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Parent and peer influences on emerging adult substance use disorder: A genetically informed study

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Abstract

The present study utilizes longitudinal data from a high-risk community sample to examine the unique effects of genetic risk, parental knowledge about the daily activities of adolescents, and peer substance use on emerging adult substance use disorders (SUDs). These effects are examined over and above a polygenic risk score. In addition, this polygenic risk score is used to examine gene–environment correlation and interaction. The results show that during older adolescence, higher adolescent genetic risk for SUDs predicts less parental knowledge, but this relation is nonsignificant in younger adolescence. Parental knowledge (using mother report) mediates the effects of parental alcohol use disorder (AUD) and adolescent genetic risk on risk for SUD, and peer substance use mediates the effect of parent AUD on offspring SUD. Finally, there are significant gene–environment interactions such that, for those at the highest levels of genetic risk, less parental knowledge and more peer substance use confers greater risk for SUDs. However, for those at medium and low genetic risk, these effects are attenuated. These findings suggest that the evocative effects of adolescent genetic risk on parenting increase with age across adolescence. They also suggest that some of the most important environmental risk factors for SUDs exert effects that vary across level of genetic propensity.

Because substance use disorders (SUDs) contribute to multiple negative physical and psychosocial outcomes (World Health Organization, 2004), identifying factors that increase risk for substance use problems is important. Among Sher's (1991) proposed and widely studied models that explain the intergenerational transmission of SUDs is the deviance-proneness pathway. In this pathway, children of parents with alcohol use disorders (AUDs) show elevated behavioral undercontrol (i.e., sensation seeking and conduct problems) and receive poor parenting. This combination places them at risk for affiliation with deviant peers and SUDs.

Sher's model (1991) considers both genetic and environmental influences and recognizes that the relations among parenting, peer influences, and SUDs may be influenced by genetic factors. However, these relations are often treated as if they are environmental in nature. We extend the previous literature by examining whether parental monitoring and affiliation with substance-using peers mediate the effects of parental AUD and adolescent polygenic risk on emerging adult SUD. We also test whether polygenic risk moderates the relations between parental monitoring and peer substance use, in predicting problematic substance use in emerging adulthood.

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Parent monitoring has often been linked to adolescent substance use outcomes (Chassin, Pillow, Curran, Molina, & Barrera, 1993; White et al., 2006). 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 adolescent self-disclosure, that is, the extent to which offspring chose to share this information with their parents. In addition, youth self-disclosure, and to a lesser extent parental solicitation of information, predicted changes in adolescent delinquency (Kerr, Stattin, & Burke, 2010). These findings suggest that *parental knowledge* is a more accurate term than parental monitoring. This distinction is important because the concept of parental monitoring may underestimate the importance of child effects.

The Putative Roles of Parent AUD, Parental Knowledge, and Peer Affiliation

Links within the deviance-proneness pathway have received substantial empirical support. Specifically, parent AUD is associated with poor parent–child relationships and less parental knowledge in younger adolescence (Latendresse et al., 2008), which in turn is related to increased substance use in older adolescence and emerging adulthood (Lac & Crano, 2009). Parents who know more about their children's lives may be better positioned to limit offspring substance use

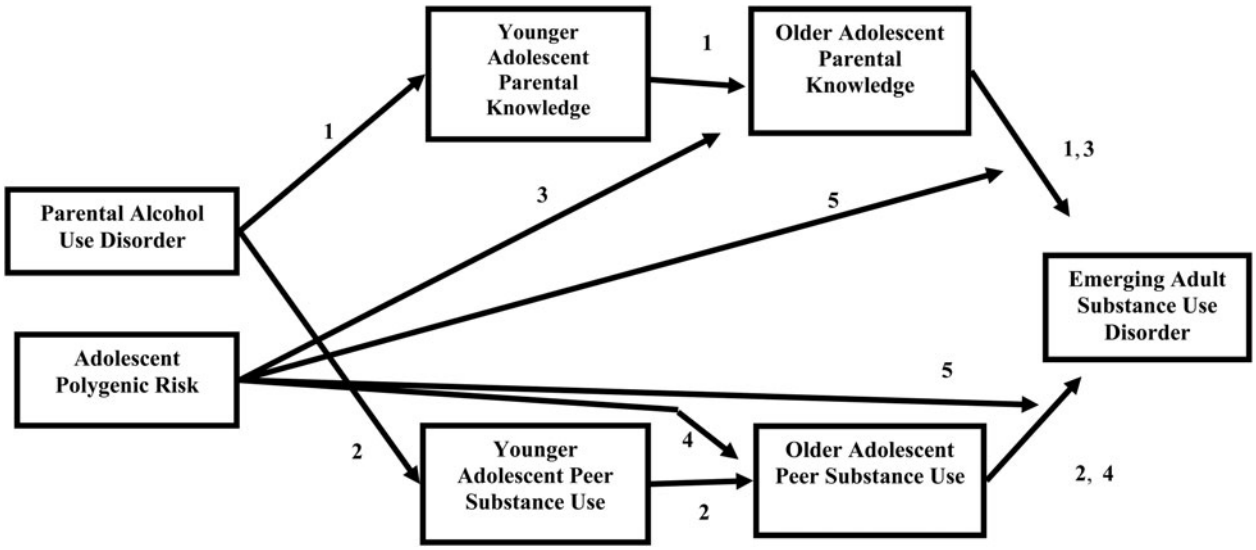

Figure 1. Conceptual model. Paths correspond to the hypothesized effects, with numbers matching the hypotheses listed in the text.

(Dishion, Capaldi, Spracklin, & Li, 1995). Therefore, our first hypothesis was that parental AUD would predict younger adolescent parental knowledge, which would affect older adolescent parental knowledge, in turn influencing risk for emerging adult SUD. In other words, together, younger and older parental knowledge would mediate the effect of parent AUD on emerging adult SUD. See the paths labeled "1" in Figure 1 for a visual depiction of this effect.

In addition to parental AUD predicting parental knowledge, parental AUD may also influence the characteristics of the adolescent's peer group, which in turn affects risk for SUDs. Parents with AUDs may model for their adolescents regular alcohol misuse with their own friends, thus communicating to their offspring the acceptability of drinking behaviors with one's peer group (White, Johnson, & Buyske, 2000). Adolescents who believe that regular alcohol misuse with peers is normative and acceptable may be more likely to have friends who also drink and potentially use drugs. Parents with AUDs may also be more likely to tolerate substance use behavior among their children's friends (Abar & Turrisi, 2008). Finally, parents with AUDs may be less psychologically and/or physically present and may therefore have less knowledge about their children's friends, making it more difficult to discourage association with a deviant peer group (Latendresse et al., 2008). For all of these reasons, children of parents with AUDs may be more likely to affiliate with a substance-using peer group. Membership in a substance-using peer group may in turn increase risk for SUDs, as these friends provide opportunities for substance use (White et al., 2006), and normalize and encourage substance use (Dishion & Owen, 2002). Our second study hypothesis was therefore that parental AUD would predict younger adolescent peer substance use, which would affect older adolescent peer substance use, in turn influencing risk for emerging adult SUD. That is, together, younger and older peer substance use would mediate the effect of parent AUD on emerging adult SUD. See the paths labeled "2" in Figure 1 for a visual depiction of this effect.

The Putative Role of Gene–Environment Correlation

Although there is evidence for direct effects of parental knowledge on offspring substance use outcomes, as well as indirect effects mediated through peer substance use, these pathways may be at least in part genetically determined. Specifically, it may be that adolescents at genetic risk for alcohol and/or drug use disorders may be more likely to engage in deviant behaviors. They may also be unlikely to disclose details about their day-to-day lives to their caregivers (Tilton-Weaver & Marshall, 2008). Their caregivers may in turn withdraw, resulting in less parental knowledge (Dishion, Nelson, & Bullock, 2004; Kerr & Stattin, 2003; Kerr, Statin, & Pakalniskiene, 2008). This is an example of an evocative gene–environment effect, such that individuals with particular genotypes evoke particular responses from their environments (Klahr & Burt, 2014; Plomin, DeFries, & Loehlin, 1977). Therefore, differences in parental knowledge may be partially determined by genetic differences between individuals (Plomin, Reiss, Hetherington, & Howe, 1994; Reiss, Neiderhiser, Hetherington, & Plomin, 2000).

