Parent and Peer Influences on Emerging Adult Substance Use Disorder: A Genetically

Informed Study

by

Kaitlin Bountress

A Dissertation Presented in Partial Fulfillment of
The Requirements for the Degree
Doctor of Philosophy

Approved May 2014 by the
Graduate Supervisory Committee:

Laurie Chassin, Chair
Keith Crnic
Kathryn Lemery-Chalfant
David MacKinnon

ARIZONA STATE UNIVERSITY

August 2015

ABSTRACT

The present study utilized longitudinal data from a high-risk community sample (n=254, 52.8% female, 47.2% children of alcoholics, 74% non-Hispanic Caucasian) to test questions concerning the effects of genetic risk, parental knowledge, and peer substance use on emerging adult substance use disorders (SUDs). Specifically, this study examined whether parental knowledge and peer substance use mediated the effects of parent alcohol use disorder (AUD) and genetic risk for behavioral undercontrol on SUD. The current study also examined whether genetic risk moderated effects of parental knowledge and peer substance use on risk for SUD. Finally, this study examined these questions over and above a genetic "control" which explained a large proportion of variance in the outcome, thereby providing a stricter test of environmental influences.

Analyses were performed in a path analysis framework. To test these research questions, the current study employed two polygenic risk scores. The first, a *theory-based* score, was formed using single-nucleotide polymorphisms (SNPs) from receptor systems implicated in the amplification of positive effects in the presence of new/exciting stimuli and/or pleasure derived from using substances. The second, an *empirically-based* score, was formed using a data-driven approach that explained a large amount of variance in SUDs. Together, these scores allowed the present study to test explanations for the relations among parent AUD, parental knowledge, peer substance use, and SUDs.

Results of the current study found that having parents with less knowledge or an AUD conferred greater risk for SUDs, but only for those at higher genetic risk for behavioral undercontrol. The current study replicated research findings suggesting that peer substance use mediated the effect of parental AUD on SUD. However, it adds to

i

this literature by suggesting that some mechanism other than increased behavioral

undercontrol explains relations among parental AUD, peer substance use, and emerging

adult SUD. Taken together, these findings indicate that children of parents with AUDs

comprise a particularly risky group, although likelihood of SUD within this group is not

uniform. These findings also suggest that some of the most important environmental risk

factors for SUDs exert effects that vary across level of genetic propensity.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Parent and Peer Influences on Emerging Adult Substance Use Disorder: A Genetically
Informed Study

Because substance disorders contribute to multiple negative outcomes including

maladaptive family relationships, careers damaged, and shortened lives (World Health

Organization, 2004; UN Office on Drugs and Crime, 2008), researchers have focused on

identifying factors that may increase risk for substance use problems. Among Sher's

(1991) proposed and widely studied models that explain the intergenerational

transmission of substance use disorders (SUDs) is the deviance-proneness pathway. In

this pathway, children of parents with alcohol use disorders (AUDs) tend to show greater

behavioral undercontrol (sensation seeking, impulsivity, and conduct problems). These

children receive poor parenting, and the combination of their undercontrol and poor

parenting places them at risk for affiliation with deviant peers and substance use

problems.

As Sher suggested, implicit in this model are both "genetic and environmental

influences." However, the extent to which some of these paths reflect genetic versus

environmental influences cannot be assumed based on "how ostensibly 'environmental' a

construct appears to be" (1991; p. 134). As Sher notes, it is possible that the relations

among parenting, peer influences, and SUDs may be influenced by genetic factors.

Despite this observation, the relations among parental AUD, parenting, peer substance

use, and offspring substance use problems have historically been treated as if they are

environmental in nature. The current study extends previous literature by examining

whether these effects that are presumed to be environmental (i.e., parental monitoring and

the substance-using peer group) predict substance use problems over and above measures

of genetic risk and gene-environment covariation. The present study also tests whether

1

genetic risk moderates the relations among parental monitoring, peer substance use, and problematic substance use in emerging adulthood.

One parenting factor that has been linked to offspring substance use outcomes is parental monitoring. Until recently, researchers assumed that information that parents acquired about their children's lives resulted from parents actively seeking out this knowledge. As a result, the term "parental monitoring" was used to describe how much parents knew about their children's activities and friends. However, Stattin and Kerr (2000) discovered that most of the variance in parental monitoring was explained by child self-disclosure, i.e., the extent to which the child chose to share this information with the caregiver. Less variance was explained by parental solicitation and control (i.e. parents actively questioning and limiting the adolescent's opportunity to make decisions without telling the caregiver). Additionally, it is youth self-disclosure and to a lesser extent parental solicitation of information that predicts changes in adolescent delinquency over time (Kerr, Stattin, & Burke, 2010). These findings suggest that "parental knowledge" is a more accurate term to describe what had previously been labeled as "parental monitoring." This distinction is important because the concept of "parental monitoring" may underestimate the importance of child effects in comparison to "parental knowledge." Accordingly, this document refers to "parental knowledge," both in describing the current study and summarizing past literature.

Research examining links in the deviance proneness pathway suggests significant relations among parent AUD, parental knowledge, peer substance use and offspring substance problems. Specifically, parent SUD disrupts the care giver's ability to monitor the child's behavior and undermines child the relationship (Latendresse, Rose, Viken,

Pulkkinen, Kaprio, & Dick, 2008), resulting in those parents having less knowledge about their children. In turn, less parental knowledge has been found to be related to offspring substance use (Lac & Crano, 2009; Martins, Storr, Alexandew, & Chilicoat, 2008; White et al., 2006). This relation may exist because parents who know more about their children's lives are in a better position to limit offspring substance use (Chilcoat & Anthony, 1996; Dishion, Capaldi, Spracklen, & Li, 1995). Although parental knowledge may be directly related to offspring substance problems, research is less clear on whether both maternal and paternal knowledge affect offspring substance use (Bogenschneider, Wu, Raffaelli, & Tsay, 1998; Chassin, Pillow, Curran, Molina, & Barrera, 1993; Webb, Bray, Getz, & Adams, 2002). The present study tests whether parental knowledge is a mediator of the effect of parent AUD on offspring substance use diagnosis, and whether the effect of mother, father and child knowledge all significantly influence risk for SUD.

In addition to parental AUD predicting parental knowledge, it may also be that having a parent with an alcohol use disorder influences the characteristics of the adolescent's peer group, which in turn affects risk for SUDs. Parents with AUDs may be more likely to model substance-using habits, be less likely to limit offspring substance use, and be less likely to have knowledge about the friends with whom their children associate (Abar & Turrisi, 2008). As a result, they may be more likely to have children who affiliate with a substance-using peer group (Dishion & Owen, 2002; Read, Wood, Kahler, Maddock, & Palfai, 2003). Membership in a substance-using peer group may increase risk for SUDs, as these friends provide opportunities to drink and/or use drugs (White et al., 2006) and influence substance use norms (Dishion & Owen, 2002). The present study examines

3

whether peer substance use is a mediator of the effect of parent AUD on offspring

substance use diagnosis.

Explanations for the Relations among Parental Knowledge, Peer Substance Use, and SUDs

Although research has found support for direct effects of parental knowledge and

peer substance use on substance use outcomes, there are multiple plausible explanations

for these findings, given the research implicating genetic risk in substance use outcomes.

First, parent and peer effects may be spurious because they are "caused" by adolescent's

genotypes, which are the "true" influences on SUD. That is, parental knowledge and

substance-using peers may exert no unique effect on young adult substance use disorders

over and above measures of genetic risk. Second, correlated adolescent genetic risk may

lessen disclosure, producing decreased parental knowledge (i.e. evocative gene-

environment correlation). Additionally, greater genetic risk for behavioral undercontrol

and substance use outcomes may increase risk for adolescent association with substance-

using peers (i.e. active gene-environment correlation), who promote excessive drinking

and drug use. Thus, parental knowledge and peer influence might mediate the effect of

adolescent genetic risk on substance use disorders. Finally, the effects of parental

knowledge and peer substance use on SUDs may be particularly strong for those at

certain levels of genetic risk (i.e. gene-environment interaction).

In order to test these potential explanations, the current study employs two

different polygenic risk scores. The first, a *theory-based* score based on prior literature,

was formed with the goal of being able to meaningfully interpret associations between

genetic risk and study variables, as well as interpret interactions between genetic risk and

peer and parenting influences. The second, an *empirically-based* score was formed using

a data-driven approach in order to explain a relatively large amount of variance in SUDs. This score was used to test whether parenting and peer effects exert unique effects over and above a genetic control variable, thus providing a stricter test of environmental influences. Together, these two gene scores allow the present study to test the plausible explanations for the relations among parental knowledge, peer substance use, and SUDs.

The Link between Genetic Risk and Study Variables

       The Theory-based Genetic Risk Score

       Genetic Influences and Risk for Behavioral Undercontrol and SUDs. In creating the theory-based gene score, single-nucleotide polymorphisms (SNPs) were chosen from theoretically plausible receptor systems that have been found to be related to behavioral undercontrol and/or substance use/abuse in at least two prior studies. This theory-based genetic risk score utilizes a relatively small number of SNPs that are hand-chosen based on prior literature. This score included SNPs from the dopamine (e.g. DRD2), opioid (e.g. OPRM1, PDYN), GABA (gamma-Aminobutyric acid, e.g. GABRA2), drug metabolism (e.g. ADH4, ADH1B), and cannabinoid (e.g. CNR1) receptor systems. Genes within these systems have been linked to the amplification of positive effects in the presence of new and exciting stimuli and/or pleasure derived from using substances (Koepp et al., 1998; Robinson & Berridge, 2003; Brady & Sinha, 2005).

       When individuals encounter potentially reinforcing stimuli, genes from the Dopamine system increase the dopamine released in the ventral (contains the nucleus accumbens, involved in reward) and dorsal striatum (involved in planning and executive function; Koepp et al., 1998). Genes from the Dopamine system also increase dopamine released in the prefrontal cortex (which regulates behavior related to future rewards; Thut

et al., 1997). Increased dopamine in these areas may result in experiencing more positive effects of exciting stimuli and an increased pursuit of additional rewarding stimuli. Similarly, the role of Dopamine receptors in substance dependence may stem from an involvement in the mesocortolimbic reward pathway, and specifically the nucleus accumbens (Koob, 1992). Research suggests that substance use increases dopamine in this area, amplifying the rewarding effects of substances (Koob, 1992). Research suggests that the Dopamine system and gene DRD2 generally are implicated in the enhanced rewarding effects of exciting stimuli and substance use. Additionally, prior research finds that the SNPs **Rs1800497, Rs1079597, Rs1799978,** and **Rs12364283** are related to conduct disorder, substance intake, and substance use diagnosis in adolescents and adults (Brody, Chen, & Beach, 2012; Dick et al., 2007; Esposito-Smythers, Spirito, Rizzo, McGeary, & Knopik, 2009; Foley et al., 2004; Hamidovic, Dlugos, Skol, Palmer, & deWit, 2009; Munafo, Matheson, & Flint, 2007; Preuss, Zill, Koller, Bondy, & Soyka, 2007; Yang et al., 2007; Yang et al., 2007).

In addition to research suggesting a link between the Dopamine system and behavioral undercontrol and substance use, research has found that receptors in the Opioid system are related to these constructs as well. Genes in the Opioid system, such as OPRM1 and PDYN affect the mesolimbic system of the brain, primarily responsible for reward. When an individual consumes alcohol or drugs, the level of opiates in the mesolimbic system increases, releasing dopamine into the nucleus accumbens and amplifying the reinforcing effects of these substances (Herz, 1997; Robinson and Berridge, 2003). Lower basal activity in some of these opiates has been found in individuals with a positive family history of substance use disorders, suggesting a state of

under arousal in those who have relatives with substance problems (Gianoulakis, DeWaele, & Thavundayil, 1996). After consuming a high dose of alcohol or drugs, the level of these opiates increases significantly in those with a family history of substance use problems (Gianoulakis, 1996; Gianoulakis, et al., 1996), potentially indicating an enhanced sensitivity to the effects of substances. It therefore appears that Opioid receptors may be related to both an individual's baseline level of arousal in reward-sensitive areas and an individual's experience of high levels of pleasure after consuming alcohol or drugs. Research has specifically linked the SNPs **Rs1799971, Rs548646** (in high Linkage Disequilibrium/LD[1] with Rs660756), and **Rs1997794** with positive response to substances and substance use disorders in adolescents and adults (Ehlers, Lind, & Wilhelmsen, 2008; Miranda et al., 2010; Ray, 2011; Taqi et al., 2011; Xuei et al., 2007; Zhang et al., 2006).

Studies have also found significant relations between GABA genes and these outcomes. One of the three types of GABA receptors, GABA(A), and specifically, the variant GABRA2, has been found to affect the mesolimbic system via the nucleus accumbens and ventral tegmental area (VTA; Fallon et al., 1978). When an individual is in the presence of exciting stimuli, GABA(A) receptors increase dopamine in the prefrontal cortex, which is important in regulating behavior related to future rewards (Moghaddam, 2002; Brady & Sinha, 2005). Therefore, these genes in the GABA system may be related to the tendency to seek out rewarding experiences in the future. Also, in the short-term, substance use alters the influence of dopamine in the processing of

---

[1] Linkage Disequilibrium means that two SNPs are non-randomly associated with each other and are more likely to be inherited together than would have been expected by chance alone. Because research has found links between Rs7016275 (which was unavailable in this dataset) and response to substances, the SNP Rs35991105 was included as part of this theoretical risk score.

reinforcing stimuli. Specifically, GABA receptors prolong the rewarding effects of dopamine in the nucleus accumbens and VTA, which may lead to increased motivation to use substances. However, in the long-term, chronic substance use is associated with a decrease in the sensitivity of GABA(A) receptor responses in the nucleus accumbens (Szmigielski, Szmigielski, & Wejman, 1992). These findings suggest that some individuals may experience more reward in using substances initially, and then once use escalates into chronic problem use, individuals at particular genetic risk must ingest more alcohol or drugs in order receive the same benefit as others. More specifically, the **SNP Rs279858** (in high LD with Rs279871) is related to increased rewarding effects of substances, higher drug and alcohol tolerance, and substance use disorders in adolescents (Brody et al 2013; Enoch, Hodgkinson, Yuan, Albaugh, Virkkunen, & Goldman, 2008).

Although most studies have been conducted with rats, recent research has additionally identified the cannabinoid system as being involved in the meso-cortico-limbic reward pathway, and the development of substance use disorders (Tanda, Munzar, & Goldberg, 2000). More specifically, following chronic cannabinoid administration and then discontinuation, some experience tolerance and severe withdrawal symptoms. These symptoms are a result of the inhibition of Dopamine in the ventral tegmental, medial forebrain bundle, and nucleus accumbens areas, which are implicated in reward (Costa, Giagnoni, & Colleoni, 2000; Rodriguez, Carrera, Navarro, Koob, & Weiss, 1997). These findings may explain why habitual users must ingest a larger amount of the drug to get the same previous effect, and why many may relapse when/if they attempt to discontinue use (van der Stelt & Marzo, 2003). More specifically, the SNP **Rs1049353** of a CB1 cannabinoid receptor gene CRN1 has been found to be related to withdrawal after

discontinuation of substances, and substance use diagnosis in adolescents and young adults (Schmidt et al., 2002; Zhang et al., 2004; Hartman et al., 2009).

Research has additionally found that genes that encode the major enzymes in drug metabolism, such as alcohol dehydrogenase (ADH), and specifically the genes ADH1B and ADH4, are implicated in alcohol use problems. After alcohol is ingested, it is metabolized in two steps: it is oxidized by alcohol dehydrogenase (ADH) to acetaldehyde, which is then oxidized to acetate by acetaldehyde dehydrogenase (ALDH). Alleles of genes in the alcohol metabolism system are related to increases in level of acetaldehyde in the blood, causing adverse responses such as dizziness, accelerated heart rate, sweating and nausea (the "flushing response"; Mulligan et al., 2003; Ducci & Goldman, 2008). Individuals who are more likely to experience these unwanted effects of alcohol may in turn be protected against alcohol use problems via decline in use. Research has specifically linked **Rs1229984** and **Rs3762894** to the physical effects of substance use (e.g. flushing), substance use, and substance use problems in adults (MacGregor, Lind, Bucholz, Hansell, Madden, Richter et al., 2008; Liu, Zhou, Hodgkinson, Yuan, Shen, Mulligan et al., 2011).

Although research implicates genetic influences in risk for behavioral undercontrol and response to substances, these effects may not be uniform across developmental period. Specifically, genes assume increasing importance with age when examining adolescents and adults (Kendler et al., 2012). Specifically, genes account for one-half of the variation during emerging adulthood, with this effect being much smaller in adolescence (Dick et al., 2007b; Rose, Dick, Viken & Kaprio, 2001). This trend may occur because developmentally-limited deviance and drinking during adolescence masks

genetic risk. These findings may also be explained by the fact that, as individuals age, they are able to exercise more freedom to make decisions consistent with their genetic risk, compared to earlier developmental periods when adults in their lives might make some of these decisions for them. Because of this trend in the literature, and in order to provide a stricter test of environmental influences, the current study examines the effect of genetic risk on SUDs in emerging adulthood.

Affiliation with Substance-using Peers: An Active Gene-environment Effect. In addition to an individual's genetic make-up being related to his/her risk of developing a SUD, genetic make-up may also be related to his/her environment. Specifically, Plomin, DeFries, & Loehlin (1977) described active gene-environment influences, in which individuals seek out environments they find "compatible and stimulating" (p.427). In the current study, this means that individuals who are more sensitive to the reinforcing effects of alcohol may be more likely to select friends who similarly enjoy drinking alcohol and using drugs (Scarr & McCartney, 1983; Dishion & Owen, 2002; Dick et al., 2007a). Although a majority of twin studies examining the influence of genetic risk on association with substance using peers have found significant genetic influences, some have not (Cleveland, Wiebe, & Rowe, 2005; Beaver et al., 2009; Fowler et al., 2007; Gillespie, Neale, Jacobson, & Kendler, 2009; Harden, Hill, Turkheimer, & Emery, 2008; Iervolino, Pike, Manke, Reiss, Hetherington, & Plomin, 2002; Walden, McGue, Iacano, Burt, & Elkins, 2004).

One potential explanation for this inconsistency is that the studies finding a significant influence of genetic effects on peer substance use/delinquency used slightly older samples—with more emerging adults and fewer early adolescents. Researchers

10

suggest that genetic influences on choice of peers would be expected to increase as individuals age and presumably, have more control over the people with whom they socialize (Brendgen, 2012; Kendler, Jacobson, Gardner, Gillespie, Aggen, & Prescott, 2007). In addition to late adolescence/emerging adulthood being an ideal age at which to examine the influence of genetic risk on peer substance use, this developmental period is also ideal for testing the effect of peer substance use on later emerging adult SUD. Specifically, it is during adolescence, and even more so in late adolescence/emerging adulthood, that individuals spend less time with family members and more time outside of the home (Larson, Richards, Moneta, Holmbeck, & Duckett, 1996; Crosnoe & Johnson, 2011). Some have even found that peer influence effects are strongest in late adolescence (Steinberg & Monahan, 2007; Monahan, Steinberg, & Cauffman, 2009). By choosing to examine peer substance use between the ages of 15 to 17, the current study attempts to capture stronger effects of genetic risk on peer substance use, and peer substance use on later emerging/young adult SUDs.

The literature examining specific genetic variants and associations with deviant peers is limited—and even more limited when only examining the 11 SNPs included in the theory-based gene score. However, some studies have found that adolescents at genetic risk to drink as measured by the DRD2 SNP Rs1125394, in high LD with Rs1079597, have friends with the same level of genetic risk (Fowler et al., 2011; Boardman, Dominique, & Fletcher, 2012). Another study found that children of parents with AUDs were more likely to have a particular genetic make-up on OPRM1 rs1799971, which in turn predicted peer substance use (Chassin et al., 2013). This research suggests that individuals with genotypes that make them susceptible to SUDs may be directly

influenced to use substances because of their own genetic make-up, but may also be indirectly influenced to use substances because they have friends with the same genotype (Fowler et al., 2011; Boardman et al., 2012). The literature examining whether peer substance use exerts a unique effect on individual SUD over and above genetic risk is small, and limited to twin studies. Some of these studies have found that adding genetic risk attenuated this effect, but peer use did predict substance use from adolescence to young adulthood over and above genetic risk (Cruz, Emery, & Turkheimer, 2012; Harden, Hill, Turkheimer, & Emery, 2008). This finding suggests that both genes and peer use exert unique, significant effects on substance use outcomes. Therefore, the current study extends previous literature by testing the hypothesis that genetic risk—in the form of a broad genetic risk score—and peer substance use exert unique significant influences on SUD.

The Effect of Parental Knowledge: An Evocative Gene-environment Effect. In contrast to active gene-environment correlation, the effect of child genetic risk on parental knowledge may reflect an evocative gene-environment effect, such that individuals with particular genotypes evoke or pull out particular responses from their environments (Plomin, DeFries, & Loehlin, 1977). For example, adolescents at genetic risk for substance use may be more likely to engage in behaviors of which parents disapprove and may be less likely to disclose their involvement in these activities (Tilton-Weaver & Marshall, 2008). This may prompt caregivers to then withdraw and give the youths more autonomy (Kerr, Statin, & Pakalniskiene, 2008; Dishion, Nelson, & Bullock, 2004; Kerr & Stattin, 2003). Past research has found support for the effect of genes on parental knowledge, with genetic factors playing a small but significant role

(Plomin, Reiss, Hetherington, & Howe, 1994; Reiss, Neiderhiser, Hetherington, & Plomin, 2000; Cleveland & Crosnoe, 2004). Others have found that the variance in parental (mother) knowledge accounted for by genetic factors was highly variable, with much more variance explained when using mother report than adolescent report (Neiderhiser et al., 2004). No studies to date have examined the effect of parental knowledge on emerging/young adult substance use outcomes over and above a polygenic risk score.

In terms of the age at which to examine parental knowledge, research has found that opportunities for parent-child interactions are more limited as adolescents age (Crosnoe & Johnson, 2011). Therefore parent-child relationships in early adolescence, before offspring begin spending more time away from the home, may be predictive of later problems. Indeed, research has found that the effects of parental knowledge on offspring delinquency and problem behavior in early/mid adolescence last into late adolescence/emerging adulthood (Li, Stanton, & Feigelman, 2000). By choosing to examine parental knowledge when adolescents are 11 to 14 years old, the current study predicted a significant effect of parental knowledge on offspring and peer substance use, and hypothesizing that adolescent genetic risk and parental knowledge exerts unique significant influences on emerging adult SUD.

