Multiplex Familial Risk for Alcohol Use Disorders and Substance Use Disorder Outcome: The Mediating Effects of Social Functioning

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Alcohol use disorders (AUD) are associated with deficits in social cognition, the mental processes involved in perceiving, attending to, remembering, thinking about, and making sense of the people in our social world. Consistent findings of impaired theory of mind and affective face processing in AUD raise questions as to whether these deficits are the consequence of neural damage associated with AUD or potentially reflect premorbid risk for alcohol-related problems. Offspring with a family history of AUD are at increased risk for substance use disorders (SUD), and some research suggests that alcohol-naïve, high-risk offspring also have deficits in social-cognitive functioning. However, evidence linking premorbid social-cognitive functioning to SUD outcome has not yet been established. Accordingly, this dissertation sought to examine specific measures of social functioning, thought to reflect underlying social-cognitive abilities, and their relationship to both familial risk status and SUD outcome. The sample included high-risk offspring (n = 137) from multiplex, alcohol-dependent families and low-risk controls (n = 122) from an ongoing longitudinal study comprising 2,387 separate evaluations. Risk-group differences were examined on parent-report measures of social competence and social problems collected during childhood, self-report measures of social support from parents and friends during adolescence, and self-report measures of personality administered in young adulthood. Structural equation modeling (SEM) was used to examine relationships between familial risk status, social functioning, adolescent alcohol use, and SUD outcome. Compared to low-risk controls, high-risk

offspring had poorer performance on measures of social functioning administered during childhood, adolescence, and young adulthood, higher rates of alcohol use during adolescence, and increased likelihood of developing SUD by young adulthood. Further, the relationship between familial risk status and SUD outcome was partially mediated by social competence in childhood, by alcohol use in adolescence, and in association with social connectedness and alienation in young adulthood. This dissertation provides preliminary evidence that social functioning is impaired among high-risk offspring before the onset of regular alcohol use and that these deficits confer additional risk for SUD above and beyond the influence of familial risk. Interventions targeting social functioning may improve outcomes among youth at high familial risk for AUD.

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1.0 Introduction

Adults with alcohol use disorders (AUD) demonstrate deficits in social cognition (Bora & Zorlu, 2017; Castellano et al., 2015; Le Berre, Fama, & Sullivan, 2017; Onuoha, Quintana, Lyvers, & Guastella, 2016; Thoma, Friedmann, & Suchan, 2013a; Thorberg, Young, Sullivan, & Lyvers, 2009; Uekermann & Daum, 2008), and emerging evidence indicates that alcohol-naïve, high-risk offspring with a family history of AUD also demonstrate atypical social-cognitive functioning, including abnormal neural activation during theory of mind and emotional face processing fMRI tasks (Cservenka, Fair, & Nagel, 2014; Glahn, Lovallo, & Fox, 2007; Hill et al., 2007; Hulvershorn et al., 2013; Peraza, Cservenka, Herting, & Nagel, 2015). Research among community and other at-risk samples has also consistently shown that family- and peer-related factors in childhood and adolescence confer risk for SUD, independent of familial risk status. However, only a small number of studies have directly investigated the role of relationships with family members and peers in SUD outcomes among youth with a family history of AUD.

Given well-established relationships between familial risk status, adolescent alcohol use, and SUD by young adulthood, a growing body of literature documenting social cognitive deficits among adults with AUD, and strong evidence that family- and peer-related factors in childhood and adolescence confer risk for SUD independent of familial risk status, closer investigation of relationships among these factors is warranted. The current study sought to examine specific measures of social functioning, thought to reflect underlying social-cognitive abilities, and their relationship to both familial risk status and SUD outcome. The sample included high-risk offspring (n = 137) from multiplex, alcohol-dependent families and low-risk controls (n = 122) from an ongoing longitudinal study comprising 2,387 separate evaluations. It was expected that offspring

with a family history of AUD would have higher rates of adolescent alcohol use and SUD by young adulthood, and that high-risk offspring would also show deficits on measures of social functioning collected during childhood, adolescence, and young adulthood. Finally, it was expected that premorbid deficits in social functioning would confer increased risk for SUD outcome by young adulthood, independent of familial risk status. The current study sought to use structural equation modeling to explore longitudinal relationships between familial risk for AUD, social functioning measured in childhood, adolescence, and young adulthood, adolescent alcohol use, and SUD outcomes. This framework allowed for assessment of potential mediation of the association between familial risk and SUD outcome by social functioning factors.

1.1 Review of the Literature

1.1.1 Alcohol Use Disorders

Alcohol use disorders (AUD) are characterized by problematic patterns of alcohol use leading to clinically significant impairment or distress and are a major public health problem in the United States and many other parts of the world (American Psychiatric Association, 2013). Data from the National Epidemiologic Survey on Alcohol and Related Conditions indicates that the lifetime prevalence of AUD is 20.9% in the United States (Grant et al., 2015). AUD is associated with deficits in numerous cognitive and emotional processes, as well as concomitant structural and functional abnormalities of the central nervous system (Oscar-Berman & Marinkovic, 2007). Accordingly, it is of great clinical interest to gain a better understanding of

the factors increasing risk for AUD in order to inform prevention and intervention efforts for affected and at-risk individuals.

1.1.1.1 Heritability of AUD

Alcohol use disorders and other substance use disorders (SUD) have complex etiologies that are influenced by interactions between genetic, environmental, and developmental processes across childhood, adolescence, and young adulthood. Twin, adoption, and family studies have provided significant evidence that AUD runs in families, and recent meta-analyses estimate the heritability of AUD to be 0.52 for males and 0.44 for females (Verhulst, Neale, & Kendler, 2015). Offspring of parents with AUD are 4-10 times more likely to develop AUD than offspring of non-alcoholics (Cloninger, Bohman, & Sigvardsson, 1981; Chassin, Curran, Hussong, & Colder, 1996; Donovan, 2004; Goodwin, Schulsinger, Hermansen, Guze, & Winokur, 1973), and offspring with particularly dense or multigenerational family histories are at even greater risk (Dawson & Grant, 1998; Hill et al., 2008; Hill, Tessner, & McDermott, 2011). Parental AUD has also been shown to increase risk for the use and abuse of other drugs in adolescence (Hussong, Huang, Serrano, Curran, & Chassin, 2012), as well as other SUD in young adulthood (Hill et al., 2008; Hill et al., 2011). Given that AUDs run in families, research examining substance-naïve, first-degree relatives of individuals with AUD has elucidated a number of biological and psychological characteristics that may reflect premorbid risk factors for AUD and other SUD. Additionally, longitudinal studies following offspring with a family history of AUD have allowed for the determination of risk and resilience factors among these high-risk offspring. Premorbid risk factors for AUD often converge with observed deficits in affected adults, indicating that the behavioral phenotype of AUD likely reflects a complex interaction of premorbid genetic and

environmental risk factors and the neurotoxic effects of alcohol and other drugs of abuse on the brain (Hill & O'Brien, 2015).

1.1.1.2 Phenotypic Characteristics of High-Risk Offspring

Among children and adolescents with a family history of AUD, several phenotypic risk factors that are predictive of SUD outcome have been identified. Deficits in response inhibition, cognitive control and emotion regulation are commonly observed in high-risk individuals (Cservenka, 2016; Hill & O'Brien, 2015). Externalizing behaviors, including oppositionality, hyperactivity, impulsivity, inattention, and sensation seeking, as well as externalizing disorders, including Attention Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, and Conduct Disorder, are observed in high-risk offspring during childhood and adolescence and are predictors of subsequent alcohol and drug use problems (Hill et al., 2008; Hill et al., 2011; Iacono, Carlson, Taylor, Elkins, & McGue, 1999; Iacono, Malone, & McGue, 2008). High-risk offspring also have a higher incidence of internalizing psychopathology, and are more likely to demonstrate anxiety and stress-reactive personality traits such as harm avoidance, low self-esteem, negative affectivity, and impaired emotion regulation (Hill et al., 2008; Hill et al., 2011; Hussong, Jones, Stein, Baucom, & Boeding, 2011). Recent research on psychological predictors of SUD in high-risk offspring has also focused on impaired reward sensitivity and decision making, as well as deficits in social cognition (Hill & O'Brien, 2015; O'Brien, Lichenstein, & Hill, 2014).

1.1.2 Social Cognition

Social cognition refers to the study of mental processes involved in perceiving, attending to, remembering, thinking about, and making sense of the people in our social world, and

encompasses a broad range of abilities (Moskowitz, 2005). Research on social cognition has rapidly grown over the past ten years cross the fields of social, cognitive, clinical, and developmental psychology and neuroscience, and social cognition has recently been designated as a major domain in the Research Domain Criteria (RDoC) framework (Gur & Gur, 2016). Deficits in social cognition are hallmark features of autism spectrum disorders and schizophrenia, and social cognition has been increasingly studied in a range of other psychiatric conditions, including AUD (Bora & Zorlu, 2017). A recent meta-analysis by Cotter et al. (2018) suggests that social cognitive deficits are a core cognitive phenotype of many psychiatric disorders, and that these deficits tend to be of similar magnitude as other, more established cognitive deficits typically observed among clinical populations (Cotter, Granger, Backx, Hobbs, Looi, & Barnett, 2018). Although numerous definitions of social cognitive have been offered, the National Institute of Mental Health (NIMH) Workshop on Social Cognition in Schizophrenia has defined social cognition as "the mental operations that underlie social interactions, including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others". This NIMH Workshop identified five key areas of study in social cognition: theory of mind/mental state attribution, social perception, social knowledge, attributional bias, and emotional processing (Green et al., 2008; Pinkham et al., 2013), though the majority of research, to date, has focused on theory of mind and social perception/emotional processing, as assessed by emotional face recognition tasks (Cotter et al., 2018).

Neuroimaging research on social cognition has allowed for the delineation of a set of neural structures and networks subserving various aspects of social thought and behavior. Both structural and functional neuroimaging studies have been used to assess the neural basis of social cognition among healthy individuals and those with psychiatric disorders. Neural regions playing an integral

role in social cognition span all four lobes of the brain and include both cortical and subcortical structures. The components of the 'social brain' include the amygdala, insula, temporoparietal junction, dorsomedial prefrontal cortex, anterior cingulate cortex (ACC), superior temporal sulcus/gyrus, posterior cingulate, retrosplenial cortex, fusiform face area, orbitofrontal cortex (OFC), and extrastriate body area (Kennedy & Adolphs, 2012).

1.1.3 Social Cognition and AUD

Individuals with AUD and other substance use disorders are more likely to experience problems in close relationships, including higher levels of interpersonal distress, greater conflict and less cohesion with family members, and low social integration and low social support (Nixon, Tivis, & Parsons, 1992; Lewis, Price, Garcia, & Nixon, 2019; Phillipot et al., 2003). Interpersonal difficulties are associated with substance use in adolescence, young adulthood, and across adulthood, and recent studies have demonstrated important associations between interpersonal problems and underlying social cognitive abilities (Kornreich et al., 2011; Maurage et al., 2011b). Research on social cognition in AUD is a rapidly growing field, as evidenced by the increasing number of empirical behavioral and neuroimaging studies, theoretical reviews, and meta-analyses published since the early 2000s (Bora & Zorlu, 2017; Castellano et al., 2015; Le Berre et al., 2017; Onuoha et al., 2016; Thoma et al., 2013a; Thorberg et al., 2009; Uekermann & Daum, 2008). Studies have consistently shown that adults with AUD show deficits in theory of mind and emotional processing, although other key areas of study in social cognition remain largely unexamined. In addition to findings of behavioral deficits and atypical task-based neural activity that are subsequently described, adults with AUD also show abnormal structural morphology of brain regions implicated in social cognition, including the amygdala, ACC, OFC, and insula

(Cardenas et al., 2011; Durazzo et al., 2011; Makris et al., 2008; Wobrock et al., 2009; Wrase et al., 2008; Xiao et al., 2015).

1.1.3.1 Theory of Mind

Adults with AUD have been shown to have deficits in theory of mind, which refers to the ability to reason about mental states of other people and to predict and understand other people's behavior on the basis of their mental state (Bosco et al., 2009; Cox, Bertoux, Turner, Moss, Locker, & Riggs, 2018; Gizewski et al., 2013; Maurage et al., 2011a, 2011b; Maurage, de Timary, Tecco, Lechantre, & Samson, 2015; Nandrino et al., 2014; Premack & Woodruff, 1978; Thoma, Winter, Juckel, & Roser, 2013b). Additionally, neuroimaging research has implicated atypical functioning of the insula in those with AUD during theory of mind tasks (Gizewski et al., 2013). Theory of mind deficits in individuals with AUD have also been demonstrated via impairments on measures of complex social communication that putatively rely on intact theory of mind ability, including humor processing and understanding and detection of faux pas and irony (Amenta, Noel, Verbanck, & Campanella, 2013; Cermak et al., 1989; Thoma et al., 2013b; Uekermann, Channon, Winkel, Schlebusch, & Daum, 2007).

1.1.3.2 Emotional Processing

Emotional processing broadly refers to perceiving, facilitating, understanding, and managing emotions (Green et al., 2008; Mayer, Salovey, Caruso, & Sitarenios, 2001). Models of emotional processing often include affect perception (i.e., the ability to recognize or 'decode' emotions from human faces), a domain well studied in AUD (for reviews, see D'Hondt, Campanella, Kornreich, Philippot, & Maurage, 2014; Donadon & de Lima Osório, 2014). Faces are multi-dimensional stimuli that convey signals of social and motivational significance, and the

ability to correctly identify emotions from facial expressions is an important social skill. Disruption of this ability may lead to misunderstandings and significant impairments in interpersonal communication; deficits in the ability to decode facial expressions of emotion are associated with low social competence, low popularity in peer groups, and higher rates of alexithymia in both healthy and clinical populations (D'Hondt et al., 2014; Grynberg et al., 2012).

Adults with AUD have consistently been shown to overestimate the intensity of negative emotions in faces and systematically over-attribute emotions of anger and contempt (Kornreich et al., 2001a; Kornreich et al., 2001b; Kornreich et al., 2002; Maurage et al., 2009; Maurage, Campanella, Philippot, Martin, & de Timary, 2008; Philippot, Kornreich, & Blairy, 2003; Philippot et al., 1999; Townshend & Duka, 2003; Valmas, Mosher Ruiz, Gansler, Sawyer, & Oscar-Berman, 2014). Deficits in decoding faces appears to be limited to emotional cues, as affected individuals are not impaired in the ability to decode non-emotional face features like gender, age range, or cultural identity (Foisy et al., 2007b). Deficits in face processing has been shown to persist after several months of abstinence (Foisy et al., 2007a; Foisy et al., 2005; Kornreich et al., 2001b), indicating these emotion-perception deficits are not solely due to the acute effect of heavy alcohol consumption. fMRI studies assessing neural activation during the presentation and/or decoding of emotional facial expressions have shown that adults with AUD show atypical activation of the amygdala, orbitofrontal cortex, insula, and anterior cingulate cortex in comparison to healthy controls (Charlet et al., 2014; Marinkovic et al., 2009; O'Daly et al., 2012; Park et al. 2015; Salloum et al., 2007).

In addition to deficits in facial affect perception, adults with AUD may show more general difficulties in understanding and managing emotions. Affected individuals have lower scores on measures of emotional intelligence (Kornreich et al., 2011), and past research has documented a

relationship between AUD and alexithymia, a term introduced by Peter Sifneos in 1972 that literally means 'no words for emotions' (Thorberg et al., 2009). Alexithymia is a multifaceted construct that has been described as difficulty identifying and communicating feelings, differentiating feelings and somatic sensations of emotional arousal, a diminuation of fantasy and imagination, and an externally oriented cognitive style (Sifneos, 1973). Several studies have shown that adults with AUD have higher levels of alexithymia than unaffected controls (Hamidi, Rostami, Farhoodi, & Abdolmanafi, 2010; Maurage et al., 2011b; Rybakowski, Ziolkowski, Zasadzka, & Brzezinski, 1988; Uzun, Ates, Cansever, & Ozsahin, 2003).

1.1.4 Social Cognition in High-Risk Offspring

Consistent findings of impaired theory of mind and emotional processing in AUD raise questions as to whether these deficits are the consequence of neural damage associated with AUD or potentially reflect premorbid risk for AUD. Although relatively few studies have examined social cognition in high-risk offspring with a family history of AUD, twin, adoption, and family studies have shown significant heritability of social cognitive abilities, with effect sizes equal to or greater than those observed for other neurocognitive skills (Constantino & Todd, 2003; Constantino & Todd, 2005; Ebstein, Israel, Chew, Zhong, & Knafo, 2010; Gur et al., 2006; Gur et al., 2007; Hughes & Cutting, 1999; Knowles et al., 2015). Deficits in social cognition are also observed in unaffected siblings of individuals with schizophrenia and autism spectrum disorders, lending further support for the hereditable nature of these deficits (Villareal et al., 2014).

One previous study has shown that young adult high-offspring who did not succumb to SUD have intact theory of mind, potentially indicating a role of this ability in predicting resilience (Kopera et al., 2014), whereas high-risk offspring from multiplex, AD families have been found

to show atypical neural activation during mental state attribution in the right middle temporal gyrus, right superior frontal gyrus, and left inferior frontal gyrus compared to low-risk controls (Hill et al., 2007). Adults with AUD also show atypical activity in the medial temporal lobe on this task (Gizewski et al., 2013), and atypical activation in prefrontal regions has also been observed in subjects with autism (Baron-Cohen et al., 1999).

A small number of additional studies have directly assessed neural activation in response to emotional faces in alcohol-naïve offspring with and without a family history of AUD (Cservenka et al., 2014; Glahn et al., 2007; Hulvershorn et al., 2013; Peraza et al., 2015). Collectively, these studies have documented atypical activation of numerous neural regions during face processing, including the amygdala, insula, and OFC. Volumetric imaging studies have also shown that alcohol-naïve high-risk offspring show volumetric reductions in these neural regions (Cservenka, 2016; Hill & O'Brien, 2015), and that volumes of the amygdala and OFC observed during adolescence prospectively predict SUD outcome in young adulthood (O'Brien & Hill, 2017). Although this body of research lends preliminary support for deficits in theory of mind and emotional processing among high-risk offspring, future research is needed to confirm and extend this finding.

1.1.5 Social Cognition and Social Functioning

Social functioning refers to an individual's interactions with their environment and the ability to fulfill their role within environments such as school/work, social activities, and relationships with peers and family (Bosc, 2000). Similarly, the domain of social cognition has also been defined more broadly as encompassing 'behavior related to contact with the context of other conspecifics' (Gur & Gur, 2016). In support of a broader definition of social cognition,

elements of more narrowly-defined social cognitive abilities (e.g. theory of mind, face processing) have been shown to correlate with more general measures of social functioning in healthy children and adults (Bosacki & Wilde, 1999; Cacioppo & Hawkley, 2009; Crick & Dodge, 1994; Ford, 1982; Lakey & Drew, 1997; Lalonde & Chandler, 1995; Liddle & Nettle, 2006; McGuire & Weisz, 1982; Nowicki & Mitchell, 1998; Rubin, Bukowski, & Parker, 1997; Walker, 2005). Furthermore, emerging evidence suggests that atypical social behavior observed in psychiatric disorders is strongly correlated with social cognitive deficits (Bishop-Fitzpatrick, Mazefsky, Eack, & Minshew, 2017; Brune, 2007; Janusz, Kirkwood, Yeates, & Taylor, 2002; Kornreich et al., 2011; Lewis et al., 2019; Maurage et al., 2011b) and abnormal functioning of neural structures involved in the processing of social cognitive information (Villareal et al., 2014).

1.1.5.1 Social Cognition and Social Functioning in AUD

Individuals with AUD frequently experience problems in interpersonal relationships, and these higher-order deficits in social functioning likely relate to abnormalities in lower-level facets of social cognition (Nixon, Tivis, & Parsons, 1992; Lewis et al., 2019). In fact, a social-psychological model of alcoholism has been proposed by Philippot and colleagues in which non-verbal emotion decoding deficits in AUD generate and exacerbate interpersonal tensions, which increase the likelihood of alcohol consumption as a coping strategy, further impairing social cognitive abilities (Philippot et al., 2003). Evidence in support of this hypothesis has been provided by several studies examining associations between social-cognitive processing and functional outcomes in individuals with AUD. Among affected individuals, impaired emotional facial expression recognition and empathy are independently associated with higher rates of interpersonal problems (Kornreich et al., 2011; Maurage et al., 2011b). Other research indicates that among adults with AUD, those who show deficits in managing, understanding, and describing

emotions have greater severity of AD (Cecero & Holmstrom, 1997; Kopera et al., 2015; Stasiewicz et al., 2012; Uzun et al., 2003; Valmas et al., 2014), increased likelihood of consuming alcohol in response to unpleasant emotions or interpersonal conflicts (Stasiewicz et al., 2012), and poorer treatment outcomes (Rupp, Derntl, Osthaus, Kemmler, & Fleischhacker, 2017). Although deficits in social cognition, and associated deficits in social functioning, among adults with AUD are often interpreted as a consequence of long-term alcohol abuse, they may reflect, in part, premorbid deficits that confer increased risk for alcohol-related problems during sensitive developmental periods of neurobiological and social maturation.