An evocative effect of genetic risk on parental knowledge may also change with development. Estimates of genetic influences on parenting, and gene–environment correlation specifically, appear to increase across adolescence (Avinun & Knafo, 2013). Changing also is the amount of time adolescents spend with their family versus outside of the home, with older adolescents spending more time away from their parents and siblings, compared to younger adolescents (Crosnoe & Johnson, 2011). As adolescents gain increasing autonomy, they are more able to make decisions that are consistent with their genotypes. Therefore, the association between genetic risk for alcohol and/or drug use disorders and evoked

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parental knowledge may increase across adolescence. Because of the potentially increasing ability of individuals to influence their parenting environments across adolescence, we were particularly interested in the impact of parental knowledge during older adolescence on later risk for SUD. Thus, we tested whether polygenic risk predicted parental knowledge both in younger and older adolescence, and whether older adolescent parental knowledge predicted risk for emerging adult SUD. Our third study hypothesis was that older adolescent parental knowledge would mediate the effect of polygenic risk on SUD. See the paths labeled "3" in Figure 1 for a visual depiction of this effect.

In Sher's (1991) deviance-proneness pathway, the effects of parenting on SUD are mediated through affiliation with substance-using peers. Although studies consistently support the importance of these peer influences, peer group affiliation may reflect genetic risk also common to risk for SUD. Adolescents at high genetic risk for SUDs may be more likely to select friends who enjoy drinking alcohol and using drugs. This may reflect either an active gene–environment correlation (in which the individual's own genes make him/her seek certain environments) or an evocative gene–environment correlation (in which an individual's own genes increase the chance that he/she will evoke particular behaviors in others; Dishion & Owen, 2002; Fowler et al., 2007; Scarr & McCartney, 1983).

There is evidence of genetic influences on peer affiliation. Twin studies find that genetic influences explain up to 37% of the variance in peer delinquency/substance use outcomes in late adolescence and emerging adulthood, but may explain only 3% of the variance in these outcomes in early adolescence (Beaver et al., 2009; Fowler et al., 2007; Iervolino et al., 2002). In addition, Fowler, Settle, and Christakis (2011) reported that there was a significant positive relation between each adolescent's genotype and his/her peers' genotype (controlling for age, sex, and ethnicity), as measured by the dopamine D2 receptor (*DRD2*) gene single nucleotide polymorphism (SNP) rs1125394. Chassin et al. (2012) found that offspring of parents with AUDs were more likely to have a particular genetic makeup on μ-opioid receptor M1 gene (*OPRM1*) rs1799971, which predicted peer substance use for males, but not for females (Chassin et al., 2012).

Although there is some evidence that genetic effects influence peer group affiliations (e.g., Christakis & Fowler, 2014), the research is not unequivocal. As stated, one explanation for this variability is that the studies finding significant genetic influences on peer substance use were conducted with older samples. During and across adolescence, individuals spend less time with family members and more time outside the home, compared to during earlier developmental periods (Crosnoe & Johnson, 2011). Therefore, as individuals begin to have more control over the people with whom they socialize, the relation between genetic risk for SUDs and choice of a substance-using peer group would be expected to increase (Kendler et al., 2007; Salvatore et al., 2014). Genetic influences on peer substance use are therefore likely to be stronger in older adolescence, compared to younger adolescence. Older adolescence may also be the ideal time to examine peer influences on substance use outcomes, because these effects are strongest during this developmental period (Steinberg & Monahan, 2007). Accordingly, the current study examined whether genetic risk significantly predicted affiliations with substance-using peers in younger and older adolescence, and whether older adolescent peer substance use influenced risk for SUD. Our fourth study hypothesis was therefore that older adolescent peer substance use would mediate the effect of genetic risk on SUD. See the paths labeled "4" in Figure 1 for a visual depiction of this effect.

The Putative Role of Gene × Environment Interaction

We have described the role of gene–environment correlation in the relations among parent knowledge, peer affiliation, and emerging adult SUDs. However, there is also literature to suggest a role for Gene × Environment interaction. Many studies report that genetic effects are stronger at higher levels of environmental risk, and environmental effects are stronger at higher levels of genetic risk (Miranda et al., 2012; Salvatore et al., 2014). Environments that provide less opportunity for substance use suppress the behavioral manifestations of genetic risk, whereas environments that allow for more substance use opportunities amplify the behavioral manifestations of genetic risk (Hicks, South, DiRago, Iacano, & McGue, 2009). These diathesis–stress interactions have been found for substance use outcomes in twin studies (Agrawal et al., 2010), as well as in studies using measured genes (Dick et al., 2007; Miranda et al., 2012). Accordingly, our fifth and final study hypothesis was that older adolescent parental knowledge and peer substance use would exert larger effects on offspring emerging adult SUDs for those at higher levels of polygenic risk for SUDs. See the paths labeled "5" in Figure 1 for a visual depiction of these effects.

Measuring Genetic Risk: Creating a Polygenic Risk Score

In order to test these questions, we created a *literature-based* score based on prior research and theory, which was formed to meaningfully represent interplay between genetic risk and study variables. In attempting to create a score measuring literature-based polygenic risk, SNPs were chosen from theoretically plausible receptor systems that have been found to be related to risk for alcohol and/or drug use disorders in at least two prior studies. A search was conducted using the terms "alcohol use disorder," "drug use disorder," "alcohol misuse," or "drug misuse" with "SNP" or "polymorphism" via Google Scholar, PubMed, and HuGE Navigator. The results of this literature search yielded SNPs from the dopamine (*DRD2*), opioid (*OPRM1*, prodynorphin [*PDYN*]), GABA (GABA receptor subunit alpha-2 [*GABRA2*]), drug metabolism (alcohol dehydrogenase 4 [*ADH4*]), and cannabinoid (endocannabinoid receptor 1 [*CNR1*]) systems. Genes within these systems are asso-

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Table 1. *SNPs used to create polygenic risk*

Gene	SNP	System	References	Phenotypes Related to SNP
DRD2/ ANKK1	Taq1A/rs1800497	Dopamine	Brody et al., 2013; Foley et al., 2004	Frequency of binge drinking, frequency of and problems associated with alcohol misuse
ADH4	Rs3762894	Drug metabolism	Liu, Zhou et al., 2011; MacGregor et al., 2008	Physical effects of alcohol use (e.g., flushing)
CNR1	Rs1049353	Cannabinoid	Hartman et al., 2009; Preuss et al., 2003	Withdrawal after discontinuation of alcohol, cannabis dependence
GABRA2	rs11503014	GABA	Enoch et al., 2010; Smelson et al., 2012	Subjective response to cocaine, heroin addiction
PDYN	rs609148 (in high LD with rs558025)	Opioid	Zhang et al., 2006; Shabalina et al., 2009	Alcohol dependence, response to opiates
OPRM1	rs495491 (in high LD with 510769)	Opioid	Zhang et al., 2006; Shabalina et al., 2009	Alcohol dependence, response to opiates
OPRM1	Rs548646; in high LD with Rs660756	Opioid	Ehlers et al., 2008; Zhang et al., 2006	Response to alcohol, opioid misuse

Note: SNP, Single nucleotide polymorphism; SUD, substance use disorder; GABA, gamma-aminobutyric acid.

ciated with pleasure derived from using substances, and more punitive effects of discontinuing substance use (Brady & Sinha, 2005; Costa, Giagnoni, & Colleoni, 2000; Koob, 1992).