Interaction Effects between the Theory-based Gene Score and Parenting and Peer Influences. There are relatively few studies examining the main effects of measured genes on parental knowledge and peer substance use or the unique effects of parenting and peers on substance use outcomes over and above measured gene scores. However, there is a somewhat larger literature exploring significant interactions between

measured genes and parental knowledge and peer substance use to predict substance use outcomes.

Many studies examining gene-environment interactions have found that genetic effects are stronger at higher levels of environmental risk, and environmental effects are stronger at higher levels of genetic risk, over and above gene-environment covariation. It may be that less stressful and more nurturing environments suppress genetic risk, whereas more stressful environments amplify it (Hicks, South, DiRago, Iacano, & McGue, 2009). These effects hold for several risk factors for adolescent externalizing behavior and adolescent and adult substance use outcomes in twin studies (Agrawal et al., 2010; Dick et al., 2007b; Guo, Elder, Cai, & Hamilton, 2009; Harden et al., 2008; Kendler, Gardner, & Dick, 2011), as well as in studies using measured genes. Specifically, these interaction effects have been found for **DRD2** (Rs1800497; Pieters et al., 2012; van der Zwaluw et al., 2010), **GABRA2** (Rs279858; Dick et al., 2009; Dick et al., 2007b), and **OPRM1** (Rs1799971; Miranda et al., 2012; Pieters et al., 2012). To date, there is no research examining gene-environment interactions to predict substance use outcomes for **OPRK1, PDYN, ADH1B, ADH4, and CNR1**.

In the current study, some individuals—because of their genetic risk—might have less of a predisposition towards pursuing exciting experiences, and thus, may not seek out delinquent activities. Therefore, parents' knowledge of their activities may be less predictive of their risk for SUDs, compared to those who are more likely to seek out exciting and potentially dangerous situations. That is, parental knowledge and peer substance use may exert larger effects on offspring SUDs for those at genetic risk.

Although most of the work on gene-environment interactions in this area find this "fan-shaped" type of interaction in which there are stronger associations between genetic risk and outcome under adverse environmental conditions, compared to under benign conditions (Dick et al., 2011), there have been some which have not. For example, one group using twin data to examine genes, peers, and substance use (Button, Stallings, Rhee, Corley, Boardman, & Hewitt, 2009) found that genetic influences were the strongest predictors of substance dependence at high and low levels of peer delinquency. There are also some studies finding interactions in which the individuals who are most responsive to the risks associated with problematic environments are also the individuals who are more likely to benefit from nurturing environments (called "differential susceptibility;" Belsky, 2005; Belsky, Bakermans-Kranenburg & van Ijzendoorn, 2007; Belsky & Pluess, 2009; Boyce & Ellis, 2005; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011). However, the studies that have found differential susceptibility effects have used temperament—not genes—as the moderator variable. The proposed study is the first to test whether, after taking into account gene-environment covariation, the effects of parental knowledge and peer substance use on emerging/young adult substance problems are stronger at higher levels of a broad genetic risk score.

The Empirically-based Genetic Risk Score and Risk for SUDs

Although a theory-based polygenic risk score is needed to interpret gene-environment correlation and gene-environment interaction, such a theory-based score may explain relatively small amounts of variance, thus resulting in an over-estimation of environmental effects. This limitation can be addressed by the inclusion of a second polygenic risk score. The goal of this second risk score is to explain a relatively large

portion of the variance in the outcome, emerging adult substance use disorder. Specifically, this score includes SNPs that are related to emerging adult SUDs, excluding SNPs that were included in the theory-driven gene score or any that were in high LD with those SNPs. However, because this gene score is empirically-derived and its goal is to simply explain variance, the present study makes no interpretations about why it may be significantly associated with study variables.

As stated previously, this empirically-derived gene score is needed to rule out plausible alternative hypotheses. Specifically, there is literature to suggest that genetic influences affect phenotypes which evoke less parental knowledge and increase the likelihood of associating with substance-using peers. As stated previously, parental knowledge and peer substance have been found in the literature to predict later substance use problems. Therefore, the genetic risk that decreases the likelihood of child disclosure and increases risk for associating with deviant peers may be the same genetic risk that elevates the chance of developing a SUD in emerging adulthood. In this way, parental knowledge and peer substance use may simply be markers of genetic risk, rather than mediators of the effect of genes on SUDs. In order to test these questions, the current study created a variable that was meant to control for genetic risk for behavioral undercontrol and SUDs. In creating this empirically-derived gene score and partialling out this genetic risk in parental knowledge, peer substance use, and SUDs, the current study created a stricter test of environmental influences, over and above this control variable.

Present Study

The present study expands on previous literature in several ways. Although the research on candidate genes has been useful in implicating particular receptor systems and genetic variants in substance use problems, many studies using measured genes tend to account for little variance in substance use outcomes. This is problematic when one considers that approximately fifty percent of the variance in substance use problems in emerging/young adulthood is explained by genetic factors. Therefore, these studies may over-estimate the contribution of environmental influences on substance use or substance use problems, after controlling for this genetic risk. The current study addresses this limitation by creating two genetic risk scores, one of which is based on prior literature, and another which is empirically-derived, and is expected to explain a great deal more variance in substance use disorders, compared to the theory-driven score. By examining the relations among parental knowledge when adolescents are age 11 to 14, peer substance use at age 15-17, and emerging/young adult substance use disorder (age 18-25)—developmental periods when these influences are thought to be relevant—the current study prospectively examines their unique effects. In so doing, the current study tests whether these "environmental" effects (i.e. parental knowledge and peer substance use) exert significant influence over and above one, both, or neither of these genetic risk scores.

After creating these two gene scores, the current study tests three main questions. First, this study examines whether parental AUD and the two gene scores predict emerging adult SUD. Second, the present study examines whether parental knowledge and peer substance use mediate the effects of parental AUD and the theory-driven gene

score on emerging adult SUD. Finally, the current study examines whether the theory-driven genetic risk score moderates the relations between parental knowledge, peer substance use, and emerging adult substance use disorder.

Based on previous work outlined above, it is hypothesized that parental alcohol use disorder, as well as both the theory- and empirically-based gene scores confer risk for SUDs. It is also hypothesized that parental knowledge and peer substance use will remain significant predictors of adult substance use disorder even after parent AUD and both genetic risk scores are added to the model. The current study additionally hypothesizes that parental knowledge and peer substance use significantly mediate the effect of parent AUD and scores on the theory-based gene score on emerging adult SUD. Finally, it is hypothesized that the theory-based gene score will moderate the effects of parental knowledge and peer use on adult SUD, such that for those at highest levels of genetic risk, parental knowledge and peer use will exert stronger effects.

Method

The Original Study

Participants. Participants for the present study were from a larger ongoing longitudinal study of familial alcoholism (Chassin, Flora, & King, 2004; Chassin, Pillow, Curran, Molina, & Barrera, 1993; Chassin, Pitts, DeLucia, & Todd, 1999). There have been six waves of data collection, with Wave 1 beginning in 1988, Wave 2 in 1989, Wave 3 in 1990, Wave 4 in 1995, Wave 5 in 2000 and Wave 6 in 2005.

The total sample at Wave 1 consisted of 454 adolescents, 246 of whom were children of alcoholics (COA), meaning that they had at least one biological alcoholic parent who was also a custodial alcoholic parent. The remaining 208 were

18

demographically matched controls who had no biological or custodial alcoholic parents. Adolescents and their families were interviewed consecutively for three years. The present study employs a subsample of alcoholic and non-alcoholic families from this larger sample.

Recruitment. COA families were recruited via court records, health maintenance organization (HMO) wellness questionnaires, and community telephone screenings. Alcoholic participants convicted of driving while intoxicated between the years 1984 and 1988 were identified by reviewing records from seven court systems. The participants who were chosen were non-Hispanic Caucasian or Hispanic, lived in the state of Arizona, and were born between 1927 and 1960. Potential indicators of alcoholism were noted from records, varying by court system, including prior alcohol-related arrests, scores of seven or higher on the Michigan Alcohol Screening Test, blood alcohol content of at least .15 at the time of arrest (Selzer, 1971), or diagnosis of probable alcoholism by a court substance abuse screening center. From these court records, 103 alcoholic families were obtained for the study.

In addition to court sources, 22 COA families were obtained through HMO wellness questionnaire responses. New members (joining between 1986 and 1988) of a large HMO were screened for the same demographic information stated above, as well as for alcoholism indicators (e.g., reporting three or more alcohol-related social consequences self-labeling as an alcoholic, or consumption of 26 or more alcoholic drinks per week).

Community telephone surveys produced an additional 120 COA families. Families located by telephone surveys were screened using the aforementioned

demographic information and alcoholism indicators. These indicators included attending

an Alcoholics Anonymous meeting, reporting that one's spouse had been alcoholic, or

hospitalization for a drinking problem. One family was located through the Veteran's

Administration outpatient alcohol treatment program.

Methods of screening began with archival data, and then proceeded to telephone

interviews (38.3% of the court and HMO potential participants were contacted). COA

families who were included in the study had a biological child between the ages of 11 and

15 of non-Hispanic Caucasian or Hispanic ethnicity who had at least one parent willing to

participate in the project, and who had no severe cognitive limitations such as mental

retardation or psychosis that might preclude an interview. Participants were all English-

speaking. In all, 327 families met these criteria, and 238 of them then agreed to

participate.

Direct verification of parental alcoholism was verified in a face-to-face interview

using the DIS, version III (Robins, Helzer, Croughan, & Ratcliff, 1981) to obtain a DSM-

III diagnosis of lifetime alcohol abuse or dependence. Interviews were conducted with

the alcoholic parent unless they refused to participate, and in those cases, he/she was

diagnosed as an alcoholic by spousal report using the Family History-Research

Diagnostic Criteria (FH-RDC, Endicott, Andreason, & Spitzer, 1975). Based on these

final criteria, 219 biological fathers and 59 biological mothers met alcoholism criteria.

Matched control families were recruited via telephone interview using reverse

directories to find families living in the same neighborhood area as the COA families.

Control families were matched according to child's age (within one year), family

composition (one-parent or two-parent), ethnicity, and socioeconomic status (based on

20

property value codes or parental income). The final criterion was that neither biological nor custodial parent met DSM-III or FH-RDC lifetime diagnosis of alcohol abuse or dependence. Seventeen families who reported indicators of alcohol problems, which were close to the diagnostic threshold, during this face-to-face interview were eliminated from the study in order to decrease the chance of being diagnosed as an alcoholic later in the project.

 Recruitment biases. There were two main sources of potential bias in recruitment for the longitudinal study; one was selective contact with COA participants and refusal to participate in the study (Chassin, Barrera, Bech, & Kossak-Fuller, 1992). The selective contact—the impact of not contacting all potential participants—was assessed by comparing the HMO and court archival records of participants who were and were not contacted. T-test and chi square analyses revealed no differences between those contacted and those not contacted on blood alcohol level at time of arrest, self-labeling as alcoholic, number of prior alcohol-related arrests, or MAST scores. However, these potential participants who were not contacted were more likely to be younger (37 versus 39 years old), from court sources (90% versus 87%), and be of Hispanic ethnicity (22% versus 18%). They were also more likely to be unmarried (64% versus 48%) and were more likely to have a lower SES rating associated with their residence (t-test or chi-square comparisons being significant at $p<.05$).

 The second source of recruitment bias was refusal to participate. Out of those families screened by telephone contacts, 73% of COA families and 77% of control families participated. Those who refused to participate were not different from participants on alcoholism indicators, age, sex, or SES ratings. However, individuals who

21

refused to participate were more likely to be Hispanic (24% versus 18%) and married (69% versus 50%) at the time of their arrest (chi-square comparisons significant at p<.05).

Refusal bias for those in the matched control sample was estimated by comparing those who agreed to participate to those 91 families who provided demographic information during the initial phone screening who ultimately refused to participate. There were no significant differences in family composition or SES ratings of their residences. There were, however, significant differences on ethnicity; both mothers and fathers who refused to participate were more likely to be Hispanic (41% versus 18% for mothers and 40% versus 22% for fathers) than those who agreed to be interviewed.

Procedure. After families provided consent for parents and assent for children, interviews were conducted at the family's residence or at the Arizona State University campus. The interviews were conducted by trained staff members who read items from a laptop computer; participants could either respond by directly entering the data into the computer or respond verbally while having the interviewers enter the data. To increase privacy of information, family members who were being interviewed simultaneously had interviews conducted in separate rooms. Interviews typically lasted one to two hours and families were paid $50 for their time and effort.

The Current study

Participants. The current study used data from Waves 1-5 of the larger parent project. At the first stage of data collection in 1988, 454 adolescents and their parents participated. Of the 454, 266 supplied genetic data. Of these 266, there were 5 cases in which the call rate was unacceptable and the genetic data were therefore not used,

resulting in a remaining 261 participants. Of these 261, 7 reported ethnicities other than Non-Hispanic Caucasian or Hispanic and were therefore eliminated. The resulting 254 participants comprised the sample for the current study.

Included versus Excluded Participants. Participants who were included in the current study's sample (N=254) were compared to those excluded from this sample (N=200; see Table 1). There were no differences between those included and excluded on mother, father or child report of parental knowledge, or ethnicity. However, those who were included in the current study sample were less likely to have friends who used substances (marginally significant), be the children of alcoholics, be male, and meet criteria for a lifetime substance use disorder between the age of 18-25. Although these differences are statistically significant, the effect sizes are small (see Table 1 for Cohen's D and Cramer's V values)[2].

Measures

Age Bands. In order to limit the age heterogeneity of participants at the times when study variables were examined, age bands were created, such that original offspring were between the ages of 11 and 14 when parental knowledge was examined, between the ages of 15 and 17 when peer substance use was examined, and between the ages of 18 and 25 when substance use disorder was examined. For the first age band, the interview age closest to age 14 was chosen to maximize the relation between parental knowledge and later peer substance use and SUD[3]. For the second and third age bands, interview age

---

[2] It is important to note that these effect sizes are also small in comparison to significant study findings which have Cohen's d values ranging from .3-.6 (closer to halfway in between small and medium effects, or medium effects).

[3] After imputing missing data, there was linear dependency between age 11-14 peer substance use and age 15-17 peer substance use, so the interview age closest to the mean of this age band (i.e. 12.5) was used for the covariate age 11-14 peer substance use.

closest to the mean of the age range was chosen (i.e. 16 and 21.5 for the first and second bands, respectively). Descriptive statistics for study variables are presented in Table 2.

Adolescent Gender. A dummy code indicating gender (52.8% female) was used as a covariate (0=Female; 1=Male).

Adolescent Ethnicity/Ancestry. The larger dataset of all participants who provided genetic data included 37 ancestry marker SNPs which—in previous literature—have differentiated Hispanics from non-Hispanic Caucasians. These were recoded to ensure that the direction of effect for each SNP's relation to Hispanic ancestry was positive, with scores of 0, 1, and 2 reflecting low, medium and high levels of Hispanic ancestry, respectively. After trichotomizing, a Principal Components Analyses on these 37 SNPs indicated that the first component explained 18.99% of the variance, with only an additional 3.36% and 3.11 % accounted for by the second and third, respectively. The scree plot indicated that the first component had an eigenvalue of 7.025, and the second through ninth components had eigenvalues between 1.243 and 1.020. Based on these findings, analyses used one component. Of the 37 ancestry marker SNPs, 32 loaded on this one component, with loadings at least as large as .3 or -.3. These 32 SNPs were included in a Factor Analysis in Mplus, using Maximum Likelihood estimation. These factor scores significantly correlated with self-reported ethnicity, both in the larger dataset ($r=.856$, $p<.001$) and in the current sample ($r=.868$, $p<.001$), suggesting that this ancestry gene score significantly differentiated between non-Hispanic Caucasians and Hispanics. This variable was coded such that higher scores indicate higher levels of Hispanic ancestry. Mplus fit statistics generally indicated good fit to the data,

24

RMSEA=.025, CFI=.943, SRMR=.027. See *Table 3* for a list of SNPs that were included in this score.

Adolescent/Emerging Adult Age. Although the age ranges for parental knowledge, peer substance use, and substance use problems were restricted, there was still variability in age bands, so self-reported age was used as a covariate in the analyses. The mean age at age bands 1 (when examining parental knowledge, age range: 11-14), 2 (when examining peer substance use, age range: 15-17) and 3 (when examining SUD, age range: 18-25) were 13.41, 15.78, and 21.21, respectively. Age band 1 age was correlated $r=.211$ ($p<.01$) with age band 2 age and correlated $r=.198$ ($p<.01$) with age band 3 age. Age band 2 and 3 ages were correlated $r=.550$ ($p<.001$).

Parent Alcohol Abuse/Dependence. Parent lifetime alcohol abuse/dependence diagnoses were obtained with a computerized version of the Diagnostic Interview Schedule (version III, Robins et al., 1981). Parents who were not interviewed were diagnosed based on spousal report using the Family History-Research Diagnostic Criteria (FH-RDC, Endicott, Andreason & Spitzer, 1975). Dichotomous dummy coded variables compared participants with at least one biological or custodial alcoholic parent (47.2%) and those with no alcoholic parents (52.8%). Parents meeting criteria were given a score of "1" and those not meeting criteria were given a score of "0."

Parental Knowledge. Parent and offspring report of knowledge about adolescent's behavior (age 11-14) was assessed via three items designed by project staff. These items assess the extent to which the parent knows about the adolescent's plans for the day, interests, and people with whom he/she associates (range: 1-5; higher scores indicate more knowledge of adolescent's life). Factor analyses were used to determine

whether mother, father and child report of items might hang together as one factor, or whether these were three separate factors.

Chi square tests revealed that a two factor model (χ^2 =132.597, df=19) fit the data significantly better than a one factor model (χ^2 =224.101, df=27), and the three factor model (χ^2 =17.859, df=12) fit significantly better than the two factor model. Therefore, the current study used three separate factors to characterize parental knowledge, with one representing mother report, one representing father report, and one representing child report of parental knowledge. Cronbach's Alphas for these three separate factors of mother, father and offspring report of knowledge were .789, .714, and .671, respectively.

Peer Substance Use. Late adolescent report of substance use in the peer group (age 15-17) was assessed via the mean of six items adapted from the Monitoring the Future Questionnaire (Johnston, O'Malley, & Bachman, 1988). These items assessed how many of their friends drink alcohol, smoke marijuana, or take other illicit drugs occasionally and regularly (range: 0-5; 0 being none and 5 being all). Cronbach's Alpha for peer substance use items was .909. To assess initial levels of this outcome, peer substance use between age 11-14 was created using these identical six items. Because of the initial skew (2.358) and kurtosis (6.347) of age 11-14 peer substance use, it was log transformed with the resulting skew and kurtosis much improved at .341 and -1.637, respectively.

Substance Use Disorder. Emerging/young adult (age 18-25) report of lifetime Substance Use Disorder was obtained from a computerized version of the Diagnostic Interview Schedule III-R (Robins, et al., 1981). Dichotomous dummy coded variables compared participants meeting lifetime criteria for alcohol or drug abuse or dependence

(38.9%) and those who did not (61.1%). Of those meeting criteria for alcohol or drug abuse or dependence, 70.5% met criteria for alcohol or drug dependence, and the remaining 29.5% met criteria for only abuse on one or more substance. To assess initial levels of this outcome, a variable was created to reflect the highest frequency of alcohol or drug use between age 11-14. These items assessed the highest frequency of use of alcohol, marijuana, amphetamines, barbiturates, tranquilizers, hallucinogens, cocaine, opiates, and inhalants (range: 0-7; 0 being never and 7 being everyday).

Genetic Risk

The extraction of DNA and plating were performed at the Department of Psychiatry at Washington University School of Medicine, and samples were genotyped at the Washington University Genome Sequencing Center. Illumina Golden Gate Technology was used to design a set of 1536 SNPs for genotyping. Checks were conducted to detect Mendelian inconsistencies, incorrect gender assignments and potentially unclear relatedness. SNPs with low call rates (< 95%) and deviations from Hardy-Weinberg equilibrium ($p < 10^{-6}$) were eliminated.

Theory-based Genetic Risk Score

In order to create a theory-driven gene score, a literature review was conducted to identify previous studies linking available SNPs in the Dopamine, GABA, Cannabinoid, Alcohol Effects, and Opioid systems (or SNPs that were in high LD with available SNPs), and behavioral undercontrol and/or substance use/misuse. See Table 4 for a list of SNPs, genes, receptor systems, references, and phenotypes related to the included SNPs. Effects of each SNP on emerging/young adult SUD were tested to determine each SNP's direction of effect, over and above the ancestry gene score. The

SNPs were then recoded to ensure that the direction of effect for each SNP was positive, with scores of 0, 1, and 2 reflecting low, medium and high levels of genetic risk, respectively. The 11 scores were then added together to create this theory-driven gene score. Each SNP's inclusion in this total score was based on finding links between it and behavioral undercontrol and/or substance use/misuse in at least two prior studies and not on its association with the phenotype of interest in this sample. This scoring method has been used by others (Morrison et al., 2007) with the rationale being that the current sample is unique from others in terms of the ancestry, age, and risk status (e.g. the sample over-sampled high risk individuals) of participants. Therefore, it was important that the risk alleles be in the direction of risk for this sample (Arpana Agrawal, personal communication January 28, 2013). This score was found to be a significant predictor of emerging/young adult SUD (β =.157, p<.05), controlling for ancestry, and explained 2.1% of the variance in substance use disorders.

In further support of this method to create a genetic risk score, 11 SNPs that were not included in either the theory or empirically-based gene score were randomly chosen from the remaining SNPs and tested as a predictor of this same phenotype (emerging/young adult SUD). These SNPs were coded to ensure that the direction of effect for each SNP on SUD was positive, with scores of 0, 1, and 2 reflecting low, medium and high levels of genetic risk, respectively (i.e. in the same way that the risk directions were determined in creating the theory-driven gene score). This gene score was not significantly related to the theory-driven score (r=-.058, p=.361). The 11 SNPs that were randomly chosen are presented in Table 5. This random gene score was not a significant predictor of emerging/young adult SUD (β =.039, p=.579), controlling for

28

ancestry. Additionally, it explained .13% of its variance, which is less than the variance explained by the gene score using SNPs based on past literature. This increases confidence in the theory-driven score.

Empirically-based Genetic Risk Score

In contrast to the theory-based gene score, the empirically-derived risk score utilized SNPs found to be related to SUDs in the current sample. Single SNP association analyses between those SNPs excluded from the theory-based gene score (and those in high LD with the SNPs in the theory-based score) and SUDs were examined in PLINK (Purcell et al., 2007). The SNPs related to this phenotype (p<.1 or lower) were retained. Relaxing the significance level used to choose SNPs produced a risk score that would explain more variance in SUDs, producing a more conservative test of environmental influences.