1.1.6 Adolescent Alcohol Use

The highest risk for the onset of alcohol use and abuse occurs during adolescence, which is a critical developmental period characterized by ongoing psychosocial and neurobiological developmental processes (Bava & Tapert, 2010; Casey, Jones, & Hare, 2008). Recent data from the Monitoring the Future National Survey indicates that six out of every ten students (61%) have consumed alcohol (more than just a few sips) by the end of high school, and nearly a quarter (23%) have done so by 8th grade. In 2016, almost half (46%) of 12th graders reported having been drunk at least once in their life (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2017). Furthermore, binge drinking, defined by the National Institute on Alcohol Abuse and Alcoholism as a pattern of drinking that brings blood alcohol concentration (BAC) levels to 0.08 grams per deciliter (which typically occurs after ~4 drinks for women and ~5 drinks for men within two hours), is particularly prevalent in adolescence and young adulthood (Courtney & Polich, 2009).

Like AUD, adolescent alcohol use is associated with a range of deleterious consequences that impact psychological, physical, interpersonal, and social functioning. Adolescent alcohol use,

and binge drinking in particular, put individuals at higher risk for academic problems, criminal and violent behavior, delinquency, risky sexual behaviors, hazardous driving, and comorbid substance use (Ellickson, Tucker, & Klein, 2003; Grigsby, Forster, Unger, & Sussman, 2016). Given the extent of brain maturation occurring during this phase in life, adolescents who use substances also appear to be vulnerable to alterations in brain functioning, cognition and behavior. Both cross-sectional and longitudinal neuroimaging research has shown that adolescent alcohol use is associated with atypical white matter integrity, cortical and subcortical volumes, and task-based neural activity (Bava & Tapert, 2010; Cservenka & Brumback, 2017; Hill, Terwillinger, & McDermott, 2013).

Importantly, several studies have shown that early-onset alcohol use is associated with the presence of AUD in adulthood (Grant & Dawson, 1997; Hingson, Hereen, & Winter, 2006; Kim et al., 2017; SAMHSA, 2014). For example, individuals who begin drinking before age 15 are four times more likely to develop AD than those starting at or after age 20 (Grant & Dawson, 1997). More recently, data from the National Survey on Drug Use and Health indicated that individuals who first used alcohol at age 14 or younger were six times more likely to develop a lifetime AUD than to those who first used alcohol after the U.S. legal limit of age 21 (SAMHSA, 2014). Unsurprisingly, many factors that confer risk for SUD in adulthood are also associated with patterns of adolescent alcohol use and abuse.

1.1.7 Environmental Risk Factors for SUD

Twin and adoption studies indicate that AUD is approximately 50% heritable and that shared environmental effects also contribute to the familial aggregation of AUDs (Verhulst, Neale, & Kendler, 2015). It is unlikely that genetic mechanisms underlying the increased risk for early-

onset substance use and SUD among offspring from multiplex, AD families operate independently from environmental characteristics of multiplex, high-risk families. Similarly, premorbid risk factors for SUD, including those in social functioning, are almost certainly influenced by both genetic and environmental factors, as well as their interactions, across development. A vast body of research with community samples, as well as samples identified to be at-risk due to factors other than parental AUD (e.g. low-socioeconomic status), has identified characteristics of the environment that confer risk and resilience for SUD. The effects of family-related characteristics and peer influences on use of alcohol and other substances during adolescence and young adulthood have been particularly well studied and supported in the extant literature (Hawkins et al., 1992; Thatcher & Clark, 2008).

1.1.7.1 Familial Characteristics Associated with Risk and Resilience

Research conducted within the framework of developmental psychology has provided a number of theoretical and empirical models of adolescent alcohol (and other substance) use that include factors from multiple ecological domains which are presumed to interact over the course of childhood and adolescence. Studies utilizing dynamic cascade models of the development of substance use highlight the importance of childhood risk factors associated with the parent and the child, as well as early parenting behaviors (Dodge et al., 2009; Eiden et al., 2016). These studies have consistently found that adolescent alcohol and drug use are influenced both directly and indirectly by family-related characteristics. Generally, parenting characterized by high levels of acceptance, supportiveness, and responsivity appears to confer resilience for adolescence substance use, whereas poor relationships with parents and low family cohesion are associated with increased risk (Dodge et al., 2009; Duncan et al., 1994; Hawkins et al., 1992; Newcomb et al., 1986; Reeb et al., 2015; Soloski et al., 2016; Thatcher & Clark, 2008; Vakalahi, 2001).

1.1.7.2 Peer Influences

Peer alcohol and drug use behaviors, as well as peer relationships, are also important risk factors for adolescent alcohol use and SUDs. Longitudinal studies have shown that peer alcohol and drug use, as well as affiliation with peers engaging in a broader range of deviant behaviors, predict adolescent alcohol use (Bray et al., 2003; Cornelius et al., 2007). Other studies have shown that affiliation with deviant peers may enhance the relationship between early risk factors and subsequent adolescent alcohol use and abuse (Giancola & Parker, 2001). However, in addition to direct modeling effects, the association between individual risk and peer substance use appears to reflect indirect selection effects, such that adolescents who are already predisposed to accelerated substance use seek out like-minded peers (Bray et al., 2003; Lynskey, Agrawal, & Heath, 2010). Thus, risk factors associated with peer alcohol and drug use may be partially explained by other premorbid risk factors.

The relative importance of family versus peer influences on substance use has been an active area of research in recent years, with some studies suggesting a stronger influence of peer influences, and others highlighting the importance of parental risk factors (Thatcher & Clark, 2008). Importantly, research examining peer- and parent-related factors simultaneously have found that characteristics of relationships with parents and peers interact to predict risk and resilience for adolescent alcohol use. For example, Nash et al. (Nash et al., 2005) found that a latent measure of family environment, which included adolescents' perceptions of parental acceptance, parental monitoring, and communication with parents, exerted significant indirect effects on adolescent alcohol use through its effects on peer influence, self-efficacy, and stress in a large sample of high school students. Similarly, non-supportive parenting in childhood has been

shown to relate to adolescent substance use indirectly via deviant peer affiliation and problem behavior (Dodge et al., 2009).

1.1.7.3 Environmental Influences in High-Risk Families

Given the importance of family environment and association with deviant peers on adolescent alcohol use and SUD among community and other at-risk samples, offspring of parents with AUD are likely at heightened risk due to both genetic and environmental influences. Indeed, parental SUD is associated with decreased levels of monitoring and supervision, poorer quality of parent-child interactions, parent-child conflict, perception of less parental warmth, and inconsistent discipline (Dunn et al., 2002). Among high-risk offspring, both alcohol-specific parenting factors (e.g. direct modeling of alcohol use, shaping of alcohol expectancies) and non-alcohol-specific parenting factors (e.g. parental monitoring, parental warmth) have been found to contribute to increased risk for adolescent alcohol use and AUDs (Ellis et al., 1997; Jacob & Johnson, 1997).

1.1.8 Summary

Substance use disorders have complex etiologies that reflect cascading genetic and environmental effects across childhood, adolescence, and young adulthood. Risk factors for the onset of use and abuse of alcohol and other substances include familial risk, early adversity and stress, and internalizing and externalizing psychopathology. Family- and peer-related factors have also been shown to exert strong influences on early substances use, such that low parental monitoring, poor parent-child relationships, and association with substance-using peers confer risk for adverse outcomes during adolescence and young adulthood.

Established environmental risk factors for SUD often relate to aspects of the individual's relationships with both family members and peers. Adults with AUD have long been known to experience problems in interpersonal relationships, with an emerging literature demonstrating specific social cognitive deficits in this population. To date, some evidence has shown that alcohol-naïve, high-risk offspring also have atypical social cognitive functioning, suggesting that observed deficits among adults with AUD may, in part, reflect premorbid risk factors for substance-related problems. However, the extent to which high-risk offspring demonstrate deficits in social cognition and associated social behavior and functioning, as well as potential relationships between premorbid deficits in social functioning and subsequent substance use outcomes among these high-risk offspring, is not well understood.

1.2 Statement of Purpose

The current study aims to add to the existing literature by examining the potentially mediating role of social functioning on the association between familial risk for AUD and SUD outcomes in young adulthood. More specifically, this study utilizes measures of social functioning collected during childhood, adolescence, and young adulthood, with constructs of interest including childhood social competence and social problems, adolescent perceptions of social support and stress from parents and peers, and alienation and social closeness self-reported in young adulthood. These domains of social functioning are hypothesized to mediate, in part, the relationship between familial risk and poor outcomes among high-risk offspring.

Social cognition has been an active area of research in schizophrenia and autism spectrum disorders, and these lines of research have successfully informed intervention design for affected

individuals (Bishop-Fitzpatrick et al., 2017; Bishop-Fitzpatrick, Minshew, & Eack, 2014). The role of social cognition is less well understood in AUD and other SUD, though there has been a recent impetus to bridge the gap between the literatures on SUD, social cognition, and social neuroscience (Bora & Zorlu, 2017; Heileg, Epstein, Nader, & Shaham, 2016). A rapidly growing body of evidence has supported the presence of social-cognitive deficits in AUD, although it remains unclear to what extent these deficits may reflect premorbid risk factors for SUD.

Functional neuroimaging studies have shown that high-risk offspring show atypical neural activation in key regions of the social brain during social-cognitive tasks (Cservenka et al., 2014; Glahn et al., 2007; Hill et al., 2007; Hulvershorn et al., 2013; Peraza et al., 2015), and behavioral studies indicate that these offspring demonstrate atypical social functioning within the domains of social competence, perceived social support, alienation, and social closeness (Barnes et al., 2000; Christensen & Bilenberg, 2000; Dunn et al., 2000; Eiden et al., 2009; Eiden et al., 2016; Elkins et al., 2004; Hill et al., 1999; Hussong et al., 2005). Importantly, prior research within other clinical populations and among typically developing children and adolescents has demonstrated associations between social cognition and these domains of social functioning (Bishop-Fitzpatrick et al., 2014; Bosacki & Wilde, 1999; Cacioppo & Hawkley, 2009; Crick & Dodge, 1994; Ford, 1982; Ladd, 2005; Lakey & Drew, 1997; Lalonde & Chandler, 1995; Liddle & Nettle, 2006; Lindner et al., 2014; McGuire & Weisz, 1982; Nowicki & Mitchell, 1998; Rubin, Bukowski, & Parker, 1997; Walker, 2005).

By testing a conceptual model that combines measures of familial risk, social functioning in childhood, adolescence, and young adulthood, adolescent substance use, and SUD outcomes, the current study is likely to allow deeper insight into the complex interplay between genetic and environmental factors associated with risk for SUD. Although we do not expect to be able to

disentangle the influence of external environmental variables, such as parental and peer influences, and the genetic factors within the child that, in turn, influence peer and parent interactions, a longitudinal examination of social functioning across development may have important implications for prevention and intervention efforts for at-risk youth. Findings of less adaptive social functioning among high-risk offspring and relationships between social functioning and SUD outcomes, would provide preliminary support for further investigations into both social functioning and social cognition in this at-risk population. Based on the extant literature on social cognition, social behavior, and risk factors for SUD, the current study was designed to test the following three main hypotheses:

1.2.1 Hypothesis 1a

High-risk offspring will have higher rates of adolescent alcohol than low-risk controls. Specifically, it is hypothesized that high-risk offspring will have earlier ages of onset of first drink and onset of regular drinking, more frequent use of alcohol during adolescence, and higher quantities of alcohol consumed before young adulthood.

1.2.2 Hypothesis 1b

High-risk offspring will have higher rates of SUD by young adulthood. Specifically, it is hypothesized high-risk offspring will be at increased risk for both alcohol and other substance use disorders compared to low-risk controls.

1.2.3 Hypothesis 2a

High-risk offspring will demonstrate deficits on measures of social functioning that were selected for analyses given their putative relationship with social cognition, as measured by childhood social competence and social problems, perceived social support and stress from parents and peers in adolescence, and self-reported alienation and social closeness in young adulthood. It is hypothesized that deficits will be observed across measures and developmental periods.

1.2.4 Hypothesis 2b

Risk-group differences on measures of social functioning collected during adolescence and young adulthood will remain significant after controlling for personal exposure to alcohol. Specifically, high-risk offspring will show deficits on measures of social functioning after controlling for the onset, frequency, and quantity per occasion of adolescent alcohol use.

1.2.5 Hypothesis 3

Deficits in social functioning will mediate the relationship between familial risk and SUD outcomes in young adulthood among high-risk offspring. Specifically, it is hypothesized that measures of social functioning collected during childhood, adolescence, and young adulthood will independently mediate the relationship between familial risk status and SUD outcome, and that these effects will remain significant after accounting for personal exposure to alcohol use in adolescence.

2.0 Methods

2.1 Participants

Participants in this study are high-risk and low-risk (control) third-generation offspring in two ongoing family studies, the Cognitive and Personality Factors in Relatives of Alcoholics family study (CPFFS) and the Biological Risk Factors in Relatives of Alcoholic Women family study (BRFFS), that selected families through their parents' generation. Rates of SUD are particularly high among offspring from these multiplex AD families (Hill et al., 2008; Hill et al., 2011), making them well suited to examine longitudinal predictors of SUD outcomes. The BRFFS and CPFFS studies have ongoing approval from the University of Pittsburgh Institutional Review Board. All participants provided consent at each visit. Children provided assent with parental consent.

2.1.1 Inclusion Criteria for High-Risk Families

The high-risk families in both family studies were identified through a proband pair of alcohol dependent (AD) siblings, one of whom was in a substance abuse treatment facility in the Pittsburgh area at the time of recruitment (late 1980's and early 1990's). Probands were screened (Diagnostic Interview Schedule [DIS]; Robins et al., 1981) for the presence of AD and other Axis I (DSM-III) psychopathology. Feighner Criteria for AD was also obtained (Feighner et al., 1972). Probands provided family history information for biological relatives in order to determine if the proband might have a same-sex sibling meeting criteria for alcohol dependence. If this appeared

to be the case, the proband assisted in the recruitment of his/her sibling who then completed the same diagnostic assessments. Probands and their families were selected if a pair of same-sexed adult siblings with an alcohol dependence diagnosis was present (sister pairs for the BRFFS study and brother pairs for the CPFFS study). Each multiplex family required the screening of approximately 100 families to meet the present goals, and for the broader goals of the family studies that included a search for developmental neurobiological markers and gene finding efforts.

2.1.2 Exclusion Criteria for High-Risk Families

The DIS was administered to all available relatives (adult probands, their siblings and parents [>90% of first-degree relatives]). Unavailable or deceased relatives were diagnosed using a minimum of two family-history reports. Targeted families were excluded if the proband or his or her first-degree relatives showed evidence of primary recurrent Major Depressive Disorder (MDD), Bipolar Disorder (BD), Primary Drug Dependence (PDD) (i.e., drug dependence preceded alcohol dependence by 1 or more years) or Schizophrenia by DSM-III criteria, the diagnostic system in place at the time the studies were initiated. Presence of Axis II disorders was not used as either an exclusionary or inclusionary condition. No attempt was made to limit the psychiatric disorders in "marrying in" spouses who represent the parents of the children/adolescents reported here. However, available spouses were diagnosed using the same methods (DIS) as members of the "target" families.

2.1.3 Selection of Control Families

Selection of control families was based on availability of a pair of same sex adult siblings. Selection of families was based on one of two methods. In the first method (Control Group I – CPFFS Study), volunteers were screened for Axis I psychopathology including alcohol and drug dependence using the DIS. Control families were selected if the volunteer's first-degree relatives (parents and siblings) were similarly free of psychopathology. In the second method (Control Group II – BRFFS Study), volunteers from the same census tract who indicated they had children between the ages of 8–18 years were screened as a potential control family in order to match the family to a high-risk family using census tract information. The control parents of these offspring were screened for parental alcohol or drug dependence.

In a previously published study (Hill et al., 2008), direct comparison of Controls Groups I and II indicated that the groups did not significantly differ in terms of socioeconomic status (SES; mean = 44.22 ± 11.8 SD for the CPFFS controls and mean = 45.99 ± 11.66 for the BRFFS controls) or in offspring rates of the presence of any psychopathology (47.2% for CPFFS and 52.8% for the BRFFS), allowing for the two control groups to be combined. Simple phobia and separation anxiety account for approximately two-thirds of the positive cases in childhood. Because the two control groups have previously been shown to be comparable in terms of demographics and outcomes, the current study was based on the offspring from both types of control families, included in an approximately equal number.

2.2 Third-Generation Offspring Procedure

Beginning in 1990, third-generation offspring of parents in the CPFFS and BRFFS who were between the ages of 8 and 18 years entered the study. These offspring were followed longitudinally at approximately yearly intervals through age 18, and biennially in young adulthood beginning at age 19. At each visit, offspring were administered a multimodal assessment that included measures of childhood behavioral problems, life stressors and supports, and personality, as well as clinical interviews to determine the presence or absence of psychiatric disorders. Offspring also provided information on their use of alcohol, cigarettes, and other drugs at each clinical follow-up. Because of the longitudinal nature of the BRFFS and CPFFS studies, age-appropriate instruments used at the time of study initiation have been retained throughout follow-up.

2.2.1 Study Sample

A total of 588 offspring were followed in the CPFFS and BRFFS. The current analyses utilized data from 259 third-generation offspring who were longitudinally followed from childhood through young adulthood and who had available data for all measures needed for the present analysis. A central aim of these analyses was to identify whether deficits in social cognition and social functioning preceded the onset of regular alcohol and other drug use in high-risk offspring. Accordingly, participants for whom data was collected only in either childhood or young adulthood were excluded from analyses (n = 113). An alternative participant-selection strategy of excluding only cases for which alcohol or substance use preceded or co-occurred with initial assessment would have likely resulted in specific removal of cases with early-onset

substance use. Instead, by limiting analyses to all offspring with available data for both childhood and young adulthood, offspring excluded from analysis were expected to only differ from included participants by age at the time the third-generation protocol was initiated.

2.3 Measures

2.3.1 Social Functioning

2.3.1.1 Child Behavior Checklist (CBCL)

Childhood social functioning was assessed with the Child Behavior Checklist (CBCL; Achenbach, 1991), a parent-report form for children ages 4-18 and is comprised of a 113-item behavior problems checklist and a seven-part social competency checklist. The scoring profile for the CBCL includes: (a) three competence scales (Activities, Social, and School); (b) a total competence scale score; (c) eight syndrome scales (Aggressive Behavior, Attention Problems, Delinquent Behavior, Social Problems, Somatic Complaints, Thought Problems, Anxious/Depressed, and Withdrawn); (d) an Internalizing problem scale score; (e) an Externalizing problem scale score; and (f) a Total problem scale score. Standard scores are scaled so that 50 is average for the youth's age and gender, with a standard deviation of 10 points. Higher scores indicate greater problems. Norms take into account both age and gender; there are separate norms for girls and boys, and separate norms for ages 4–11 and ages 12–18.

Normative data for the CBCL were drawn from a subset of children without disabilities in a national sample assessed in 1989. This sample (n = 2,368) was chosen to be representative of the 48 contiguous U.S. states with respect to ethnicity, SES, geographical region, and urban-suburban-

rural residences. The normative sample was compared to a 'referred' sample of children who had received referral for mental health services or special education classes for behavioral/emotional problems within the past year. With regard to reliability, the CBCL composite behavior problem scores (i.e., Internalizing, Externalizing, and Total Problems) have been shown to have excellent internal consistency and one-week test-retest coefficients ($r \geq 0.89$). Syndrome scales have been shown to have moderate reliability (internal consistency and one-week test-retest coefficients both averaging 0.80), whereas the competence scales have moderate test-retest reliability (0.80) but low internal consistency (0.50). The CBCL is widely used in both research and clinical practice with youths (Achenbach & Rescorla, 2001). The current project analyzed data from the Social Competence scale and Social Problems scale of the parent-report CBCL collected between participant age 7 – 18 (mean = 11.32 years). T-scores, adjusted for child age and sex, were used in all analyses.

The CBCL Social Competence subscale includes (1) the number of organizations, clubs, teams, or groups that the child belongs to (Item III-A; none or 1= 0, 2 = 1, 3+ = 2, raw scores range from 0 – 2, with higher scores indicating participation in more organizations), (2) the mean level of participation in these organizations compared to others of the same age (Item III-B; for each organization listed in III-A, less than average = 0, average = 1, more than average/above average = 2; raw scores range from 0 – 2, with higher scores indicating higher levels of participation), (3) number of friends (Item V-1; none or 1 = 0, 2 or 3 = 1, 3 or more = 2; raw scores range from 0 – 2, with higher scores indicating more friends), (4) times per week the child does things with friends outside of school (Item V-2; <1 = 0, 1 or 2 = 1, ≥ 3 = 2; raw scores range from 0 – 2, with higher scores indicating more contact with friends outside of school), (5) how well the child gets along with siblings, peers, and parents compared to other children his/her age (mean of Items VI-A – VI-

C; for each item, worse = 0, average = 1, better = 2; raw scores range from 0 – 2), and (6) how well the child does things alone compared to others of his/her age (Item VI-D; worse = 0, average = 1, better = 2; raw scores range from 0 – 2). The Social Competence raw score is calculated by summing these six items; scores range from 0 – 12, with higher scores indicating higher competence.

