Substance use related Dopamine Polygenic Risk Score	-0.04	0.03	0.15	0.02	0.02	0.32	-0.11	0.04	0.01	-0.11	0.12	0.33
High Sexual Abuse Sub-group*Substance Use Related Dopamine Polygenic Risk Score	0.00	0.02	0.89	0.02	0.01	0.11	-0.07	0.03	0.01	-0.05	0.03	0.16
High Physical Abuse Sub-group *Substance Use Related Dopamine Polygenic Risk Score	-0.01	0.02	0.83	-0.01	0.01	0.19	0.05	0.04	0.27	-0.03	0.03	0.26
Respondent's Education level	-0.04	0.04	0.24	0.06	0.03	0.09	-0.13	0.06	0.04	-0.19	0.06	0.00
Parent's Education Level	0.04	0.04	0.34	0.06	0.03	0.08	0.01	0.07	0.91	0.01	0.07	0.95
Respondent's Age at Wave 3	-0.04	0.14	0.79	0.13	0.12	0.31	-0.31	0.23	0.17	0.11	0.40	0.77
Respondent's Age at Wave 4	-0.03	0.14	0.83	-0.15	0.12	0.22	0.23	0.23	0.32	-0.25	0.41	0.54
Biological Sex	0.24	0.02	0.00	0.20	0.03	0.00	0.18	0.05	0.00	0.10	0.07	0.15

Note: Standardized estimates presented in table; 1 - either substance use or alcohol use or marijuana use or other drug use depending on the phenotype evaluated as outcome

Appendix Table A4 Estimating Indirect Effects for Physical Intimate Partner Violence via Substance use for Dopamine Related substance use Polygenic Risk Score model

Substance use						
	High Sexual Abuse Sub-group			High Physical Abuse Sub-group		
	β	*s.e.*	*p*	β	*s.e.*	*p*
Physical Intimate Partner Violence	0.00	0.00	0.60	0.00	0.00	0.91
Alcohol Use						
	High Sexual Abuse Sub-group			High Physical Abuse Sub-group		
	β	*s.e.*	*p*	β	*s.e.*	*p*
Physical Intimate Partner Violence	0.00	0.00	0.88	0.00	0.00	0.16
Marijuana Use						
	High Sexual Abuse Sub-group			High Physical Abuse Sub-group		
	β	*s.e.*	*p*	β	*s.e.*	*p*
Physical Intimate Partner Violence	0.00	0.01	0.82	0.00	0.01	0.81
Illicit Drug Use						
	High Sexual Abuse Sub-group			High Physical Abuse Sub-group		
	β	*s.e.*	*p*	β	*s.e.*	*p*
Physical Intimate Partner Violence	-0.02	0.02	0.74	0.02	0.03	0.79

Note: Standardized estimates presented in table; Indirect effects were estimated above and beyond all covariates and interaction between substance use genetic risk

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