While conducting association analyses in PLINK (Purcell et al., 2007), 23 males were identified who were heterozygous on one, two, or three SNPs on the X chromosome, which is impossible. Because out of hundreds of participants and thousands of SNPs a few errors of this nature is not uncommon, and there was such a relatively low number of errors of this kind (Arpana Agrawal, personal communication December 17, 2012), values for these males on these SNPs were set to be missing, and these males were included in the analyses for the current study. These analyses resulted in 139 SNPs significantly associated with emerging/young adult substance use disorders. However, after "pruning" for SNP relatedness when linkage disequilibrium was 0.8 or higher (PLINK; Purcell et al., 2007), 30 SNPs were retained for the creation of this empirically-based gene score (a list of these SNPs can be found in *Table 6*). These 30 SNPs were

recoded to ensure that the direction of effect for each SNP was positive, with scores of 0, 1, and 2 reflecting low, medium and high levels of genetic risk, respectively. Frequencies for all 30 SNPs are presented in Table 7. This score was found to be a significant predictor of emerging/young adult SUD (β =.552, p<.001), controlling for ancestry, and explained 29.2% of the variance in substance use disorders.

Although it is less of a concern because the objective of this score was to create a liberal measure of genetic risk, using this method may have resulted in false positives effects. Many procedures to control for the possibility of Type I errors with multiple tests often result in a reduction in power (e.g. Bonferroni). Therefore, as an alternative approach, control of the False Discovery Rate (FDR) has recently been used (Benjamini & Hochberg, 1995). This procedure seeks to control the percentage of significant results that are false positives. A typical p-value of .05 indicates that 5 percent of tests will result in false positives. However, a FDR corrected p-value of .05 indicates that 5 percent of significant tests will result in false positives. This approach is a great deal less conservative than the Bonferroni method and has more power to find true significant results, while maintaining control of false positives (Shaffer, 1995).

FDR-adjusted p-values were computed in SAS 9.3 (SAS Institute, Cary NC) under the PROC MULT TEST procedure. Analyses in SAS indicated that of the 30 SNPs that were significantly (p<.05) or marginally significantly (p<.1) related to substance use disorder between age 18-25, all 30 had FDR-adjusted p-values that were marginally significantly (p<.1) related to the same outcome. Therefore, all 30 of these SNPs were used when creating the empirically-based genetic risk score. See *Table 6* for the standard and FDR-adjusted p-values for the 30 SNPs that were used to create this score.

Data Analytic Strategy

The first hypothesis was that parental AUD and the theory-based gene score would predict parental knowledge, peer substance use, and emerging/young adult SUD, and that the empirically-based gene score would be related to emerging adult SUDs. The second hypothesis was that parental knowledge and peer alcohol/drug use would partially mediate the effects of parental alcoholism and the theory-based gene score on emerging/young adult SUD. The third and final study hypothesis was that the theory-based gene score would interact with parental knowledge and peer substance use to predict SUD, such that knowledge and peer use would exert stronger effects at higher levels of genetic risk.

To reduce nonessential multicollinearity, continuous variables were centered prior to conducting analyses (Cohen, Cohen, West & Aiken, 2003). The inclusion of covariates increase the power of a statistical test by minimizing uncontrolled variability, and accounting for variance that would otherwise be thought of as error. In testing the study hypotheses, a number of covariates were used because of their hypothesized associations with the variables of theoretical interest. The covariates were: adolescent ancestry, adolescent gender, age at each age band (e.g. parental knowledge was examined when the adolescent was age 11-14, so that age between 11 and 14 were used as covariates in predicting age 11-14 parental knowledge), and any significant interactions among covariates and between covariates and predictors. Additionally, earlier levels of peer substance use (age 11-14) and own substance use (age 11-14) were used as covariates in the prediction of peer substance use at ages 15-17 and SUD at ages 18-25. Finally, although the estimates are not necessarily of substantive interest, the current study

models estimated effects of the empirically-based gene score on parental knowledge and peer substance use, in order to provide a stricter test of environmental influences on these variables.

In order to test study hypotheses, a model-building approach was used to examine the relations among covariates, parental AUD, genetic risk scores, parental knowledge, peer substance use, and emerging adult SUD. This particular model building approach was used to examine important theoretical questions. First, this method was used to test whether adding genetic risk scores as predictors resulted in a model that fit the data better than a model that ignored genetic effects (i.e. the "traditional" understanding of the deviance proneness pathway). Second, this method was used to test whether—if genetic influences add substantially to model fit—these gene effects vary by levels of other variables (i.e. estimating gene-environment interaction effects).

A chi square difference test, in addition to fit statistics (i.e. CFI, RMSEA, and WRMR) was used to determine whether a simple model (Model 1), more complicated model (Model 2), or most complicated model (Model 3) fit the data best. See Table 10 for the parameters that were freely estimated and constrained to zero in each model. In Model 1, the covariate main effects of gender, ancestry, and age, in predicting parental knowledge, peer substance use and SUD were freely estimated. Additionally, in predicting age 15-17 peer substance use and age 18-25 SUD, own substance use and peer substance use between ages 11-14 were also used as covariates and freely estimated. The effects of parental alcoholism, parent knowledge, and peer substance use on SUDs were also freely estimated.

Within this Model 1, however, the main effects of the theory-based and empirically-based gene scores on parental knowledge, peer substance use, and SUD were fixed to zero. Additionally, the interaction effects between the theory-based gene score and parental alcoholism, ancestry, gender, and age in predicting parental knowledge, peer substance use and SUDs were fixed to zero. The interaction between knowledge and the theory-based gene score predicting peer substance use, and the interactions between the theory-based gene score and parental knowledge and peer substance use to predict SUD were also fixed to zero. Broadly, Model 1 tests the relations among the variables in the deviance proneness pathway as they have historically be treated, as if all relations are "environmental" effects (e.g. the effects of parental knowledge and peer substance use on emerging adult SUD), ignoring genetic influences.

In order to move from Model 1 to Model 2, the main effects of the theory-based and empirically-based gene scores on parental knowledge, peer substance use, and SUD were freely estimated. The interaction effects between the theory-based gene score and parental alcoholism, ancestry, gender, and age in predicting parental knowledge, peer substance use and SUD were fixed to zero. The interaction between knowledge and the theory-based gene score predicting peer substance use, and the interactions between the theory-based gene score and parental knowledge and peer substance use to predict SUD were again still fixed to zero. That is, Model 2 adds the main effects of genetic risk to the prediction of parental knowledge, peer substance use and emerging adult SUDs.

In moving from Model 2 to Model 3, the interaction effects between the theory-based gene score and parental alcoholism, ancestry, gender, and age in predicting parental knowledge, peer substance use and SUDs were freely estimated. The interaction

between knowledge and the theory-based gene score predicting peer substance use, and the interactions between the theory-based gene score and parental knowledge and peer substance use to predict SUD were also freely estimated. That is, Model 3 adds gene-environment interactions, and tests the question of whether genetic effects vary by levels of other variables.

This model building strategy was used for models with mother-, father-, and child-report of parental knowledge. Following previous methodology for nested model testing (Schermelleh-Engel, Moosbrugger, & Muller, 2003), chi square statistics were utilized to compare the fit of Model 1 to Model 2. If the chi square difference test was significant, the null hypothesis of equal fit for both models was rejected and Model 2 was retained. Once the best fitting model for each reporter of parental knowledge was chosen, non-significant interaction terms that were not hypothesized (i.e. covariate by covariate or covariate by predictor interaction terms) were dropped. After dropping these non-significant interactions, all remaining interactions were probed using simple slope analyses (Aiken & West, 1991).

Current study hypotheses involved the prediction of dependent variables that were continuous and categorical. Therefore, models used the weighted least squares estimator with mean and variance adjustments (WLSMV), which computes ordinary least squares (OLS) parameter estimates for continuous outcomes and probit parameter estimates for categorical outcomes. Missing data on endogenous variables were estimated as a function of the observed exogenous variables under the missingness at random assumption (Schafer & Graham, 2002). Because the WLSMV estimator provides probit regression estimates, which cannot be converted to odds ratios (as logit regression estimates can),

there are no odds ratios in this document despite the prediction of a dichotomous outcome (Cohen, Cohen, West, & Aiken, 2003; Muthén & Muthén, 1998-2010).

Researchers consider an acceptable chi-square goodness of fit test statistic to be one whose p-value is >.05, although the significance of chi square is affected by sample size (Saris, Satorra, & van der Veld, 2009). In addition, the models were assessed for goodness of fit based on whether the values of the following fit indices were consistent with accepted standards (i.e. Hu & Bentler, 1999; Muthén & Muthén, 1998-2010): Comparative Fit Index (CFI): $\geq$.95, Root Mean Square Error of Approximation (RMSEA) $\leq$ .06, and Weighted Root Mean Square Residual (WRMR) <.90. The mediated effects of parental alcoholism and the theory-based gene score on emerging adult SUDs through parental knowledge and peer substance use were tested using the Model Indirect statement in Mplus (Muthén & Muthén, 1998-2010).

Results

Correlations

Zero-order correlations among study variables are in Table 8. Note that the covariates child gender, ancestry, age, and earlier levels of own and peer use predicted some study variables. Specifically, according to adolescent and mother report, parents know more about the lives of females compared to males, and males are more likely to be diagnosed with a SUD. Additionally, there was a trend such that males had higher scores on the theory-based gene score.

Interestingly, adolescents of stronger Hispanic ancestry have fathers who report knowing less about their lives. Adolescents with stronger Hispanic ancestry are also less likely to

be children of alcoholics and are at higher genetic risk (according to the empirical score) for SUDs[4].

Higher early levels of substance use were associated with parental alcoholism, less father, mother and child reported knowledge, more later peer substance use, and higher likelihood of emerging adult SUD. Higher early levels of peer use were associated with parental alcoholism, less child reported parental knowledge, higher later levels of peer substance use, and greater likelihood of SUD.

In terms of relations between age and study variables, individuals who were older at age band 2 (age 15-17) were more likely to have friends who used substances at age band 2. Individuals who were older at age band 3 (age 18-25) were more likely to meet criteria for a SUD.

Children of parents with alcohol use disorders (AUDs) were more likely to have mothers and fathers who reported knowing less about their lives, were more likely to have friends who use substances, and were more likely to meet criteria for a SUD. Higher levels of mother knowledge were associated with higher levels of father knowledge and children's report of their parents' knowledge. Father and child report of knowledge predicted peer substance use, such that higher levels of knowledge were associated with having fewer friends who used substances. Only child report of knowledge was related to substance use disorder in emerging adulthood, such that more knowledge was associated with less risk for a SUD. Having more friends who use substances predicted increased chance of developing a SUD and was associated with higher genetic risk for SUDs according to the empirically-based gene score. Emerging adult SUD was related to higher

_____

[4] Although it seems contradictory for those with higher scores on the Hispanic ancestry score to be less likely to be children of alcoholics and more likely to have higher genetic risk on the empirically-based gene score, parental AUD and the empirically-based gene score are actually not significantly associated.

scores on the theoretical and empirically-based gene scores, and the two gene scores were also significantly related to one another.

Regression diagnostics

Mplus does not yield regression diagnostics, so study models were estimated in OLS and logistic regression using SPSS to examine the potential influence of outliers on model results. No extreme abnormalities were detected; therefore, no outlying cases were deleted from the analyses.

Path Analyses (N=254)

Mother Report of Knowledge: Nested Model Test. Model 1 using mother report of parental knowledge suggested poor fit to the data, χ^2= 207.889, df=86, p<.001; RMSEA=.076; CFI=.554; WRMR=1.240. Model 2 yielded better fit, χ^2= 179.874, df=80, p<.001; RMSEA=0.067; CFI=.671; WRMR=1.101. The difference between chi square statistics (28.015, 6 dfs) exceeded the critical value of 12.592, suggesting that the null hypothesis of equal fit for both models should be rejected, and Model 2 was retained. Model 3 suggested good fit to the data, χ^2= 160.794, df=70, p<.001; RMSEA=0.063; CFI=.660; WRMR=1.065. The difference between chi square statistics (19.08, 10 dfs) did exceed the critical value of 18.307, suggesting that the null hypothesis of equal fit for both models should be rejected, so Model 3 was retained.

Mother report of knowledge: Final trimmed model. Figure 1 and Table 11 present the results of the final mother model (N=254). Results indicate that no predictors or covariates were significantly related to mother knowledge. In the prediction of age 15-17 peer substance use, older children had more friends who used substances (b= .165, *SE*=.473, *p* < .1). Additionally, earlier substance use (b= 0.297, *SE*=.122, *p* < .05) and

earlier peer substance use (b= 0.567, *SE*=.083, *p* < .001) predicted peer substance use, such that those with higher earlier levels of own and peer substance use were more likely to have friends who used substances. Additionally, children of alcoholics were more likely to have friends who used substances (b= 0.337, *SE*=.175, *p* < .01). No other predictors or covariates were significantly related to peer substance use.

In predicting age 18-25 lifetime SUD, the empirically-based gene score (b= 0.489, *SE*=.255, *p* < .001) predicted likelihood of disorder, such that higher genetic risk predicted higher chance of developing a SUD. Additionally, children of alcoholics (b= 0.182, *SE*=.224, *p* < .05), males (b= 0.191, *SE*=.199, *p* < .01), and those with more friends who used substances between age 15-17 (b= 0.280, *SE*=.209, *p* < .05) were more likely to develop a SUD. Those of lower Hispanic ancestry (b= -0.108, *SE*=.101, *p* < .1) were also more likely to develop a substance use disorder. Additionally, those between age 18-25 who were older were at greater risk for SUDs (b= 0.239, *SE*=.664, *p* < .05). The interactions of genetic risk by parental alcoholism (b=.154, *SE*=.107, *p* < .1) and genetic risk by parental knowledge (b=-0.195, *SE*=.153, *p* < .1) were marginally significant. These interactions indicate that for COAs, greater genetic risk was associated with greater risk for SUD (b= .375, *SE*=.033, *p* < .01), but there was no relation for non-COAs (b= .056, *SE*=.031, *NS*). Additionally, there was no relation between parental knowledge and SUD for those at medium (b=-0.126, *SE*=.220, *NS*) and low levels of genetic risk (b= -.076, *SE*=.105, *NS*). However, for those at high levels of genetic risk, as parental knowledge decreased, risk for SUD increased (b=-0.226, *SE*=.088, *p* < .05).

Mother report of knowledge: Indirect effects of parent AUD and genetic risk through peers and parenting (Testing Mediation and Moderated Mediation[5]).

Mediation. The theory-based gene score did not significantly predict peer substance use (b=.029, *SE*=.473, NS), but having more friends who used substances did prospectively predict higher likelihood of developing a SUD (b=0.280, *SE*=.209, *p* < .05). The indirect effect of genetic risk on emerging adult SUD through the substance-using peer group was non- significant (*CI:-.343-.371*). The effect of the theory-based gene score on mother knowledge was also not significant (b=.029, SE=.358, NS). The overall effect of mother knowledge on later SUD was non-significant (b=-0.126, *SE*=.220, *NS*). The indirect effect of genetic risk on SUD through mother knowledge was non-significant (CIs: -.207-.190). The direct effect of genetic risk on SUD was not significant (b=-.126, *SE*=.814, *NS*), over and above other predictors and covariates.

Children of parents with AUDs were more likely to have friends who used substances (b=0.337, *SE*=.175, *p* < .01), and having more friends who used substances prospectively predicted higher likelihood of developing a SUD (b=0.280, *SE*=.109, *p* < .05). This indirect effect of parental alcoholism on emerging adult SUD through the substance-using peer group was significant (95% CI:.016-.203).

Moderated Mediation. There was no relation between parental alcoholism and mother reported knowledge (b=-0.156, *SE*=.116, NS). However, there was an effect of mother knowledge on later SUD for those at high (b=-0.226, *SE*=.088, *p* < .05), but not

---

[5] For mother-, father-, and child-report models, the current study tested whether parental knowledge and peer substance use mediated the effects of the theory-based score on emerging adult SUD, and whether peer substance use mediated the effect of parental AUD on emerging adult SUD. Because genetic risk moderated the effect of parental knowledge on emerging adult SUD, the current study tested whether the effect of parental AUD on emerging adult SUD through parental knowledge varied by level of genetic risk on the theory-based score (i.e. moderated mediation).

medium (b=-0.126, *SE*=.220*, NS*) or low levels of genetic risk (b=-.076, *SE*=.105, *NS*).

The indirect effect of parental alcoholism on emerging adult SUD through mother

knowledge was non-significant for those at high, medium and low levels of genetic risk,

respectively (CI:-.016-.107; CI: -.060-.128; CI:-.025-.066). There was therefore no

evidence of moderated mediation. The direct main effect of parental alcoholism on

emerging adult SUD was significant (b=.182, *SE*=.224, *p* < .05), indicating that having a

parent with an AUD increased risk for developing a substance use problem, over and

above all other predictors and covariates.

Father report of knowledge: Nested model test. Model 1 using father report of

parental knowledge suggested poor fit to the data, χ^2= 221.583, df=84, p<.01;

RMSEA=.080; CFI=.525; WRMR=1.290. Model 2 also yielded poor fit, χ^2= 184.375,

df=80, p<.01; RMSEA=0.073; CFI=.634; WRMR=1.157. The difference between chi

square statistics (37.208, 6 dfs) exceeded the critical value of 12.592, suggesting that the

null hypothesis of equal fit for both models should be rejected, and Model 2 was retained.

Model 3 suggested good fit to the data, χ^2= 163.381, df=70, p<.01; RMSEA=0.073;

CFI=.673; WRMR=1.079. The difference between chi square statistics (20.994, 10 dfs)

exceeded the critical value of 19.307, so Model 3 was retained.

Father report of knowledge: Final trimmed model. Figure 2 and Table 12

present the results of the final father model. Results indicate that the empirically-based

gene score predicted father report of knowledge, such that higher levels of genetic risk

was associated with less father knowledge (b=.211, SE=.130, p<.1). In the prediction of

age 15-17 peer substance use, children of alcoholics (b=.309, SE=.196, p<.01) and those

with more friends who used substances between age 11-14 (b=.448, SE=.196, p<.01) were more likely to have friends who used substances.

In predicting emerging adult SUD, those with higher scores on the empirical score (b=.635, SE=.246, p<.001), males (b=.280, SE=.208, p<.01), and those who were older within the 18-25 age range (b=.270, SE=.640, p<.01) were more likely to meet criteria for a SUD. Additionally, those with more friends who used substances were at greater risk for a SUD (b=.451, SE=.232, p<.05). The interactions of genetic risk by parental alcoholism (b=-0.301, *SE=*.093, *p=*.055) and genetic risk by parental knowledge (b=-0.301, *SE=*.137, *p < .1*) were marginally significant. These interactions indicate that for COAs, greater genetic risk was associated with greater risk for SUDs (b=.421, *SE=*.036, *p < .05*), but there was no relation for non-COAs (b=.127, *SE=*.038, *NS*). Additionally, there was no relation between parental knowledge and SUD for those at low levels of genetic risk on the theory-based score (b=-.053, *SE=*.103, *NS*). However, for those at medium (b=-0.355 *SE=*.315, *p<.05*) and high levels of genetic risk on the theory-based score, as parental knowledge decreased, risk for SUD increased (b=-0.125, *SE=*.085, *p < .05*).

Father report of knowledge: Indirect effects of parent AUD and genetic risk through peers and parenting (Testing Mediation and Moderated Mediation)

Mediation. The effect of the theory-based gene score on peer substance use was not significant (b=.024, *SE=*.125, p<.001). The effect of peer substance use on emerging adult SUD was however significant (b=451, *SE=*.232, p<.05). The indirect effect of the theory-based gene score on emerging adult SUD through the substance-using peer group was non-significant (CI:-.118-.150). The effect of the theory-based gene score on father knowledge was also not significant (b=.102, SE=.325, NS). Additionally, the overall

effect of father knowledge on later SUD was non-significant (b=-0.355 *SE*=.315, *NS*). This indirect effect of the theory-based gene score on SUD through father knowledge was also non-significant (CI: -.407-.270). The direct effect of the theory-based gene score on SUD was non-significant (b=-.021, *SE*=.660, *NS*), over and above other predictors and covariates.

Children of parents with AUDs were more likely to have friends who used substances (b=0.309, *SE*=.126, *p* < .01). Having more friends who used substances prospectively predicted higher likelihood of developing a SUD (b=0.452, *SE*=.102, *p* < .05). This indirect effect of parental alcoholism on emerging adult SUD through the substance-using peer group was significant (CI: .025-.284).

Moderated Mediation. There was no relation between parental alcoholism and father reported knowledge (b=-.150, *SE*=.125, NS). However, the relation between father knowledge and later SUD was significant for those at high (b=-0.125, *SE*=.085, *p* < .05) and medium (b=-0.355 *SE*=.315, *p<.05*) but not low levels of genetic risk on the theory-based gene score (b=-.053, *SE*=.103, *NS*). The indirect effect of parental alcoholism on emerging adult SUD through father knowledge was also non-significant for those at high, medium and low levels of genetic risk (CI:-.015-.074, -.062-.241, -.030-.059). Therefore, there was no evidence of moderated mediation. The direct main effect of parental alcoholism on emerging adult SUD was significant (b=.225, *SE*=.241, *p<.05*), indicating that having a parent with an AUD did increase risk for developing a substance use problem, over and above all other predictors and covariates.

Child Report of Knowledge: Nested Model Test. Model 1 using child report of parental knowledge suggested poor fit to the data, χ^2= 214.527, df=86, p<.01;

RMSEA=.078; CFI=.583; WRMR=1.261. Model 2 yielded better fit, χ^2= 173.942, df=80, p<.01; RMSEA=0.069; CFI=.691; WRMR=1.115. The difference between chi square statistics (40.585, 6 dfs) exceeded the critical value of 12.592, suggesting that the null hypothesis of equal fit for both models should be rejected, and the Model 2 was retained. Model 3 also suggested good fit to the data, χ^2= 154.047, df=70, p<.01; RMSEA=0.070; CFI=.727; WRMR=1.045. The difference between chi square statistics (19.895, 10 dfs) exceeded the critical value of 19.307, so Model 3 was retained.