The Social Problems scale is comprised of 8 items assessing social immaturity (i.e., acts too young for his/her age, clings to adults or too dependent, poorly coordinated or clumsy, and prefers playing with younger children) and peer rejection (i.e., doesn't get along with other children, gets teased a lot, not liked by other children). All items are scored on a 3-point scale, and caregivers report whether each behavioral item is not true (0), somewhat or sometimes true (1), or very true or often true (2). The Social Problems scale score is determined by summing responses to these 11 items. Raw scores range from 0 – 16, with higher scores indicating more social problems.

2.3.1.2 Life Stressors and Social Resources Inventory – Youth Form (LISRES-Y)

Adolescent social functioning was assessed with the Life Stressors and Social Resources Inventory – Youth Form (LISRES-Y; Moos & Moos, 1994), a self-report paper-and-pencil measure for youth ages 12-18 years designed to assess stable sources of psychosocial stress as well as social resources that might influence the effect of stressors on the well-being of youth. Nine Life Stressor scores (Physical Health, Home and Money, Parents, Siblings, Extended Family, School, Friends, Boyfriend/Girlfriend, Negative Life Events) and 7 Social Resource scores (Parents, Siblings, Extended Family, School, Friends, Boyfriend/Girlfriend, Positive Life Events) are derived from 209 items.

The LISRES-Y was normed on 400 youth (179 boys and 221 girls), and its scales have been shown to have moderate-to-high internal consistency ($.68 < \alpha < .93$). Significant differences have been observed between healthy controls and youth with depression, conduct disorder, and medical conditions. Previous research has shown that both of the LISRES-Y Parent scales have the highest correlations with measures of child and adolescent functioning (Crehan & Oosterhof, 1998). The current study analyzed data from the LISRES-Y Parental Stressors scale, the Parental Resources scale, the Peer Stressors scale, and Peer Resources scale, collected between participant age 12 – 18 (mean = 13.95 years).

The Parental Stressors and Resources scales are comprised of separate scores for mothers and fathers; Maternal Stressors and Resources are assessed with 7 and 5 items assessing negative and positive aspects, respectively, of maternal support. Sample items include "How often can you count on [your mother] to help you when you need it?" and "How often is [your mother] critical or disapproving of you?" Paternal Stressors and Resources subscales are conceptually identical to the Maternal measures. For all four subscales, responses are scored on a 5-point scale, ranging from 0 (never) to 4 (often). The Parental Stressors score is a sum of the Maternal Stressor and Paternal Stressor subscales; raw scores range from 0 – 28, with higher scores reflecting higher perceived stress. Similarly, the Parental Resources score is a sum of the Maternal Resources and Paternal Resources subscales; raw scores range from 0 – 20, with higher scores reflecting lesser perceived support.

The Peer Stressors and Resources scales consist of 6 and 10 items, respectively. Sample items include “How often are any of your friends critical or disapproving of you?” and “How often can you count on any of your friends to help you when you need it?”. Responses are scored on a 5-point scale, ranging from 0 (never) to 4 (often). Raw scores on the Peer Stressors scale range

from 0 – 24, with higher scores reflecting higher perceived stress. Raw scores on the Peer Resources scale range from 0 – 40, with higher scores reflecting lesser perceived support.

2.3.1.3 Multidimensional Personality Questionnaire (MPQ)

Young adult social functioning was assessed with the Multidimensional Personality Questionnaire (MPQ; Tellegen, 1982), a self-report measure that includes 276 true-false items and yields scores on 10 different personality scales which compose three trait superfactors. Constraint is a combination of the Traditionalism, Harm Avoidance, and Control scales; Negative Emotionality is a combination of the Aggression, Alienation, and Stress Reaction scales; and Positive Emotionality is a combination of the Achievement, Social Potency, Well-Being, and Social Closeness scales.

MPQ norms were derived from a community sample of 1,350 (675 men / 675 women) in Minnesota ages 20 to 60, drawn from the Minnesota Twin and Family Registry. The MPQ has been shown to have good discriminant validity and high internal consistency (median $\alpha = 0.85$). The 30-day test-retest reliability is also high (median $\alpha = 0.89$) (Tellegen, 1985). A notable strength of this measure is the ability to assess trait, as opposed to state, personality characteristics, as demonstrated by the high interclass correlations among twins reared apart for traits such as alienation (Tellegen et al., 1988). The current study analyzed data from the MPQ Alienation and Social Closeness scales collected between participant age 17 – 24 (mean = 22.24 years).

The MPQ Alienation scale is comprised of 20 true-false items and raw scores range from 0 - 20. Individuals who score high on this scale describe themselves as believing that others wish them harm, being victims of false and nasty rumors, having been betrayed and deceived, feeling used by friends, feeling pushed around, and having had a lot of bad luck. The MPQ Social

Closeness scale is comprised of 21 true-false items and raw scores range from 0 - 21. Individuals who score high on this scale describe themselves as sociable, liking to be with people, taking pleasure in and valuing close personal ties, warm and affectionate, and turning to others for comfort and help.

2.3.2 Substance Use

2.3.2.1 Kiddie Schedule for Affective Disorders and Schizophrenia-Present Episode (K-SADS-P)

The Kiddie Schedule for Affective Disorders and Schizophrenia-Present Episode (K-SADS-P; Chambers et al., 1985) is a semi-structured interview administered by trained clinicians to both children and parents in order to diagnose DSM-III mental disorders in children ages 6 – 18. The K-SADS-P assesses symptoms that have occurred within the week preceding the interview, as well as symptoms that have occurred within the last 12 months. The K-SADS-P has been shown to have good inter-rater reliability (range 93 – 100%) and good-to-excellent test-retest reliability ($0.67 \leq \kappa \leq 1.00$) (Kaufman et al., 1997). The K-SADS-P is widely used in both research and clinical practice with children and adolescents.

Offspring in the BRFFS and CPFFS studies, ages 8 to 18, and his/her parent were separately administered the K-SADS-P by trained, Masters' level, clinical interviewers and an advanced resident in child psychiatry at approximately yearly intervals. Using DSM-III criteria that has been used throughout the follow-up, K-SADS interviewers and the resident independently provided scores for each diagnosis. A best-estimate diagnosis based on these four blinded interviews was completed in the presence of a third clinician who facilitated discussion to resolve

diagnostic disagreements if needed. Age of onset, usual and maximum quantity, and usual and maximum frequency of alcohol and drug use were also assessed via the K-SADS-P.

2.3.2.2 Composite International Diagnostic Interview (CIDI)

The Composite International Diagnostic Interview (CIDI; Janca et al., 1992) is a fully structured interview used to assess psychiatric disorders according to DSM-III and ICD-10 diagnostic criteria. The CIDI has been shown to have good inter-rater reliability ($0.67 \leq \kappa \leq 0.99$) (Wittchen et al., 1991) and validity (overall $\kappa = 0.77$; Janca et al., 1992). Offspring in the BRFFS and CPFFS studies, ages 19 and older, were administered the CIDI at approximately biennial intervals to determine the presence or absence of DSM-IV diagnoses.

2.3.2.3 Composite International Diagnostic Interview Substance Abuse Module (CIDI-SAM)

The Composite International Diagnostic Interview Substance Abuse Module (CIDI-SAM; Compton et al., 1996; Cottler et al., 1989) is a fully structured interview used to assess past and current substance abuse diagnoses for alcohol, tobacco, and nine classes of psychoactive drugs according to multiple diagnostic systems (i.e., DMS-III, DSM-III-R, DSM-IV, Feighner, RDC, and ICD-10). The CIDI-SAM has been shown to have good test-retest reliability for DSM-III (average $\kappa = 0.84$) (Cottler et al., 1989) and DSM-IV substance use disorders (average $\kappa = 0.78$); however, test-retest reliability is lower for cannabis use disorders ($\kappa = 0.56$) (Compton et al., 1996). Offspring in the BRFFS and CPFFS studies, ages 19 and older, were also administered the CIDI-SAM at approximately biennial follow-up visits to measure the quantity, frequency, and pattern of substance use.

2.3.3 Covariates and Confounds

2.3.3.1 Hollingshead Four-Factor Index of Socioeconomic Status

The Hollingshead Four-Factor Index of Socioeconomic Status (Hollingshead, 1975) was used to assess SES at each clinical follow-up visit. Parental SES was calculated from the education and occupation of both parents at the time of the first childhood assessment during childhood and adolescence, and young adult SES calculated beginning at age 19 based on the offspring's education and occupation. The current study examined the effect of SES on hypothesized structural models by utilizing data from the Hollingshead Four-Factor Index collected at the time of study entry.

2.3.3.2 Drinking and Drug Use During Pregnancy Interview

Each mother was administered a structured interview, the Drinking and Drug Use During Pregnancy, at the time her child was entered into the follow-up study. The interview covered her alcohol, cigarette, and other drug use during each of her pregnancies so that the quantity and frequency of these substances could be determined. The interview format was developed in our laboratory and was designed to measure typical and maximal daily use by obtaining information for each of several substances, noting the quantity per occasion and the frequency of use. Daily use was multiplied by the number of days in each trimester and accumulated for all three trimesters, allowing for the total amount used throughout pregnancy to be calculated. Because drug use involved varying quantities taken by various routes (smoking, intravenous, and inhalation), no attempt was made to analyze these data using quantity estimates. Rather, the number of days any drug was used was calculated and used in the analyses. If the mother had multiple children, she was queried concerning each child separately. Multiple manuscripts have been published from

our lab concerning data from this instrument (Hill, Lowers, Locke-Wellman, & Shen, 2000a; Hill, Shen, Locke-Wellman, Rickin, & Lowers, 2005; O'Brien & Hill, 2014; Sharma & Hill, 2017).

2.4 Analytic Plan

2.4.1 Data Selection

Among offspring selected for inclusion in the current analyses, age at study entry ranged from 7 to 18 years. Seventy five percent of high- and low-risk offspring entered the study by age 13. To minimize the effect of developmental differences on measures of interest, a decision was made to use data from the first visit in which each participant completed age-appropriate measures of social functioning. The means and standard errors for age at study entry, age at each measure of social functioning, and age at last clinical follow-up are presented in Table 2.

2.4.2 Data Analyses

The primary goals of this study were to examine relationships between familial risk status, social functioning assessed in childhood, adolescence, and young adulthood, adolescent alcohol use, and SUD outcome by young adulthood. Analyses exploring the main effects of familial risk status on observed variables of interest were conducted in SPSS (IBM Corp., 2016); risk-group differences on measures of social functioning were assessed with linear mixed models in order to account for random effects due to the presence of multiple siblings from the same family in the dataset (i.e., non-independence of observations), and alcohol use measures were examined using

generalized linear mixed models to also account for the non-normal distribution of these variables. SUD outcome was assessed using Cox regression survival analyses, which allows for censoring of observations for which survival time is incomplete and correctly incorporates information from both censored and uncensored observations in estimating important model parameters.

This study also sought to use structural equation modeling (SEM) to examine more complex, longitudinal relationships among risk, social functioning, and substance use and abuse. SEM refers to a collection of related statistical techniques used to evaluate the validity of substantive theories with empirical data. SEM is a hypothesis-driven analytic technique, and its overarching goal is to determine whether a hypothesized theoretical model is consistent with the data collected to reflect this theory. Statistically, SEM is related to general linear modeling (GLM), and SEM allows for the examination of a set of relationships between one or more independent variables, either continuous or discrete, and one or more dependent variables, either continuous or discrete. SEM has rapidly gained popularity across a number of disciplines in the past two decades, and there are several significant advantages to the use of these statistical techniques (Kline, 2016; Lei & Wu, 2007; Ullman, 2006).

One significant advantage of SEM, as compared to other GLM techniques, is its ability to study the relationships among latent constructs that are indicated by multiple measures. Latent, unobserved variables are those which cannot be measured directly, but are inferred by responses to a number of observable indicator variables (e.g. intelligence, reading ability, or social functioning). Latent factors are presumed to causally influence an individual's performance on observable measures, and SEM utilizes confirmatory factor analysis (CFA) to verify hypothesized factor structures. Using observed variables as indicators of latent factors rather than components of a scale allows for estimation and removal of measurement error associated with the observed

variables. In general, measuring hypothetical constructs with multiple observed indicators, rather than single indicators, tends to increase the reliability of factor measurement (Kline, 2016).

SEM is also an effective and direct tool for modeling mediation, indirect effects, and other complex relationships among variables in both cross-sectional and longitudinal studies; variables in SEM models can serve both as a source variable (i.e., an exogenous, independent variable) and a result variable (i.e., an endogenous, dependent variable), allowing for analyses of mediation (Kline, 2016; Lei & Wu, 2007; Ullman, 2006).

In conventional SEM, all latent variables and indicators are assumed to be independent across units. However, recent advances in generalized linear latent and mixed modeling (GLLAMM; Rabe-Hesketh, Skrondal, & Zheng, 2007) allow for the specification of SEM models that include latent and observed variables varying at different levels, and also allow the for the modeling of censored outcome variables. Thus, SEM was identified as the most appropriate technique to address the current studies aims.

To evaluate the study's first hypothesis, a model was estimated with familial risk as an exogenous, independent variable, SUD onset as an endogenous, censored, dependent variable, and adolescent alcohol use as a latent factor dependent on risk but predictive of SUD onset (Model A; Figure 6). To examine the effect of familial risk status on measures of social functioning, as well as interrelationships among social functioning measures collected during different developmental periods, familial risk was modeled as an exogenous, independent variable predicting four latent social functioning factors: childhood social functioning (measured by the CBCL Social Competence and Social Problems scales), adolescent social support - parents (modeled by the LISRES-Y Parent Stressor and Parent Resource scales), adolescent social support – peers (modeled by the LISRES-Y Friend Stressor and Friend Resource scale), and young adult social

functioning (modeled by the MPQ Alienation and Social Closeness scales; Model B, Figure 8. The third hypothesized model (Model C, Figure 10) aimed to examine whether social functioning mediated the relationship between familial risk status and SUD outcome and allowed for examination of relationships among all constructs of interest, as well as the ability to examine indirect influences of familial risk on SUD outcome via both social functioning and adolescent alcohol use. In the hypothesized model, latent factors of childhood social functioning, adolescent parent and peer support, young adult social functioning, and adolescent alcohol use were measured as previously described above for hypothesized Models A and B. All SEM analyses were conducted in M*plus* (Muthén & Muthén, 2017) and broadly followed the guidelines established by Kline (2016).

3.0 Results

3.1 Preliminary Analyses

3.1.1 Sample Characteristics

A total of 137 high-risk (62 male, 75 female) and 122 low-risk (74 male, 48 female) offspring from 170 separate family pedigrees were included in the current analyses. Eighty-five high-risk and 85 low-risk pedigrees were represented; there were 101 pedigrees from which one third-generation offspring was included (HR = 47, LR = 54), 53 pedigrees from which two third-generation offspring were included (HR = 27, LR = 26), 12 pedigrees from which three third-generation offspring were included (HR = 8, LR = 4), and 4 pedigrees from which four third-generation offspring were included (HR = 3, LR = 1). A family identification number was included as a random effect in all data analyses to account for non-independence of observations from siblings within the same nuclear family.

Among the high-risk offspring, there were 102 participants with a parent diagnosed with alcohol dependence (AD): 25 participants for whom both parents were affected and 77 participants for whom one parent was affected and one parent was unaffected. Additionally, there were 17 high-risk offspring with both biological parents unaffected by AD and 18 high-risk offspring for whom one parent's AD status was known to be negative and the co-parent's AD status was unavailable. Importantly, the number of second-degree relatives affected by AD was similar (i.e., > 3.0) regardless of parental AD status (**Table 1**).

Demographic data for high- and low-risk offspring are presented in **Table 2.** High- and low-risk groups had similar age at study entry [$F(1,139.87) = 0.95$, $p = 0.33$], age at CBCL assessment [$F(1,139.74) = 0.86$, $p = 0.36$], age at LISRES-Y assessment [$F(1,142.77) = 0.02$, $p = 0.88$], and age at MPQ assessment [$F(1,175.75) = 3.04$, $p = 0.10$]. High- and low-risk participants did not differ on the total number of assessments across the study [$F(1,155.55) < 0.01$, $p = 0.97$], number of assessments in childhood/adolescence [$F(1,143.76) = 0.65$, $p = 0.42$], or number of assessments in young adulthood [$F(1,161.39) = 1.52$, $p = 0.22$]. High-risk offspring were significantly older (i.e., by < 1.5 years) than low-risk controls at age of last assessment [$F(1,164.79) = 8.27$, $p = 0.01$]. Participants were followed for an average of 14.4 years (SD = 4.8) and data from a total of 2,387 assessments were used in the current analyses.

High- and low-risk groups had similar racial/ethnic composition [$\chi 2 = 2.66$, $p = 0.45$]. The percent of male versus female offspring in the high- and low-risk samples was significantly different [$\chi 2 = 6.14$, $p = 0.02$], such that there was a higher percentage of female offspring in the high-risk (54.7%) than low-risk (39.3%) group. High-risk offspring had significantly lower SES than low-risk controls [$F(1,167.10) = 19.85$, $p < 0.001$], though groups were in adjacent social strata (skilled craftsmen, clerical, sales workers and medium business, minor professional, technical, respectively; Hollingshead, 1975). All subsequent analyses included sex and SES as covariates.

3.2 Main Effects of Familial Risk

3.2.1 Adolescent Alcohol Use

A total of 190 offspring reported any alcohol use prior to the age of 19, with high-risk offspring (n = 119) significantly more likely to endorse adolescent alcohol use than low-risk controls (n = 71; $\chi 2 = 27.13$, $p < 0.001$). To examine the hypothesis that high-risk offspring would have higher rates of adolescent alcohol use, generalized linear mixed models (described above) with risk as the independent variable were conducted within the sample of subjects who reported any alcohol use during adolescence. Unstandardized means for high- and low-risk offspring are reported in Table 3 and presented in Figure 1 and Figure 2.

3.2.1.1 Age of Onset

Among adolescents who reported any alcohol use during adolescence, high-risk offspring had significantly earlier ages at first drink [$F(1,72.52) = 4.14$, $p = .04$] and age of onset of regular (i.e., monthly) drinking than low-risk controls [$F(1,76.05) = 14.00$, $p = 0.001$].

3.2.1.2 Frequency of Drinking

Risk groups did not differ on measures of usual frequency of drinking [$F = 0.98$, $p = 0.32$] or maximum frequency of drinking [$F = 0.47$, $p = 0.49$].

3.2.1.3 Quantity per Occasion

High-risk offspring reported higher usual quantity per occasion [QPO; $F(1,85.49) = 3.99$, $p = 0.049$] and higher maximum QPO [$F(1,72.99) = 5.34$, $p = 0.02$]. Binge-drinking, which was

defined as 5 or more drinks for males and 4 or more drinks for females, was more prevalent among high-risk offspring ($\chi 2 = 26.58$, $p < 0.001$). Both high-risk males ($\chi 2 = 20.85$, $p < 0.001$) and high-risk females ($\chi 2 = 5.56$, $p = 0.02$) were more likely to engage in binge drinking than sex-matched low-risk controls.

3.2.2 Substance Use Disorder Outcome

In order to provide an age of onset for SUD that covered both childhood/adolescence and young adulthood, SUD outcome data was derived from Kiddie Schedule for Affective Disorders and Schizophrenia – Present Version (K-SADS-P), Composite International Diagnostic Interview (CIDI), and CIDI-Substance Abuse Module (CIDI-SAM) data collected at each clinical follow-up visit that occurred across adolescence and young adulthood. Age of SUD onset was also derived from these measures. Given the increased risk for both alcohol and drug use disorders among high risk offspring (Hill et al., 2008; Hill et al., 2011), individuals meeting criteria for alcohol abuse, alcohol dependence, drug abuse, and/or drug dependence were classified as SUD positive. K-SADS data, collected across multiple longitudinal assessments, was also used to determine measures of adolescent alcohol use.

To examine the hypothesis that high-risk offspring would have higher rates of SUD by young adulthood, Cox regression survival analyses (also described above) were performed. High-risk offspring were significantly more likely to develop an SUD in young adulthood than low-risk offspring (B = 1.25, Wald = 25.52, $p < 0.001$; Figure 5). Both high-risk males (B = 1.35, Wald = 18.76, $p < 0.001$) and high-risk females (B = 1.24, Wald = 8.88, $p < 0.01$) were more likely to develop SUD by young adulthood than sex-matched low-risk controls.

3.2.3 Social Functioning

General linear mixed models were used to analyze the hypothesis that high-risk offspring would have deficits in social functioning measured in childhood, adolescence, and young adulthood. High-risk offspring had significantly lower scores than low-risk controls on the Social Competence scale of the CBCL [$F(1,152.46) = 6.15$, $p = 0.014$], the LISRES-Y Parent Resources scale [$F(1,136.95) = 4.55$, $p = 0.035$], the LISRES-Y Friend Resources scale [$F(1,156.31) = 4.54$, $p = 0.035$], and the MPQ Social Closeness scale [$F(1,112.37) = 4.25$, $p = 0.042$], and significantly higher scores than low-risk controls on the LISRES-Y Parent Stressors scale [$F(1,135.16) = 17.07$, $p < .0001$], LISRES-Y Friend Stressors scale [$F(1,150.01) = 14.94$, $p < 0.001$], and MPQ Alienation scale [$F(1,101.04) = 10.75$, $p = 0.001$]. High- and low-risk offspring did not significantly differ on the Social Problems scale of the CBCL [$F(1,153.13) = 0.41$, $p = 0.52$]. Unstandardized means for high- and low-risk offspring are reported in Table 4 and standardized (z) scores for high- and low-risk offspring on measures of social functioning are presented in Figure 3.