In examining SNPs from these receptor systems specifically, the SNP rs1800497 within the gene *DRD2* is associated with increased risk for higher frequency of binge drinking and frequency of and problems associated with substance misuse among adolescents (Brody, Chen, & Beach, 2013; Foley et al., 2004). Research has also found associations between rs3762894 (*ADH4*) and adverse effects of alcohol use (e.g., flushing; Liu et al., 2011; MacGregor et al., 2008). In addition, prior work has found support for the association between the SNP rs1049353 (*CNR1*) within the cannabinoid system and unpleasant effects following discontinuation of alcohol use, as well as cannabis dependence (Hartman et al., 2009; Preuss, Koller, Zill, Bondy, & Soyka, 2003). Research also found associations between *GABRA2* SNP rs11503014 and subjective response to cocaine and heroin addiction (Enoch, 2010; Smelson et al., 2012). Finally, the SNP rs609148 (in high linkage disequilibrium [LD][1] with rs558025), rs495491 (in high LD with rs510769), rs548646 (in high LD with rs660756) within the genes *OPRM1* and *PDYN* are associated with increased rewarding effects of alcohol, as well as alcohol use and drug (i.e., opioid) misuse in adolescents and adults (Ehlers, Lind, & Wilhelmsen, 2008; Shabalina et al., 2009; Zhang et al., 2006). By creating a polygenic risk score using SNPs from theoretically plausible receptor systems, the current study is able to interpret significant main and interaction effects involving this gene score. See Table 1 for more information on included SNPs.

In general, these genetic effects on alcohol and drug use disorders have explained increasing amounts of variance as individuals move from adolescence into adulthood (Dick et al., 2007; Kendler et al., 2012). 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 freedom to make decisions consistent with their genetic risk, compared to earlier developmental periods when adults in their lives might make 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 predictors of emerging adult SUD.

Present Study

In summary, the current study had five main study hypotheses. First, we hypothesized that together, younger and older parental knowledge would mediate the effect of parental AUD on emerging adult SUD, and second, that younger and older peer substance use would mediate this effect. Third, we predicted that older adolescent parental knowledge would mediate the effect of adolescent genetic risk for SUDs on propensity for developing a SUD (no such hypothesis is made about younger adolescent parental knowledge). Fourth, we predicted that older (but not younger) adolescent peer substance use would mediate the effect of adolescent genetic risk on propensity for developing a SUD. Fifth, we predicted that the effects of older adolescent parental knowledge and peer substance use on emerging adult SUD would be stronger for those at higher level of genetic risk. We examined these hypotheses after controlling for earlier levels of outcome variables, as well as ancestry, gender, and age.

Method

The original study

Participants were a subsample from a larger longitudinal study of familial alcoholism in a large metropolitan area in

1. Linkage disequilibrium means that two SNPs are nonrandomly associated with each other and are more likely to be inherited together than would have been expected by chance alone. Because research has found associations between Rs609148 (which is unavailable in this data set) and response to substances, the SNP Rs558025 is included as part of this risk score.

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the Southwest United States. 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 had at least one biological alcoholic parent who was also a custodial alcoholic parent (i.e., child of an alcoholic). The remaining 208 were controls, matched on neighborhood, child's age, number of parents in the household, and ethnicity, who had no biological or custodial alcoholic parents. At Wave 1 of the study, families in which one or more caregivers met criteria for an AUD reported lower levels of education. However, families with and without parent AUD were comparable on family income and the likelihood of a parent being unemployed. Adolescents and their families were interviewed annually for 3 years for the first three waves, and then 5, 10, and 15 years later for the last three waves.

In terms of sociodemographic characteristics in the larger sample, the average total yearly household income of original participants in 1988 was $43,000. The range in reported household incomes was $6,000 to $180,000, with about 10% of families reporting household incomes of $22,000 or less a year. In addition, on average, mothers and fathers completed high school or had taken some college classes. The overwhelming result was that most (80%) families reported that both biological parents lived at home with the children. The large proportion of two-biological parent families was created by the selection criterion that the alcoholic parent be both biological and custodial and then matching nonalcoholic and alcohol samples in family structure. Other adolescents lived with only their biological mother (7% of the sample), biological father (1%), or some other relative (12%). Additional details of sample recruitment and representativeness are reported elsewhere (Chassin, Barrera, Bech, & Kossak-Fuller, 1992).

The current subsample

The current study used data from Waves 1–5 of the larger parent project. Of the 454 Wave 1 adolescent participants, 266 supplied genetic data. Of these 266, there were 5 cases in which the call rate was unacceptable, resulting in 261 remaining participants. Of these 261, 7 reported ethnicities other than non-Hispanic Caucasian or Hispanic, and were eliminated. The resulting 254 comprised the subsample for the current study.

Participants who were included in the subsample (N = 254) were compared to those excluded (N = 200). Of the 254 adolescents included in current study analyses, 120 (47.2%) had at least one parent with an AUD and 134 (52.8%) did not. In addition, 120 (47.2%) attended at least some college. There were no differences between those included and excluded on age, ethnicity, education level achieved by the offspring (i.e., emerging adults, between the ages of 18 and 25), younger or older adolescent mother or offspring report of parental knowledge, younger or older adolescent peer substance use, or on younger adolescent own substance use. Those who met inclusion criteria and who were included in the subsample were less likely to be children of alcoholics, male, and to meet criteria for a lifetime SUD between the ages of 18 and 25. However, the magnitude of these significant differences was small,[2] suggesting minimal bias in terms of sample characteristics.

Measures

Age bands. Age bands were created in order to limit the age heterogeneity of participants at the times when study variables were examined. The first age band captured peer substance use, adolescent substance use, and parental knowledge when the adolescent was between ages 11 and 14 (mean age = 12.93; "younger adolescence"). The second age band captured peer substance use and parental knowledge when adolescents were between ages 15 and 17 (mean age = 15.93; "older adolescence").[3] The third age band captured emerging adult SUD when the individual was between ages 18 and 25 (mean age = 21.22). 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. A factor score of SNPs reflecting Hispanic ancestry was used as a covariate. Scores were derived from 37 ancestry marker SNPs, which, in previous literature, have differentiated Hispanics from non-Hispanic Caucasians (Tian et al., 2007). These were coded to ensure that higher scores indicated more Caucasian and less Hispanic ancestry, with scores of 0, 1, and 2 reflecting low, medium, and high levels of Caucasian ancestry, respectively. After trichotomizing, a principal components analyses of 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 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 0.3 or –0.3. These 32 SNPs were included in a factor analysis in Mplus, and these factor scores significantly correlated with self-reported ethnicity (r = .868, p < .001). Mplus fit statistics for the one-factor model showed good fit, root mean square error of approximation (RMSEA) = 0.025, comparative fit index (CFI) = 0.943, standard root mean square residual = 0.027.

2. Cramer *V*s (*small* = 0.1, *moderate* = 0.3) were 0.107 (emerging adult SUD), 0.127 (gender), and 0.157 (parent AUD).
3. Because of the frequency of interviews, some of participants' data points were not used in study analyses. If, for example, an individual was interviewed at ages 13, 14, 15, 20, and 25, the data from the interview in which he/she was closest in age to the middle of each age band (i.e., 12.5, 16, and 21.5) were used. Therefore, in this example, this participant's data at ages 13, 15, and 20 would have been used (and data from interviews at ages 14 and 25 would not have been used).