Child Report of Knowledge: Final Trimmed Model. Figure 3 and Table 13 present the results of the final child model. Results indicate that gender predicted child report of parental knowledge, such that girls reported their parents knew more about their lives (b=-.387, SE=.162, p<.05). Additionally, those who were of higher genetic risk on the empirically-based gene score had parents who knew less about their lives (b=-.193, SE=.054, p<.1). In the prediction of age 15-17 peer substance use, children of alcoholics (b=.301, SE=.181, p<.01) and females (b=-.183, SE=.184, p<.1) were more likely to have friends who used substances. Additionally, older adolescents (b=.242, SE=.214, p<.05) and those who had earlier had more friends who used substances (b=.471, SE=.085, p<.001) were more likely to report friends who used substances.

In predicting emerging adult SUD, those who were higher on the empirically-based gene score (b=.637, SE=.244, p<.001) and those who had more friends who used substances when they were younger (b=.269, SE=.117, p<.01) were at higher risk for SUD. Additionally, those who were male (b=.229, SE=.379, p<.01), and who were older in the 18-25 age range (b=.179, SE=.103, p<.01) were more likely to meet criteria for a SUD. The interactions of the theory-based gene score by parental alcoholism (b=-0.301,

43

SE=.140, *p*<.05) and genetic risk by parental knowledge (b=-0.301, *SE*=.231, *p* < .1)

were marginally significant. These interactions indicate that for COAs, greater genetic

risk was associated with greater risk for SUD (b=.354, *SE*=.032, *p* < .01), but there was

no relation for non-COAs (b=.106, *SE*=.034, *NS*). Additionally, there was no relation

between parental knowledge and SUD for those at medium (b=-0.037, *SE*=.308, *NS*) and

low levels of genetic risk (b=-.075, *SE*=.081, *NS*). However, for those at high levels of

genetic risk on the theory-driven gene score, as parental knowledge decreased, risk for

SUD increased (b=-0.193, *SE*=.072, *p* < .05).

Child report of knowledge: Indirect effects of parent AUD and genetic risk through peers and parenting (Testing Mediation and Moderated Mediation)

Mediation. The effect of the theory-based score on peer substance use was non-

significant (b=.017, SE=.446, NS), but the effect of peer substance use on emerging adult

SUD was significant (b=0.269, SE=.317, p<.01). This indirect effect of the theory-based

score on emerging adult SUD through the substance-using peer group was non-

significant (CI:-.395-.415). The effect of genetic risk on child reported parental

knowledge was also not significant (b=.084, SE=.403, NS). The overall main effect of

parental knowledge on later SUD was non-significant (b=-0.037, *SE*=.308, *NS*). This

indirect effect of genetic risk on SUD through child reported parental knowledge was

non-significant (CI: -.270-.287). The main direct effect of genetic risk on SUD was non-

significant (b=-.129, *SE*=1.254, *NS*), over and above other predictors and covariates.

Children of parents with AUDs were more likely to have friends who used

substances (b=0.301, *SE*=.085, *p* < .001). Having more friends who used substances

prospectively predicted higher likelihood of developing a SUD (b=.269, SE=.117, p<.01).

The indirect effect of parental alcoholism on emerging adult SUD through the substance-using peer group was significant (CI: .010-.177).

   Moderated Mediation. There was no relation between parental alcoholism and child reported parental knowledge (b=.014, *SE*=.151, NS). Additionally, the relation between parental knowledge and later SUD depended on level of genetic risk. Specifically, there was no relation between parental knowledge and SUD for those at medium (b=-0.037, *SE*=.308, *NS*) and low levels of genetic risk on the theory-based gene score (b=-.075, *SE*=.081, *NS*). However, for those at high levels of genetic risk on the theory-based gene score, as parental knowledge decreased, risk for SUD increased (b=-0.193, *SE*=.072, *p* < .05). The indirect effects of parental alcoholism on emerging adult SUD through child reported parental knowledge were also non-significant for those at high, medium, and low levels of genetic risk on the theory-based gene score *(CI:-.061-.068,-.104-.101,-.039-.034).* Therefore, there was no evidence of moderated mediation. The direct main effect of parental alcoholism on emerging adult SUD was also non-significant (*b*=.067, *SE*=.367, NS), indicating that having a parent with an AUD did not increase risk for developing a substance use problem, over and above all other predictors and covariates.

Path Analyses for Those with and without Genetic Data (N=447)

   The same model building approach was tested in the full sample of participants to examine whether results held when using a larger sample. This sample of 447 participants included those who had or had not provided genetic data, excluding only 7 of the original participants on the grounds that they self-reported ethnicities other than Non-Hispanic Caucasian or Hispanic.

Mother Report of Knowledge: Nested Model Test (Full Sample). Using the same model-building methodology with the larger sample yielded retention of the same model (Model 3). This model yielded good fit, $\chi^2= 81.280$, df=41, p<.05; RMSEA=0.047; CFI=.955; WRMR=.635. The findings using this larger sample were similar to the model using the smaller sample, with a few exceptions. Namely, in predicting mother knowledge, children of alcoholics had mothers who knew less about their lives (b=-.161, *SE*=.083, *p* < .05). Additionally, those at lower risk on the empirically-based gene score (b=-1.210, *SE*=.607, *p* < .05), those of higher Hispanic ancestry (b=.416, *SE*=.103, *p* < .05), and older individuals had mothers knew more about their lives (b=.323, *SE*=.236, *p* < .1). See Appendix for Table 14 and Figure 4 depicting the findings from the larger sample.

Father Report of Knowledge: Nested Model Test (Full Sample). Using the same model-building methodology with the larger sample yielded retention of the same model (Model 3). Model 3 showed good fit to the data, $\chi^2= 75.804$, df=48, p<.01; RMSEA=0.036; CFI=.945; WRMR=.704. The findings using this larger sample were similar to the model using the smaller sample, with a few exceptions. Namely, child ancestry predicted father report of knowledge (b=-.192, *SE*=.066, *p*<.1) such that children of more Hispanic ancestry had fathers who reported knowing less about their lives. See Appendix for Table 15 and Figure 5 depicting the findings from the larger sample.

Child report of knowledge: Nested model test (Full Sample). Using the same model-building methodology with the larger sample yielded retention of the same model (Model 3). Model 3 showed good fit to the data, $\chi^2= 71.142$, df=48, p<.01;

RMSEA=0.038; CFI=0.964; WRMR=0.676. The findings using this larger sample were similar to the model using the smaller sample, with a few exceptions. Specifically, higher risk on the theory-based gene score predicted less child reported parent knowledge (b=-.166, SE=.374, p<.1). Additionally, those with higher earlier levels of substance use were at higher risk for SUDs in the larger sample (b=.145, SE=.072, p<.05). See Appendix for Table 16 and Figure 6 depicting the findings from the larger sample.

Additional Study Analyses

The models presented up to this point attempted to answer specific questions about the unique effects of genetic risk, parent AUD, parental knowledge, and peer substance use on emerging adult SUDs, over and above covariates. However, there was some concern that study findings might have changed substantially if two covariates, the empirically-based gene score and age 11-14 adolescent substance use, had been omitted. If many non-significant effects became significant after omitting one or both of these covariates, there would be strong theoretical implications for the necessity of including these control variables in future research.

Omitting the Empirically-based Gene Score. The current study sought to create an empirically-based genetic risk score in an effort to explain as much variance as possible in emerging adult SUD. The current study arrived at findings that hold even with the inclusion of this key covariate. Therefore, because this "control" variable explained so much of the variance in emerging adult SUDs, there was a question about whether other findings have been obscured by the omission of the empirically-based gene score. After omitting the empirically-based gene score from study analyses, most study findings did not change. However, a few coefficients that were non-significant or marginally

47

significant, became statistically significant (p<.05). First, in the first father model (N=254), ancestry, which had been a marginally significant predictor of father knowledge, became a significant predictor (b=-.204, SE=.064, p<.05). Additionally, in the first child report model (N=254) the main effect of parental alcohol use disorder became a significant predictor of emerging adult SUD after dropping the empirically-based gene score (b=.260, SE=.210, p<.01). Several findings also changed in the models using the larger sample. For instance, after dropping the empirically-based gene score, age 11-14 adolescent substance use became a significant predictor of SUD in the larger mother model (N=447; b=.233, SE=.094, p<.01). Additionally, in the larger father model (N=447), as was the case in the smaller father model, ancestry became a significant predictor of father knowledge (b=-.278, SE=.061, p<.01).

It was important in the current study to control for earlier levels of problematic drinking in order to rule out reciprocal relations between early drinking, parental knowledge and peer substance use. However, by including highest frequency of substance use between age 11-14 as a covariate, current study models are predicting change in problematic substance use between age 11-14 and age 18-25. There was specific concern about the effect of genetic influences on emerging adult SUDs, controlling for earlier levels of problematic use. For example, it may have been that genetic influences would appear weaker after controlling for early levels of substance use, especially for individuals who displayed a high frequency of early problematic substance use. After omitting early substance use as a covariate, some coefficients that had been non-significant or marginally significant became significant (p<.05). For example, in the first mother model (N=254) age band 2 age (age between15-17) which

had been a marginally significant predictor of age 15-17 peer substance use became a significant predictor (b=.277, SE=.195, p<.01). Additionally, in the larger father model (N=447), the empirically-based gene score became a significant predictor of father knowledge (b=-1.031, SE=.552, p<.05).

Executive Summary of Findings

  Models Using Mother Report of Knowledge. Most key findings of interest held across the two models using mother report of parental knowledge (N=254 and N=447). Specifically, children of alcoholics and adolescents with more friends who used substances earlier had friends who later used more substances. Additionally, those at higher genetic risk on the empirically-based gene score were at greater risk for a SUD. Additionally, children of alcoholics, and males were at greater risk for SUDs. Those with more friends who used substances were at greater risk for a substance use disorder, and peer substance use partially mediated the effect of parent AUD on emerging adult SUD. The two significant interactions involving the theory-based gene score indicate that for COAs, more genetic risk predicted greater risk for SUDs, but for non-COAs this relation was non-significant. Additionally, for those at high level of genetic risk, less parental knowledge predicted greater risk for SUDs. For those at medium and low levels however there was no relation.

  Models using Father Report of Knowledge. Most key findings of interest held across the two models using father report of parental knowledge (N=254 and N=447). Specifically, those with parents with AUDs and those who had friends who used more substances earlier were more likely to have friends who later used substances. Additionally, higher levels of genetic risk on the empirical score conferred greater risk

for a SUD, as did being the child of an alcoholic or male. Those with friends who used substances were more likely to develop a SUD, and peer substance use partially mediated the effect of parent AUD on emerging adult SUD. The two significant interactions involving the theory-based gene score indicate that for COAs, more genetic risk predicted greater risk for SUDs, but for non-COAs this relation was non-significant. Additionally, for those at high level of genetic risk, less father reported knowledge predicted greater risk for SUDs. For those at medium and low levels however there was no relation.

Models using Child Report of Knowledge. Most key findings of interest held across the two models using child report of parental knowledge (N=254 and N=447). Specifically, children at higher risk on the empirically-based gene score reported that their parents knew less about their lives, as did males. The adolescents whose parents had an alcohol use disorder, and those at higher genetic risk on the empirically-based gene score were more likely to have friends who used substances. Males, children of alcoholics, and those at higher genetic risk on the empirically-based gene score were at higher risk for SUDs. Those with more friends who used substances were also at greater risk for developing a SUD, and peer substance use partially mediated the effect of parent AUD on emerging adult SUD. The two significant interactions involving the theory-based gene score indicate that for COAs, more genetic risk predicted greater risk for SUDs, but for non-COAs this relation was non-significant. Additionally, for those at high level of genetic risk, less child reported parental knowledge predicted greater risk for SUDs. For those at medium and low levels however there was no relation.

Discussion

The present study had three goals. First, after creating one theory-based and one empirically-based genetic risk score, this study tested whether parental AUD and the theory-based gene score predicted parental knowledge, peer substance use, and emerging adult SUDs. Second, the present study tested whether parental knowledge and peer substance use mediated the relations between parental AUD and the theory-based genetic risk score, and emerging adult SUD. Finally, it examined whether the theory-based genetic risk score moderated the relations among parental knowledge, peer substance use, and emerging adult substance use disorder.

This study provides a number of important contributions. First, creating the two genetic risk scores allowed for the examination of novel study questions using innovative methods. Specifically, the relations among parental alcoholism, parental knowledge, peer substance use, and offspring substance use disorder have historically been treated as if they are environmental in nature. The few studies which have examined relations among these constructs using a genetically-informative design have for the most part utilized single SNPs which explain minimal variance in phenotypes. Therefore, these studies are limited in their ability to discern the unique effects of environmental influences, such as peers and parenting, over and above gene-environment covariation (i.e. the relation between genetic risk and peer and parenting influences). Additionally, few studies have also examined whether a theory-based gene score might moderate the relations among these constructs. The current study is unique in that is the first to have utilized both a theory-based gene score which allowed for the interpretation of gene-environment interaction effects, as well as an empirically-derived genetic risk score, which explained a

51

relatively large proportion of the variance in SUDs, acting as a "control" for genetic influences. Together, these two gene scores offer a new way of analyzing genetic risk, while also clarifying relations among constructs within Sher's deviance-proneness pathway.

The current study also contributed to the literature in replicating previous findings that parental AUD influences peer substance use which affects risk for emerging adult SUD (Monahan, Steinberg, & Cauffman, 2009; Steinberg, Fletcher, & Darling, 1994). However, it was the first to find that this effect was maintained in the context of polygenic risk scores. In addition, the current study found that genetic risk moderated the effects of parental knowledge such that less parental knowledge conferred greater risk for SUDs for those at higher levels of genetic risk for behavioral undercontrol and problematic substance use. Finally, this study contributes to current literature pertaining to diathesis stress models by finding that only for children of parents with AUDs does higher genetic risk for behavioral undercontrol and maladaptive substance use yield greater likelihood of developing a substance use disorder. Importantly, these main study findings also held across reporter and subsamples of those with and without genetic data (using missing data techniques), increasing confidence that they are reliable. Taken together, these findings indicate that children of parents with alcohol use disorders comprise a particularly risky group, although risk of developing a SUD within this group is not uniform. These results also indicate that some of the most important environmental risk factors for SUDs, such as parental knowledge, exert varying effects across levels of genetic risk. Each of these main study findings will be discussed in turn.

Peer Substance use as a Mediator of the Effect of Parent AUD and Genetic Risk on Emerging Adult SUD

The current study predicted that peer substance use would partially mediate the effect of parental alcoholism on emerging adult SUD, and support was found for this hypothesis. Specifically, children of alcoholics were more likely to have friends who drank alcohol and used drugs, which in turn prospectively predicted increased risk for emerging adult substance use disorders. Literature suggests that parents with SUDs are more likely to model substance use, are less likely to limit offspring drinking, and are more likely to have behaviorally under-controlled children (Abar & Turrisi, 2008; Sher, 1991). All of these factors increase the chance that adolescents both develop SUDs and associate with deviant peers (Hicks, Krueger, Iacano, McGue, & Patrick, 2004; Kendler, Sundquist, Ohlsson, Palmer, Maes, Winkleby, & Sundquist, 2012). Adolescents who are impulsive and sensation seeking and whose parents engage in less monitoring are more likely to associate with peers who use substances and who encourage substance use behaviors.

There is a very large literature suggesting that peer substance use increases risk for later substance use problems, as friends who drink alcohol and use drugs may provide access and opportunity for substance use, model substance use behavior, and indirectly influence substance use norms use for those around them (Borsari & Carey, 2001; Dishion & Owen, 2002). The current study replicated this finding. However, the fact that this finding was obtained over and above gene-environment correlation suggests that children of parents with AUDs are at risk for associating with substance-using peers because of some mechanism beyond simply being genetically or environmentally at risk for behavioral undercontrol.

In fact, peer substance use did not mediate the effect of genetic risk on SUDs. That is, there was no evidence of a genetically based peer selection process in which genetically high risk children select deviant peers who in turn, influence SUD. The literature examining genetic influences on an individual's choice of peer group is mixed, with stronger effects appearing in older samples and in some cases, only among males (Beaver et al., 2009; Chassin, et al., 2012; Iervolino et al., 2002). This trend may appear because as individuals age, they gain freedom to associate with those whose behaviors are more consistent with their genotypes. In fact, as compared to the non-significant zero-order correlations between the theory-based gene score and age 11-14, and age 15-17 peer substance use, the correlation between this score and age 18-25 peer substance use was significant[6] in the current study sample, with higher genetic risk conferring greater risk for associating with substance-using peers.

Interaction of Parental Knowledge and Genetic Risk to Predict SUD

The present study predicted that there would be a significant interaction between genetic risk and parental knowledge to predict SUD, and found such an effect. Specifically, for those at higher levels of genetic risk, less parental knowledge predicted higher risk for SUD. However, for those at medium and low levels of genetic risk, parental knowledge did not affect risk for SUD. For adolescents who have the propensity to seek new and dangerous experiences and use substances, having parents who know little about their lives provides further opportunity to escalate in their substance use and develop substance-related problems.

Genetically informed studies involving parenting have generally found that genetic influences are stronger at higher levels of environmental risk and environmental

---

[6] This zero-order correlation was r=.176 (p<.01).

influences are stronger at higher levels of genetic risk. Specifically, recent work has found interactions between parental knowledge and genetic risk to predict adolescent externalizing behavior and smoking, such that the genotype exerts a stronger influence in environments with less monitoring (Dick et al., 2011; Dick et al., 2009; Miranda et al., 2012). These studies suggest that environments that constrain opportunities for problematic substance use suppress or weaken the effects of genetic risk. These findings are also consistent with a review of the gene-environment interaction literature finding this same pattern for adolescent risk taking and externalizing in general, rather than substance use specifically (Young-Wolff, Enoch, & Prescott, 2011). The fact that this interaction effect was obtained over and above gene-environment correlation (as indicated by both the theory-based and empirically-derived gene scores) indicates that parental knowledge exerts a unique, significant effect on emerging adult SUD for a subset of individuals. Therefore, this significant gene-environment interaction effect is consistent with previous literature. However, this finding adds to prior work by extending it to clinical substance disorders outcomes and ruling out the possibility that parental knowledge is simply a marker of genetic risk for behavioral undercontrol and problematic substance use in the prediction of emerging adult SUD.

Interaction of Genetic Risk and Parental AUD to Predict Emerging Adult SUD

The current study also found a significant interaction between parental AUD and child genetic risk to predict emerging adult risk for SUD. For children of parents without AUDs, there was no relation between genetic risk and SUD. However, for children of parents with AUDs, higher genetic risk for behavioral undercontrol and substance use predicted greater likelihood of developing a substance use problem, and this effect held

over and above the main and interaction effects of parental knowledge. Parents with AUDs have been found to provide access to substances, model maladaptive drinking behavior, and provide permissive parenting (Abar, Abar, & Turrisi, 2010). Therefore, for adolescents at high genetic risk, having parents who provide access to alcohol or drugs, model substance use, and/or are permissive regarding substance use exacerbates the likelihood of developing a SUD. In the absence of this maladaptive parenting environment, adolescents at high genetic risk may have less access or opportunity to obtain alcohol or drugs, decreasing likelihood of a substance use problem.

Parental Knowledge as a Mediator of the Effect of Parent AUD on Emerging Adult SUD

The current study hypothesized that parental alcoholism would predict parental knowledge, which in turn would predict offspring SUD. Specifically, it was hypothesized that parents with AUDs would have less knowledge about their children's lives, which in turn would increase risk for offspring SUD. Parental alcoholism was related to mother and father report of parental knowledge in the zero-order correlations, suggesting that an association does exist between these variables. However, the correlations with mother and father knowledge became non-significant after controlling for age 11-14 adolescent substance use. This suggests that the relation between parental alcoholism and parent-reported parental knowledge can be accounted for by the adolescent's early substance use. Although the current study did not test this question specifically, early problematic substance use may fully mediate the relation between parental alcoholism and parental knowledge, with the relation between parental AUD and parental knowledge being better explained by adolescent alcohol and drug use. Indeed, research has found that adolescents

who use substances and engage in behaviors they believe their parents would disapprove are unlikely to disclose their involvement in these activities (Tilton-Weaver & Marshall, 2008). These actions likely prompt caregivers to withdraw from youths (Kerr et al., 2008; Dishion et al., 2004; Kerr & Stattin, 2003). These findings generally suggest that after taking early adolescent substance use into account, parental alcoholism is no longer associated with less parental knowledge.

In terms of the main effect of parental knowledge on emerging adult SUD, only for father report did less parental knowledge yield higher risk for SUD. For child and mother report, there was no main effect of parental knowledge on SUD, although there was significant moderation by genetic risk. In the current study, the average level of mother knowledge was high, unlike the average level for father knowledge which was relatively low. Therefore, it may be that a ceiling effect of mother report of parental knowledge made it difficult for mother knowledge to significantly predict risk for SUDs. This trend may in part explain why mother knowledge only predicted risk for SUDs among those at high genetic risk. It may have been that for those at high genetic risk, any slight change in mother knowledge influenced the offspring's risk for SUD. However, for father report, parental knowledge predicted risk for SUD among those at either high or medium levels of genetic risk.

Parental Knowledge as a Mediator of the Effect of Genetic Risk on Emerging Adult SUD

It was also predicted that the theory-based gene score would predict parental knowledge (i.e. evocative gene-environment correlation), which in turn would predict emerging adult SUD. Specifically, it was hypothesized that higher genetic risk for

behavioral undercontrol in adolescents would present caregivers with a particularly

difficult phenotype to attempt to parent. There was generally no such relation found

between the theory-based gene score and parental knowledge (with the exception of a

marginally significant effect in the model using child report in the larger sample).

However, one possibility for the lack of significant association is that this gene score was

meant in part to capture risk for behavioral undercontrol, and genetic effects on

externalizing outcomes are relatively small in adolescence (Dick et al., 2006). If genetic

effects on behavioral undercontrol do not emerge until older ages, one might actually not

expect a significant relation between this theory-based gene score and evoked parental

knowledge in adolescence when adolescents are age 11-14. Indeed, the limited research

examining evocative gene-environment correlation across development generally

suggests increasing effects between childhood and adulthood (Jaffee & Price, 2007;

Beam & Turkheimer, 2013). In the current study, the zero-order correlations between this

theory-based gene score and later adolescent (age 13-17) parental knowledge were

significant or trending towards significant[7]. Therefore, future research interested in

detecting evocative gene-environment associations should attempt to measure parenting

constructs in later adolescence.

The current study may have also failed to find an association between the theory-

based gene score and parental knowledge because of a limitation in the manner in which

the score was constructed. Specifically, SNPs related to both conduct disorder as well as

response to alcohol and drugs were used in the creation of this theory-based gene score.