3.3 Covariates of Interest

Given significant differences in SES and gender composition in the high- and low-risk samples, the main effects of these demographics on variables of interest was examined. Additionally, the main effect of personal exposure to alcohol on social functioning variables was examined.

3.3.1 Main Effects of Sex

There was no significant main effect of sex on CBCL Social Competence [$F(1,256.44) = 0.73$, $p = 0.79$], CBCL Social Problems [$F(1,254.80) = 1.03$, $p = 0.31$], LISRES-Y Parent Stressors [$F(1,251.56) = 0.76$, $p = 0.39$], LISRES-Y Friend Stressors [$F(1,254.05) < 0.001$, $p = 0.99$], or MPQ Alienation [$F(1,251.99) = 0.17$, $p = 0.68$]. There were significant main effects of sex on LISRES-Y Friend Resources [$F(1,247.08) = 13.55$, $p < 0.001$] and MPQ Social Closeness [$F(1,256.65) = 7.82$, $p = 0.006$], such that females had higher scores than males. There was also a significant main effect of sex on LISRES-Y Parent Resources, such that males had higher scores than females [$F(1,245.86) = 4.34$, $p = 0.041$], though the strength of this relationship was attenuated when familial risk status was included as a covariate [$F(1,244.19) = 3.18$, $p = 0.08$]. Standardized (z) scores for high- and low-risk male and female offspring on measures of social functioning are presented in Figure 4. No significant risk by sex interactions were observed (all $p > 0.20$).

Across the sample, SUD outcome did not significantly differ by sex ($B = 0.23$, Wald = 1.23, $p = 0.27$). Among offspring who reported any adolescent alcohol use, there were significant main effects of sex on usual QPO [$F(1,126.05) = 9.23$, $p = 0.003$] and maximum QPO [$F(1,127.97) = 6.26$, $p = 0.01$] such that males reported drinking higher quantities than females. No effects of sex were observed on usual [$F(1,126.70) = 0.01$, $p = 0.99$] or maximum frequency of drinking [$F(1,128.00) = 0.15$, $p = 0.70$]. No significant risk by sex interactions were observed (all $p > 0.20$).

3.3.2 Main Effects of Socioeconomic Status

There were significant main effects of SES on CBCL Social Problems [F(66,192.00) = 1.39, p = 0.045], MPQ Alienation [F(66,121.86) = 1.47, p = 0.033], and MPQ Social Closeness [F(66,128.55) = 1.45, p = 0.038]. Marginal effects of SES were observed on CBCL Social Competence [F(66,131.09) = 1.35, p = 0.08], Parent Stressors [F(66,111.00) = 1.37, p = 0.08], Parent Resources [F(66,140.54) = 1.39, p = 0.055] and Friend Resources [F(66,139.65) = 1.38, p = 0.059]. There was also a main effect of SES on Friend Stressors [F(66,86.62) = 1.60, p = 0.021], though the strength of this relationship was attenuated when familial risk status was included as a covariate [F(1,171.08) = 0.97, p = 0.33]. For the aforementioned effects, lower SES was associated with poorer social functioning. No significant risk by SES interaction effects were observed for these variables (all $p > 0.20$).

Across the sample, SUD outcome was significantly affected by SES (B = -0.033, Wald = 14.56, $p < 0.001$), such that lower SES predicted a higher likelihood of SUD. Among offspring who reported any adolescent alcohol use, there were marginally significant effects of SES on usual QPO [F(59,93.51) = 1.42, p = 0.06] and maximum QPO [F(59,72.15) = 1.39, p = 0.09]. No effects of SES were observed on usual [F(59,81.66) = 0.55, p = 0.99] or maximum frequency of drinking [F(59,128.00) = 0.69, p = 0.95]. No significant risk by SES interaction effects were observed for SUD outcome ($p > 0.20$).

3.3.3 Main Effects of Personal Alcohol Exposure

Among offspring who reported using any alcohol use before the age of LISRES-Y or MPQ assessment, the lifetime number of drinks consumed prior to each social functioning assessment

was calculated by multiplying usual frequency of drinking by usual quantity per occasion for each age after the onset of alcohol use, then summing across childhood visits prior to age at the time of assessment. Linear mixed models were then repeated with risk as the independent variable, social functioning measures as the dependent variables, and total number of drinks before assessment as a covariate. Across the sample, there were 44 participants (HR = 30, LR = 14) who reported alcohol use prior to LISRES-Y assessment, with personal exposure ranging from 12 – 1892 total alcoholic drinks. High-risk offspring were more likely than low-risk offspring to have had personal exposure to alcohol before the LISRES-Y ($\chi 2 = 4.97$, $p = 0.03$), though amount of exposure at the time of the LISRES-Y did not differ by risk status within this subsample [$F(1,42) = 1.83$, $p = 0.19$]. Among offspring who had personal exposure to alcohol before LISRES-Y data was collected, there was no significant relationship between total number of lifetime drinks and scores on the Parent Stressor scale [$F(1,29.74) = 0.001$, $p = 0.98$], Parent Resource scale [$F(1,23.78) = 2.71$, $p = 0.12$], Friend Stressor scale [$F(1,18.91) = 1.02$, $p = 0.33$], or Friend Resource scale [$F(1,0.52)= 0.72$, $p = 0.64$].

There were 188 participants (HR = 116, LR = 72) for whom age of onset of regular (i.e., monthly) drinking preceded the age of MPQ assessment, with personal exposure ranging from 12 – 3336 total alcoholic drinks. High-risk offspring were more likely than low-risk offspring to have had personal exposure to alcohol before the MPQ ($\chi 2 = 21.35$, $p < 0.001$), though amount of exposure at the time of assessment did not differ by risk status within this subsample [$F(1,120.35) = 0.52$, $p = 0.47$]. After controlling for total personal exposure to alcohol at the time of MPQ assessment, risk-group differences remained significant for both the Alienation [$F(1,106.43) = 10.00$, $p < 0.01$] and Social Closeness scales [$F(1,113.04) = 4.30$, $p = 0.04$]. There was no main

effect of total alcohol exposure on either MPQ scale [$F(1,252.05) = 1.02$, $p = 0.31$ and $F(1,254.95) = 0.08$, $p = 0.78$, respectively].

3.3.4 Main Effects of Prenatal Exposures

3.3.4.1 Prenatal Alcohol Exposure

Mothers of 69 offspring (HR = 53, LR = 16) reported using any alcohol during pregnancy, and high-risk offspring were significantly more likely to have been exposed to alcohol prenatally than low-risk controls ($\chi 2 = 21.59$, $p < 0.001$). Among offspring whose mothers reported any alcohol use during pregnancy, total number of drinks ranged from 3 to 2160 (mean = 135.17, median = 27.00), and was marginally higher among high-risk families [$F(1,51.83) = 3.04$, $p = 0.09$]. After accounting for familial risk status, offspring with prenatal alcohol exposure did not differ from unexposed participants on measures of social competence [$F(1,253.82) = 1.44$, $p = 0.23$], social problems [$F(1,249.74) < 0.01$, $p = 0.94$], parent stressors [$F(1,253.49) = 1.60$, $p = 0.21$], parent resources [$F(1,253.88) < 0.01$, $p = 0.96$], friend stressors [$F(1,253.90) = 0.27$, $p = 0.60$], friend resources [$F(1,254.98) = 2.72$, $p = 0.10$], or social closeness [$F(1,236.68) = 0.04$, $p = 0.85$]. Prenatal alcohol exposure was associated with significantly higher alienation scores [$F(1,241.73) = 4.85$, $p = 0.03$].

Among offspring with any prenatal alcohol exposure, higher rates of maternal alcohol use during pregnancy (i.e., more total drinks) were significantly associated with lower scores on the CBCL Social Competence scale [$F(34,5.20) = 11.42$, $p < 0.01$] and LISRES-Y Parent Resources scale [$F(34,32.00) = 1.98$, $p = 0.03$]. Dose-dependent relationships were not observed for the CBCL Social Problems scale, LISRES-Y Parent Stressor scale, LISRES-Y Peer Stressor scale, LISRES-Y Peer Resources scale, MPQ Alienation scale, or MPQ Social Closeness scale (all $p >$

0.20). After controlling for familial risk status, there was not a statistically significant difference in SUD outcome between individuals with and without prenatal drug exposure in this sample (B = 0.04, SE = 0.33, Wald = 0.02, $p = 0.90$), nor was there a significant effect of amount of prenatal exposure among offspring whose mothers reported any alcohol use during pregnancy (B < 0.01, SE < 0.01, Wald = 0.57, $p = 0.45$). Among offspring with any prenatal alcohol exposure, no dose-dependent relationships were observed on measures of adolescent alcohol use (all $p > 0.40$).

3.3.4.2 Prenatal Drug Exposure

Mothers of 22 offspring (HR = 21, LR = 1) reported using any drugs during pregnancy, and high-risk offspring were significantly more likely to have been exposed to drugs prenatally than low-risk controls ($\chi 2 = 17.48$, $p < 0.001$). Number of days of drug use ranged from 3 to 270 (mean = 69.41, median = 15.00). Risk group differences in number of days of use were not analyzed due to the presence of only one affected low-risk offspring. After accounting for familial risk status, offspring with prenatal drug exposure did not differ from unexposed participants on the CBCL Social Competence scale [$F(1,159.2) = 2.29$, $p = 0.13$], CBCL Social Problems scale [$F(1,162.32) < 0.01$, $p = 0.96$], LISRES-Y Parent Stressor scale [$F(1,143.28) = 2.41$, $p = 0.12$], LISRES-Y Parent Resource scale [$F(1,153.57) = 1.60$, $p = 0.21$], or LISRES-Y Friend Stressor scale [$F(1,152.55) = 2.03$, $p = 0.16$]. There was a significant effect of any prenatal drug exposure on LISRES-Y Friend Resources [$F(1,151.45) = 5.69$, $p = 0.02$], such that offspring with prenatal exposure had lower scores than unexposed offspring. Individuals with any prenatal drug exposure also had marginally higher scores on the MPQ Alienation scale [$F(1,186) = 3.93$, $p = 0.05$] and marginally lower scores on the MPQ Social Closeness scale [$F(1,186) = 3.47$, $p = 0.06$]. Analyses of the main effect of number of days of drug use during pregnancy among offspring with any prenatal drug exposure were not conducted due to the small sample size (n = 22). After controlling

for familial risk status, there were not a statistically significant differences in SUD outcome between individuals with and without prenatal drug exposure in this sample (B = -0.11, SE = 0.22, Wald = 0.26, $p = 0.61$), nor was there a significant effect of amount of prenatal exposure among offspring whose mothers reported any drug use during pregnancy (B < 0.01, SE < 0.01, Wald = 0.18, p = 0.67).

3.3.4.3 Prenatal Cigarette Exposure

Mothers of 70 offspring (HR = 56, LR = 14) reported using any cigarettes during pregnancy, and high-risk offspring were significantly more likely to have been exposed to cigarettes prenatally than low-risk offspring ($\chi 2 = 28.28$, $p < 0.001$). Among offspring whose mothers reported any cigarette use during pregnancy, total packs of cigarettes ranged from 18 to 810 (mean = 158.14, median = 135.00), and total packs of cigarettes during pregnancy did not significantly differ between risk groups [$F(1,49.95) = 1.57$, $p = 0.22$]. Offspring of mothers who used cigarettes during pregnancy had significantly higher scores on the CBCL Social Problems scale [$F(1,132.22) = 7.86$, $p < 0.01$] and MPQ Alienation scale [$F(1,186.00) = 12.96$, $p < 0.001$], and significantly lower scores on the LISRES-Y Friend Resource scale [$F(1,129.45) = 6.99$, $p < 0.01$], than offspring without any prenatal cigarette exposure. Offspring with prenatal cigarette exposure did not differ from unexposed offspring on the CBCL Social Competence scale [$F(1,142.94) = 0.83$, $p = 0.36$], LISRES-Y Parent Stressor scale [$F(1,114.92) = 1.05$, $p = 0.31$], LISRES-Y Friend Stressor scale [$F(1,124.76) < 0.01$, $p = 0.97$], LISRES-Y Parent Resource scale [$F(1,137.07) = 0.75$, $p = 0.39$], or MPQ Social Closeness scale [$F(1,186.00) < 0.01$, $p = 0.94$].

Among offspring with any prenatal cigarette exposure, no significant relationships were observed between the number of packs of cigarettes used during pregnancy and measures of social functioning (all $p > 0.50$). After controlling for familial risk status, there was not a statistically

significant difference in SUD outcome between individuals with and without prenatal cigarette exposure in this sample (B = -0.03, SE = 0.23, Wald = 0.01, p = 0.91), nor was there a significant effect of amount of prenatal exposure among offspring whose mothers reported any cigarette use during pregnancy (B < 0.01, SE < 0.01, Wald = 0.18, p = 0.67).

3.4 Structural Equation Modeling

Structural equation modeling (SEM) was utilized to examine longitudinal relationships among measures of social functioning, familial risk status, adolescent alcohol use, and SUD outcome, and to address the three study hypotheses. SEM was deemed to be an appropriate procedure for the current study because of its ability to examine complex relationships with predictors simultaneously using multivariate analyses, model familial relatedness/nested data, control for error, and operate with non-normal data (Kline, 2016; Lei & Wu, 2007; Ullman, 2006).

To evaluate the three hypothesized models, confirmatory factor analysis (CFA) was first used to evaluate the measurement model. For models with poor fit, model re-specification was conducted and fit was re-assessed. After a measurement model with good fit was identified, path analysis was conducted to examine relationships among observed and latent constructs of interest. Full models were estimated with all paths between latent factors freely estimated and with fixed parameters consistent with study hypotheses.

All models were estimated using the MLR command in Mplus which allows for maximum likelihood parameter estimates with standard errors and chi-square test statistics that are robust to non-normality and non-independence of observations (Satorra, 2000). Due to the presence of continuous, non-normal outcome variables, chi-square difference testing for nested models was

calculated with the Satorra-Bentler scaled chi-square difference test (Satorra & Bentler, 2010). Because traditional model fit indices in Mplus are not generated with censored outcome variables, all models that included SUD outcome were respecified using a binary indicator of SUD outcome (yes vs. no) and estimated using weighted least square means and variance (WLSMV).

The following fit statistics were examined when evaluating overall model fit. The Model Chi-Square (χ_2) statistic assesses overall fit in terms of the discrepancy between the sample and fitted covariance matrices. The associated null hypothesis presumes that the model fits the sample perfectly, so smaller χ_2 values, and higher associated *p* values, are associated with better model fit. A generally supported cut-off value for this statistic is $p > 0.05$. The Root Mean Standard Error of Approximation (RMSEA) is a parsimony-adjusted index and values closer to 0 represent a good fit, with a cut-off value of RMSEA < 0.08 for a good-fitting model. The value of the Non-Normed Fit Index, also called the Tucker Lewis Index (TLI) corresponds to the percentage by which the model of interest improves fit relative to the null model, and values equal to or higher than 0.95, which indicate improvement of fit by at least 95%, suggest good fit. The Comparative Fit Index (CFI) is a revised form of the TLI that is less sensitive to sample size. Like the TLI, this index compares the fit of the target model to the fit of the null model, and values equal to or greater than 0.90 indicate good fit. The Standardized Root Mean Square Residual (SRMR) reflects the square-root of the difference between the residuals of the sample covariance matrix and the hypothesized model; lower values indicate better fit, with a cutoff value of < 0.08. Lastly, the weighted root mean square residual (WRMR) uses a variance-weighted approach that is well-suited for models whose variables measured on different scales or have widely unequal variances. The WRMR is also appropriate for use with categorical variables and non-normally distributed data; values <1.0 reflect adequate model fit. Model fit statistics, reported below, are presented in Table 7.

With regard to missing data, the current study selected a subset of high- and low-risk offspring for whom data on all measures of interest was available in order to facilitate examination of longitudinal associations between age-appropriate measures of social functioning, adolescent alcohol use, and SUD outcome.

3.4.1 Hypothesis 1: Risk, Adolescent Alcohol Use, and Substance Use Disorder Outcome

The first hypothesized model (Model A) examined relationships between familial risk, adolescent alcohol use, and SUD outcome. Risk status was considered an independent, observed variable, and SUD status in young adulthood was modeled as an observed outcome with survival analysis. In the hypothesized model, adolescent alcohol use was modeled as a latent variable comprised of usual quantity per occasion and maximum quantity per occasion, calculated across annual childhood K-SADS assessments. Significant paths were hypothesized among all three constructs.

3.4.1.1 Correlations Among Alcohol Use Variables

Bivariate correlations, as well as partial correlations controlling for the effects of familial risk status and sex, were calculated among the six observed measures of adolescent alcohol use: age at first drink, age of onset of regular (i.e., monthly) drinking, usual frequency, maximum frequency, usual quantity per occasion (QPO), and maximum QPO (Table 5). For adolescents who reported alcohol use during adolescence (n = 190), significant relationships were observed among variables assessing age of onset, frequency of use, and QPO. Specifically, the two age of onset variables (i.e., age at first drink and age of onset of regular drinking) were significantly correlated ($r = 0.54$, $p < 0.001$); onset of regular drinking, but not age at first drink, was

significantly related to usual and maximum frequency of drinking (r = -0.24, $p = 0.001$; r = -0.26, $p = 0.001$), as well usual and maximum QPO (r = -0.25, $p = 0.001$; r = -0.31, $p < 0.001$). Significant pairwise correlations were also observed for all relationships among measures of frequency and QPO ($0.42 \leq r \leq 0.83$, all $p < 0.001$), with particularly high coefficients for the pairs of frequency (b = 0.58) and QPO (b = 0.84) measures.

3.4.1.2 Measurement Model A

Confirmatory factory analysis (CFA) was used to examine the initially hypothesized latent factor comprised of usual QPO and maximum QPO and its relationship to both familial risk status and SUD outcome (Figure 6). However, the latent variable covariance matrix of the estimated model was not positive definite, and modification indices indicated a high degree of collinearity between usual and maximum QPO. Age of onset of regular (i.e., monthly) drinking has also been shown to have a significant relationship with both familial risk status and SUD outcome, and a modified model was estimated in which the latent factor adolescent alcohol use comprised maximum QPO and onset of regular (i.e., monthly) drinking (Figure 7). This model showed good fit to the data [($\chi 2(2) = 7.12$, $p = 0.03$, RMSEA = 0.08, CFI = 0.96, TLI = 0.83, SRMR = 0.05] and was retained.

3.4.1.3 Structural Model A

Analysis of the structural model indicated significant paths between familial risk and adolescent alcohol use (b = -0.38, $p < 0.001$), familial risk and SUD outcome (b = -0.29, $p < 0.001$), and adolescent alcohol use and SUD outcome (b = 0.49, $p < 0.001$). There was no significant effect of sex on adolescent alcohol use (b = -0.07, $p = 0.32$), though the effect of sex on SUD outcome was marginally significant (b = -0.10, $p = 0.06$). Both the direct (b = -0.29, SE = 0.07, $p < 0.001$)

and indirect (b = -0.19, SE = 0.05, $p < 0.001$) pathways between familial risk and SUD onset were significant (Figure 7).

3.4.2 Hypothesis 2: Risk and Social Functioning

The second hypothesized model (Model B) examined the influence of familial risk status on social functioning assessed in childhood, adolescence, and young adulthood, and also examined interrelationships among social functioning assessed at each timepoint. In the hypothesized model, childhood social functioning was modeled as a latent variable comprised of the CBCL Social Competence scale and the CBCL Social Problems scale. Latent variables of Adolescent Parent Support and Adolescent Peer Support were comprised of the LISRES-Y Parent and Peer Stress and Resources scales, respectively, and Young Adult Social Functioning was comprised of the MPQ Alienation and MPQ Social Closeness scales.

3.4.2.1 Correlations Among Social Functioning Variables

Bivariate correlations and partial correlations controlling for the effects of familial risk status and sex were calculated among the six observed measures of social functioning (Table 6). After controlling for the effects of risk and sex, significant correlations were observed between CBCL Social Competence and Social Problems (r = -0.24, $p < 0.001$), LISRES-Y Parent Stressors and Parent Resources (r = -0.55, $p < 0.001$), LISRES-Y Peer Stressors and Peer Resources (r = -0.31, $p < 0.001$), and MPQ Alienation and Social Closeness (r = -0.41, $p < 0.001$).