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Table 2. *Descriptive statistics*

Variable	Min.	Max.	Mean (*SD*)	Skew	Kurtosis
Younger adolescent					
Mother report of knowledge	2.67	5	4.48 (0.60)	−0.970	0.372
Child report of parent knowledge	1	4.33	2.17 (0.76)	−0.672	0.131
Older adolescent					
Mother report of knowledge	1	5	4.24 (0.68)	−1.051	2.361
Child report of parent knowledge	1	4.33	2.05 (0.70)	−0.626	0.581
Peer substance use					
Younger adolescent	0	3.67	0.88 (0.87)	1.177	0.719
Older adolescent	0	4.86	2.02 (1.02)	0.237	−1.631
Younger adolescents' own substance use	0	6	0.61 (1.01)	1.992	4.300
Ancestry gene score	−3.39	1.17	0.06 (0.91)	−1.403	1.070
Polygenic risk	2	9	5.84 (1.53)	−0.148	−0.261
Parent alcoholism status			47.2% diagnosed		
Emerging adult alcohol or drug diagnosis			38.9% diagnosed		
Emerging adult gender			52.8% female		

Adolescent age. Self-reported age at age band 1 (age 11–14) was used as a covariate in predicting younger adolescent parental knowledge, peer substance use, and substance use (all at ages 11–14). The mean age at age band 1 was 12.93.

Parent alcohol abuse/dependence. Parent lifetime alcohol abuse/dependence diagnoses were obtained with a computerized version of the Diagnostic Interview Schedule (version III; Robins, Helzer, Croughan, & Ratcliff, 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). The parent alcohol abuse/dependence variable was measured at the beginning of the original study when the adolescents were between the ages of 11 and 15 (i.e., generally corresponding to the age when "younger adolescent" constructs were examined in the current study).

Analyses ($\chi^2 = 23.884$) indicated that those with one parent with an AUD ($p < .01$) or two parents with AUDs ($p < .001$) were more likely to develop a SUD, compared to those whose parents had not had an AUD. However, there were no differences in risk for offspring SUD between those with one versus two parents with an AUD (*ns*). There were also no differences in risk as a function of the gender of the parent with the AUD either among male offspring ($\chi^2 = 2.269$, *ns*) or female offspring ($\chi^2 = 1.375$, *ns*). Specifically, 59.1% of males with a father with an AUD, 50% of males with a mother with an AUD, and 66.7% of males with a mother and a father with an AUD met criteria for a SUD. In addition, 46.8% of females with a father with an AUD, 40% of females with a mother with an AUD, and 66.7% of females with a mother and a father met criteria for a SUD. Accordingly, parent AUD was treated as a dichotomous variable, either absent in both parents (0; 52.8% of sample) or present in one or two parents (1; 47.2% of sample).[4]

Parental knowledge. Mother and offspring report of knowledge about the adolescent's behavior (ages 11–14, "younger adolescence," and 15–17, "older adolescence,") was assessed via three items designed by project staff. These items assess the extent to which the parents talked with the adolescent about his/her plans for the day, had a "pretty good idea" about the adolescent's interests and whereabouts, and generally knew the people with whom he/she associated (range = 1–5; higher scores indicate more knowledge). These items have been shown to have good predictive validity in terms of their associations with peer substance use and offspring substance use (Chassin et al., 1993). The Cronbach α values for mother and offspring report of knowledge were 0.78 and 0.60 in younger adolescence and 0.82 and 0.63[5] in older adolescence, respectively.

Peer substance use. Adolescent report of substance use in the peer group (ages 11–14 and 15–17) was assessed with the mean of six items adapted from the Monitoring the Future Questionnaire (Johnston, O'Malley, & Bachman, 1988).

4. This lack of increase in risk based upon parent AUD could potentially be explained by assortative mating for endophentypes of AUD, such that more basic personality characteristics (and not necessarily AUD) may confer risk for poor parenting and/or offspring psychopathology.

5. One explanation for the lower αs in adolescent report is that the first item involved parents actually talking with adolescents in order to gather information, and the second two allowed for sharing of information by the child or the soliciting of information by the parent. The means of the first item at ages 11–14 and 15–17 (2.67–2.77) were larger than the means of the last two items (1.80–1.94) using adolescent report. The means for all three items at each of the two time points were much larger and more similar to one another when using mother report (4.1–4.5). This suggests that if parents ask about adolescents' plans (but not about their interests or friends) and adolescents themselves do not volunteer information about their interests or friends, the correlations between the last two items might be larger than the correlations involving the first item, when using adolescent report. This trend may not hold using mother report if mothers believe they are knowledgeable about their adolescent's plans, interests, and friends. Correlations between the last two items were generally larger (.41–.46) than those involving the first item (.24–.31) when using adolescent report. Correlations among mother-reported items were generally consistent and much larger (.62–.70).

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These items assessed how many of their friends drink alcohol, smoke marijuana, or take other illicit drugs occasionally and regularly (range = 0–5; 0 = *none* and 5 = *all*). The Cronbach α values were 0.92 in younger adolescence and 0.94 in older adolescence.

SUD. Emerging adult (ages 18–25) diagnoses of lifetime SUD were obtained from a computerized version of the Diagnostic Interview Schedule (Robins et al., 1981). Dichotomous dummy-coded variables compared participants meeting lifetime criteria for alcohol or drug abuse or dependence (38.9%) with 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 of one or more substances.

To assess a precursor of this outcome at ages 11–14 (and thus establish prospective prediction), a variable was created to reflect the highest frequency of alcohol or drug use in younger adolescence. These items assessed the highest frequency of use of alcohol, marijuana, amphetamines, barbiturates, tranquilizers, hallucinogens, cocaine, opiates, and inhalants (range = 0–7; 0 = *never* and 7 = *every day*).

Polygenic risk

DNA extraction 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 1,536 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.

To create literature-based polygenic risk, a literature review was conducted to identify previous studies associating available SNPs in the dopamine, GABA, cannabinoid, alcohol effects, and opioid systems (or SNPs that were in high LD with available SNPs), and SUD. Inclusion was based on finding associations between the SNP and SUD in at least two prior studies and not on its association with the phenotype of interest in this sample (see Table 1 for a list). In addition, in order to be included in this literature-based score, prior literature had to agree on the allele that confers greater risk for SUD. When prior work (between two and six studies) disagreed about the risk allele direction, findings from studies including those most similar to current study participants (e.g., in terms of ethnicity, being from a high-risk community sample) were prioritized. These criteria resulted in seven SNPs that were used to create this polygenic risk score.

Using prior literature to determine the direction of risk, SNPs were coded additively to indicate low, medium, and high levels of genetic risk (0, 1, 2) based on the number of risk alleles inherited. The seven scores were then summed, as is standard practice (Morrison et al., 2007).[6] This score was related to emerging adult SUD in the zero-order correlations ($r = .128$, $p < .05$). In terms of its main effect on SUD in study models, this score was significantly or marginally significantly predictive (βs were 0.203 and 0.233, $p < .1$ and $p < .05$, respectively). This score explained 1.63% of the variance in emerging adult SUD.[7]

Although this polygenic risk score only explained 1.63% of the variance in emerging adult SUD, others have commented on the problem of "missing heritability." That is, there is a large gap between the heritability of a trait and the variance accounted for by measured genetic associations (Plomin & Simpson, 2013). The magnitude of variance explained by this risk score is consistent with other studies utilizing polygenic risk scores to predict substance use outcomes in adolescents and young adults (e.g., variance explained ranging from 0.5%–2%; Davis & Loxton, 2013; Derringer et al., 2012).

In further support of this method, seven SNPs that were not included in the polygenic risk were randomly chosen from the remaining SNPs. These SNPs were added together, used to create a polygenic score, and tested as a predictor of this same phenotype. These SNPs were coded such 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. This random gene score did not predict emerging adult SUD (β = –0.062, *ns*). In addition, it explained 0.02% of the variance, which is less than the variance explained by the current study's polygenic risk score. This analysis increases our confidence in the current study's measure of polygenic risk.