Therefore, the SNPs related to response to substances may have washed out the effects of

---

[7] The correlations between the theory gene score and age 13-17 parental knowledge ranged from r=-.117 (p=.1) to r=-.229 (p<.05), indicating that higher genetic risk for disinhibition was associated with less parental knowledge.

the SNPs related to conduct disorder, which was hypothesized to evoke less parental knowledge from caregivers. Researchers aiming to find a gene-environment correlation (e.g. a correlation between genetic risk and parenting) should attempt to create a gene score that captures propensity for a one-dimensional phenotype that is likely to evoke an aversive response from parents.

One final explanation for the lack of consistent relation between the theory-based score and parental knowledge may be that there were a relatively small number of SNPs comprising the theory-based gene score, as well as a relatively small sample on which analyses were conducted. Therefore, the current study may have been under-powered to detect this effect. Future research would benefit from testing this question in a larger sample with a theory-based gene score using a larger number of SNPs.

In further attempting to examine whether parental knowledge mediated the effect of genetic risk on emerging adult SUD, the current study tested whether parental knowledge predicted risk for offspring SUD. Prior work which has found that only for father report (Chassin et al., 1993) does parental knowledge predict later offspring substance use outcomes may have been capturing the effect at medium levels of genetic risk. The current study found that at medium and high levels of genetic risk, father-reported knowledge predicted emerging adult SUD. However, only at high levels of genetic risk did mother- and child-reported knowledge predict risk for emerging adult substance use disorder. These findings suggest that parental knowledge exerts the strongest effect in influencing risk for emerging adult SUD among those at greater genetic risk for behavioral disinhibition and maladaptive substance use. They also

suggest that the effect of father-reported knowledge on risk for SUD extends to offspring at medium levels of genetic risk.

Interaction of Genetic Risk and Peer Substance Use to Predict Emerging Adult SUD

Based on previous work examining gene-environment interactions, this study hypothesized that there would be an interaction between genetic risk and peer substance use to predict SUD, but this interaction was not significant. However, most of the literature using measured genes to examine gene-environment interaction effects to predict externalizing behavior or substance use outcomes has involved parenting. Therefore, it is difficult to say whether the current study's lack of significant interaction between genetic risk and peer substance use to predict risk for SUD is necessarily inconsistent with prior work.

The limited work involving measured genes that has examined deviant peer affiliations found a significant interaction between the A118G SNP of the OPRM1 gene and deviant peer affiliations. Specifically, for those at higher levels of genetic risk, more peer substance use predicted greater risk for an AUD, although literature is mixed on whether this relation only holds for females or males and females (Chassin et al., 2012; Miranda et al., 2012). The A118G SNP from the OPRM1 gene is primarily implicated in amplifying the rewarding effects of substances. One other study failed to find a significant interaction between the VNTR SNP of DRD4 (implication in sensation seeking and impulsivity) and deviant peer associations to predict adolescent substance use (van der Zwaluw, Larsen, and Engels, 2011) Therefore, it may be that using SNPs related to behavioral undercontrol as opposed to response to substances influences the potential for an interaction with peer affiliations to predict substance use outcomes. The

current study used a broad genetic risk score using SNPs from receptor systems implicated in both behavioral undercontrol and response to substances, and it may be that including SNPs from both types of systems interfered with the ability of the gene score to interact with peer substance use to significant predict SUDs.

Implications of Findings for Prevention and Intervention Programs

The findings from the present study have implications for prevention and intervention programs. First, the finding that parental knowledge exerts a stronger effect on risk for emerging adult SUD for those at higher levels of genetic risk for behavioral disinhibition is important for prioritizing intervention efforts. Specifically, this finding suggests that there is a link between parental knowledge and later risk for SUDs for a subset of adolescents. Therefore, the extent to which parents are aware of their children's day-to-day activities exerts a lasting impact on their risk for substance use disorders. The literature examining how parents obtain information about their children's lives indicates that child disclosure, rather than parent solicitation of information, explains a great deal of the variance (Kerr & Stattin, 2003). However, even if child self-disclosure drives parental knowledge, other parenting constructs such as sensitivity and control may increase parent-child closeness, and in turn, the likelihood that adolescents voluntarily disclose information to parents (Vieno, Nation, Pastore, & Santinello, 2009). Additionally, it may be that adolescents who are engaging in deviant acts and associating with substance-using peers withdraw from their parents, and that their parents in turn withdraw from the adolescents. In these cases, educating parents about the role of active, nurturing and non-controlling parenting techniques in evoking adolescent self-disclosure,

61

especially for children who are at higher genetic risk, may be important in decreasing the likelihood of emerging adult SUDs.

Next, the finding that peer substance use mediated the effect of parent AUD on emerging adult SUD, over and above genetic risk for behavioral undercontrol is noteworthy. Prior work had implicated multiple possible mechanisms in the link from parental AUD to peer substance use and emerging adult SUD. However, the current study findings suggest that some mechanism other than simply genetic/temperamental risk explains why children of parents with AUDs are at risk for peer substance use and in turn substance use disorders. Specifically, parents with AUDs are unlikely to limit offspring drinking and are more likely to model drinking behaviors, so perhaps it is these parenting behaviors that allow for adolescents to associate with deviant peers. Intervention work should emphasize to parents with AUDs the importance of talking with adolescents about the reasons to limit/discontinue drinking, and engage in more adaptive behaviors in place of drinking.

Finally, the finding that greater genetic risk for behavioral undercontrol and SUDs increase risk for emerging adult SUDs for children of parents with AUDs only has important implications. It may be that the combination of higher genetic risk and parents who provide access to substances or model drinking behaviors (among parents with AUDs) confers the greatest risk for SUDs among emerging adults. This finding suggests that intervention work should discuss with parents with AUDs the necessity of limiting access of adolescents to substances, especially for those at highest genetic risk for behavioral undercontrol and substance use disorders.

Limitations

Although the present study found important effects involving genetic risk to predict parental knowledge, peer substance use, and emerging adult SUDs, it is important to consider its limitations. First, parent genotype was not measured, so the extent to which parents' genetic risk influences parenting (i.e. passive gene-environment correlation) could not be tested. Indeed, prior research has found evidence for significant passive gene-environment effects (Rice, Lewis, Harold, & Thapar, 2013). Future research should therefore attempt to test competing theories of gene-environment correlation, specifically whether passive and/or active gene-environment correlation predict parenting behaviors.

Second, the theory-based gene score was meant to capture risk for behavioral undercontrol and risk for SUDs, both of which were hypothesized to evoke reduced parental knowledge and increased risk for associating with deviant peers. However, as stated, this score's significant relation to emerging adult SUDs but no other study variables suggests that the SNPs involved in response to substances and risk for problematic substance use may have been over-powering the SNPs that were meant to capture risk for conduct problems and behavioral undercontrol. This is one potential explanation for why no evocative gene-environment correlation was observed. Future researchers hoping to find such a gene-environment correlation should attempt to create a gene score that captures risk for a unidimensional phenotype that has been shown in the literature to evoke an aversive response from parents.

Third, in creating both the empirically-based and theory-based gene scores, a number of assumptions were made. Specifically, the current study assumed that SNP

effects were linear, that each SNP did not interact with others, and that each SNP did not moderate main effects in different ways. It would be ideal if future research in this area could test whether creating gene scores under these assumptions influences study findings.

Finally, the effects of measured genes on outcomes tend to be very small and explain fractions of a percent of variance (Bierut, 2011). There were a number of marginally significant main and interaction effects, suggesting that perhaps the current study was under-powered to detect some of these effects. Therefore, future work should attempt to examine relations among these study variables in a larger sample that would have more power to detect effects involving genes.

Conclusions and Summary

In summary, this study provides important contributions. First, over and above gene-environment correlation, the current study found that less parental knowledge predicted greater risk for SUDs for those at higher genetic risk for behavioral undercontrol. This study also adds to current literature by finding that only for children of parents with AUDs does higher genetic risk for behavioral undercontrol and maladaptive substance use yield greater likelihood of developing a SUD. Finally, the current study replicates previous research finding that peer substance use mediated the effect of parental AUD on emerging adult SUD. However, it adds to this literature by suggesting that some mechanism other than simply increased behavioral undercontrol explains relations among parental AUD, peer substance use, and emerging adult SUD. These main study findings were also robust across reporter and sample. Taken together, these findings indicate that children of parents with AUDs comprise a particularly risky group,

although likelihood of SUD within this group is not uniform. These findings also suggest

that some of the most important environmental risk factors for SUDs, such as parental

knowledge, exert non-uniform effects that vary across level of genetic propensity.

Table 1. *Comparing Participants Included in this Sample to those Excluded from this Sample.*

	Included		Excluded				
	N	Mean (SD)	N	Mean (SD)	T	P value	Effect size
Age 11-14 Father Knowledge	87	3.97 (.56)	64	4.08 (.63)	1.120	.265	
Age 11-14 Mother Knowledge	105	4.47 (.60)	85	4.44 (.54)	-.491	.624	
Age 11-14 Child report of Parent Knowledge	105	3.93 (.76)	85	3.86 (.77)	.638	.524	
Age 15-17 Peer Substance Use	122	.88 (.87)	104	1.09 (.94)	1.722	.086	Cohen's D (.2=small, .5=medium) .23
	N	% of included	N	% of excluded	Chi-Square	P value	
G1 alcoholism status Non-alcoholic=0 Alcoholic=1	134 120	52.8% 47.2%	74 126	37% 63%	11.19	.001	Cramer's V (.1=small, .3=moderate) .164
G2 Age 18-25 alcohol or drug diagnosis Non-diagnosed=0 Diagnosed=1	149 95	61.1% 38.9%	85 84	50.3% 49.7%	4.716	.019	.128
G2 Gender Female=0 Male=1	134 120	52.8% 47.2%	80 120	40% 60%	7.307	.004	.118
G2 Ethnicity 1=Non-Hispanic Caucasian 2=Hispanic	188 66	74% 26%	141 44	76.2% 23.8%	.276	.340	

Table 2. *Descriptive Information Pertaining to Current Study Sample.*

Variable Name	Min.	Max.	Mean (SD)	Skew	Kurtosis
Age 11-14 Father Knowledge	2	5	3.97(.57)	-.505	1.771
Age 11-14 Mother Knowledge	2.67	5	4.48 (.60)	-.970	.372
Age 11-14 Child report of Parent Knowledge	1	4.33	2.07 (.76)	.672	.131
Age 15-17 Peer Substance Use	0	3.67	.88 (.87)	1.177	.719
Ancestry Gene Score	-3.39	1.17	.06 (.91)	-1.403	1.070
Theory-based gene Score	9	19	13.87 (1.95)	-.017	.130
Empirically-based gene Score	92	168	130.32 (14.67)	.078	-.467
				%	
G1 alcoholism status				47.2% diagnosed	
G2 Age 18-25 alcohol or drug diagnosis				38.9% diagnosed	
G2 Gender				52.8% female	

Table 3. *SNPs Included in the Ancestry Gene Score.*

	SNP	Gene
1.	rs883399	ADAM17
2.	rs1572396	ATRNL1
3.	rs730570	C14orf70
4.	rs953786	C18orf17
5.	rs1931059	DLGAP3
6.	rs262838	DOCK2
7.	rs6587216	EPN2
8.	rs9847748	FAM19A4
9.	rs762656	HCFC1
10.	rs1475930	IGLC3
11.	rs901304	KCNH7
12.	rs2384319	KIF3C
13.	rs1417999	LOC347275
14.	rs1648180	LOC387820
15.	rs9937955	LOC729945
16.	rs1951936	MPP7
17.	rs300152	MSGN1
18.	rs4478653	MTAP
19.	rs7995033	MTMR6
20.	rs2065160	NFASC
21.	rs7504	NR0B2
22.	rs1638567	POLD4
23.	rs734329	PPP1R2P9
24.	rs2165139	RBP2
25.	rs2065982	RFC3
26.	rs814597	ROPN1L
27.	rs2439522	SDC2
28.	rs1426654	SLC24A5
29.	rs1418032	STK35
30.	rs9295009	WDR27
31.	rs2380316	WDR44
32.	rs17638989	ZNF564

Table 4. *SNPs Used to Create the Theory-based Genetic Risk Score*

	Gene	SNP	System	References	Phenotype related to SNP
1.	DRD2/ ANKK1	Taq1A/Rs18 00497	Dopamine	Brody et al 2012; Foley, Loh, Innes, Williams, Tannenberg, Harper, & Dodd, 2004; Esposito-Smythers, Spirito, Rizzo, McGeary, & Knopik, 2009; Munafo, Matheson, & Flint, 2007	Conduct disorder, substance use intake, SUDs
2.	DRD2/ ANKK1	Taq1B/Rs10 79597	Dopamine	Yang, Kranzler, Zhao, Gruen, Luo, & Gelernter, 2007; Preuss, Zill, Koller, Bondy, & Soyka, 2007	Conduct disorder, substance use intake, SUDs
3.	DRD2/ ANKK1	Rs1799978	Dopamine	Dick, Wang, Plunkett, Aliev, Hinrichs, Bertelsen, et al., 2007; Yang et al., 2007	Conduct disorder, substance use intake, SUDs
4.	DRD2/ ANKK1	rs12364283	Dopamine	Hamidovic, Dlugos, Skol, Palmer, & deWit, 2009; Yang et al., 2007	Conduct disorder, substance use intake, SUDs
5.	GABRA 2	Rs279858; in high LD with Rs279871	GABA	Dick, Bierut, Hinrichs, Fox, Bucholz, Kramer, et al., 2006; Enoch, Hodgkinson, Yuan, Albaugh, Virkkunen, & Goldman, 2008	Rewarding effects of substances, tolerance, and SUDs
6.	OPRM1	Rs1799971	Opioid	Miranda, Ray, Justus, Meyerson, Knopik, McGeary, et al., 2010; Ray, 2011	Rewarding effects of substances
7.	OPRM1	Rs548646; in high LD with Rs660756	Opioid	Zhang, Luo, Kranzler, Lappalainen, Yang, Krupitksy, et al., 2006; Ehlers, Lind, & Wilhelmsen, 2008	Rewarding effects of substances
8.	PDYN	Rs1997794	Opioid	Xuei, Flury-Wetherill, Bierut, Dick, Nurnberger, Foroud, et ak., 2007; Taqi, Bazov, Watanabe, Nyberg, Yakovleva, & Bakalkin, 2011	Rewarding effects of substances
9.	ADH1B	Rs1229984	Drug Metabolism	MacGregor, Lind, Bucholz, Hansell, Madden, Richter et al., 2008; Liu, Zhou, Hodgkinson, Yuan, Shen, Mulligan et al., 2011	Physical effects of substance use (e.g. flushing)
10.	ADH4	Rs3762894	Drug Metabolism	MacGregor, Lind, Bucholz, Hansell, Madden, Richter et al., 2008; Liu, Zhou, Hodgkinson, Yuan, Shen, Mulligan et al., 2011	Physical effects of substance use (e.g. flushing)
11.	CNR1	Rs1049353	Cannabinoid	Schmidt, Samochowiec, Finckh, Fiszer-Piosik, Horodnicki, Wendel, et al., 2002; Zhang, Ishiguro, Ohtsuki, Carillo, Walther, Onaivi, et al., 2004; Hartman, Hopfer, Haberstick, Rhee, Crowley, Corley, et al., 2009	Withdrawal after discontinuation, SUDs

Table 5. *11 SNPs Randomly Chosen from those Remaining after Creating Theory-based Genetic Risk Score.*

	SNP	Gene	System
1.	rs567807	ARRB1	Adrenergic
2.	rs180095	DRD4	Dopamine
3.	rs2283139	SLC18A2	Dopamine
4.	rs5970292	GABRA3	GABA
5.	rs731779	HTR2A	Serotonin
6.	rs11055682	GRIN2B	NMDA
7.	rs219881	GRIN2B	NMDA
8.	rs1336978	SORCS1	Other
9.	rs1719982	LOC388459	Other
10.	rs2427400	NTSR1	Signal Transduction
11.	rs4792887	CRHR1	Stress

Table 6. *30 SNPs Used to Create the Empirically-based Genetic Risk Score.*

SNP Number	SNP	Standard p-value	FDR-adjusted p-value
1	rs333113	0.0009	0.074133
2	rs420817	0.0027	0.074133
3	rs497576	0.0086	0.078396
4	rs524468	0.0107	0.078396
5	rs167770	0.0109	0.078396
6	rs851027	0.0116	0.078396
7	rs363526	0.0129	0.078396
8	rs324029	0.0134	0.078396
9	rs753572	0.0217	0.086379
10	rs893584	0.0245	0.086379
11	rs36017	0.0256	0.086379
12	rs252965	0.03	0.086379
13	rs660361	0.0317	0.086379
14	rs782449	0.0386	0.089831
15	rs525631	0.0416	0.089831
16	rs963468	0.0427	0.089831
17	rs279841	0.0431	0.089831
18	rs324594	0.0529	0.0973
19	rs909525	0.0541	0.0973
20	rs576386	0.0592	0.0973
21	rs520865	0.0601	0.0973
22	rs904092	0.0643	0.0973
23	rs623580	0.0692	0.0973
24	rs732215	0.0805	0.097904
25	rs182637	0.0854	0.097904
26	rs412974	0.0867	0.097904

SNP Number	SNP	Standard p-value	FDR-adjusted p-value
27	rs722651	0.0894	0.097904
28	rs363338	0.0965	0.097904
29	rs279843	0.097	0.097904
30	rs362936	0.0972	0.097904

Table 7. *Frequencies of 30 SNPs Included in Empirically-based Genetic Risk Score.*

SNP	% 0's	% 1's	% 2's
rs167770	45.7	42.1	12.2
rs182637	.4	68.6	31
rs252965	2.8	23.3	74
rs279841	16.1	52.4	31.5
rs279843	16.1	53.1	30.7
rs324029	45.7	41.3	13
rs324594	57.1	35.8	7.1
rs333113	6.7	37.8	55.5
rs36017	22.1	46.2	31.6
rs362936	.4	3.9	95.7
rs363338	10.6	45.3	44.1
rs363526	42.5	42.9	14.6
rs412974	58.7	37	4.3
rs420817	31.1	47.6	21.3
rs497576	22	52	26
rs520865	18.1	45.7	36.2
rs524468	50.8	41.7	7.5
rs525631	34.6	49.2	16.1
rs576386	35.4	48.8	15.7
rs623580	12.6	47.8	39.5
rs660361	21.7	48	30.3
rs722651	35.4	45.7	18.9
rs732215	33.9	41.3	24.8
rs753572	39.4	47.6	13
rs7824449	28.8	51.7	19.6
rs851027	11	43.7	45.3
rs893584	32.7	50	17.3
rs904092	2	23.6	74.4
rs909525	54.7	23.3	22
rs963468	15.1	47.2	37.7

Table 8. Correlations between Covariates and Study Variables

	Child Gender	Child Ancestry	Band 1 Age	Band 2 Age	Band 3 Age	Band 1 Substance Use	Band 1 Peer Substance Use
Child Gender	--						
Child Ancestry	-.026	--					
Band 1 Age	-.041	-.171**	--				
Band 2 Age	.070	-.091	.211***	--			
Band 3 Age	.122*	-.001	.198**	.550***	--		
Band 1 Substance Use	.066	-.045	.192**	.099†	-.007	--	
Band 1 Peer Substance Use	-.057	-.179**	.029	.249***	.128*	.595***	--
Parental Alcoholism	-.027	-.165**	-.049	-.147*	-.044	.125**	.149*
Father Report of Knowledge	-.041	-.178**	.010	.022	-.133*	-.129**	-.037
Mother Report of Knowledge	-.138*	.084	-.081	-.199**	.066	-.148*	-.070
Child Report of Parents' Knowledge	-.264***	.085	-.026	-.335***	.004	-.224***	-.237***
Band 2 Peer Substance Use	-.066	-.049	.087	.266***	.160**	.525***	.513***
Band 3 SUD	.156**	-.068	-.053	-.093	.122*	.262***	.221***
Theory gene Score	.098†	.038	.126*	.055	-.021	.055	-.075
Empirical gene Score	.042	.208***	.206***	.089	.003	.061	.069

N=254, although exact *n* varies across reporter. ***p<.001, **p<.01,*p<.05, †*p< .1*; gender is coded 0=Female, 1=Male; Ancestry score is coded such that higher scores mean more Hispanic ancestry; Parental Alcoholism 0=non-COA, 1=COA; Substance Use Diagnoses is 0=no diagnosis, 1=diagnosis.

Table 9. Correlations between Study Variables

	Parental Alcoholism	Father Report of Knowledge	Mother Report of Knowledge	Child Report of Parents' Knowledge	Band 2 Peer Substance Use	Theory-based gene Score	Empirically-based gene Score
Father Report of Knowledge	-.183**	--					
Mother Report of Knowledge	-.154**	.311***	--				
Child Report of Parents' Knowledge	.013	.278***	.363***	--			
Band 2 Peer Substance Use	.289***	-.407***	-.047	-.223***	--		
Band 3 SUD	.288***	.054	-.122	-.217***	.269***	--	
Theory gene Score	.090	.060	.091	.030	.048	.140*	--
Empirical gene Score	.069	.026	.039	-.068	.138*	.506***	.214***

N=254, although exact *n* varies across reporter. ***$p<.001$, **$p<.01$,*$p<.05$, †$p<.1$;
Parental Alcoholism 0=non-COA, 1=COA; Substance Use Diagnoses is 0=no diagnosis, 1=diagnosis.