3.4.2.2 Measurement Model B

The hypothesized structural model examining relationships between familial risk status and social functioning included four latent social functioning variables, such that the first variable was comprised of the CBCL Social Competence and Social Problems scale, the second by the LISRES-Y Parent Stressors and Parent Resources scales, the third by the LISRES-Y Friend Stressors and Friend Resources scales, and the fourth by the MPQ Alienation and Social Closeness scales (Figure 8). The CFA performed on this model resulted in a non-positive definite covariance matrix and modification indices indicated a high degree of collinearity between LISRES-Y Parent Stressors and LISRES-Y Parent Resources. A modified model was estimated in which an observed composite score of the LISRES-Y Parent Stressors and LISRES-Y Parent Resources was used in place of a latent factor with two indicators. This model showed good fit to the observed data ($\chi 2(11) = 32.07$, $p < 0.01$; RMSEA = 0.08, CI = 0.047 to 0.115; CFI = 0.90; TLI = 0.78, SRMR = 0.05) and was retained. Factor loadings for the latent constructs of Child Social Functioning, Adolescent Peer Support, and Young Adult Social Functioning were all significant ($p < 0.001$; Figure 9).

3.4.2.3 Structural Model B

Analysis of the structural model (Figure 9) indicated significant relationships between familial risk and the three latent variables; childhood social functioning (b = 0.23, $p = 0.02$), adolescent peer support (b = -0.35, $p < 0.01$), and young adult social functioning (b = -0.24, $p < 0.01$). Risk was also significantly related to the observed composite variable of adolescent parent support (-0.26, $p < 0.01$). Significant relationships between social functioning variables were also observed. Childhood social functioning was related to adolescent peer support (b = -0.64, $p < 0.001$) and young adult social functioning (b = -0.45, $p <0.001$), but not adolescent parent support

(b = -0.24, p = 0.29). Adolescent peer support was related to adolescent parent support (b = 0.93, $p < 0.001$) and young adult social functioning (b = 0.63, $p < 0.001$), and adolescent parent support related to young adult social functioning (b = 0.44, $p < 0.001$). There was a significant relationship between sex and adolescent peer support (b = -0.21, p = 0.04), but sex did not significantly relate to childhood social functioning (b = 0.08, p = 0.46), adolescent parent support (b = 0.08, p = 0.24), or young adult social functioning (b = -0.15, p = 0.11).

3.4.3 Hypothesis 3: Mediation by Social Functioning

The third hypothesized model (Model C) aimed to examine whether social functioning mediated the relationship between familial risk status and SUD outcome and allowed for examination of relationships among all constructs of interest, as well as the ability to examine indirect influences of familial risk on SUD outcome via both social functioning and adolescent alcohol use. In the hypothesized model, latent factors of childhood social functioning, adolescent parent and peer support, young adult social functioning, and adolescent alcohol use were measured as previously described above for hypothesized Models A and B.

3.4.3.1 Measurement Model C

First, the hypothesized baseline model was assessed with all possible pathways between observed and latent variables freely estimated by the model (Figure 10). As had occurred with estimation of Model B, the latent variable covariance matrix of the estimated model was not positive definite, and modification indices indicated a high degree of collinearity between LISRES-Y Parent Stressors and LISRES-Y Parent Resources. Accordingly, a modified model was estimated in which an observed composite score of the LISRES-Y Parent Stressors and

LISRES-Y Parent Resources was used in place of a latent factor with two indicators (Figure 11). The modified baseline model, with all paths freely estimated, was found to fit the observed data adequately well ($\chi 2(32) = 47.92$, $p = 0.04$; RMSEA = 0.04, CI = 0.01 to 0.07; CFI = 0.95; TLI = 0.89, WRMR = 0.66).

3.4.3.2 Structural Model C

In the baseline model (Figure 11), main effects of familial risk were observed on childhood social functioning (b = 0.22, $p = 0.04$), adolescent peer support (b = -0.27, $p < 0.02$), adolescent alcohol use (b = 0.38, $p < 0.001$), and young adult social functioning (b = -0.27, $p < 0.01$). There was not a significant relationship between risk and adolescent parent support (b = 0.06, $p = 0.94$). With regard to SUD outcome, significant paths were observed from childhood social functioning (b = -0.35, $p = 0.03$), adolescent alcohol use (b = -0.46, $p < 0.001$), and young adult social functioning (b = 0.37, $p < 0.01$). Neither adolescent peer (b = -0.24, $p = 0.17$) nor parent (b = -0.08, $p = 0.50$) support was a significant predictor of SUD outcome. Familial risk status was found to have a significant indirect effect on SUD outcome via adolescent alcohol use (b = -0.18, $p < 0.01$) and a marginally significant indirect effect via young adult social functioning (b = -0.10, $p = 0.06$). The direct path between risk and SUD outcome was also marginally significant (b = -0.19, $p = 0.09$). A significant path was observed between sex and adolescent peer support (b = -0.21, $p = 0.01$), and there was a marginally significant relationship between sex and young adult social functioning (b = -0.15, $p = 0.07$).

3.4.3.3 Model C Respecification

In order to identify the most parsimonious model explaining relationships among variables of interest, an iterative series of nested models were estimated. First, paths between risk and all

other variables of interest were fixed at zero. Overall model fit was poor ($\chi 2(29) = 134.86$, $p < 0.001$; RMSEA = 0.12, CI = 0.01 to 0.14; CFI = 0.46; TLI = 0.18, WRMR = 1.64) and parameter estimates were not interpreted. When paths between childhood social functioning and all other variables of interest were fixed at zero, estimation did not converge and no model was able to be fit to the data.

Next, paths between young adult social functioning and all other variables of interest were fixed at zero. The respecified model fit the data more poorly than the baseline model ($\chi 2(32) = 69.14$, $p < 0.001$; RMSEA = 0.07, CI = 0.05 to 0.09; CFI = 0.85; TLI = 0.75, WRMR = 1.04), though similar significant relationships among remaining variables were observed. Additionally, significant paths between childhood social functioning and SUD outcome (b = -0.30, $p < 0.01$), as well as adolescent peer support and SUD outcome (b = 0.25, $p = 0.03$) emerged.

A model with improved overall fit was identified when paths involving both adolescent parent support and adolescent peer support were fixed at zero; $\chi 2(15) = 25.76$, $p = 0.041$; RMSEA = 0.05, CI = 0.01 to 0.09; CFI = 0.95; TLI = 0.88, WRMR = 0.60. Parameter estimates indicated that sex did not significantly relate to any latent or observed variables in the model, and a final model was estimated in which these relationships were fixed at zero. The overall model fit was further improved ($\chi 2(12) = 15.67$, $p = 0.21$; RMSEA = 0.03, CI = 0.01 to 0.08; CFI = 0.98; TLI = 0.96, WRMR = 0.49), and a final model was accepted with the following effects of interest (Figure 12). Using Satorra-Bentler's Maximum Likelihood Mean Adjusted Chi-Square Difference Test, this model was shown to be a significantly better fit to the data than the originally accepted Model C ($\chi 2$ (20) = 32.14, $p = 0.04$).

In the final model, familial risk status was significantly related to childhood social functioning (b = 0.21, $p < 0.05$), adolescent alcohol use (b = -0.38, $p < 0.001$), and young adult

social functioning (b = -0.24, $p < 0.01$), and each of these variables was significantly related to SUD outcome (familial risk: b = -0.17, $p < 0.05$; childhood social functioning: b = -0.19, $p < 0.05$; adolescent alcohol use: b = 0.46, $p < 0.001$; young adult social functioning: b = 0.33, $p < 0.01$) . The relationship between child and young adult social functioning was significant (b = -0.40, $p < 0.001$), though, contrary to hypotheses, neither childhood (b = 0.02, $p = 0.83$) nor young adult (b = -0.13, $p = 0.15$) social functioning was significantly related to adolescent alcohol use. Significant indirect pathways between familial risk and SUD outcome were identified via each latent construct independently, though no significant paths between familial risk and SUD outcome via any two latent constructs were observed (all $p > 0.40$). Parameter estimates for the final mediation model are presented in Figure 12.

4.0 Discussion

4.1 Summary

The current study aimed to examine: 1) whether there were risk-group differences in adolescent alcohol use and SUD outcome in a sample of offspring at high and low familial risk for AUD; 2) whether high-risk offspring had deficits on measures of social functioning collected during childhood, adolescence, and young adulthood; and 3) whether deficits in social functioning mediated the relationship between familial risk status and SUD outcome by young adulthood. The results indicated that high-risk offspring were more likely to engage in alcohol use during adolescence and develop SUD by young adulthood, and had lower scores on parent- and self-report measures of social functioning across developmental periods. Furthermore, less adaptive social functioning reported during both childhood and young adulthood partially mediated the relationship between risk and SUD outcome.

4.2 Familial Risk, Adolescent Alcohol Use, and Substance Use Disorder Outcome

Consistent with this study's hypotheses, high-risk offspring from multiplex families were more likely to engage in alcohol use as adolescents, had earlier onsets of regular (i.e., monthly) drinking, consumed greater usual and maximum quantities of alcohol per occasion after the onset of regular drinking, and were more likely to engage in binge drinking than low-risk controls. High-risk offspring were also significantly more likely to develop SUD by young adulthood and had

higher rates of alcohol, drug, and polysubstance use disorders than low-risk controls. These findings are consistent with extant research on the increased risk for problematic use of alcohol and other substances among those at high familial risk for AUD.

Twin, adoption, and family studies have provided significant evidence that AUD runs in families, and recent meta-analyses estimate the heritability of AUD to be 0.52 for males and 0.44 for females (Verhulst, Neale, & Kendler, 2015). Offspring of parents with AD are 4-10 times more likely to develop AUD than offspring of non-alcoholics (Cloninger, Bohman, & Sigvardsson, 1981; Chassin, Curran, Hussong, & Colder, 1996; Donovan, 2004; Goodwin, Schulsinger, Hermansen, Guze, & Winokur, 1973), and offspring with particularly dense or multigenerational family histories are at even greater risk (Dawson & Grant, 1998; Hill et al., 2008; Hill, Tessner, & McDermott, 2011). Parental AUD has also been shown to increase risk for the use and abuse of other drugs in adolescence (Hussong, Huang, Serrano, Curran, & Chassin, 2012), as well as other SUD in young adulthood (Hill et al., 2008; Hill et al., 2011). Thus, results indicating heavier drinking (i.e., greater quantity per occasion) and higher rates of SUD among high-risk offspring in the current sample are consistent with prior research demonstrating increased risk of both adolescent alcohol use and SUD by young adulthood among those at high familial risk for AUD.

Although high-risk offspring consumed greater usual and maximum quantities of alcohol per occasion and were more likely to engage in binge drinking, high- and low-risk offspring were not found to differ on measures of usual and maximum frequency of alcohol use during adolescence. Post-hoc analyses indicated that there were significant risk-group differences in usual frequency of drinking in young adulthood, such that high-risk offspring reported using alcohol more frequently than low-risk controls (HR M = 5.5 occasions per month, LR M = 3 occasions per month, $p < 0.001$). These findings are consistent with the social control/opportunity

model of genetic risk for a range of substance use outcomes, which suggests that genetic influences are greater when social control is reduced (e.g., low parental monitoring) or social opportunity is high (e.g., affiliations with deviant peers) because these environments provide individuals with more opportunity to express any genetic predisposition (Cooke et al., 2015; Dick et al., 2007; Shanahan & Hofer, 2005). Similarly, twin studies have indicated that the relative importance of genetic influences on alcohol outcomes increases as individuals enter young adulthood, at which time the influence of both formal (e.g. legal prohibition) and information (e.g. parental supervision) social controls may be reduced or removed (Dick, 2011). In the current study, adolescent alcohol use was assessed between the ages of 8 – 18, and thus only captured alcohol use before the legal age of 21. Other environmental factors likely affect the frequency of access to alcohol during adolescence and thus, this measure of use may not accurately reflect patterns of alcohol use once it becomes legally available. In contrast, quantity of alcohol consumed per occasion may be more closely related to characteristics of the individual and less sensitive to social controls. The relationship between frequency of drinking and familial risk status may be dependent on the age at which this measure is assessed, such that family history predicts frequency of drinking in young adulthood, but not adolescence.

The broader literature on adolescent alcohol use, and well as the prevalence of AUD and other SUD across the lifespan, has identified significant sex differences on metrics of use and abuse of alcohol and other substances, as well as some evidence of sex-specific trajectories of risk and resilience (Dir, Bell, Adams, & Hulvershorn, 2017; Schulte, Ramo, & Brown, 2009). In the current study, usual and maximum quantity of alcohol per occasion among adolescents reporting any alcohol use did show significant effects of sex, such than males reported greater usual and maximum quantities per occasion than females. However, neither rates of adolescent alcohol use

nor SUD status by young adulthood significantly differed by sex, such that both male and female high-risk offspring were more likely to report adverse outcomes compared to low-risk controls. Although these results diverge from findings in community samples, they are consistent with prior research on offspring from multiplex AD families in which sex differences are attenuated among those at ultra-high risk for AUD (Hill et al., 2008; Hill et al., 2011).

4.3 Familial Risk and Social Functioning

Based on the emerging literature demonstrating deficits in social cognition and social functioning among high-risk offspring, this project examined whether familial risk affected measures of social functioning collected during childhood, adolescence, and young adulthood. The results showed that high-risk offspring had poorer performance on measures of social functioning collected across developmental periods: in childhood (mean age = 11.3 years, range = 7 – 18 years), high-risk offspring were rated by parents as less socially competent and as having more social problems; in adolescence (mean age = 13.7 years, range = 12 – 18 years), high-risk youth reported more stressors, as well as fewer resources, in relationships with parents and peers; and, in young adulthood (mean age = 19.9 years, range = 17 – 24 years), these high-risk offspring reported more alienation and less closeness in social relationships. Stability of social functioning across developmental periods was also observed, as parent-report measures of social functioning collected in childhood were significant predictors of self-reported social support in adolescence and alienation and social closeness in young adulthood.

4.3.1 Childhood Social Competence and Social Problems

The findings in the current study converge with prior research demonstrating that offspring with a family history of AUD are described as less socially competent and as having more social problems than their peers by parents, teachers, and classmates in childhood (Christensen & Bilenberg, 2000; Eiden, Colder, Edwards, & Leonard, 2009; Eiden et al., 2016; Hussong, Zucker, Wong, Fitzgerald, & Puttler, 2005). Social competence is a broadly adaptive individual-differences characteristic that encompasses several related interpersonal skills. In childhood, social competence reflects social cognition, emotional self-regulation, positive communication, and prosocial relationships with family members, peers, and teachers (Ladd, 2005). Prior studies have shown that social cognitive abilities account for a large proportion of variance in social competence (Ford, 1982). More specifically, social competence has been shown to correlate with individual differences in theory of mind (Bosacki & Wilde, 1999; Lalonde & Chandler, 1995; Liddle & Nettle, 2006; McGuire & Weisz, 1982; Rubin et al., 1997; Walker, 2005) and emotional face processing abilities (Nowicki & Mitchell, 1998). Social adjustment, a related concept encompassing the degree to which children get along with their peers, the extent to which they engage in adaptive, competent social behavior, and the degree to which they inhibit aversive, incompetent behavior, has also been theoretically and empirically linked to social cognitive abilities (Crick & Dodge, 1994). Previous research has also shown that offspring from multiplex, AD families show more inhibited play behavior with other children in childhood, and spend significantly more time staring, less time speaking, and more time proximate to their parent than low-risk controls (Hill, Lowers, Locke, Snidman, & Kagan, 1999). These behaviors have previously been shown to relate to an inhibited temperament, which in turn predicts a tendency to

be socially avoidant in unfamiliar social situations (Kagan, Reznick, Snidman, Gibbons, & Johnson, 1988).

4.3.2 Adolescent Social Supports and Stressors

High-risk offspring reported more stressors and fewer supports in relationships with both parents and peers, indicating lower perceived social support than low-risk controls in adolescence (mean age = 13.7 years, range = 12 – 18 years). Individuals with AUD and other SUD frequently report problems in interpersonal relationships and low levels of perceived social support (Moak & Agrawal, 2010; Peirce, Frone, Russell, Cooper, & Mudar, 2000), and some research has reported that high-risk offspring are more likely to report lower levels of perceived social support (Barnes, Reifman, Farrell, & Dintcheff, 2000; Dunn et al., 2002) than low-risk controls. In contrast, one previous study demonstrated that, in a sample of high- and low-risk offspring (ages 14 – 21) in which participants with early-onset SUD were excluded from analyses, familial risk status was not significantly related to perceived social support from either family or friends (Averna & Hesselbrock, 2001). However, it is unclear whether this sample reflected relatively resilient high-risk youth who were free of substance-related problems in adolescence and young adulthood. Thus, these results may not generalize to offspring with early-onset adolescent alcohol use or SUD by young adulthood.

Social support has been broadly defined as 'support accessible to an individual through social ties to other individuals, groups, and the larger community' (Lin, Ensel, Simeone, & Kuo, 1979), with perceived social support referring to subjective perceptions of available supports. Early theories of perceived social support inferred strong relationships between perceived and actual received supportiveness, though subsequent research failed to demonstrate significant

associations between these constructs. Instead, many studies have shown that perceived social support is a stronger predictor of mental health outcome than actual or observed social support (Lakey & Drew, 1997). Accordingly, some researchers have hypothesized that perceived social support is a construct best understood as a social-cognitive correlate. In support of this hypothesis, perceived social support has been shown to influence how children, adolescents, and adults interpret novel supportive behaviors, as well as their ability to recall both supportive and unsupportive behaviors (Lakey & Drew, 1997). Recent neuroimaging studies with healthy young adults have provided evidence for common neural underpinnings of perceived social support and social cognition; perceived social support has been found to significantly correlate with GM volumes of the amygdala, cingulate cortex, fusiform cortex, and insula (Che et al., 2014; Li et al., 2014; Sato et al., 2016). Thus, observed deficits on measures of perceived social support from family members and friends among high-risk offspring may partially reflect underlying social cognitive abilities. Nonetheless, it is possible that risk-group differences in this sample reflect exogenous environmental consequences associated with parental AUD rather than genetically driven risk factors within the individual.

4.3.3 Young Adult Alienation and Social Closeness

High-risk offspring had elevated scores on the alienation subscale and reduced scores on the social closeness subscale of the MPQ in young adulthood (mean age = 19.9 years, range = 17 – 24 years). These results are consistent with prior studies documenting that high-risk young adults, both with and without SUD, report higher alienation and lower social closeness than low-risk offspring (Elkins, McGue, Malone, & Iacono, 2004), and that adults with AUD and their non-

affected adult relatives report higher levels of alienation than controls from low-risk families (Hill et al., 1990; McGue, Slutske, Taylor, & Iacono, 1997).

Alienation is a psychological construct comprising feelings of powerlessness, meaninglessness, normlessness, isolation and self-estrangement (Seeman, 1959), and social closeness typically refers to perceived connections, or connectedness, with other individuals. As personality constructs demonstrated to show high heritability and stability (Tellegen, 1982; Tellegen, 1988), high alienation characterizes individuals who feel they are the victim of bad luck, are often mistreated, are the target of false rumors, that others wish them harm, and that they have betrayed and used by friends. In contrast, low alienation characterizes individuals who do not see themselves as victims, feel they are treated fairly, and do not feel taken advantage of (Tellegen, 1982). Individuals high on social closeness are described as sociable, warm and affectionate, liking people, taking pleasure in and valuing close interpersonal ties, and turning to others for comfort and help. In contrast, individuals low on social closeness are described as liking to be alone, not minding pulling up roots, aloof and distant, and preferring to work problems out on their own (Tellegen, 1982). Alienation and social closeness are theoretically related to perceived social isolation, which has been shown to relate to both social cognition and social behavior (Cacioppo & Hawkley, 2009). The current study suggests that high-risk offspring are more likely to report high alienation and low social closeness in young adulthood, and lend support for the role of premorbid deficits in social functioning in the problematic interpersonal relationships associated with substance use disorders.

4.4 Mediation of the Relationship Between Risk and Outcome by Social Functioning

The central aim of the current study was to examine whether measures of social functioning, collected separately in childhood, adolescence, and young adulthood, mediated the relationship between familial risk for AUD and SUD outcome in young adulthood. Structural equation models encompassing all constructs of interest indicated that there were main effects of childhood social functioning, adolescent alcohol use, and young adult social functioning on SUD outcome. In contrast, neither adolescent peer nor parent support were significant predictors of SUD outcome. Similarly, familial risk status had significant, indirect effects on SUD outcome by young adulthood via parent-reported social competence and problems in childhood and self-reported alienation and social closeness in young adulthood, but not adolescent social support from parents or peers.

4.4.1 Familial Risk, Childhood Social Competence and Social Problems, and Substance Use Disorder Outcome

Childhood social functioning, measured by the CBCL Social Competence and Social Problems scales, was significantly affected by familial risk status, and, in turn, was a significant predictor of SUD outcome. Importantly, childhood social functioning was assessed between the ages of 7 and 18 years, and all participants were assessed prior to age of onset of alcohol and other substance use. These findings provide strong evidence that lower levels of adaptive social functioning reported in childhood reflect premorbid risk for SUD outcomes that is independent of offspring substance use. Results are consistent with prior research demonstrating that social

competence in childhood predicts a number of important outcomes later in life, including problematic use of alcohol and other substances (Jones, Greenberg, & Crowley, 2015).

Interestingly, childhood social competence and social problems were not found to be significant predictors of adolescent alcohol use. Similarly, one previous study examining social competence and adolescent substance use among high-risk offspring analyzed, but did not find support for, this relationship (Eiden et al., 2016). Nonetheless, these results diverge from research on samples of other at-risk youth populations, in which higher social competence has been shown to exert a protective effect on adolescent substance use (Caplan et al., 1992; Fishbein et al., 2006). Additional research is needed to clarify the relationships among familial risk, childhood social competence, and adolescent alcohol use behaviors among high-risk offspring.