Data analytic strategy

To reduce nonessential multicollinearity, continuous variables were centered (Cohen, Cohen, West, & Aiken, 2003). Covariates were adolescent ancestry, gender, and age band 1 age (age 11–14). Because there were both continuous and categorical dependent variables models, we used the weighted least squares estimator with mean and variance adjustments (WLSMV), which computes ordinary least squares parameter estimates for continuous outcomes and probit parameter estimates for categorical outcomes. Because the

6. The receptor systems from which the included SNPs come (i.e., dopamine, GABA, cannabinoid, alcohol effects, and opioid) influence reward sensitivity, and specifically the amplification of pleasure derived from using alcohol and/or illicit drugs (Brady & Sinha, 2005; Costa, Giagnoni, & Colleoni, 2000; Koob, 1992). Therefore, higher risk on one of these SNPs was thought to similarly impact risk for alcohol, marijuana, and other illicit drug misuse. Thus, each SNP used to compute this score was weighted equally.
7. Although all seven of these SNPs are thought to amplify positive effects or negative effects that result from discontinuing alcohol and drugs, they are thought to represent unique genetic risks. Using SNAP proxy search revealed that none of the SNPs were in LD (defined here with $r^2 \geq .6$) with one another (Johnson et al., 2008). Because these SNPs represent unique genetic risks, we feel confident summing them to create a polygenic risk score.

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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 et al., 2003; Muthén & Muthén, 1998–2011). However, the *categorical is* function in Mplus was used, indicating to the program that the outcome variable is a categorical variable. WLSMV uses a four-stage process to estimate missing data, with the first two stages using full information at maximum likelihood estimation (Muthén & Satorra, 1995), and then techniques similar to pairwise deletion are used in the last two steps. Prior work suggests that full information maximum at likelihood produces unbiased estimates under the missing at random assumption (Enders & Bandalos, 2001).

Missing data on endogenous variables were estimated as a function of the observed exogenous variables under the missingness at random assumption (Schafer & Graham, 2002). As Shafer and Graham point out, there is no way to test whether missing at random holds in a data set without following up with nonresponders. However, it is possible to examine whether earlier values on a construct predict missingness on that same construct at the next time point (which would suggest a missing not at random pattern). Using this method, we did not find a significant association between young adolescent parental knowledge and older adolescent missing parent knowledge data. We also did not find a relation between young adolescent peer substance use and older adolescent missing peer substance use data. In addition, there was no association between younger adolescent substance use and missing substance use diagnosis in emerging adulthood. Therefore, we conclude that our data are missing at random.[8]

Models were assessed for goodness of fit using the chi-square goodness of fit test statistic, CFI $\geq$ 0.95, RMSEA $\leq$ 0.08, and weighted root mean square residual (WRMR) $<$ 0.90 (Hu & Bentler, 1999; Yu & Muthén, 2002). The mediated effects of parental alcoholism and polygenic risk on emerging adult SUDs through parental knowledge and peer substance use were tested using the Model Indirect and Sobel statements in Mplus (Muthén & Muthén, 1998–2010).

Regression diagnostics

Because Mplus does not yield regression diagnostics, models were estimated in ordinary least squares and logistic regression using SPSS to examine the influence of outliers on results. No abnormalities were detected; therefore, no cases were deleted from the analyses.

8. All 254 participants had complete data on gender, age, parental alcoholism status, and genetic risk. In terms of missing data on other key study variables, the missing data rates ranged from 1.5% missing (on ancestry and emerging adult SUD) to 40% missing (mother and child knowledge variables in older adolescence). However, this large amount of missing data is likely due at least in part to the fact that we created an age-based data set. Therefore, not all data collected at each wave could be utilized in examining relations among constructs at specific ages.

Results

Correlations

Table 3 gives the zero-order pearson (between two continuous variables), tetrachoric (two dichotomous variables), and biserial (dichotomous and continuous variables) correlations. In terms of covariates, according to mother report, older adolescents at the first age band (i.e., ages 11–14) have mothers who know less about their lives, and are more likely to drink alcohol and have friends who use substances. Compared to males, females have parents who know more about their lives (by mother report), and more friends who use substances in younger adolescence. However, males are more likely to meet criteria for age 18–25 SUD. Those of greater Caucasian ancestry have mothers who know more about their lives in older adolescence (by child report).

In terms of predictors, offspring of parents with AUDs have parents who know less about their lives (by mother report), are more likely to have friends who use substances, and are more likely to meet criteria for SUD. Higher scores on polygenic risk were significantly associated with less adolescent and mother-reported knowledge in older (but not younger) adolescence, and were significantly associated with greater risk for emerging adult SUD.

More younger adolescent substance use was generally associated with less adolescent mother- and child-reported knowledge. Younger adolescent substance use also conferred risk for later association with substance-using peers and emerging adult SUD. Greater younger adolescent peer substance use was associated with less younger adolescent child-reported knowledge, greater younger adolescent substance use, and emerging adult SUD. Finally, less mother- (in younger and older adolescence) and child-reported knowledge (in older adolescence) in older and younger adolescence were associated with older adolescent peer substance use, as well as emerging adult SUD.

Final study models

Separate models using mother and adolescent report of parental knowledge were estimated. Because of the hypotheses about polygenic risk predicting parental knowledge and peer substance use across developmental periods, paths from this polygenic risk score to younger and older adolescent parental knowledge and peer substance use were estimated. Prior work (Keller, 2014) suggests that confounders may exert significant influences on outcomes via interactions with genetic and environmental a prior predictors. Therefore, covariate by covariate and covariate by predictor interactions were estimated, and when not significant, were dropped from final models.

The models using mother and adolescent report of knowledge (N = 254) showed good fit to the data (mother report: RMSEA = 0.065, CFI = 0.805, WRMR = 0.796, see Table 4; adolescent report: RMSEA = 0.078, CFI = 0.728, WRMR = 0.888, see Table 5). In terms of covariate effects,

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Table 3. *Correlations between study variables*

	1	2	3	4	5	6	7	8	9	10	11	12
1. Age band 1 age	—											
2. Child gender	–.063	—										
3. Ancestry	–.120*	–.027	—									
4. Gene score	–.010	–.013	.153*	—								
5. Parental alcoholism	.144*	–.027	–.166*	.055	—							
6. Younger adolescent mother knowledge	–.128*	–.201**	–.037	–.022	–.167*	—						
7. Younger adolescent child knowledge	–.022	–.071	.052	–.081	–.067	.178**	—					
8. Older adolescent mother knowledge	–.140*	–.211**	.031	–.167*	–.225**	.460***	.112*	—				
9. Older adolescent child knowledge	–.026	–.096	.117*	–.129*	–.107	.064	.164*	.319***	—			
10. Younger adolescent peer substance use	.165**	–.132*	–.108	–.061	.349***	–.066	–.232**	.039	–.050	—		
11. Older adolescent peer substance use	.227**	–.077	–.107†	.113†	.355***	–.231**	.088	–.141*	–.221**	.556***	—	
12. Younger adolescent own substance use	.176**	.044	.037	–.089	.169**	–.120*	–.014	–.167**	–.174*	.336***	.421***	—
13. Emerging adult SUD	.175**	.207**	−0.081	.128*	.360***	–.086	–.226***	–.291***	–.288***	.466***	.352***	.316***

Note: $N = 254$, although exact n varies across reporter. SUD, Substance use diagnosis. Gender is coded 0 = female, 1 = male. Ancestry score is coded such that higher scores mean more Caucasian ancestry. Parental alcoholism, 0 = non-child of alcoholic (COA), 1 = COA; SUD, 0 = no diagnosis, 1 = diagnosis.
†$p < .1$. *$p < .05$. **$p < .01$. ***$p < .001$.