Table 10. *Specific Parameters to be Freely Estimated and Constrained in the Model-building Approach.*

Parameters	Model 1	Model 2	Model 3
Covariates gender, ancestry, and age in predicting parental knowledge, peer substance use and SUD	**Freely Estimated**	**Freely Estimated**	**Freely Estimated**
Adolescents' substance use and peer substance use between the ages of 11-14 in predicting age 15-17 peer substance use and age 18-25 SUD	**Freely Estimated**	**Freely Estimated**	**Freely Estimated**
Effects of parental alcoholism, parental knowledge, and peer substance use on SUDs	**Freely Estimated**	**Freely Estimated**	**Freely Estimated**
Main effects of the theoretical and empirically-based gene scores on parental knowledge, peer substance use, and SUD	Constrained to zero	**Freely Estimated**	**Freely Estimated**
Interaction effects between the theory-based gene score and parental alcoholism, ancestry, gender, and age in predicting parental knowledge, peer substance use and SUDs	Constrained to zero	Constrained to zero	**Freely Estimated**
Interaction between knowledge and the theory-based gene score predicting peer substance use, and the interactions between the theory-based gene score and parental knowledge and peer substance use to predict SUD	Constrained to zero	Constrained to zero	**Freely Estimated**

Table 11. *Results of Model using Mother Report of Parental Knowledge (N=254)*

Predictor	Age 11-14 Mother Reported Knowledge		Age 15-17 Peer Substance Use		Age 18-25 Substance Use Disorder	
	B	*SE*	*B*	*SE*	*B*	*SE*
Theory-based gene Score	.043	.358	.029	.473	-.126	.814
Empirically-based gene Score	.043	.139	.127	.162	.589***	.255
Parent Alcohol Use Disorder (AUD)	-.156	.116	.337***	.105	.182*	.224
Child Gender	-.116	.125	-.053	.165	.191**	.199
Child Ancestry	.069	.043	-.049	.076	-.108†	.101
Age Band 1 Age (11-14)	-.028	-.043				
Age Band 2 Age (15-17)			.165†	.210		
Age Band 3 Age (18-25)					.239**	.664
Age 11-14 Own Substance Use			.297*	.122	.041	.154
Age 11-14 Peer Substance Use			.678***	.083		
Age 15-17 Peer Substance Use					.280*	.109
Age 11-14 Mother Knowledge				.231	-.044	.220
Theory-based gene X Parent AUD					.154†	.107
Theory-based gene X Age 11-14 Mother Knowledge				.114	-.195†	.153
Theory-based gene X Age 15-17 Peer Substance Use					-.106	.744

Note. †$p< .10$, *$p<.05$, **$p<.01$, ***$p<.001$. $N=201$. *B*= Standardized regression coefficient. *SE*= Standard error. Parental AUD is coded 0 for children of non-alcoholics and 1 for children of alcoholics. Gender is coded 0 for females and 1 for males.

Table 12. *Results of Model using Father Report of Parental Knowledge (N=254)*

Predictor	Age 11-14 Father Reported Knowledge		Age 15-17 Peer Substance Use		Age 18-25 Substance Use Disorder	
	B	*SE*	*B*	*SE*	*B*	*SE*
Theory-based gene Score	.102	.325	.024	.439	-.021	.660
Empirically-based gene Score	-.211†	.130	-.176	.169	.735***	.246
Parent Alcohol Use Disorder (AUD)	-.150	.125	.309**	.126	.225*	.241
Child Gender	-.115	.123			.206**	.208
Child Ancestry	-.129	.067	-.016	.170	-.079	.095
Age Band 1 Age (11-14)	.099	.143				
Age Band 2 Age (15-17)			.197	.309		
Age Band 3 Age (18-25)					.279**	.640
Age 11-14 Own Substance Use			.140	.130	.094	.159
Age 11-14 Peer Substance Use			.341***	.502		
Age 15-17 Peer Substance Use					.451*	.117
Age 11-14 Father Knowledge			-.345	.387	-.355*	.315
Theory-based gene X Parent AUD					.203†	.093
Theory-based gene X Age 11-14 Father Knowledge			.307	.170	-.216†	.137
Theory-based gene X Age 15-17 Peer Substance Use					-.111	.547

Note. †*p< .10, *p<.05, **p<.01, ***p<.001.N=201. B=* Standardized regression coefficient. *SE=* Standard error. Parental AUD is coded 0 for children of non-alcoholics and 1 for children of alcoholics. Gender is coded 0 for females and 1 for males.

Table 13. *Results of Model using Child Report of Parental Knowledge (N=254)*

Predictor	Age 11-14 Child Reported Knowledge		Age 15-17 Peer Substance Use		Age 18-25 Substance Use Disorder	
	B	*SE*	*B*	*SE*	*B*	*SE*
Theory-based gene Score	.084	.403	.017	.446	-.129	1.254
Empirically-based gene Score	-.193†	.054	.063	.055	.537***	.244
Parent Alcohol Use Disorder (AUD)	.014	.151	.301***	.181	.067	.367
Child Gender	-.253	.162	-.183†	.184	.223**	.379
Child Ancestry	.099	.088	-.054	.088	-.095	.242
Age Band 1 Age (11-14)	.076	.151				
Age Band 2 Age (15-17)			.242*	.214		
Age Band 3 Age (18-25)					.179**	.103
Age 11-14 Own Substance Use				.100	-.115	.251
Age 11-14 Peer Substance Use			.471***	.085	.269**	.317
Age 15-17 Peer Substance Use						
Age 11-14 Child Knowledge			-.343	.181	-1.573	.308
Theory-based gene X Parental AUD					.135*	.140
Theory-based gene X Age 11-14 Child Knowledge			.008	.554	-.141†	.231
Theory-based gene X Age 15-17 Peer Substance Use					-.215	.166

Note. †*p< .10, *p<.05, **p<.01, ***p<.001.N*=201. *B*= Standardized regression coefficient. *SE*= Standard error. Parental AUD is coded 0 for children of non-alcoholics and 1 for children of alcoholics. Gender is coded 0 for females and 1 for males.
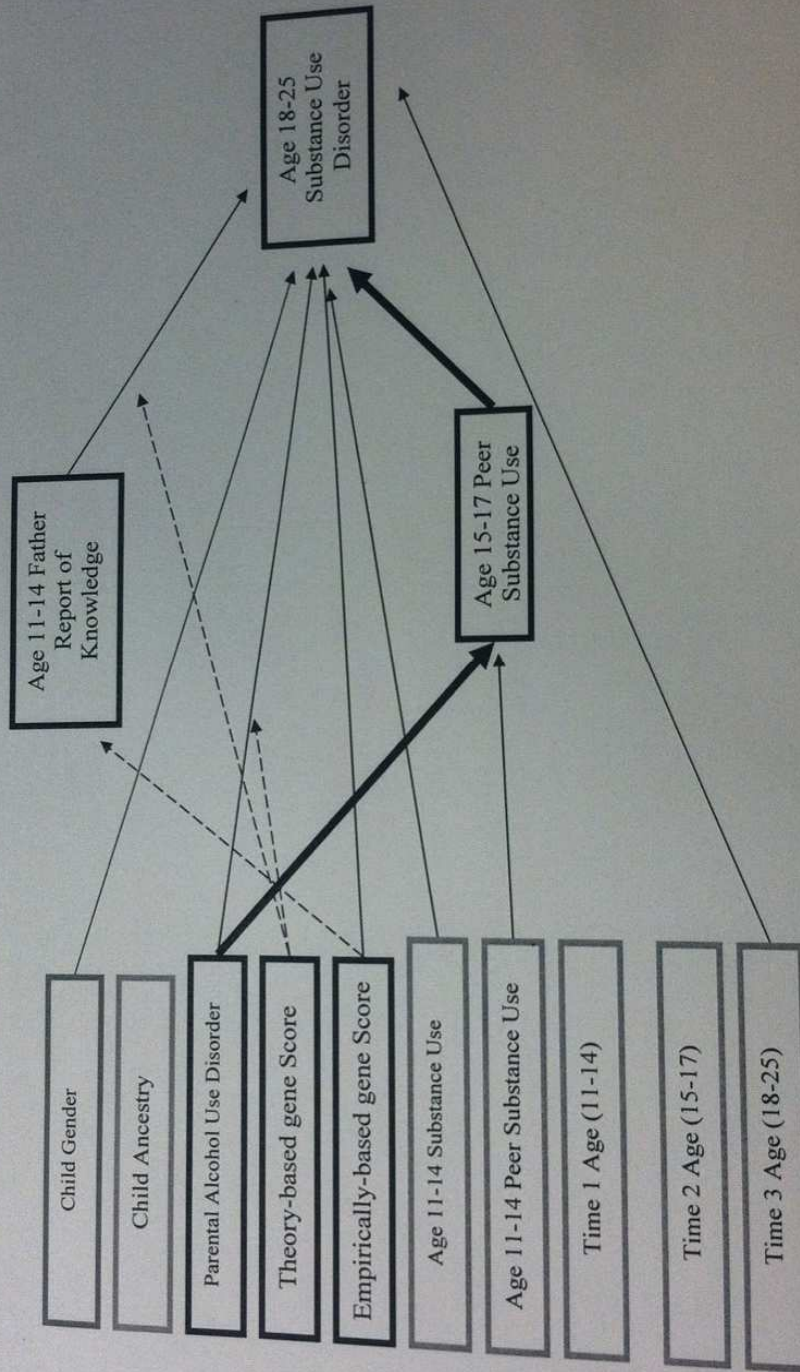
Figure 1. *Final Mother Model (N=254).*
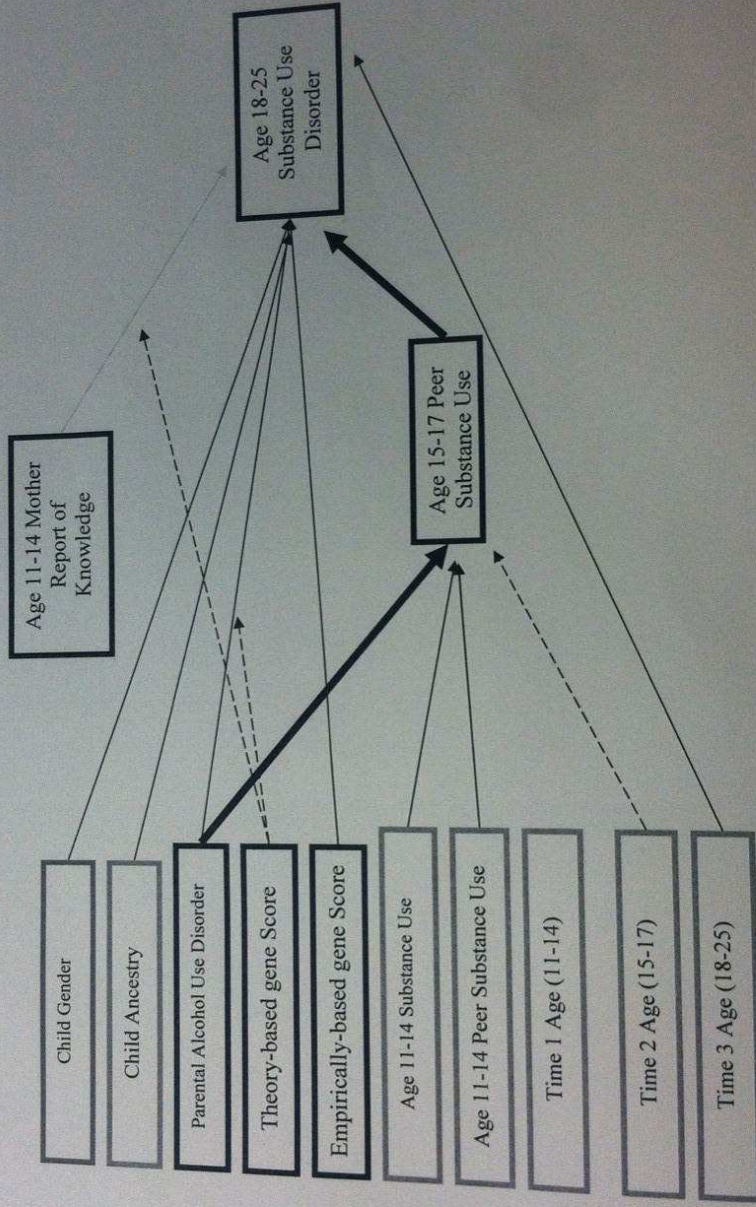
Solid lines indicate significant effects (p<.05), dashed lines indicate marginally significant effects (p<.1), and bolded paths indicate significant mediation effects.

Figure 2. *Final Father Model (N=254).*

Solid lines indicate significant effects (p<.05), dashed lines indicate marginally significant effects (p<.1), and bolded paths indicate NS effects (the only NS paths that are shown are those involved in moderated effects). Bolded black paths indicate significant mediation effects.

Figure 3. *Final Child Model (N=254).*

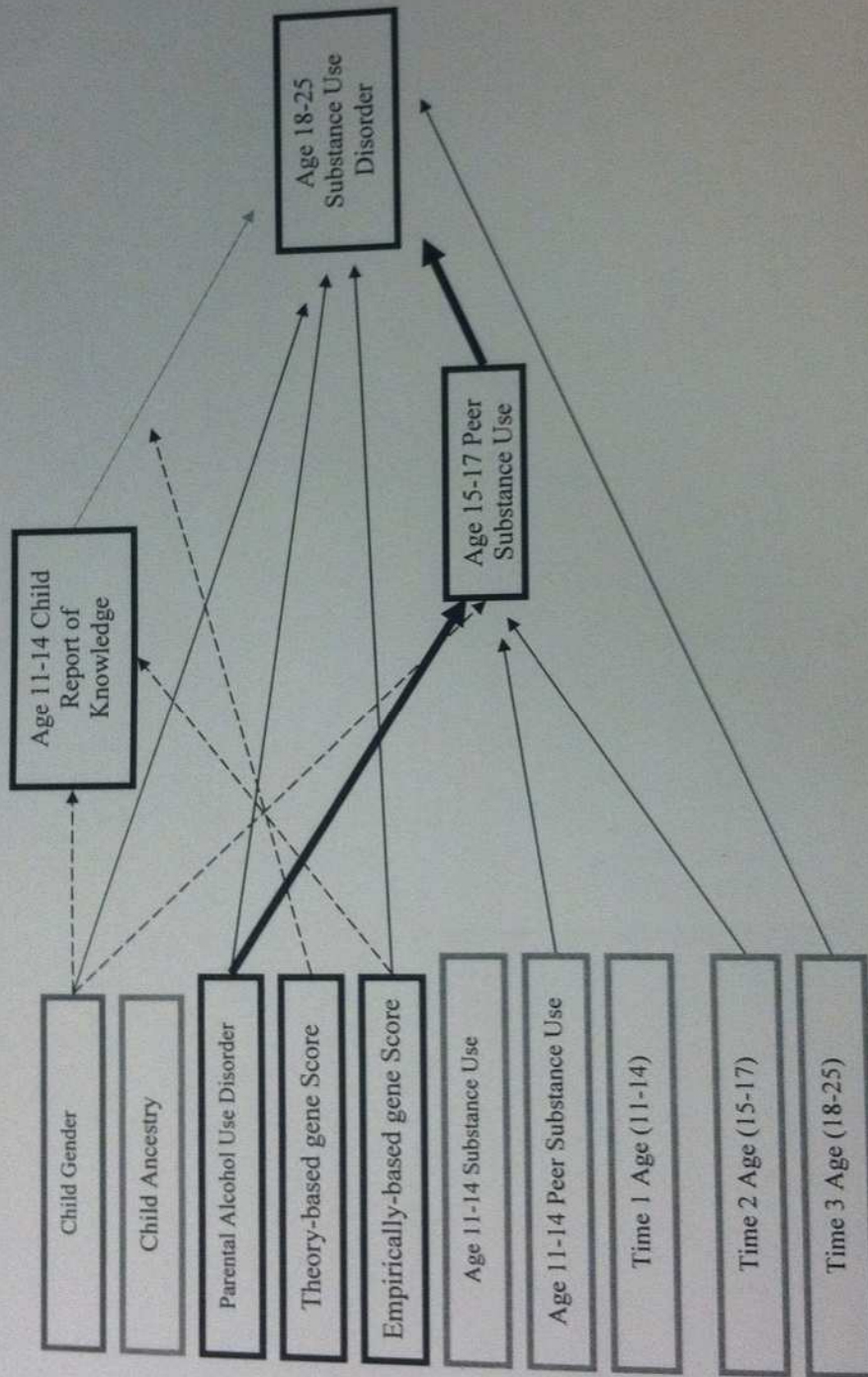Solid lines indicate significant effects (p<.05), dashed lines indicate marginally significant effects (p<.1), and bolded paths indicate significant mediation effects. Bolded moderated paths indicate significant mediation.

82

REFERENCES

Abar, C., Abar, B., & Turrisi, R. (2010). The impact of parental modeling and permissibility on alcohol use and experienced negative drinking consequences in college. *Addictive Behaviors*, 34, 541-547.

Abar, C. & Turrisi, R. (2008). How important are parents during the college years? A longitudinal perspective of indirect influences parents yield on their college teens' alcohol use. *Addictive Behaviors*, 33, 1360-1368.

Agrawal, A., Balasubramanian, S., Smith, E.K., Pamela, A.F., Bucholz, K.K., Heath, A.C. et al. (2010). Peer substance involvement modifies genetic influences on regular substance involvement in young women. *Addiction*, 105, 1844-1853.

Agrawal, A., Edenberg, H.J., Forund, T., Bierut, L.J, Dunne, G., Hinrichs, A.L. et al. (2006). Association of GABRA2 with drug dependence in the collaborative study of the genetic of alcoholism sample. *Behavior Genetics*, 36, 640-650.

Aiken, L. & West, S. (1991). Multiple Regression: Testing and Interpreting Interactions. Newbury Park, CA: Sage.

Beaver, K.M., Shutt, J.E., Boutwell, B.B., Ratchford, M., Roberts, K., & Barnes, J.C. (2009). Genetic and environmental influences on levels of self-control and delinquent peer affiliation. Results from a longitudinal sample of adolescent twins. *Criminal Justice and Behavior*, 36, 41-60.

Belsky, J. (2005). Differential susceptibility to rearing influence: An evolutionary hypothesis and some evidence. In B. Ellis & D. Bjorklund (Eds.), Origins of the social mind: Evolutionary psychology and child development (pp. 139–163). New York: Guilford.

Belsky, J., Bakermans-Kranenburg, M., & van IJzendoorn, M. (2007). For better and for worse: Differential susceptibility to environmental influences. *Current Directions in Psychological Science, 16,* 300–304.

Belsky, J. & Pluess, M. (2009). Beyond Diathesis Stress: Differential susceptibility to environmental influences. *Psychological Bulletin*, 135, 885-908.

Benjamini, Y. & Hochberg, Y. (1995). Controlling the false discover rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society*, Series B (Methodological), 57, 289-300.

Bierut, L.J. (2011). Genetic vulnerability and susceptibility to substance dependence. *Neuron Cell Press*, 69, 618-627.

Boardman, J.D., Dominique, B.W., & Fletcher, J.M. (2012). How social and genetic factors predict friendship networks. *Proceedings of the National Academy of Sciences of the United States of America*, 109, 17377-17381.

Bogenschneider, K., Wu, M., Raffaelli, M., & Tsay, J.C. (1998). Parent influences on adolescent peer orientation and substance use: the interface of parenting practices and values. *Child Development,* 69, 1672–88.

Borsari, B. & Carey, K.B. (2001). Peer influences on college drinking: A review of the research. *Journal of Substance Abuse*, 13, 391-424.

Boyce, W., & Ellis, B. (2005). Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology*, 17, 271–301.

Brady, K.T. & Sinha, R. (2005). Co-occurring mental and substance use disorders: the neurobiological effects of chronic stress. *American Journal of Psychiatry,* 162, 1483–93.

Brendgen, M. (2012). Genetics and peer relations: A review. *Journal of Research on Adolescence*, 22, 419-437.

Brody, G.H., Chen, Y., & Beach, S.R.H. (2013). Differential suceptibility to prevention: GABAergic, dopaminergic, and multilocus effects. *Journal of Child Psychology and Psychiatry*, 1-9.

Button, T. M., Stallings, M.C., Rhee, S.H., Corley, R.P., Boardman, J.D., & Hewitt, J.K. (2009). Perceived peer delinquency and the genetic predisposition for substance dependence vulnerability. *Drug and Alcohol Dependence*, 1, 1-8.

Chassin, L., Barrera, M., Bech, K., & Kossak-Fuller, J. (1992). Recruiting a community sample of adolescent children of alcoholics: A comparison of three subject sources. *Journal of Studies on Alcohol, 53,* 316-319.

Chassin, L., Flora, D. B., & King, K. M. (2004). Trajectories of alcohol and drug use and dependence from adolescence to adulthood: The effects of familial alcoholism and personality *Journal of Abnormal Psychology*, 113,483–498.

Chassin, L., Lee, M., Cho, Y., Wang, F. L., Agrawal, A., Sher, K.J., & Lynskey, M.T. (2013). Testing multiple levels of influence in the intergenerational transmission of alcohol disorders from a developmental perspective: The example of alcohol using peers and mu-opioid reception M1 variation. *Development and Psychopathology*, 24, 953-967.

Chassin, L., Pillow, D.R., Curran, P.J., Molina, B.S., & Barrera, M. (1993). Relations of parental alcoholism to early adolescent substance use: a test of three mediating mechanisms. *Journal of Abnormal Psychology,* 102, 3–19.

Chassin, L., Pitts, S. C., Delucia, C., & Todd, M. (1999). A longitudinal study of children of alcoholics: Predicting young adult substance abuse disorders, anxiety, and depression. *Journal of Abnormal Psychology,* 108, 106–119.

Chen, D., Liu, F., Shang, Q., Song, X., Miao, X., & Wang, Z. (2011). Association between polymorphisms of DRD2 and DRD4 and Opioid Dependence: Evidence from the current studies. *American Journal of Medical Genetics. Part B: Neuropsychiatric genetics*, 156, 661-670.

Chen, Y., Ysou, H., Kuo, H., Fang, C., Wang, S., Ho, I. et al. (2013). OPRM1 genetic polymorphisms are associated with the plasma nicotine metabolite cotinine concentration in methadone maintenance patients: A cross-sectional study. *Journal of Human Genetics*, 58, 84-90.

Chilcoat, H. & Anthony, J. (1996). Impact of parent monitoring on initiation of drug use through late childhood. *Journal of the American Academy of Child and Adolescent Psychiatry*, 35, 91–100.

Clarke, T., Krause, K., Li, T., Schumann, G. (2009). Genetic Study: An association of prodynorphin polymorphisms and opioid dependence in females in a Chinese population. *Addiction Biology*, 14, 366-370.

Cleveland, H. H. & Crosnoe, R. (2004). Individual variation and family-community ties: A behavioral genetic analysis of the intergenerational closure in the lives of adolescents. *Journal of Adolescent Research,* 19,174–91.

Cleveland, H. H., Wiebe, R. P., & Rowe, D. C. (2005). Sources of exposure to smoking and drinking friends among adolescents: A behavioral-genetic evaluation. *The Journal of Genetic Psychology, 166,* 153–169.

Cloninger, C., Sigvardsson, Reich, & Bohman, M. (1986). In *Genetic and biological markers for drug abuse and alcoholism*, NIDA/NIAAA Research Monograph. Washington, D.C.: U.S. Government Printing Office.