4.4.2 Familial Risk, Perceived Social Support in Adolescence, and Substance Use Disorder Outcome

Contrary to hypotheses, perceived social support from parents and peers during adolescence was not significantly related to either adolescent alcohol use or SUD outcome, though main effects of familial risk were observed such that high-risk offspring reported more stressors and fewer supports in relationships with both parents and peers. Previous research indicates that associations between perceived social support and adolescent substance use are complex, such that strong supportive peer networks may confer either resilience or risk for early-onset substance use and abuse (Aseltine & Gore, 2000; Peirce, Frone, Russell, & Cooper, 1994; Windle, 2000). Among high-risk offspring, perceived social support from friends has been shown to mediate the relationship between familial risk status and alcohol use during adolescence (Averna & Hesselbrock, 2001), such that higher perceived social support from peers was associated with

heavier alcohol use regardless of familial risk status. In contrast, among adults with a family history of AUD, lower perceived social support was predictive of greater quantities of alcohol consumption and more alcohol-related problems (Ohannessian & Hesselbrock, 1993).

The nature of the association between perceived support from peers and alcohol-related behaviors is further complicated by relationships between premorbid risk factors for early-onset substance use and association with substance-using peers. Some evidence suggests that the relationship between individual risk and peer substance use reflects both direct modeling effects as well as indirect selection effects, such that adolescents who are already predisposed to accelerated substance use seek out like-minded peers (Bray et al., 2003; Lynskey, Agrawal, & Heath, 2010). Thus, it is unclear whether friend relationships precede and influence substance use or if substance use leads to a certain selection of friends.

The lack of effects between perceived social support from parents and peers in adolescence and metrics of adolescent alcohol use may also relate to the previously described social control/opportunity model of genetic risk for SUD, which suggests that the impact of genetic influences may be attenuated in adolescence when social control is relatively high and social opportunity is relatively low (Cooke et al., 2015; Dick et al., 2007; Shanahan & Hofer, 2005). Future research is needed to clarify the extent to which perceived social support from parents and peers confers risk among offspring at high familial risk for AUD.

4.4.3 Familial Risk, Young Adult Alienation and Social Closeness, and Substance Use Disorder Outcome

Young adult social functioning, measured by the MPQ Alienation and Social Closeness scales, was significantly affected by familial risk status, and, in turn, was significantly related to

SUD outcome. High-risk offspring reported higher alienation and lower social closeness, and high alienation and low social closeness scores were associated with increased rates of SUD. These results are consistent with previous research in community and treatment samples of adolescents that have shown that alienation correlates with AUD symptoms (Javdani, Finy, & Verona, 2014) and prospectively predicts substance use outcomes in young adulthood (Bond et al., 2007; Caspi et al., 1997).

The current findings regarding risk-group differences on young-adult measures of social functioning may suggest that less adaptive social functioning confers premorbid risk for SUD. Alternatively, it is possible that risk-group differences measured in young adulthood are the consequence of heavier use of alcohol and other substances in adolescence. In an attempt to disentangle cause from consequence, measures of adolescent alcohol use (i.e., age of onset, usual and maximum frequency of drinking, and usual and maximum quantity per occasion) were included as statistical covariates in models including familial risk, MPQ data, and SUD outcome. The results of these analyses indicated that none of the measures of personal exposure to alcohol significantly affected scores on the relevant MPQ scales, and risk-group differences remained significant after accounting for these metrics. Furthermore, previous research has shown that high-risk young adults with and without SUD report higher alienation and lower social closeness than low-risk offspring (Elkins, McGue, Malone, & Iacono, 2004) and that both adults with AUD and their non-affected first-degree adult relatives report higher levels of alienation than controls from low-risk families (Hill et al., 1990; McGue, Slutske, Taylor, & Iacono, 1997). Thus, findings in the current study, and prior research demonstrating associations between familial risk for AUD, alienation, as well as social closeness among those unaffected by SUD, suggest that less adaptive

social functioning among high-risk offspring is not explained by heavy personal exposure to alcohol and other substances.

4.5 Clinical Implications and Future Directions

The results of this study have a number of potential implications that may be used to inform future clinical research and practice. First, low social competence and high social problems in childhood were found to be significant, premorbid risk factors for SUD outcomes in young adulthood. Social functioning in childhood was found to be a significant predictor of self-reported alienation and social closeness in young adulthood, providing evidence for stability of less adaptive social functioning across development. Numerous studies have shown that interventions in childhood and adolescence targeting social competence are associated with improvements in social skills and associated reductions in adverse outcomes (Skeen et al., 2019; Spence, 2003). Thus, youth with family histories of AUD who demonstrate low social competence in childhood may be especially important to identify for intervention and prevention services. However, future research is needed to specifically examine the extent to which interventions shown to be efficacious in community and other at-risk samples have a positive impact on youth at ultra-high familial risk for AUD and other SUD.

Second, social cognition has been an active area of research in schizophrenia and autism spectrum disorders, and these lines of research have successfully informed intervention design for affected individuals and have been associated with improvements in social functioning and other treatment outcomes (Bishop-Fitzpatrick et al., 2017; Bishop-Fitzpatrick, Minshew, & Eack, 2014). Although the present study did not assess social cognition, risk-group differences on measures of

more general social functioning lend support for future research examining facial affect perception, theory of mind, and other social-cognitive skills among high-risk youth. Research establishing the presence of underlying social cognitive deficits among offspring with a family history of AUD would likely benefit the development of treatment modalities most effective for at-risk and affected youth. Furthermore, clarifying the profile of social cognitive strengths and weaknesses among substance-naïve, high-risk youth may also inform the development of interventions for adolescents and young adults affected by SUD.

Relatedly, there has been a recent impetus in the field of addiction research to examine the social context in which the use and abuse of alcohol and other drugs occur (de Wit & Sayette, 2019). Findings from the current study highlight the potential role of premorbid deficits in social functioning in problematic substance use in young adulthood, and lend further support for the need to study substance use with ecologically valid research designs.

Finally, although perceived social support and stress in relationships with parents was not found to be significant predictors of SUD outcome in the current sample, these constructs were sensitive to familial risk status. Given strong empirical support for the efficacy of interventions targeting parent-child relationships in reducing risk for adolescent substance use and SUD outcome (Van Ryzin, Roseth, Fosco, Lee, & Chen, 2016), future research is needed to examine the characteristics of the parent-child relationship that confer both risk and resilience among high-risk families.

4.6 Strengths and Limitations

The current study has a number of strengths. The use of a prospective, longitudinal design and focus on pedigrees at ultra-high risk for SUD allowed for the assessment of antecedent risk factors and consequent adverse outcomes in the same individuals. SUD outcomes were assessed via multimodal clinical inquiry (i.e., open-ended clinical interviews with a child psychiatrist and separate semi-structured K-SADS interviews with offspring and their parent) and determined based on best-estimate diagnostic conferences. Further, social functioning data were collected via both parent and offspring report and significant correlations were observed between parent-report measures collected during childhood and self-report measures collected during young adulthood. Nonetheless, the results should be interpreted in light of a number of limitations.

4.6.1 Sample

The use of offspring from multiplex, AD families may be viewed as either a strength or weakness of the current study. On the positive side, families with increased transmission for AD are ideal for finding endophenotypic characteristics associated with familial risk. However, these families are not representative of AD families in the general population; follow-up of offspring from these multiplex families indicates an exceptionally high rate of AUD and substance use by young adulthood (Hill et al., 2008, 2011). Although these families may not be representative of AUD families in the general population, the study of multiplex families provides an efficient means for identifying risk factors and genetic variation that can then be taken to population samples for replication.

4.6.2 Self-Report Measures

The current study relies heavily on self-report measures, and it is possible that genetic risk for AUD influences the *perceptions* of social constructs of interest in the current study, in addition to the constructs themselves. For example, parents with AUD may endorse higher rates of offspring social problems in childhood due to actual deficits in social behaviors and/or due to increased frustration with offspring social problems. Similarly, high-risk offspring may report lower perceived parental social support due to differences in the behavior of their parents and/or due to differences in their perceptions of those behaviors. Future research utilizing multiple reporters, including individuals from outside the family (e.g. teachers) will be needed to disentangle these effects. On the positive side, measures of adolescent substance use that were used in this study were based on independent interviews with both parents and children, and both structured (i.e., K-SADS) and unstructured interviews (i.e., interviews with residents in psychiatry) were used to achieve consensus diagnoses. Furthermore, this study used both parent-report (i.e., CBCL) and self-report (i.e., LISRES-Y and MPQ) measures of social functioning at different time points, and significant relationships were observed between parent-reported social competence in childhood and self-reported alienation and social closeness in young adulthood.

4.6.3 Adolescent Substance Use

The current study examined the effects of personal exposure to alcohol on measures of social functioning and SUD outcome, but the effects of personal exposures to substances other than alcohol were beyond the scope of this analysis. Extant research has begun to elucidate the cognitive, neurobiological, and psychiatric consequences associated with adolescent use of

marijuana (Jacobus & Tapert, 2014; Lubman, Cheetham, & Yucel, 2015), and findings in the current study should be interpreted in light of the fact that adolescent use of marijuana and other substances were not examined. Nonetheless, previous analyses of the broader sample of third-generation offspring from which participants in the current study were selected (Hill et al., 2008; Hill et al., 2011) have been shown to have high rates of alcohol use during adolescence (i.e., 73.4% of substance-using adolescents) and lower rates of cannabis use prior to young adulthood (i.e., 23.7% of substance-using adolescents). Future research in our laboratory is planned to examine the influence of use and abuse of drugs other than alcohol on social functioning across childhood, adolescence, and young adulthood.

4.6.4 Data Analyses

Structural equation modeling is typically conducted with large samples. However, there is no simple rule of thumb regarding adequate sample size in SEM analyses. Rather, sample size requirements are influenced by model complexity, measurement error in observed variables, the distribution and scaling of outcome variables, and other characteristics of hypothesized models and selected measures. It should also be noted that previous studies utilizing SEM techniques in similar sample sizes have been able to adequately detect both direct and indirect associations of interest (e.g. Eiden et al., 2016). Nonetheless, the current study sought to address potential limitations due to sample size by first studying simpler subcomponents of the full hypothesized structural model (Models A and B), and by utilizing other GLM techniques less dependent on sample size (i.e., generalized linear mixed models and Cox Regression survival analyses) to confirm findings of interest.

4.7 Conclusion

In summary, the current study provides evidence that high-risk offspring from multiplex, alcohol-dependent families show less adaptive social functioning in childhood, adolescence, and young adulthood. Social competence and social problems in childhood and alienation and social closeness in young adulthood were independent predictors of SUD outcome, such that lower competence and social closeness, and higher rates of social problems and alienation, conferred risk for adverse outcomes. Notably, familial risk status had significant, indirect effects on SUD outcome via social functioning assessed in childhood and young adulthood, confirming hypothesized mechanisms of mediation. Although risk-group differences were observed on adolescent self-report measures of perceived social support from parents and peers, these measures did not significantly influence patterns of adolescent alcohol use or SUD outcomes.

A notable strength of this study is the use of longitudinal data collected during childhood, adolescence, and young adulthood, which allowed for direct assessment of the possibly confounding effect of personal exposure to alcohol on the relationships between familial risk, social functioning, and SUD outcome. Specifically, high-risk offspring were rated as less socially competent and as having more social problems than low-risk controls prior to the onset of use and abuse of alcohol and other substances, and lesser perceived social support in adolescence was independent of personal exposure to alcohol for youth whose onset of regular use preceded adolescent assessment. Risk group differences on self-report measures of alienation and social closeness were also not attenuated by personal exposure to alcohol prior to age at MPQ assessment. In fact, SEM analyses indicated that indirect effects of familial risk on SUD outcome appeared to operate independently through either premorbid deficits in social functioning or increased rates of

adolescent alcohol use, as no significant associations emerged between measures of adolescent alcohol use and social functioning in childhood, adolescence, or young adulthood.

Taken together, these findings indicate that high-risk offspring demonstrate deficits in social functioning in childhood, adolescence, and young adulthood, and that these deficits are not explained by increased rates of early alcohol use among high-risk participants. Among those at high familial risk for AUD, offspring who were rated as less socially competent and as having more social problems in childhood were at especially high risk for developing SUD by young adulthood. These offspring were also more likely to report higher alienation and lower social closeness in young adulthood, which in turn explained additional variance in SUD outcome. Findings from the current study may have important implications for the development of prevention and intervention strategies for youth at highest risk for substance use disorders.

Appendix A Tables

Table 1: Mean Number of Second-Degree Relatives by Parental AD Status and Risk Group

	High-Risk (*n* = 137)			Low-Risk (*n* = 122)		
	N	Mean	SD	*N*	Mean	SD
Neither Parent AD	17	3.24	1.95	89	0.29	0.74
Both Parents AD	25	3.60	2.31	0	0.60	0.97
One Parent Known AD+	77	3.18	2.08	10[a]	0.09	0.43
One Parent Known AD-	18	3.39	1.29	23[b]	0.28	0.72
Total Pairs	137			122		

AD = alcohol dependent.

[a] These co-parents were not part of the targeted low-risk pedigrees but married into the family and accordingly were reported to have AD by the spouse.

[b] Second-degree relative number was unavailable for 1 participant in this group.

Table 2: Demographic Data by Familial Risk Status

	High-Risk (*n* = 137)		Low-Risk (*n* = 122)			
	n/mean	%/SE	*n*/mean	%/SE	χ_2/F	*p*
Sex					6.14	.02
Male	62	45.3%	74	60.7%		
Female	75	54.7%	48	39.3%		
Race/Ethnicity					2.66	.45
Caucasian	124	90.5%	116	95.1%		
Black	11	8.0%	5	4.1%		
Biracial	2	1.5%	1	0.8%		
Socioeconomic Status	37.84	1.27	45.80	1.26	19.85	<.001
Age at Study Entry	11.24	0.27	11.61	0.27	0.95	.33
CBCL Age	11.26	0.27	11.62	0.27	0.86	.36
LISRES-Y Age	13.77	0.17	13.73	0.18	0.02	.88
MPQ Age	20.35	0.34	19.51	0.35	3.04	.10
Age at Last Follow-Up	26.42	0.40	24.78	0.41	8.27	<.01
Number of Assessments	8.98	0.33	9.00	0.34	0.01	.97
Child/Adolescent Assessments	5.67	0.27	5.97	0.27	0.65	.42
Young Adult Assessments	3.30	0.16	3.02	0.16	1.52	.22

CBCL = Child Behavior Checklist; LISRES-Y = Life Stressors and Resources Inventory – Youth Version; MPQ = Multidimensional Personality Questionnaire. [a] Socioeconomic status was measured at the time of study entry with the Hollingshead Four Factor Index; risk groups were in adjacent social strata. Means and standard errors were calculated using linear mixed models and are adjusted to account for non-independence of observations from participants within the same nuclear families. Adjusted means and standard errors were highly similar to unadjusted means and standard errors. For example, the unadjusted mean age at study entry was 11.14 (standard error = 0.24) for high-risk offspring, compared to an adjusted mean of 11.24 (adjusted standard error = 0.27). Among low-risk offspring, the unadjusted mean age at study entry was 11.52 (standard error = 0.24), compared to an adjusted mean of 11.61 (adjusted standard error = 0.27).

Table 3: Substance Use Data by Familial Risk Status

	High-Risk (n = 137)		Low-Risk (n = 122)		$\chi 2$/F	p
	n/mean	%/SE	n/mean	%/SE		
Any Adolescent Alcohol Use	119	86.9%	71	58.2%	27.13	<.001
Age of Onset – First Drink[a]	14.98	0.21	15.70	0.26	4.48	.04
Age of Onset – Regular Drinking [a]	15.54	0.25	16.92	0.29	12.27	.001
Usual Frequency[a]	36.07	5.65	45.21	7.31	0.98	.32
Maximum Frequency[a]	86.55	9.60	75.87	12.22	0.47	.49
Average QPO[a]	4.64	0.32	3.60	0.39	3.99	<.05
Maximum QPO[a]	5.54	0.37	4.17	0.45	4.27	.04
Any Binge Drinking	90	65.7%	41	33.6%	26.58	<.001
Lifetime SUD Diagnosis	73	53.3%	21	17.2%	36.32	<.001
AUD only	19	13.9%	6	4.9%	5.94	.01
DUD only	17	12.4%	6	4.9%	4.48	.03
AUD & DUD	37	27.0%	9	7.4%	17.03	<.001

AUD = alcohol use disorder; DUD = drug use disorder; SUD = substance use disorder; QPO = quantity per occasion; [a] = analysis conducted among offspring who reported any adolescent alcohol use. Means and standard errors were calculated using linear mixed models and are adjusted to account for non-independence of observations from participants within the same nuclear families.

Table 4: Social Functioning Data by Familial Risk Status

	High-Risk (*n* = 137)		Low-Risk (*n* = 122)			
	Mean	SE	Mean	SE	F	*p*
CBCL						
Social Competence	46.23	0.67	48.62	0.69	6.15	0.014
Social Problems	53.25	0.51	52.77	0.53	0.41	0.520
LISRES-Y						
Parent Stressors	9.39	0.45	6.72	0.46	17.07	<0.001
Parent Resources	14.95	0.37	16.07	0.38	4.55	0.035
Friend Stressors	5.40	0.28	3.88	0.28	14.94	<0.001
Friend Resources	29.67	0.50	31.12	0.51	4.54	0.035
MPQ						
Alienation	4.77	0.35	3.13	0.36	10.75	0.001
Social Closeness	16.35	0.42	17.60	0.44	4.24	0.042

CBCL = Child Behavior Checklist; LISRES-Y = Life Stressors and Social Resources Inventory – Youth Version; MPQ = Multidimensional Personality Questionnaire

Means and standard errors were calculated using linear mixed models and are adjusted to account for non-independence of observations from participants within the same nuclear families

Table 5: Correlations Among Adolescent Alcohol Use Measures

	Onset First	Onset Reg	Usual Freq	Max Freq	Usual QPO	Max QPO
Risk	**.16***	**.28*****	.07	-.05	-.09	**-.16***
Onset First	-	**.55*****	-.03	-.09	-.01	-.08
Onset Reg	**.54*****	-	**-.20****	**-.25****	**-.21****	**-.30*****
Usual Freq	-.05	**-.24****	-	**.59*****	**.41*****	**.39*****
Max Freq	-.10	**-.26****	**.58*****	-	**.48*****	**.55*****
Usual QPO	-.01	**-.25****	**.44*****	**.49*****	-	**.85*****
Max QPO	-.07	**-.31*****	**.42*****	**.55*****	**.84*****	-

Zero-order correlations are presented above the diagonal and partial correlations (controlling for risk and sex) are presented below the diagonal

*** $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$**

Table 6: Correlations Among Social Functioning Measures

	Soc Comp	Soc Prob	Par Stress	Par Res	Peer Stress	Peer Res	Alienation	Soc Close
Risk	**.16***	-.04	.04	.07	**-.25*****	.12	**-.20****	.10
SocComp	-	**-.24*****	.01	.02	-.07	**.27*****	**-.17****	**.24*****
SocProb	**-.24*****	-	.05	.02	**.17****	**-.25*****	.07	-.10
ParStress	.01	**.18****	-	**.99*****	.01	-.07	.04	-.07
ParRes	.04	**-.24*****	**-.55*****	-	-.05	-.03	.01	-.04
PeerStress	-.03	**.17****	**.48*****	**-.37*****	-	**-.32*****	**.20****	**-.19****
PeerRes	**.26*****	**-.24*****	**-.24*****	**.43*****	**-.31*****	-	**-.30*****	**.36*****
Alienation	**-.14***	.06	**.28*****	**-.22*****	**.16***	**-.29*****	-	**-.41*****
SocClose	**.23*****	-.09	**-.16****	**.19****	**-.17****	**.33*****	**-.41*****	-

Zero-order correlations are presented above the diagonal and partial correlations (controlling for risk and sex) are presented below the diagonal; SocComp = Child Behavior Checklist [CBCL] Social Competence; SocProb = CBCL Social Problems; ParStress = Life Stressors and Social Resources Inventory – Youth Version [LISRES-Y] Parent Stressors; ParRes = LISRES-Y Parent Resources; PeerStress = LISRES-Y Friend Stressors; PeerRes = LISRES-Y Friend Resources; Alienation = Multidimensional Personality Questionnaire [MPQ] Alienation; SocClose = MPQ Social Closeness