Table 4. *Results of longitudinal model using mother report of parental knowledge (N = 254)*

	Younger Adolescent						Older Adolescent					
	Mother Reported Knowledge		Peer Substance Use		Own Substance Use		Mother Reported Knowledge		Peer Substance Use		Emerging Adult SUD	
Predictor	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*
Gender	−0.229**	0.090	−0.082	0.056	0.055	0.147					0.258**	0.178
Ancestry	−0.067	0.043	−0.097	0.026	0.090	0.096					−0.044	0.111
Band 1 age (age 11–14)	−0.086	0.046	−0.113	0.030	0.103	0.084						
Polygenic risk	−0.006	0.024	−0.044	0.021	−0.044	0.046	−0.241*	0.032	−0.011	0.062	0.203†	0.071
Parental AUD	−0.164*	0.087	0.418**	0.098	0.170***	0.163	−0.058	0.144	−0.026	0.237	0.130	0.220
Younger adolescent												
Mother knowledge							0.443***	0.092	0.189	0.186		
Peer substance use							−0.210	0.224	0.669***	0.587		
Own substance use							−0.060	0.099	0.291*	0.100	0.081	0.123
Older adolescent												
Mother knowledge											−0.115	0.180
Peer substance use											0.551**	0.180
Polygenic Risk × Older Adolescent Mother Knowledge											−0.461*	0.223
Polygenic Risk × Older Adolescent Peer Substance Use											0.540**	0.720

Note: B, Standardized regression coefficient; AUD, alcohol use disorder. Parental AUD is coded 0 for children of nonalcoholics and 1 for children of alcoholics. Gender is coded 0 for females and 1 for males.
†$p < .1$. *$p < .05$. **$p < .01$. ***$p < .001$.

Table 5. *Results of longitudinal model using adolescent report of parental knowledge (N = 254)*

	Younger Adolescent						Older Adolescent					
	Child Reported Knowledge		Peer Substance Use		Own Substance Use		Child Reported Knowledge		Peer Substance Use		Emerging Adult SUD	
Predictor	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*
Gender	−0.076	0.128	−0.145†	0.177	0.041	0.151					0.234**	0.173
Ancestry	0.082	0.067	−0.095	0.096	0.047	0.107					−0.010	0.101
Band 1 age (age 11–14)	0.004	0.072	0.076	0.093	0.173*	0.084						
		0.036	−0.003	0.049					−0.067	0.050		
Polygenic risk	−0.048				−0.098	0.044	−0.177*	0.034			0.233*	0.069
Parental AUD	−0.073	0.127	0.333**	0.239	0.189*	0.165	−0.167	0.181	0.122	0.185	0.136	0.230
Younger adolescent												
Child knowledge							0.537***	0.097	−0.125	0.126		
Peer substance use							0.265	0.130	0.498**	0.138		
Own substance use							−0.290*	0.080	0.152	0.129	0.390**	0.148
Older adolescent												
Child knowledge											−0.043	0.136
Peer substance use											0.457***	0.156
Polygenic Risk × Older Adolescent Child Knowledge											−0.187*	0.224
Polygenic Risk × Older Adolescent Peer Substance Use											0.510**	1.005

Note: B, Standardized regression coefficient; AUD, alcohol use disorder. Parental AUD is coded 0 for children of nonalcoholics and 1 for children of alcoholics. Gender is coded 0 for females and 1 for males.
†$p < .1$. *$p < .05$. **$p < .01$. ***$p < .001$.

in both the mother report and adolescent report of knowledge models, more younger adolescent knowledge was related to older adolescent knowledge, and more younger adolescent peer use conferred risk for increased older adolescent peer use. In the mother-report model, more younger adolescent own substance use predicted increased risk for more older adolescent peer use. In addition, in both models, males were more likely to meet criteria for a SUD in emerging adulthood. Mothers reported that they knew more about the lives of their daughters, compared to their sons, in younger adolescence, but adolescent report did not yield this same trend. Finally, more younger adolescent substance use was associated with decreased parent knowledge in older adolescence, according to adolescent (but not mother) report.

Hypothesized effects. The first hypothesis posited that together, younger and older adolescent parental knowledge would mediate the effect of parental AUD on emerging adult SUD. Findings indicate that parental AUD was associated with mother report, but not adolescent report, of younger adolescent parental knowledge. For both mother report and adolescent report, younger adolescent knowledge predicted older adolescent knowledge. The effect of older adolescent parental knowledge on emerging adult SUD was significant for those at high levels of genetic risk. The indirect effect of parent AUD on SUD through younger adolescent and older adolescent parental knowledge was significant for those at high levels of genetic risk using mother report (confidence interval [CI] = 0.016–0.061, $p < .05$). This indirect effect was not significant for those at medium (CI = –0.020 to 0.053) or low levels (CI = –0.046 to 0.081) of parental knowledge using mother report. This indirect effect was nonsignificant for those at high (CI = –0.001 to 0.046), medium (CI = –0.014 to 0.021), and low levels of genetic risk (CI = –0.054 to 0.075) when using adolescent report. Therefore, our first hypothesis was supported in mother report (for those at high genetic risk) but not in adolescent report.

The second hypothesis was that peer substance use would mediate the effect of parental AUD on emerging adult SUD. For models using both mother report and adolescent report of knowledge, parental AUD was associated with greater likelihood of associating with younger adolescent substance-using peers. Having more younger adolescent substance-using peers was associated with greater affiliation with older adolescent substance-using peers. Finally, older adolescents with more substance-using peers who used substances were more likely to meet criteria for a SUD in emerging adulthood, with this effect particularly strong for those at highest and medium levels of genetic risk. This indirect effect of parent AUD on SUD through younger and older adolescent peer substance use was significant for those at highest (mother report: CI = 0.109–0.809, $p < .01$; adolescent report: CI = 0.028–0.394, $p < .01$), medium (mother report: CI = 0.106–0.775, $p < .05$; adolescent report: CI = 0.015–0.321, $p < .05$), and lowest levels of genetic risk (mother report: CI = 0.102–0.741, $p < .05$; adolescent report: CI = 0.011–0.203, $p < .05$).

The third hypothesis posited that older adolescent parental knowledge would mediate the effect of genetic risk on emerging adult SUD. For both mother report and adolescent report, the effect of polygenic risk on older (but not younger) adolescent parental knowledge was significant. In addition, the effect of older adolescent parental knowledge on emerging adult SUD was significant for those at highest, but not medium or low, levels of genetic risk. The indirect effect of the genetic risk score on SUD through older adolescent parental knowledge was significant when examining the effect of parental knowledge on SUD at highest levels of genetic risk (mother report: CI = 0.018–0.115, $p < .05$; adolescent report: 0.001–0.045, $p < .05$). This indirect effect was not significant at medium (mother report: CI = –0.020–0.053; adolescent report: CI = –0.014–0.023) or low levels of genetic risk (mother report: CI = –0.076–0.065; adolescent report: CI = –0.075–0.051).

The fourth study hypothesis was that older adolescent peer substance use would mediate the effect of genetic risk on emerging adult SUD. In both models, the effect of polygenic risk on older adolescent peer substance use was nonsignificant, but peer substance use predicted emerging adult SUD, and this effect was particularly strong for those at highest and medium levels of genetic risk. This indirect effect was nonsignificant for those at highest (mother report CI = 0.091–0.084, *ns*; adolescent report CI = –0.095 to 0.052, *ns*), medium (mother report CI = –0.089 to 0.081, *ns*; adolescent report CI = –0.076 to 0.039, *ns*), and lowest levels of genetic risk (mother report CI = –0.085 to 0.079, *ns*; adolescent report CI = –0.034 to 0.018, *ns*).

The fifth and final hypothesis was that the effect of older adolescent parental knowledge and older adolescent peer substance use on risk for SUD would be stronger for those at highest levels of genetic risk. In both models, polygenic risk interacted with knowledge to predict emerging adult SUD. Specifically, less mother- ($\beta = –0.351$, $p < .05$) and adolescent-reported ($\beta = –0.213$, $p < .05$) parent knowledge conferred greater risk for SUD, but only for those at highest levels of genetic risk. There was no relation between mother- ($\beta = –0.115$, *ns*; $\beta = 0.081$, *ns*) or adolescent-reported ($\beta = –0.043$, *ns*; $\beta = 0.096$, *ns*) knowledge and risk for SUD for those at medium or low levels of risk, respectively. See Figures 2–5 for graphical depictions of and regions of significance for these interactions involving genetic risk and parental knowledge.