Cohen, J., Cohen, P., West, S, & Aiken, L. (2003). *Applied multiple regression/correlation analysis for the behavioral sciences* (3rd ed.). Mahwah, NJ: Lawrence Erlbaum.

Costa, B., Giagnoni, G., Colleoni, M. (2000) Precipitated and spontaneous withdrawal in rats tolerant to anandamide. *Psychopharmacology,* 149, 121–128.

Crosnoe, J. & Johnson, M. (2011). Research on Adolescence in the Twenty-First Century. *Annual Review of Sociology*, 37, 439-460.

Cruz, J., Emery, R.E., & Turkheimer, E. (2012). Peer network drinking predicts increased alcohol use from adolescence to early adulthood after controlling for genetic and shared environmental selection. *Developmental Psychology*, 48, 1390-1402.

Dick, D.M., Bierut, L., Hinrichs, A., Fox, L., Bucholz, K.K., Kramer, J. et al. (2006). The role of GABRA2 in risk for conduct disorder and alcohol and drug dependence across developmental stages. *Behavior Genetics*, 36, 577-590.

Dick, D.M., Latendresse, S.J., Lansford, J.E., Budde, J.P., Goate, K.A., Dodge, K.A. et al. (2009). Role of GABRA2 in trajectories of externalizing behavior across development and evidence of moderation by parental monitoring. *Archives of General Psychiatry*, 66, 649-657.

Dick, D.M., Meyers, J.L., Latendresse, S.J., Creemers, H.E., Lansford, J.E., Pettit, G.S. et al. (2011). CHRIM2: Parental monitoring, and adolescent externalizing behavior: Evidence for gene-environment interaction. *Psychological Science*, 22, 481-489.

Dick, D.M., Viken, R., Purcell, S., Kaprio, J., Pulkkinen, L., & Rose, R.J. (2007a). Parental monitoring moderates the importance of genetic and environmental influences on adolescent smoking. *Journal of Abnormal Psychology*, 116, 213–8.

Dick, D.M., Wang, J.C., Plunkett, J., Aliev, F., Hinrichs, A., Bertelsen, S., et al. (2007b). Family-based association analyses of alcohol dependence phenotypes across DRD2 and neighboring gene ANKK1. *Alcoholism: Clinical and Experimental Research*, 31, 1645–1653.

Dishion, T.J., Capaldi, D., Spracklin, K.M., Li, F. (1995). Peer ecology of male adolescent drug use. *Development and Psychopathology,* 7, 803–824.

Dishion, T.J. & McMahon, R.J. (1998). Parental monitoring and the prevention of child and adolescent problem behavior: A conceptual and empirical formulation. *Clinical Child and family Psychology Review, 1,* 61–75.

Dishion, T.J., Nelson, S.N., & Bullock, B.M. (2004). Premature adolescent autonomy: Parent disengagement and deviant peer process in the amplification of problem behavior. *Journal on Adolescence*, 27, 515–530.

Dishion, T. J., & Owen, L. (2002). A longitudinal analysis of friendships and substance use: Bidirectional influence from adolescence to adulthood. *Developmental Psychology, 38*, 480–491.

Ducci, F. & Goldman, D. (2008). Genetic approaches to addiction: genes and alcohol. *Addiction*, 103, 1414–1428.

Edenberg, H. & Foroud, T. (2004). The genetics of alcoholsim: identifying specific genes through family studies. *Addiction Biology*, 11, 386-396.

Ehlers, C.L., Liang, T., & Gizer, I.R. (2012). ADH and ALDH polymorphisms and alcohol dependence in Mexican and Native Americans. *American Journal of Drug and Alcohol Abuse*, 38, 389 –394.

Ehlers, C.L., Lind, P.A., & Wilhelmsen, K.C. (2008). Association between single nucleotide polymorphisms in the mu opioid receptor gene (OPRM1) and self-reported responses to alcohol in American Indians. *BioMed Central Medical Genetics*, 9, 1-11.

Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2011). Differential susceptibility to the environment: An evolutionary–neurodevelopmental theory. *Development and Psychopathology*, 23, 7–28.

Endicott, J., Andreason, N. and Spitzer, R. (1975). *Family history research diagnostic criteria*, New York State Psychiatric Institute, Biometrics Research Department, New York.

Enoch, M., Hodgkinson, C.A., Yuan, Q., Albaugh, B., Virkkunen, M., & Goldman, D. (2008). GABRG1 and GABRA2 as independent predictors for alcoholism in two populations. *Neuropychopharmacology*, 34, 1245-1254

Esposito-Smythers, C., Spirito, A., Rizzo, C., McGeary, J.E., & Knopik, V.S. (2009). Associations of the DRD2 Taq1A Polymorphism with impulsivity and substance use: Preliminary results from a clinical sample of adolescents. *Pharmacology, biochemistry, and behavior*, 93, 306-312.

Fallon, J. H. & Moore, R. Y. (1978). Catecholamine innervation of the basal forebrain. Topography of the dopamine projection to the basal forebrain and neostriatum. *The Journal of Comparative Neurology.*180, 545–580.

Foley, P.F., Loh, E.W., Innes, D.J., Williams, S.M., Tannenberg, A.E.G., Harper, C.G. et al. (2004). Association studies of neurotransmitter gene polymorphisms in alcoholic Caucasians. *Annals New York Academy of Science*, 1025, 39-46.

Fowler, J.H., Settle, J.E., & Christakis, N.A. (2011). Correlated genotypes in friendship networks. *Proceedings of the National Academy of Sciences*, 108, 1993-1997.

Fowler, T., Shelton, K., Lifford, K., Rice, F., McBride, A., Ivan, N. et al. (2007). Genetic and environmental influences on the relationship between peer alcohol use and own alcohol use in adolescents. *Addiction*, 102, 894-903.

Franke, P., Wang, T., Nothen, M.M., Knapp, M., Neidt, H., Albrecht, S. et al. (2001). Non-replication of association between Opioid-receptor gene (OPRM1) A118G polymorphism and substance dependence. *American Journal of Medical Genetics (Neuropsychiatric Genetics)*, 105, 114-119.

Gianoulakis, C. (1996). Implications of endogenous opioids and dopamine in alcoholism: human and basic science studies. *Alcohol and Alcoholism*, 1, 33-42.

Gianoulakis, C., DeWaele, J.P., & Thavundayil, J. (1996). Implications of the endogenous Opioid system in excessive ethanol consumption. *Alcohol*, 13, 19–23.

Gillespie, N., Neale, M.C., Jacobson, K., & Kendler, K.S. (2009). Modeling the genetic and environmental association between peer group deviance and cannabis in male twins. *Addiction*, 104, 420-429.

Guo, G., Elder, G.H., Cai, T., & Hamilton, N. (2009). Gene-environment interactions: Peers' alcohol use moderates genetic contribution to adolescent drinking behavior. *Social Science Research*, 38, 213-224.

Hallikainen, T., Hietala, J., Kauhanen, J., Pohjalainen, T., Syvalahti, E., Salonen, J.T. et al. (2003). Ethanol consumption and DRD2 gene Taq1A Polymorphism among socially drinking males. *American Journal of Medical Genetics*, 119A, 152-155.

Hamidovic, A., Dlugos, A., Skol, A., Palmer, A.A., & deWit, H. (2009). Evaluation of genetic variability in the Dopamine Receptor D2 in relation to behavioral inhibition and impulsivity/sensation seeking: An exploratory study with d-Amphetamine in healthy participants. *Experimental and Clinical Psychopharmacology*, 17, 374-383.

Han, D.H., Yoon, S.J., Sung, Y.H., Lee, Y.S., Kee, B.S., Lyoo, I.K. et al. (2008). A preliminary study: Novelty seeking, frontal executive function and dopamine receptor (D2) Taq1 A gene polymorphism in patients with methamphetamine dependence. *Comprehensive Psychiatry*, 387-392.

Harden, K.P., Hill, J.E., Turkheimer, E., & Emery, R.E. (2008). Gene-environment correlation and interaction in peer effects on adolescent alcohol and tobacco use. *Behavioral Genetics*, 38, 339–347.

Hartman, C.A.,Hopfer, C.J., Haberstick, B., Rhee, S.H., Crowley, T.J. Corley, R.P. et al. (2009). The association between cannabinoid receptor 1 gene (CNR1) and cannabis dependence symptoms in adolescents and young adults. *Drug and Alcohol Dependence*, 104, 11-16.

Herz, A. (1997). Endogenous opioid systems and alcohol addiction. *Psychopharmacology*, 129, 99-111.

Hicks, B. M., Krueger, R.F., Iacano, W.G., McGue, M., & Patrick, C.J. (2004). Family transmission and heritability of externalizing disorders. *Archives of General Psychiatry*, 61, 922-928.

Hicks, B.M., South, S.C., DiRago, A.C., Iacano, W.G., & McGue, M. (2009). Environmental adversity and increasing genetic risk for externalizing disorders. *Archives of General Psychiatry*, 66, 640-648.

Hu, L. & Bentler, A. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling: A Multidisciplinary Journal*, 6, 1-55.

Hubacek, J.A., Pikhart, H., Peasey, A., Kubinova, R., & Boback, M.(2012). ADH1B Polymorphism, alcohol consumption, and binge drinking in Slavic Caucasians: Results from the Czech HAPIEE study. *Alcoholism: Clinical and Experimental Research*, 36, 900-905.

Iervolino, A.C., Pike, A., Manke, B., Reiss, D., Hetherington, E.M., & Plomin, R. (2002). Genetic and environmental influences in adolescent peer socialization: Evidence from two genetically sensitive designs. *Child Development*, 73, 162-174.

Johnston, L. D., O'Malley, P. M. & Bachman, J. G. (1988). National Survey Results on Drug Use 1975-1983. Washington D.C.: National Institute on Drug Abuse.

Hicks, B. M., Krueger, R.F., Iacano, W.G., McGue, M., & Patrick, C.J. (2004). Family transmission and heritability of externalizing disorders. *Archives of General Psychiatry*, 61, 922-928.

Kendler, K.S., Chen, X., Dick, D., Maes, H., Gillespie, N., Neale, M.C. et al. (2012). Recent advances in the genetic epidemiology and molecular genetics of substance use disorders.

Kendler, K.S., Gardner, C., & Dick, D.M. (2011). Predicting alcohol consumption in adolescence from alcohol-specific and general externalizing genetic risk factors, key environmental exposures and their interaction. *Psychological Medicine*, 41, 1507-1516.

Kendler, K.S., Jacobsen, K.C., Gardner, C.O., Gillespie, N., Aggen, S.A., & Prescott, C.A. (2007). Creating a social world. A developmental twin study of peer-group deviance. *Archives of General Psychiatry*, 64, 938-965.

Kendler, K.S., Karkowski, L.M., Neale, M.C., & Prescott, C.A. (2000). Illicit psychoactive substance use, heavy use, abuse, and dependence in a U.S. population-based sample of male twins. *Journal of the American Medical Association Psychiatry*, 57, 261-269.

Kendler, K.S., Sundquist, K., Ohlsson, H., Palmer, K., Maes, H., Winkleby, M.A., & Sundquist, J. (2012). Genetic and familial environmental influences on the risk for drug abuse: A National Adoption Study. *Archives of General Psychiatry*, 69, 690-697.

Kerr, M., & Stattin, H. (2003). Parenting of adolescents: Action or reaction? In A. C. Crouter, & A. Booth (Eds.), Children's influence on family dynamics: The neglected side of family relationships (pp. 121–151). Mahwah, NJ: Erlbaum.

Kerr, M., Stattin, H., & Burke, W.J. (2010). A reinterpretation of parental monitoring in longitudinal perspective. *Journal of research on adolescence*, 20, 39-64.

Kerr, M., Stattin, H., & Pakalniskiene, V. (2008) Parents react to adolescent problem behaviors by worrying more and monitoring less. What can parents do? New insights into the role of parents in adolescent problem behaviors. Wiley, London.

Kim, Y. & Neff, J.A. (2010). Direct and indirect effects of parental influence upon adolescent alcohol use: A structural equation modeling analysis. *Journal of Child and Adolescent Substance Abuse*, 19, 244-260.

King, K. & Chassin, L. (2004). Mediating and Moderated Effects of Adolescent Behavioral Undercontrol and Parenting in the Prediction of Drug Use Disorders in Emerging Adulthood. *Psychology of Addictive Behaviors*, 18, 239-249.

Koepp, M.J., Gunn, R.N., Lawrence, A.D., Cunningham, V.J., Berridge, A. K.C., Robinson, et al. (1998). Evidence for striatal dopamine release during a video game, *Nature*, 393, 266–268.

Koob, G.F. (1992). Drugs of abuse: Anatomy, pharmacology, and function of reward pathways. Trends in Pharmacological Sciences, 13, 177-184.

Krueger, R.F., South, S., Johnson, W., & Iacano, W. (2008). The heritability of personality is not always 50%: Gene-environment interactions and correlations between personality and parenting. *Journal of Personality*, 76, 1485-1521.

Lac, A. & Crano, W.D. (2009). Monitoring matters: Meta-analytic review reveals the reliable linkage of parental monitoring with adolescent marijuana use. *Perspectives on Psychological Science*, 4, 578–586.

Laird, R.D., Pettit, G.S., Bates, J.E., & Dodge, K.A. (2003). Parents' monitoring-relevant knowledge and adolescents' delinquent behavior: Evidence of correlated developmental changes and reciprocal influences. *Child Development*, 74, 752-768.

Larson, R.W., Richards, M.H., Moneta, G.H., Holmbeck, G., & Duckett, E. (1996). Changes in adolescents' daily interactions with their families from ages 10 to 18: Disengagement and transformation. *Developmental Psychology*, 32, 744-754.

Latendresse, S.J., Rose, R.J., Viken, R.J., Pulkkinen, L., Kaprio, J., & Dick, D.M. (2008). Parenting mechanisms in links between parents' and adolescents' alcohol use behaviors. *Alcoholism: Clinical and Experimental Research*, 32, 322-330.

Levran, O., Yuferov, V., & Kreek, M.J. (2012). The genetics of the opioid system and specific drug addictions. *Human Genetics*, 131, 823-842.

Li, X., Stanton, B., & Feigelman, S. (2000). Impact of perceived parental monitoring on adolescent risk behavior over 4 years. *Journal of Adolescent Health*, 27, 49-56.

Liu, J., Zhou, Z., Hodgkinson, C.A., Yuan, Q.,Shen, P., Mulligan, C.J. et al. (2011). Haplotype-based study of the association of alcohol-metabolizing genes with alcohol dependence in four independent populations. *Alcoholism: Clinical and Experimental Research*, 35, 304-316.

MacGregor, S., Lind, P.A., Bucholz,K.K., Hansell, N.K., Madden,P.A.F., Richter, M.M. et al. (2008). Associations of ADH and ALDH2 gene variation with self-report alcohol reactions, consumption and dependence: An integrated analysis. *Human Molecular Genetics*, 18, 580-593.

Martins, S.S., Storr, C. L., Alexande, P.K., & Chilicoat, H.D. (2008). Adolescent ecstasy and other drug use in the National Survey of parents and youth: The role of sensation-seeking, parental monitoring and peer's drug use. *Addictive Behaviors*, 33, 919-933.

Miranda, R., Ray, L., Justus, A., Meyerson, L.A., Knopik, V.S., McGeary, J. et al. (2010). Initial evidence of an association between OPRM1 and adolescent alcohol misuse. *Alcoholism: Clinical and Experimental Research*, 34, 112-122.

Miranda, R., Reynolds, E., Ray, L., Justus, A., Knopik, V.S., McGeary, J. et al. (2012). Preliminary evidence for a gene-environment interaction in predicting alcohol use disorders in adolescents. *Alcoholism: Clinical and Experimental Research*, 37, 325-331.

Moghaddam, B. (2002). Stress activation of glutamate neurotransmission in the pre-frontal cortex: Implications for dopamine-associated psychiatric disorders. *Biological Psychiatry*, 51, 775-787.

Monahan, K., Steinberg, L., & Cauffman, E. (2009). Affiliation with antisocial peers, susceptibility to peer influence, and antisocial behavior during the transition to adulthood. *Developmental Psychology, 45*, 1520-1530.

Morrison, A.C., Bare, L.A., Chambless, L.E., Ellis, S.G., Malloy, M., Kane, J.P. et al. (2007). Prediction of Coronary Heart Disease using a genetic risk score: The Atherosclerosis risk in communities study. *American Journal of Epidemiology*, 166, 28-35.

Mulligan, C.J., Robin, R.W., Osier, M.V., Sambuughin, N., Goldfarb, L.G., Kittles, R.A. et al. (2003). Allelic variation at alcohol metabolism genes (ADH1B, ADH1C,

ALDH2) and alcohol dependence in an American Indian population. *Human Genetics*, 113, 325-336.

Munafo, M.R., Matheson, I.J., & Flint, J. (2007). Association of the DRD2 gene Taq1A polymorphism and alcoholism: A meta-analysis of case-control studies and evidence of publication bias. *Molecular Psychiatry*, 12, 454-461.

Muthén, B.O. & Muthén, L.K. (1998-2011). *Version 6.1, Computer Software and Manual*. Los Angeles, CA: Muthén and Muthén.

Neiderhiser, J.M., Reiss, D., Pedersen, N.L., Lichtenstein, P., Spotts, E.L., Hansson, K. et al. (2004). Genetic and environmental influences on mothering of adolescents: A comparison of two samples. *Developmental Psychology*, 40, 335-351.

Noble, E. (2000). Addiction and its reward process through polymorphisms of the D2 dopamine receptor gene: A review. *European Psychiatry*, 15, 79-89.

Pieters, S., Van Der Zwaluw, Van Der Vorst, H., Wiers, R.W., Smeets, H., Lambrichs, E. (2012). The moderating effect of alcohol-specific parental rule-setting on the relation between the Dopamine D2 receptor gene (DRD2), the mu-Opioid receptor gene (OPRM1) and alcohol use in young adolescents. *Alcohol and Alcoholism*, 47, 663-670.

Plomin, R., DeFries, J., & Loehlin, J. (1977). Genotype-environment interaction and correlation in the analysis of human behavior. *Psychological Bulletin,* 84, 309-322.

Plomin, R., Reiss, D., Hetherington, E.M., & Howe, G.W. (1994). Nature and nurture: Genetic contributions to measures of the family environment. *Developmental Psychology*, 30, 32-43.

Preuss, U.W., Zill, P., Koller, G., Bondy, B., & Soyka, M. (2007). D2 dopamine receptor gene haplotypes and their influence on alcohol and tobacco consumption magnitude in alcohol-dependent individuals. *Alcohol and Alcoholism*, 42, 258-266.

Purcell, S., Heale, B., Todd-Brown, K., Thomas, L., Ferreira, M., Bender, D. et al. (2007). PLINK: a toolset for whole-genome association and population based linkage analysis. *American Journal of Human Genetics*, 81, 559–575.

Ray, L.A. (2011). Stress-Induced and Cue-Induced Craving for Alcohol in Heavy Drinkers: Preliminary Evidence of Genetic Moderation by the OPRM1 and CRH-BP Genes. *Alcoholism: Clinical and Experimental Research*, 35, 166-174.

Read, J. P., Wood, M.D., Kahler, C. W., Maddock, J. E.,& Palfai, T. P. (2003). Examining the role of drinking motives in college student alcohol use and problems. *Psychology of Addictive Behaviors*, 17, 13–23.

Reiss, D., Neiderhiser, J.M., Hetherington, E.M., & Plomin, R. (2000). *The Relationship Code: Deciphering Genetic and Social Influences on Adolescent Development*. Cambridge, MA: Harvard Univ. Press.

Rhee, S.H., Hewitt, J.K., Young, S.E., Corley, R.P., Crowley, T. J., & Stallings, M.C. (2003). Genetic and environmental influences on substance initiation, use, and problem use in adolescents. *Archives of General Psychiatry*, 60, 1256-1264.

Rice, F., Lewis, G. Harold, G.T., & Thapar, A. (2013). Examining the role of passive gene-environment correlation in childhood depression using a novel genetically sensitive design. *Development and Psychopathology*, 25, 37-50.

Robins, L.N., Helzer, J.E., Croughan, J., & Ratcliff, K.S. (1981). National Institute of Mental Health Diagnostic Interview Schedule. Its history, characteristics, and validity. *Archives of General Psychiatry*, 38, 381-9.

Robinson, T.E. & Berridge, K.C. *(2003)* Addiction. *Annual Review of Psychology, 54,* 25–53.

Rodriguez, F., Carrera, M.R., Navarro, M., Koob, G.F., & Weiss, F. (1997). Activation of Corticotropin-releasing factor in the limbic system during cannabinoid withdrawal. *Science*, 276, 2050-2054.

Rose, R.J., Dick, D.M., Viken, R.J., & Kaprio, J. (2001). Gene-environment interaction in patterns of adolescent drinking: Regional residency moderates longitudinal influences on alcohol use. *Alcoholism: Clinical and Experimental Research,* 25, 637-643.

Sakai, J.T., Stallings, M.C., Crowley, T.J., Gelhorn, H.L., McQueen, M.B., & Ehringer, M.A. (2010). Test of association between GABRA2 (SNP rs279871) and adolescent conduct/alcohol use disorders utilizing a sample of clinic referred youth with serious substance and conduct problems, controls, and available first degree relatives. *Drug and Alcohol Dependence*, 106, 199-203.

Saris, W. E., Satorra, A., & van der Veld, W. (2009). Testing structural equation models or detection of misspecifications? *Structural Equation Modeling: A Multidisciplinary Journal*, 16, 561-582.

Schafer, J. L. & Graham, J.W. (2002). Missing data: Our view of the state of the art. *Psychological Methods*, 7, 147-177.

Schermelleh-Engel, K., Moosbrugger, H., & Muller, H. (2003). Evaluating the fit of structural equation models: Tests of significance and descriptive goodness-of-fit measures. *Methods of Psychological Research Online*, 8, 23-74.

Schuckit, M. (1985). Genetics and the risk for alcoholism. *Journal of the American Medical Association*, 253, 2614-2617.

Scarr, S. & McCartney, K. (1983). How people make their own environments: A theory of genotype-environment effects. *Child Development*, 54, 424-435.

Schmidt, L.G., Samochowiec, J., Finckh, U., Fiszer-Piosik, E., Horodnicki, J., Wendel, B. et al. (2002). Association of a CB1 cannabinoid receptor gene (CNR1) polymorphism with severe alcohol dependence. *Drug and Alcohol Dependence*, 65, 221-224.

Selzer, M.D. (1971). The Michigan Alcoholism Screening Test: The quest for a new diagnostic instrument. *American Journal of Psychiatry*, 127, 1653-1659.