*** $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$**

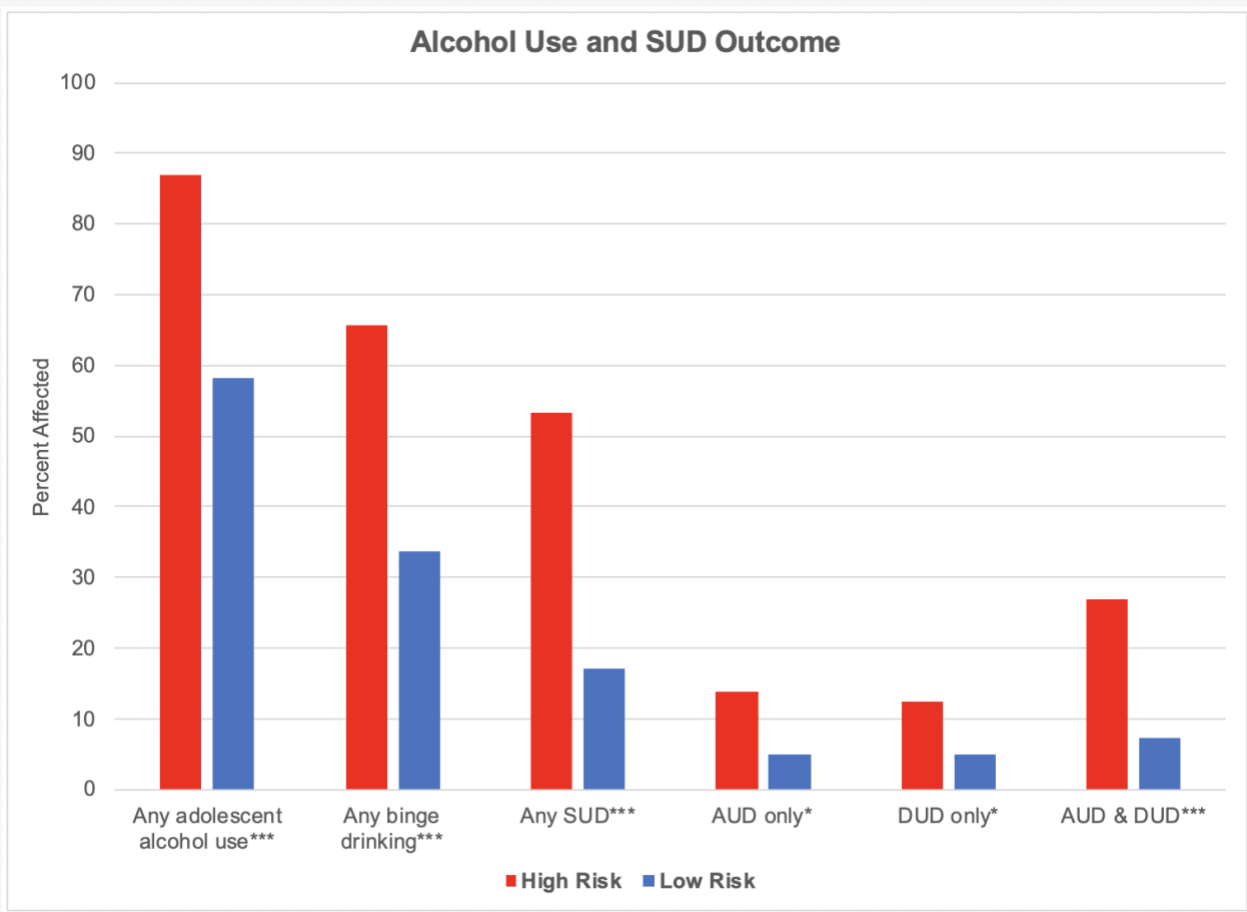
Table 7: Model Fit Statistics for Structural Equation Models

	χ^2	*p*	RMSEA	CFI	TLI	SRMR	WRMR
Model A (Figure 7)	7.12	0.03	0.08	0.96	0.83	0.05	
Model B (Figure 9)	32.07	0.01	0.08	0.90	0.78	0.06	
Model C (Figure 11)	47.92	0.04	0.04	0.95	0.89		0.66
Model C – Re-specified (Figure 12)	15.67	0.21	0.03	0.98	0.96		0.49

CFI = Comparative Fit Index; RMSEA = Root Mean Standard Error of Approximation; SRMR = Standardized Root Mean Square Residual; TLI = Tucker Lewis Index; WRMR = Weighted Root Mean Square Residual

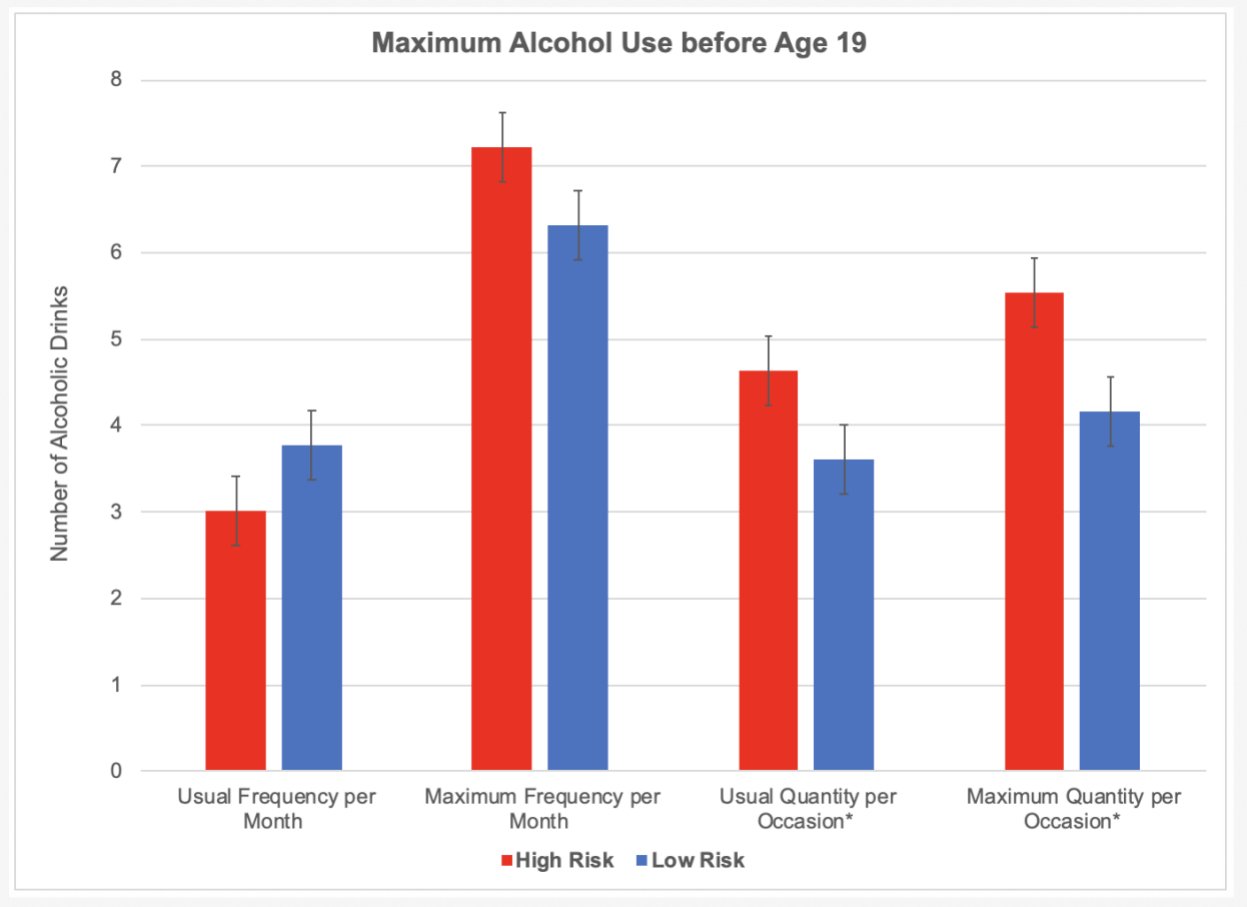
Appendix B Figures

Figure 1: Rates of Adolescent Alcohol Use and SUD for High-Risk and Low-Risk Offspring



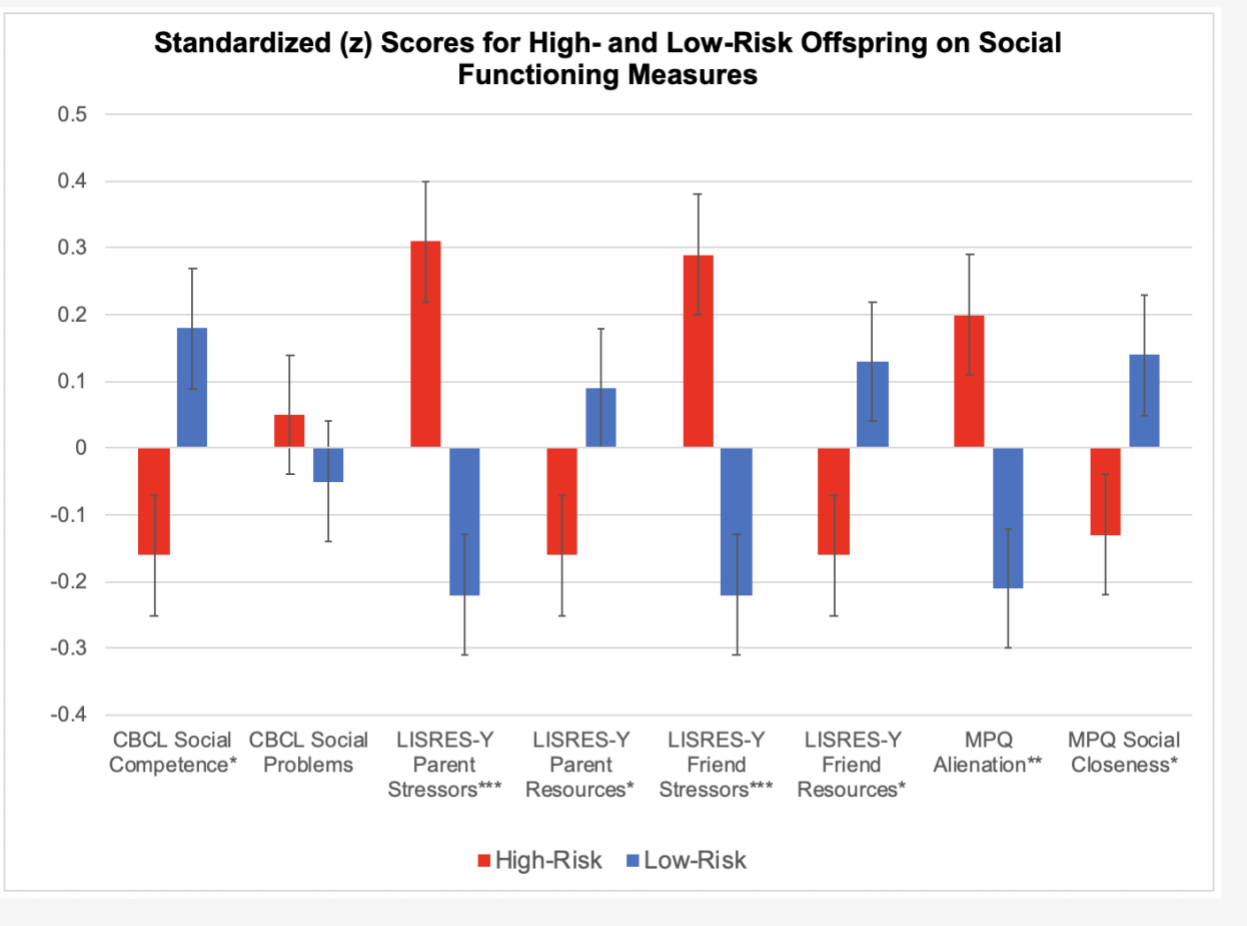
***p* < 0.05, ****p* < 0.01, *****p* < 0.001

Figure 2: Unstandardized Means and Standard Errors for High-Risk and Low-Risk Offspring on Adolescent Alcohol Use Variables



***p* < 0.05, ****p* < 0.01, *****p* < 0.001**

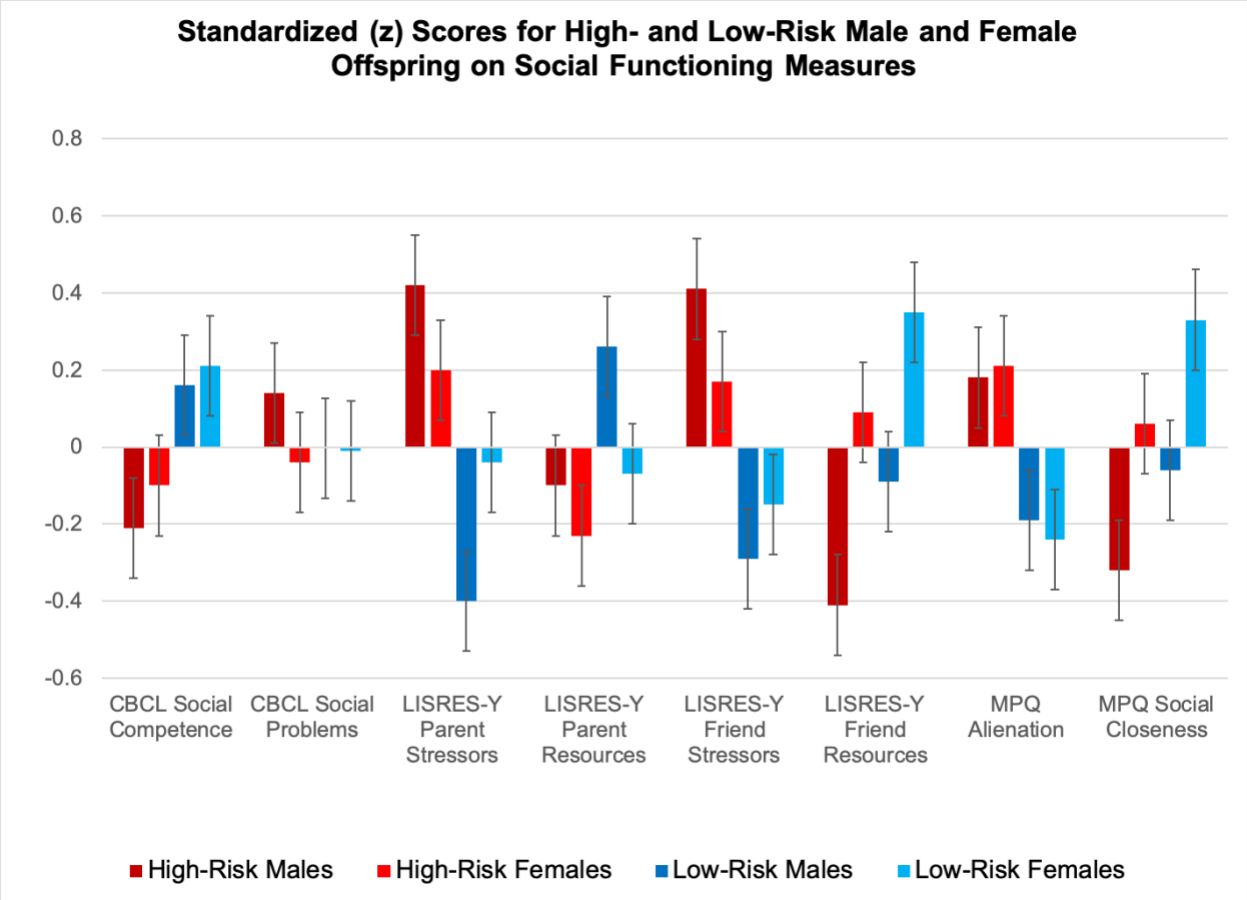
Figure 3: Standardized Means and Standard Errors for High-Risk and Low-Risk Offspring on Social Functioning Variables



CBCL = Child Behavior Checklist; LISRES-Y = Life Stressors and Resources Inventory – Youth Version; MPQ = Multidimensional Personality Questionnaire

***p* < 0.05, ****p* < 0.01, *****p* < 0.001**

Figure 4: Standardized (z) Scores for High-Risk and Low-Risk Male and Female Offspring on Measures of Social Functioning



CBCL = Child Behavior Checklist; LISRES-Y = Life Stressors and Resources Inventory – Youth Version; MPQ = Multidimensional Personality Questionnaire

Figure 5: Kaplan–Meier Survival Analysis of Age at Onset of Substance Use Disorder by Risk Status

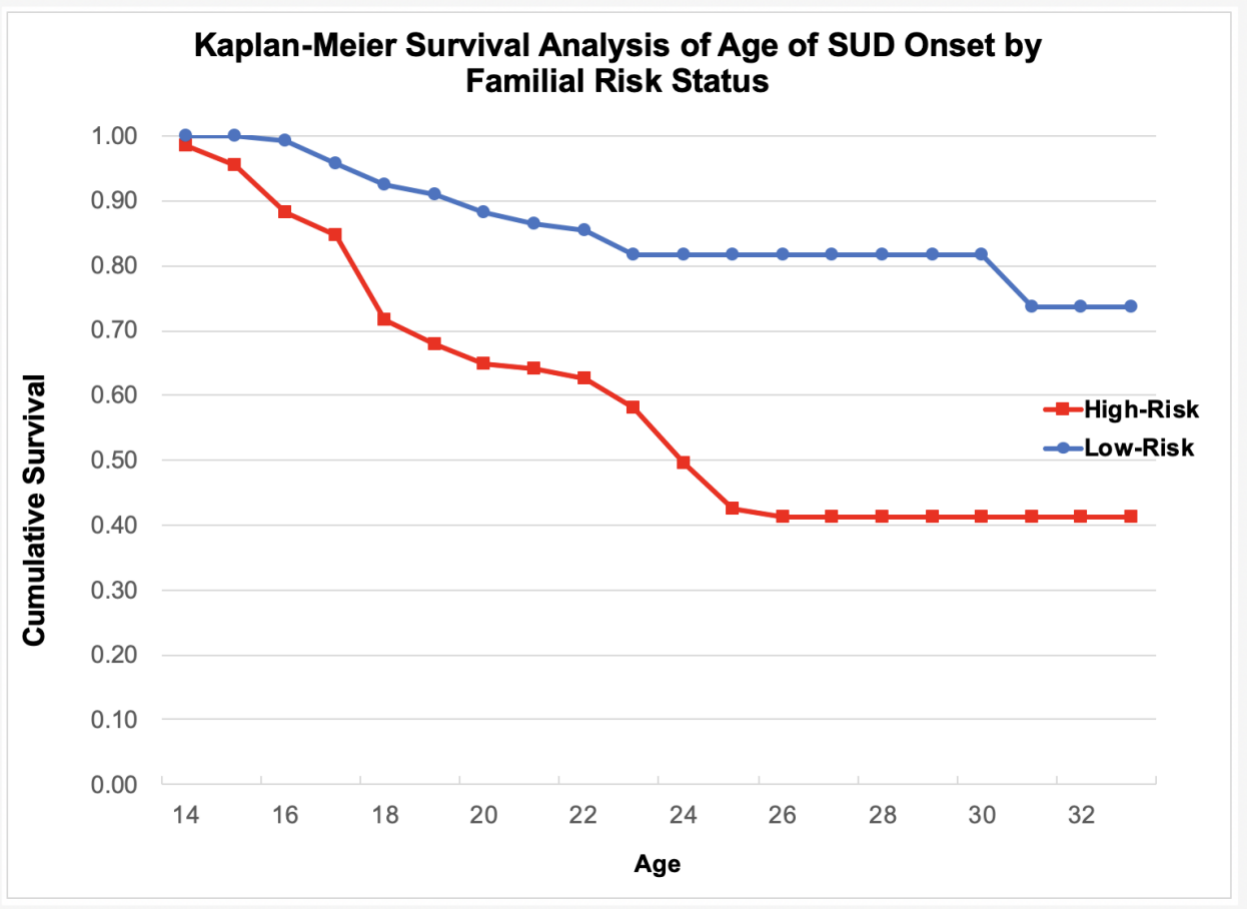
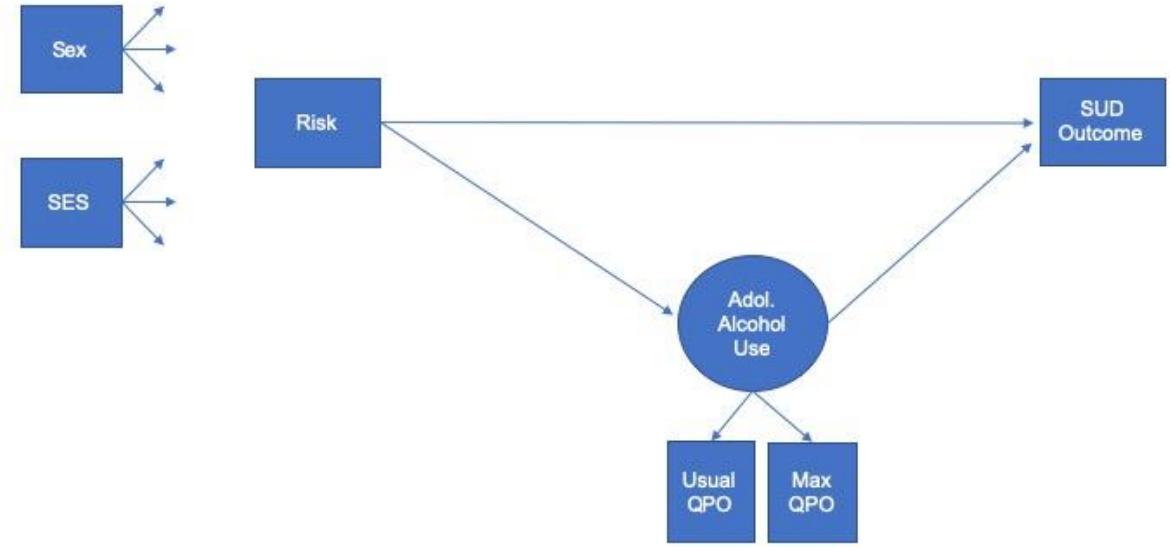
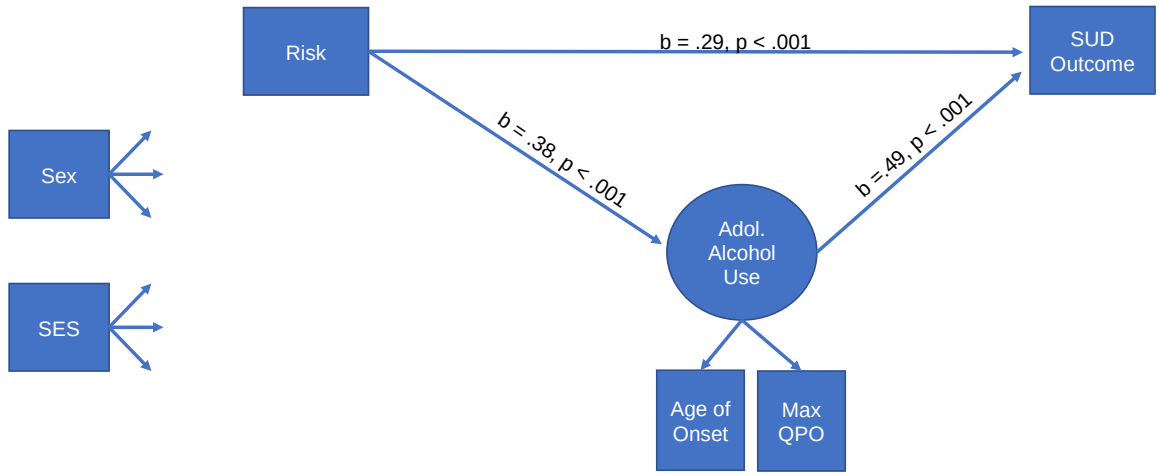