In addition, in both models, polygenic risk interacted with older adolescent peer substance use to predict emerging adult SUD. Specifically, in both mother- and adolescent-report models, more older adolescent peer substance use increased risk for emerging adult SUD. However, this effect was stronger in both models when examining those at highest ($\beta = 0.684$, $p < .001$; $\beta = 0.636$, $p < .001$) and medium levels of genetic risk ($\beta = 0.551$, $p < .001$; $\beta = 0.457$, $p < .001$), compared to those at lowest levels of genetic

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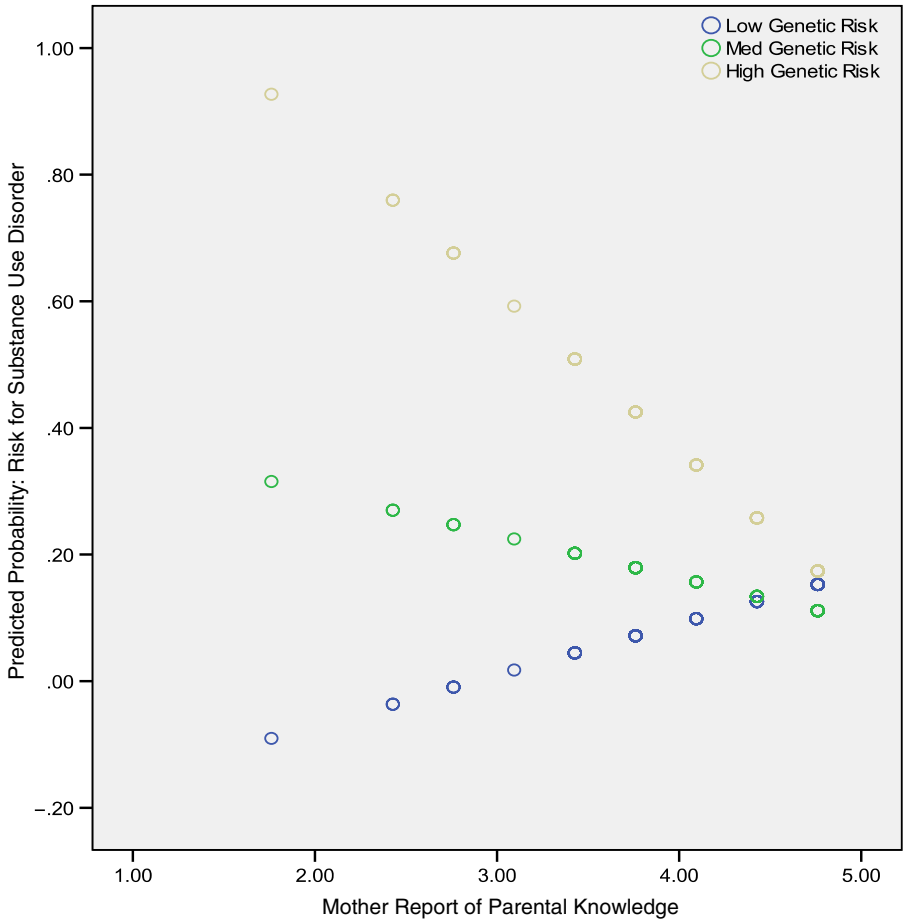

Figure 2. (Color online) Interaction between mother-reported parental knowledge and genetic risk to predict substance use disorder ($N = 254$).

risk ($\beta = 0.447$, $p < .05$; $\beta = 0.303$, $p < .05$), respectively.[9] See Figures 6–9 for graphical depictions of and regions of significance for these interactions involving genetic risk and peer substance use.

Alternative analyses: Substituting dependence for abuse/dependence

Because DSM substance abuse diagnoses may overdiagnose disorder, we tested models that restricted emerging adult SUD to dependence only, which produced few changes in findings. In both mother- and adolescent-report models with this substitution, gender no longer predicted substance dependence. In the mother-report model, an additional finding was detected. Specifically, more younger adolescent peer substance use conferred risk for less older adolescent parental knowledge ($\beta = –0.421$, $p < .05$).

Discussion

The current study had five hypotheses. First, we hypothesized that together, younger and older parental knowledge would mediate the effect of parental AUD on emerging adult SUD. Second, we predicted that younger and older peer substance use would mediate the effect of parental AUD on emerging adult SUD. Third, we hypothesized that older adolescent parental knowledge would mediate the effect of adolescent genetic risk for SUDs on propensity for developing a SUD (no such hypothesis was made about younger adolescent parental knowledge). Fourth, we hypothesized that older adolescent peer substance use would mediate the effect of adolescent genetic risk on propensity for developing a SUD (no such hypothesis was made about younger adolescent peer substance use). Fifth, we predicted that the effects of

9. The interaction terms for genetic risk and parental knowledge and genetic risk and peer substance use pertain to effects that are independent of the main effects of parental knowledge and polygenic risk, and peer substance use and polygenic risk, respectively (Cohen, Cohen, West, & Aiken, 2003). However, in order to test whether these interactions were influenced by effects of polygenic risk on parental knowledge or polygenic risk on peer substance use when examining the interactions between these constructs, we set the path from genetic risk to older adolescent parental knowledge, and then the effect of genetic risk to older adolescent peer substance use to zero. The interactions between parental knowledge and genetic risk ($p < .05$) and peer substance use and genetic risk remained significant ($p < .01$) in both models, suggesting that these interactions were not produced by significant gene–environment correlations.

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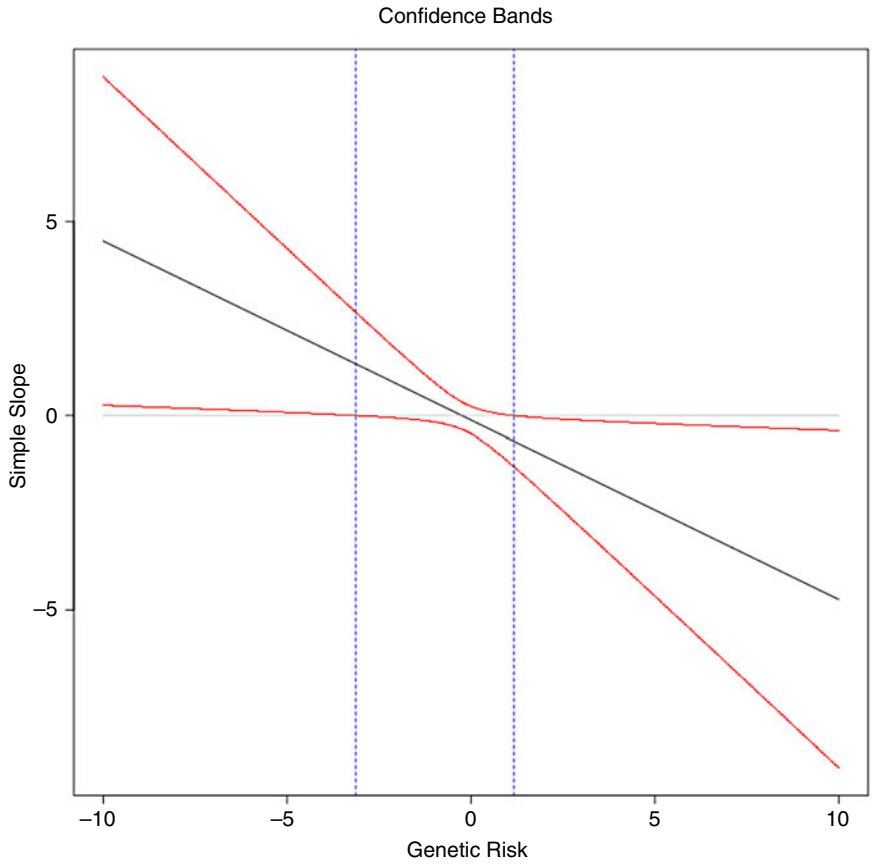

Figure 3. (Color online) Regions of significance ($p < .05$) for interaction between parental knowledge and genetic risk to predict substance use disorder (mother report of knowledge model). Regression coefficients are nonsignificant at values of the moderator falling *within* the region (–3.14 to 1.17; gene score mean = 0, *SD* = 1.53). However, because very few individuals have gene scores below –3.14, it can be concluded that the simple slope of substance use disorder regressed on parental knowledge is significantly different from zero ($p < .05$) for values of genetic risk at or above 1.17, which is about 0.75 *SD* above the mean.

older adolescent parental knowledge and peer substance use on emerging adult SUD would be stronger for those at higher level of genetic risk.