Shaffer, J. (1995). Multiple hypotheses-testing. *Annual Review of Psychology, 4*6, 561–584.

Sher, K. (1991). Children of alcoholics: A critical appraisal of theory and research. Chicago: University of Chicago Press.

Sherva, R., Rice, J.P., Neuman, R.J., Rochberg, N., Saccone, N.L., Bierut, L.J. (2009). Associations and interactions between SNPs in the alcohol metabolizing genes and alcoholism phenotypes in European Americans. *Alcoholism: Clinical and Experimental Research*, 33, 848-857.

Stattin, H. & Kerr, M. (2000). Parental monitoring: A reinterpretation. *Child Development*, 71, 1072-1085.

Steinberg, L., Fletcher, A., & Darling, N. (1994). Parental monitoring and peer influences on adolescent substance use. *Pediatrics*, 93, 1060-1064.

Steinberg, L & Monahan, K. (2007). Age differences in resistance to peer influence. *Developmental Psychology*, 43, 1531–1543.

Stoolmiller, M. (1994). Antisocial behavior, delinquent peer association and unsupervised wandering for boys: Growth and change from childhood to early adolescence. *Multivariate Behavioral Research*, 29, 263-288.

Szmigielski, A., Szmigielska, H. & Wejman, I. (1992). The effect of single and prolonged ethanol administration of the sensitivity of central GABA-A and benzodiazephine receptors in vivo. *Polish journal of pharmacology and pharmacy*, 4, 271-280.

Tanda, G., Munzar, P., & Goldberg, S.R. (2000). Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel monkeys. *Nature Neuroscience*, 3, 1073-1074.

Taqi,M.M., Bazov, I., Watanabe, H., Nyberg, F., Yakovleva, T., & Bakalkin, G. (2011). Prodynorphin promoter SNP associated with alcohol dependence forms

noncanonical AP-1 binding site that may influence gene expression in human brain. *Brain Research*, 1385, 18-25.

Thut, G., Schultz, W., Roelcke, U. Nienhusmeier, M., Missimer, J., Maguire, R.P. et al. (1997). Activation of the human brain by monetary reward. *Neuroreport,* 8, 1225–1228.

Tilton-Weaver, L. C., & Marshall, S. K. (2008). Adolescents' agency in information management. In M. Kerr, H. Stattin, R. C. M. E. Engels (Eds.), What can parents do? New insights into the role of parents in adolescent problem behavior (pp. 11-41). West Sussex, UK: Wiley.

United Nations Office on Drugs and Crime (2008). World Drug Report. Vienna Austria: United Nations Publication.

van der Stelt, M. & Marzo, V. (2003). The endocannabinoid system in the basal ganglia and in the mesolimbic reward system: Implications for neurological and psychiatric disorders. *European Journal of Pharmacology*, 480, 133-150.

van den Wildenberg, E., Wiers, R.W., Dessers, J., Janssen, R., Lambrichs, E.H. et al.(2007). A functional polymorphism of the Opioid receptor gene (OPRM1) influences cue-induced craving for alcohol in male heavy drinkers. *Alcoholism: Clinical and Experimental Research*, 31, 1-10.

van der Zwaluw, C.S., Engles, R.C. M.E., Vermulst, A.A., Franke, B., Buitelaar, J., Verkes, R.J. et al. (2010). *Molecular Psychiatry*, 15, 727-735.

van der Zwaluw, C.S., Laresen, H., & Engels, R.C. M. E. (2012). Best friends and alcohol use in adolescence: The role of the Dopamine D4 receptor gene. *Addiction Biology*, 17, 1036-1045.

Vieno, A., Nation, M., Pastore, M., & Santinello, M. (2009). Parenting and antisocial behavior: A model of the relationship between adolescent self-disclosure, parental closeness, parental control, and adolescent antisocial behavior. *Developmental Psychology*, 45, 1509-1519.

Walden, B., McGue, M., Iacano, W.G., Burt,A., & Elkins, I. (2004). Identifying shared environmental contributions to early substance use: The respective roles or peers and parents. *Journal of Abnormal Psychology*, 113, 440-450.

Webb, J.A., Bray, J.H., Getz, J.G., & Adams, G. (2002). Gender, perceived parental monitoring, and behavioral adjustment: Influences on adolescents alcohol use. *American Journal of Orthopsychiatry*, 72, 392-400.

White, H.R., McMorris, B.J., Catalano, R.F., Fleming, C.B., Haggert, K.P., & Abbott, R.D. (2006). Increases in alcohol and marijuana use during the transition out of high school into emerging adulthood: The effects of leaving home, going to

college, and high school protective factors. *Journal of Studies on Alcohol*, 67, 810-822.

World Health Organization (WHO; 2004). Global Status Report on Alcohol. Geneva, Switzerland: Marketing and Dissemination, World Health Organization.

Xuei, X., Flury-Wetherill, L., Bierut, L., Dick, D., Nurnberger, J., Foroud, T. et ak. (2007). The opioid system in alcohol and drug dependence: Family-based association study. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 144B, 877-884.

Yang, B., Kranzler, H.R., Zhao, H., Gruen, J.R., Luo, X., & Gelernter, J. (2007). Association of haplotypic variants in DRD2, ANKK1, TTC12, and NCAM to alcohol dependence in independent case-control and family samples. *Human Molecular Genetics*, 16, 2844-2853.

Zhang, P., Ishiguro, H., Ohtsuki, T., Carillo, F., Walther, D., Onaivi, E.S. et al. (2004). Human cannabinoid receptor 1: 5' exons, candidate regulatory regions, polymorphisms, haplotypes, and association with polysubstance abuse. *Molecular Psychiatry*, 9, 916-931.

Zhang, H., Luo, X., Kranzler, H.R., Lappalainen,J., Yang, B., Krupitksy, E. et al., (2006). Association between two mu-opioid receptor gene (OPRM1) haplotype blocks and drug or alcohol dependence. *Human Molecular Genetics*, 15, 807-819.

APPENDIX A

TABLES AND FIGURES OF MOTHER, FATHER, AND CHILD MODELS USING

THE FULL SAMPLE (N=447)

Table 14. *Results of Model using Mother Report of Parental Knowledge (N=447)*

Predictor	Age 11-14 Mother Reported Knowledge		Age 15-17 Peer Substance Use		Age 18-25 Substance Use Disorder	
	B	*SE*	*B*	*SE*	*B*	*SE*
Theory-based gene Score	.225	.462	.098	.427	-.125	.618
Empirically-based gene Score	-1.210*	.607	.028	.164	.578***	.093
Parent Alcohol Use Disorder (AUD)	-.161*	.083	.321***	.141	.221**	.162
Child Gender	-.007	.083	-.015	.130	.228***	.133
Child Ancestry	.416*	.103	-.042	.097	-.038	.100
Age Band 1 Age (11-14)	.323†	.236				
Age Band 2 Age (15-17)			.020	.298		
Age Band 3 Age (18-25)					.123†	.046
Age 11-14 Own Substance Use			-.073	.147	.113	.100
Age 11-14 Peer Substance Use			.581***	.093		
Age 15-17 Peer Substance Use					.403***	.127
Age 11-14 Mother Knowledge			.190	.322	-.157	.322
Theory-based gene X Mother Knowledge					.141*	.084
Theory-based gene X Mother Knowledge			.221	.213	-.257*	.157
Theory-based gene X Peer Substance Use					-.079	.517

Note. †*p< .10, *p<.05, **p<.01, ***p<.001.N=447. B=* Standardized regression coefficient. *SE=* Standard error. Parental AUD is coded 0 for children of non-alcoholics and 1 for children of alcoholics. Gender is coded 0 for females and 1 for males.

Table 15. *Results of Model using Father Report of Parental Knowledge (N=447)*

Predictor	Age 11-14 Father Reported Knowledge		Age 15-17 Peer Substance Use		Age 18-25 Substance Use Disorder	
	B	SE	B	SE	B	SE
Theory-based gene Score	.258	.297	.146	.582	-.316	.737
Empirically-based gene Score	-.181	.142	-.021	.191	.719***	.210
Parent Alcohol Use Disorder (AUD)	-.084	.100	.316***	.139	.273***	.154
Child Gender	-.037	.101	-.013	.130	.237***	.134
Child Ancestry	-.192†	.066	-.040	.106	-.015	.107
Age Band 1 Age (11-14)	.022	.125				
Age Band 2 Age (15-17)			-.060	.334		
Age Band 3 Age (18-25)					.132*	.094
Age 11-14 Own Substance Use			-.108	.135	.056	.104
Age 11-14 Peer Substance Use			.626***	.111		
Age 15-17 Peer Substance Use					.339**	.131
Age 11-14 Father Knowledge			.105	.322	-.245*	.212
Theory-based gene X Father Knowledge			.402	.209	.275**	.102
Theory-based gene X Father Knowledge					-.214†	.118
Theory-based gene X Peer Substance Use					-.060	.520

Note. †*p*< .10, *p*<.05, **p*<.01, ***p*<.001.*N=447*. *B*= Standardized regression coefficient. *SE*= Standard error. Parental AUD is coded 0 for children of non-alcoholics and 1 for children of alcoholics. Gender is coded 0 for females and 1 for males.

Table 16. *Results of Model using Child Report of Parental Knowledge (N=447)*

Predictor	Age 11-14 Child Reported Knowledge		Age 15-17 Peer Substance Use		Age 18-25 Substance Use Disorder	
	B	*SE*	*B*	*SE*	*B*	*SE*
Theory-based gene Score	.166†	.374	.193	.517	-.137	.614
Empirically-based gene Score	-.160†	.042	.039	.042	.817***	.024
Parent Alcohol Use Disorder (AUD)	-.013	.115	.394***	.163	.287***	.135
Child Gender	-.166*	.115	-.036	.153	.215***	.126
Child Ancestry	.086	.084	.094	.101	-.108†	.067
Age Band 1 Age (11-14)	-.093	.151				
Age Band 2 Age (15-17)			-.148	.251		
Age Band 3 Age (18-25)					.059	.041
Age 11-14 Own Substance Use			.785***	.167	.145*	.072
Age 11-14 Peer Substance Use			.901***	.114		
Age 15-17 Peer Substance Use					.195**	.086
Age 11-14 Child Knowledge			-.224	.171	-.041	.113
Theory-based gene X Child Knowledge					.153*	.092
Theory-based gene X Child Knowledge			-.026	.078	-.146*	.052
Theory-based gene X Peer Substance Use					-.103	.454

Note. †*p< .10, *p<.05, **p<.01, ***p<.001.N=447. B=* Standardized regression coefficient. *SE=* Standard error. Parental AUD is coded 0 for children of non-alcoholics and 1 for children of alcoholics. Gender is coded 0 for females and 1 for males.
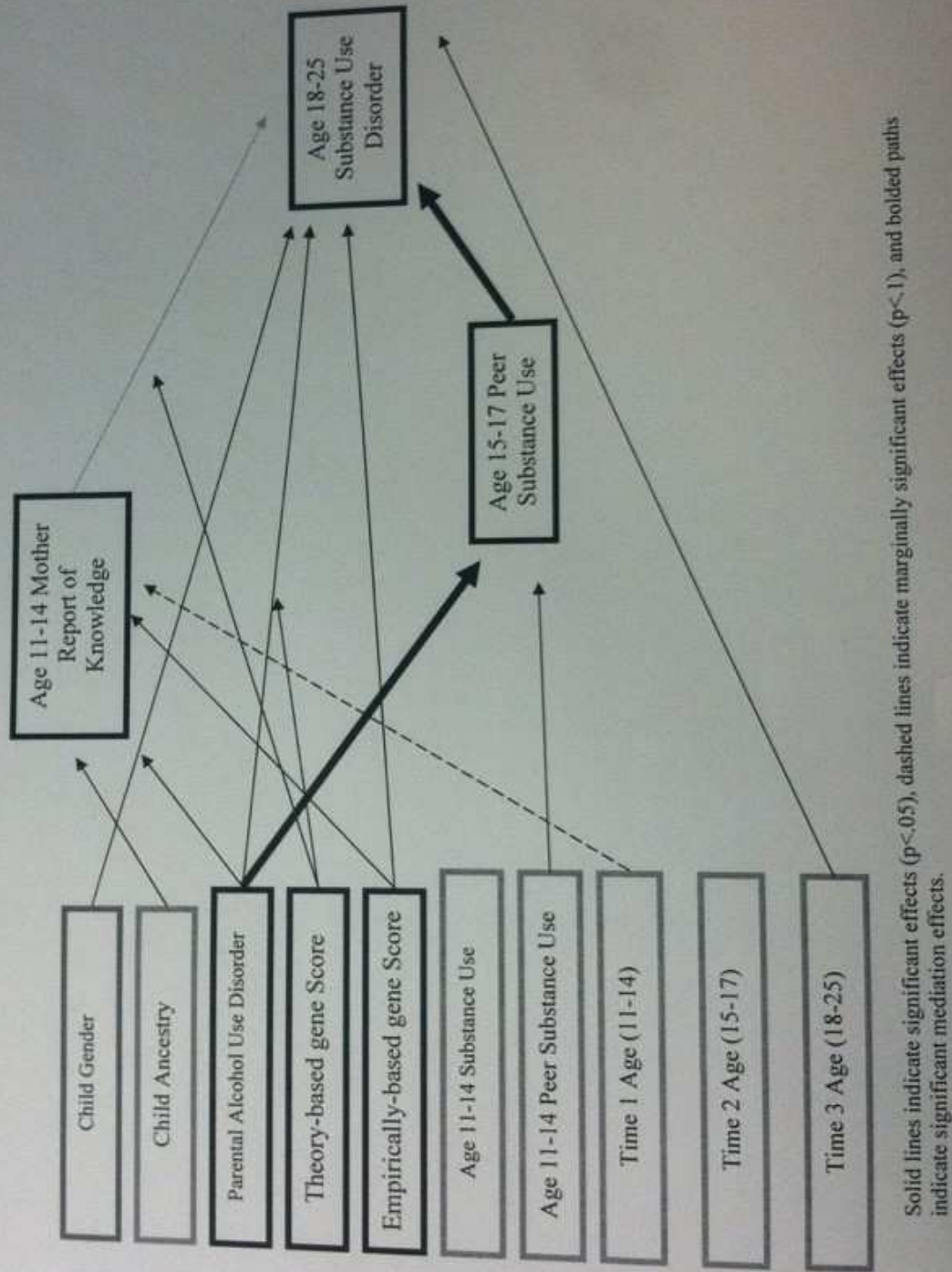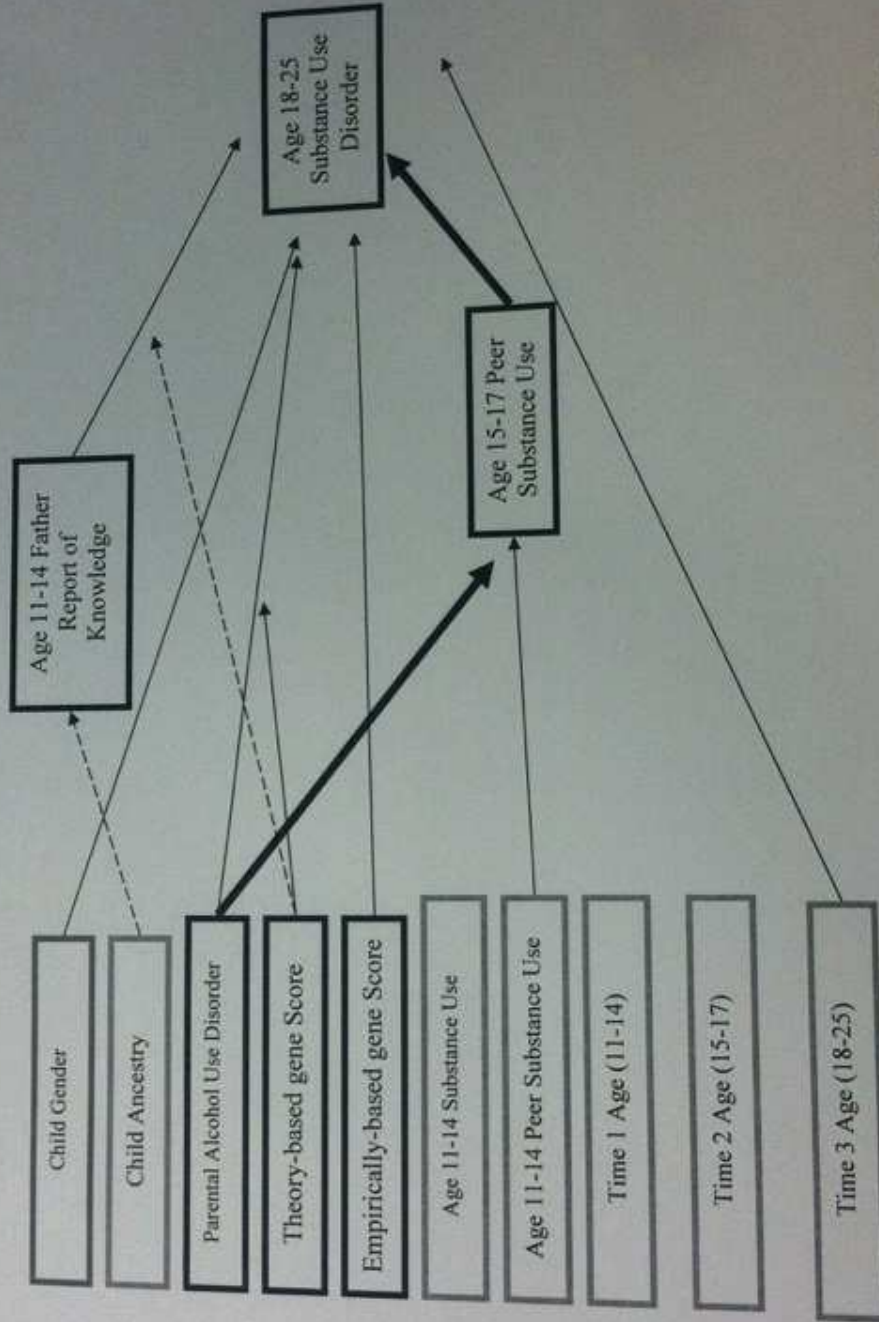
Figure 4. *Final Mother Model (N=447).*

Solid lines indicate significant effects (p<.05), dashed lines indicate marginally significant effects (p<.1), and bolded paths indicate significant mediation effects.

Figure 5. *Final Father Model (N=447).*

Solid lines indicate significant effects (p<.05), dashed lines indicate marginally significant effects (p<.1), and bolded paths indicate significant mediation effects.
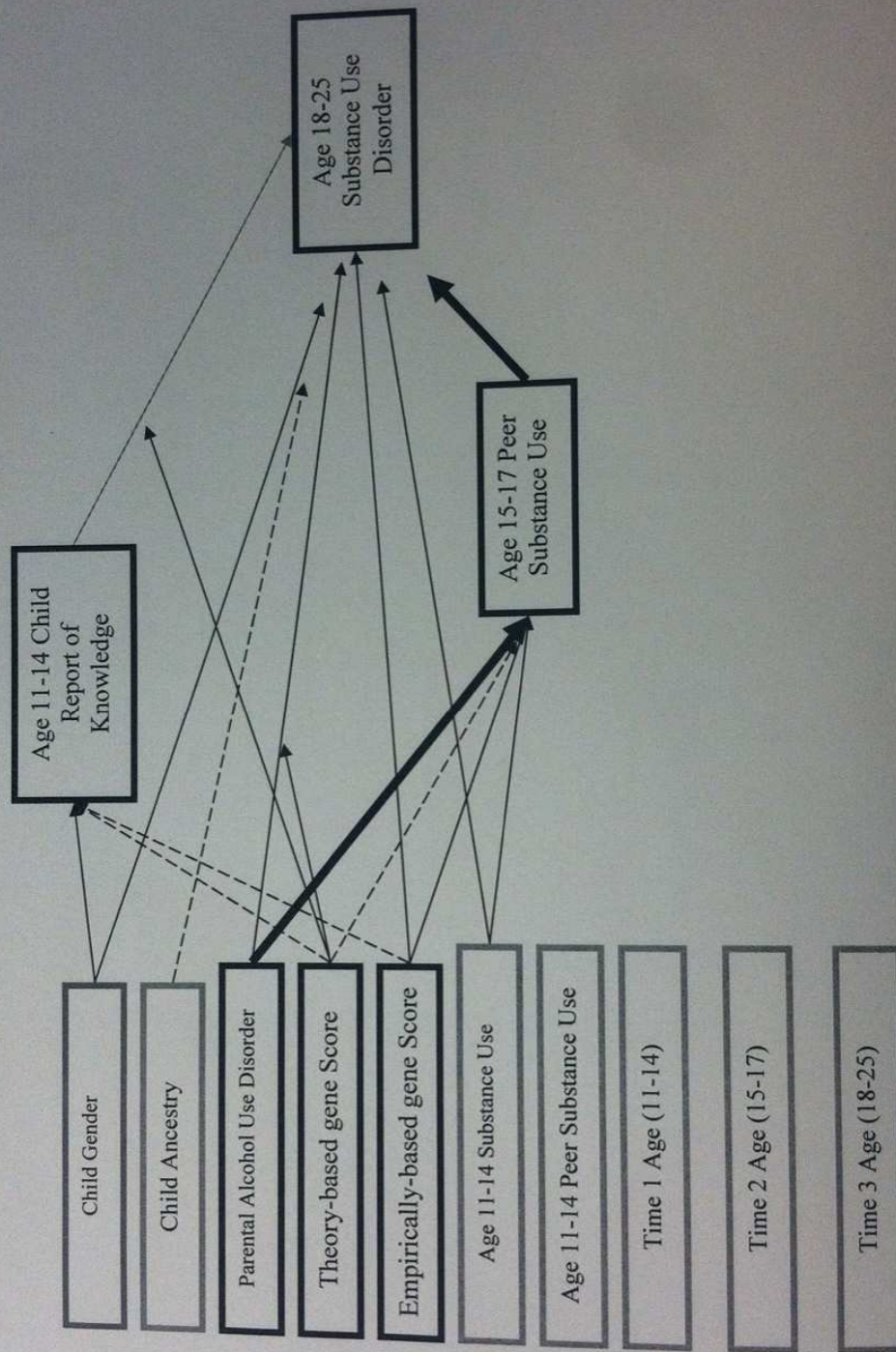
Figure 6. *Final Child Model (N=447).*

Solid lines indicate significant effects (p<.05), dashed lines indicate marginally significant effects (p<.1), and bolded paths indicate significant mediation effects.