Figure 6: Hypothesized Model for Relationships Among Familial Risk, Adolescent Alcohol Use, and SUD Outcome



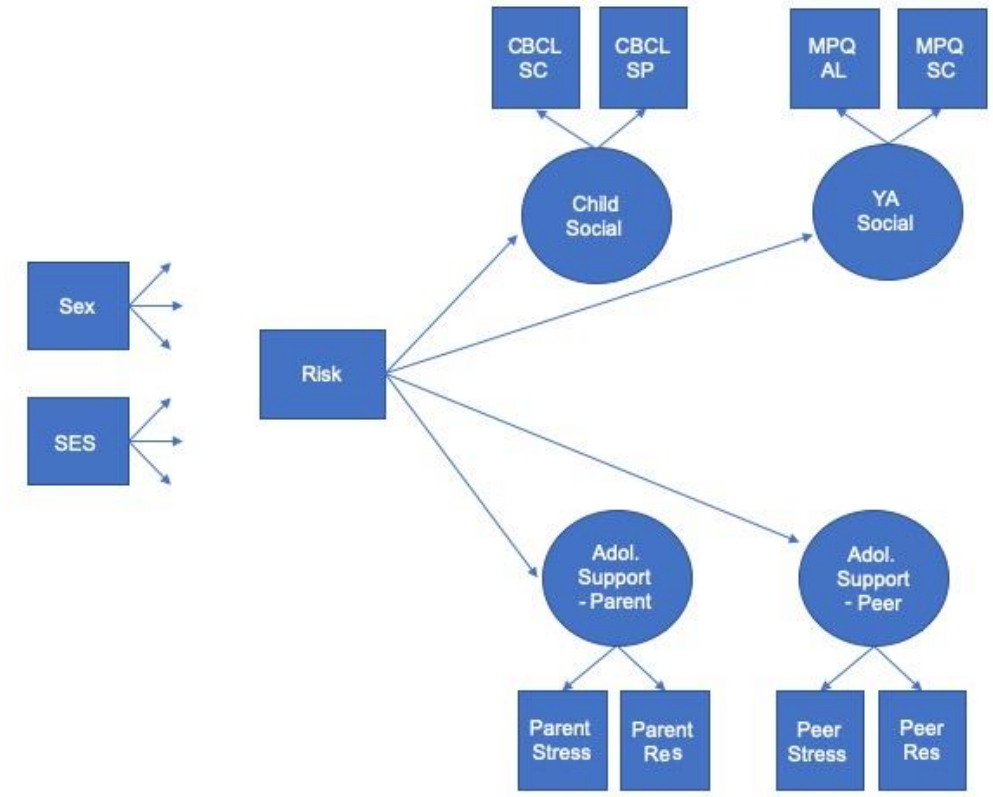
Adol. = Adolescent; Max QPO = Maximum quantity per occasion; Usual QPO = Usual quantity per occasion; SUD = Substance use disorder; SES = socioeconomic status

Figure 7: Final Model for Relationships Among Familial Risk, Adolescent Alcohol Use, and SUD Outcome



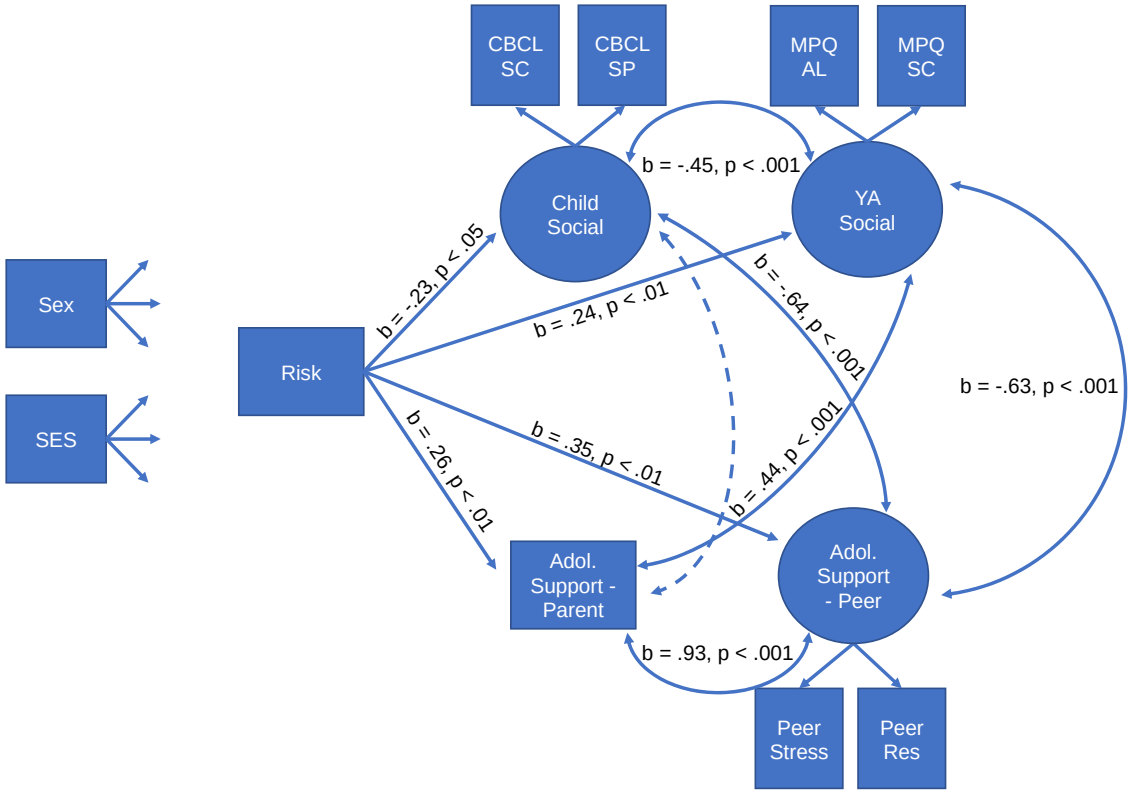
Adol. = Adolescent; Max QPO = Maximum quantity per occasion; SUD = Substance use disorder; SES = socioeconomic status

Figure 8: Hypothesized Model for Relationships Among Familial Risk and Social Functioning Variables



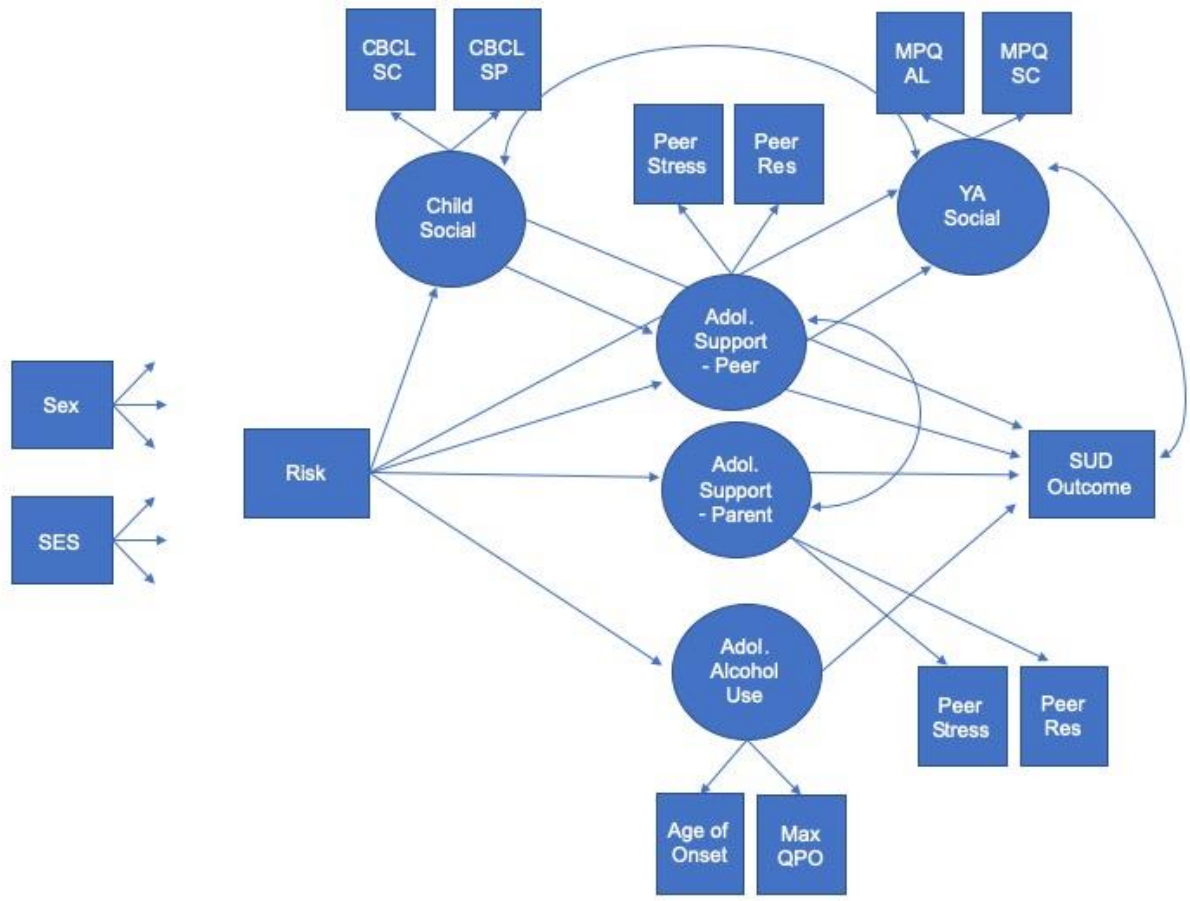
Adol. = Adolescent; CBCL SC = Child Behavior Checklist Social Competence; CBCL SP = Child Behavior Checklist Social Problems; Parent Stress = LISRES-Y Parent Stressor scale; Parent Res = LISRES-Y Parent Resources scale; Peer Stress = LISRES-Y Peer Stressor scale; Peer Res = LISRES-Y Peer Resources scale; MPQ AL = Multidimensional Personality Questionnaire Alienation scale; MPQ SC = Multidimensional Personality Questionnaire Social Closeness scale; SES = socioeconomic status

Figure 9: Final Model for Relationships Among Familial Risk and Social Functioning Variables



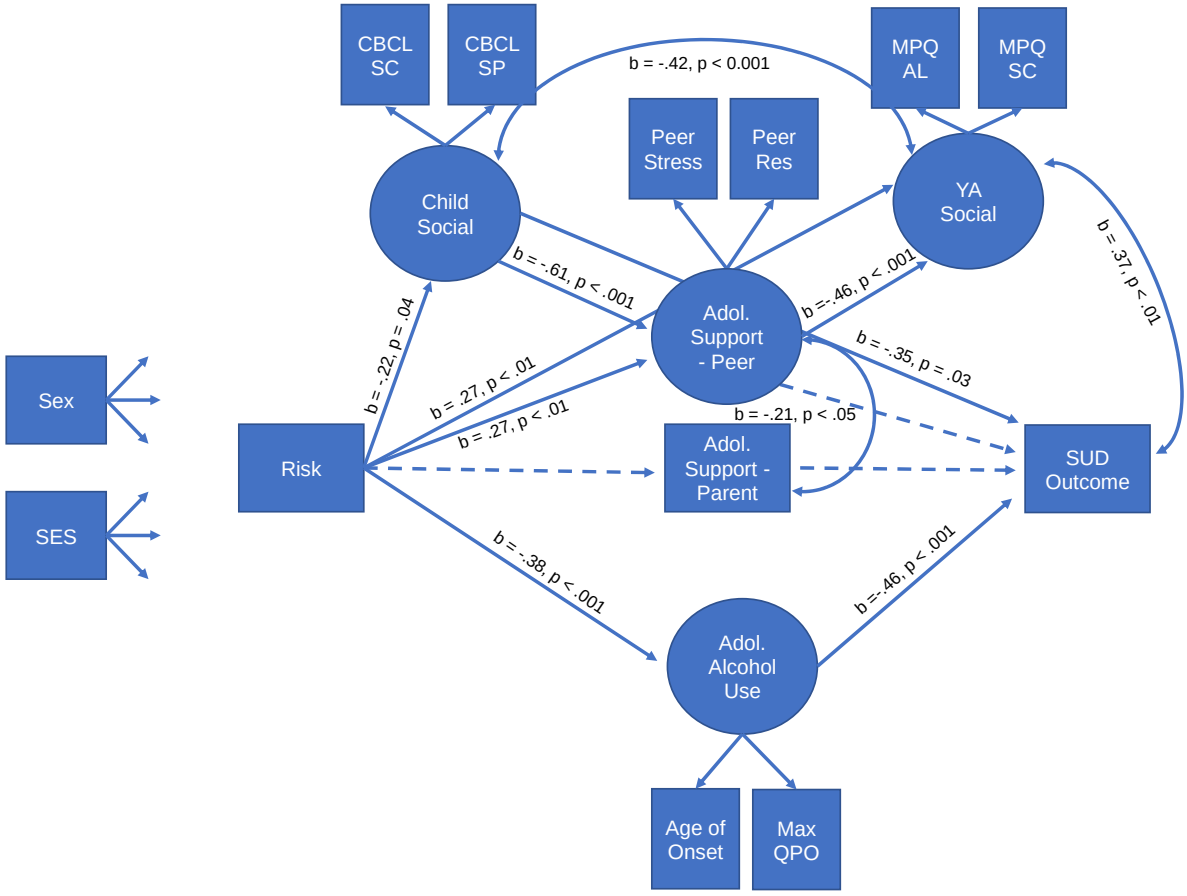
Adol. = Adolescent; CBCL SC = Child Behavior Checklist Social Competence; CBCL SP = Child Behavior Checklist Social Problems; Adol. Support – Parent = LISRES-Y Parent Stressor + Resource scales; Peer Stress = LISRES-Y Peer Stressor scale; Peer Res = LISRES-Y Peer Resources scale; MPQ AL = Multidimensional Personality Questionnaire Alienation scale; MPQ SC = Multidimensional Personality Questionnaire Social Closeness scale; SES = socioeconomic status; YA = young adult

Figure 10: Hypothesized Model for Relationships Among Familial Risk, Social Functioning Variables, Adolescent Alcohol Use, and SUD Outcome



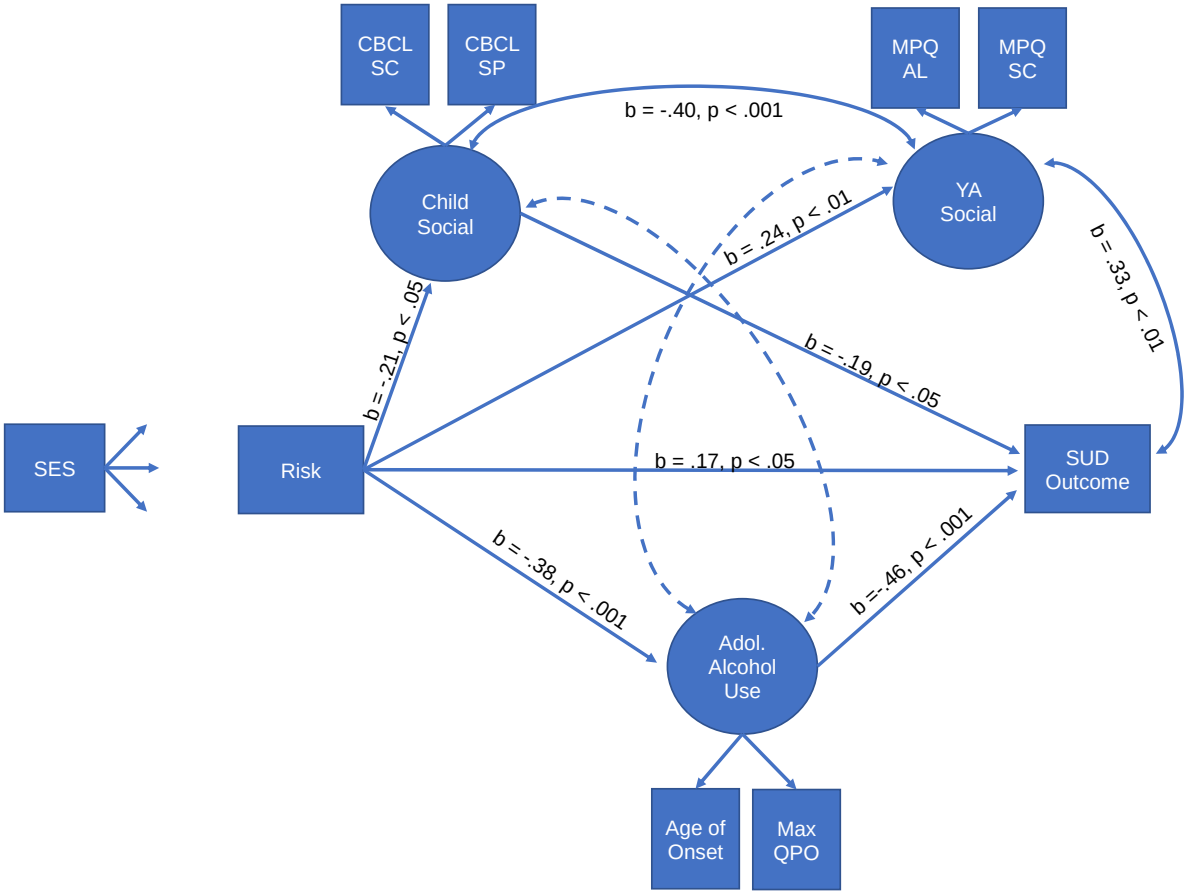
Adol. = Adolescent; CBCL SC = Child Behavior Checklist Social Competence; CBCL SP = Child Behavior Checklist Social Problems; Teen Support – Parent = LISRES-Y Parent Stressor + Resource scales; Peer Stress = LISRES-Y Peer Stressor scale; Peer Res = LISRES-Y Peer Resources scale; MPQ AL = Multidimensional Personality Questionnaire Alienation scale; MPQ SC = Multidimensional Personality Questionnaire Social Closeness scale; SES = socioeconomic status; YA = young adult

Figure 11: Modified Model for Relationships Among Familial Risk, Social Functioning Variables, Adolescent Alcohol Use, and SUD Outcome



Adol. = Adolescent; CBCL SC = Child Behavior Checklist Social Competence; CBCL SP = Child Behavior Checklist Social Problems; Teen Support – Parent = LISRES-Y Parent Stressor + Resource scales; Peer Stress = LISRES-Y Peer Stressor scale; Peer Res = LISRES-Y Peer Resources scale; MPQ AL = Multidimensional Personality Questionnaire Alienation scale; MPQ SC = Multidimensional Personality Questionnaire Social Closeness scale; SES = socioeconomic status; YA = young adult

Figure 12: Trimmed Model for Relationships Among Familial Risk, Social Functioning Variables, Adolescent Alcohol Use, and SUD Outcome



Adol. = Adolescent; CBCL SC = Child Behavior Checklist Social Competence; CBCL SP = Child Behavior Checklist Social Problems; MPQ AL = Multidimensional Personality Questionnaire Alienation scale; MPQ SC = Multidimensional Personality Questionnaire Social Closeness scale; SES = socioeconomic status; YA = young adult

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