In terms of the first study hypothesis, findings showed that younger and older parental knowledge together mediated the effect of parent AUD on risk for SUD for those at highest levels of genetic risk using mother report of knowledge. Compared to parents without alcohol disorders, parents with AUDs may have less knowledge about their offspring's activities and interests both because they are inconsistently involved in monitoring and also because their children may be difficult to monitor because of their genetic risk (Klahr & Burt, 2014; Latendresse et al., 2008). The fact that this effect of parent AUD on mother knowledge was significant over and above young adolescent substance use and genetic risk suggests that caregivers do play a unique role in obtaining information about the life of their adolescents (over and above how potentially difficult the adolescent is to monitor). In addition to parent AUD predicting younger adolescent mother-reported parental knowledge (which in turn influenced older adolescent knowledge), less older adolescent parental knowledge predicted greater risk for a SUD among offspring at higher genetic risk. This association was only significant for those at highest levels of genetic risk, which is consistent with a diathesis–stress Gene × Environment interaction in which adverse environments have the most negative effects on the most vulnerable individuals.

That this link between parent AUD and adolescent report of knowledge (and in turn the indirect effect to predict emerging adult SUD) was nonsignificant may be partially attributable to adolescents reporting the knowledge that their parents collectively provided (i.e., not separated by mother and father). Thus, the nondisordered parent may compensate for the parent with an AUD. Therefore, when adolescents were asked about parental knowledge, they may have estimated it by averaging across parents, and this may have obscured the link between parental AUD and parental knowledge when using adolescent report.

In terms of the second study hypothesis, together, younger and older peer substance use mediated the effect of parental AUD on emerging adult SUD (for those at all levels of genetic risk). Specifically, children of alcoholic parents were more likely to have friends who used substances, which increased their risk for SUDs. Parents with SUDs are more

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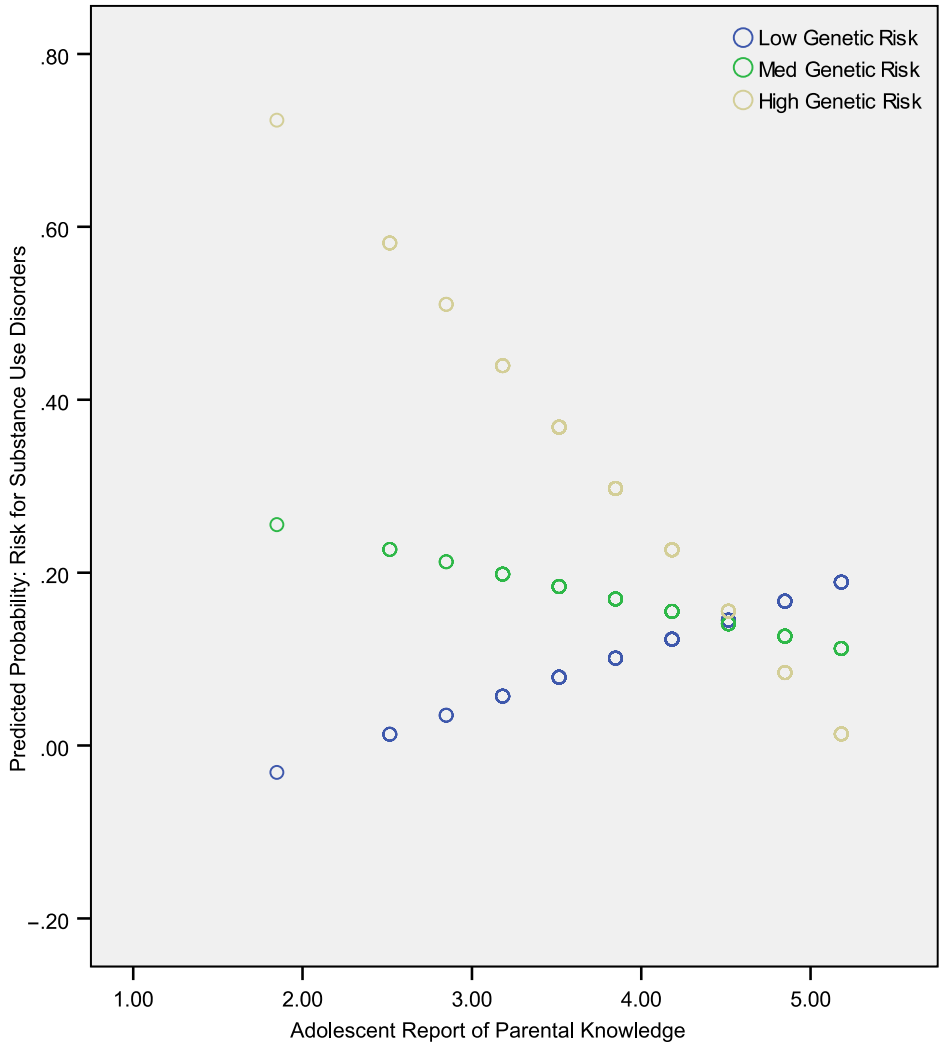

Figure 4. (Color online) Interaction between adolescent-reported parental knowledge and genetic risk to predict substance use disorder ($N = 254$).

likely to model substance use, are less likely to limit offspring drinking, and are more likely to have behaviorally undercontrolled children (Abar & Turrisi, 2008; Sher, 1991). All of these factors increase the chance that children of alcoholic parents would associate with deviant peers (Hicks, Krueger, Iacano, McGue, & Patrick, 2004; Kendler et al., 2012).

There is a large literature suggesting that peer substance use increases risk for later substance problems, as substance-using friends provide access and opportunity for substance use and influence norms that promote substance use (Borsari & Carey, 2001; Dishion & Owen, 2002). We replicated and extended this finding by demonstrating that the association between peer substance use and later SUD is still present over and above earlier levels of adolescents' own substance use and a polygenic risk score. This finding is important in the context of younger and older adolescent peer substance use together mediating the effect of parental AUD on emerging adult AUD. Specifically, these findings suggest that children of parents with AUDs are at risk for associating with substance-using peers because of some mechanism beyond their own initial levels of substance use, and being genetically at risk for substance misuse. Peer substance use did not mediate the effect of genetic risk on SUDs.

In terms of the third study hypothesis, older adolescent parental knowledge mediated the effect of polygenic risk on risk for SUDs, with the effect of parental knowledge on SUDs only significant for those at highest levels of genetic risk. In addition, the finding that polygenic risk for SUDs was related to older, but not younger, adolescent parental knowledge is consistent with previous literature suggesting that gene–environment effects on substance use, as well as evocative gene–environment correlations become stronger across adolescence (Salvatore et al., 2014). As individuals move through adolescence, they are more likely to make decisions that are consistent with their genotypes, with these choices affecting their caregivers and home environments. For instance, adolescents at higher genetic risk for SUDs may be more easily able to engage in deviant behaviors as they age, and as a result, may withdraw from their caregivers. Parents may in turn then have less knowledge about these adolescents' lives.

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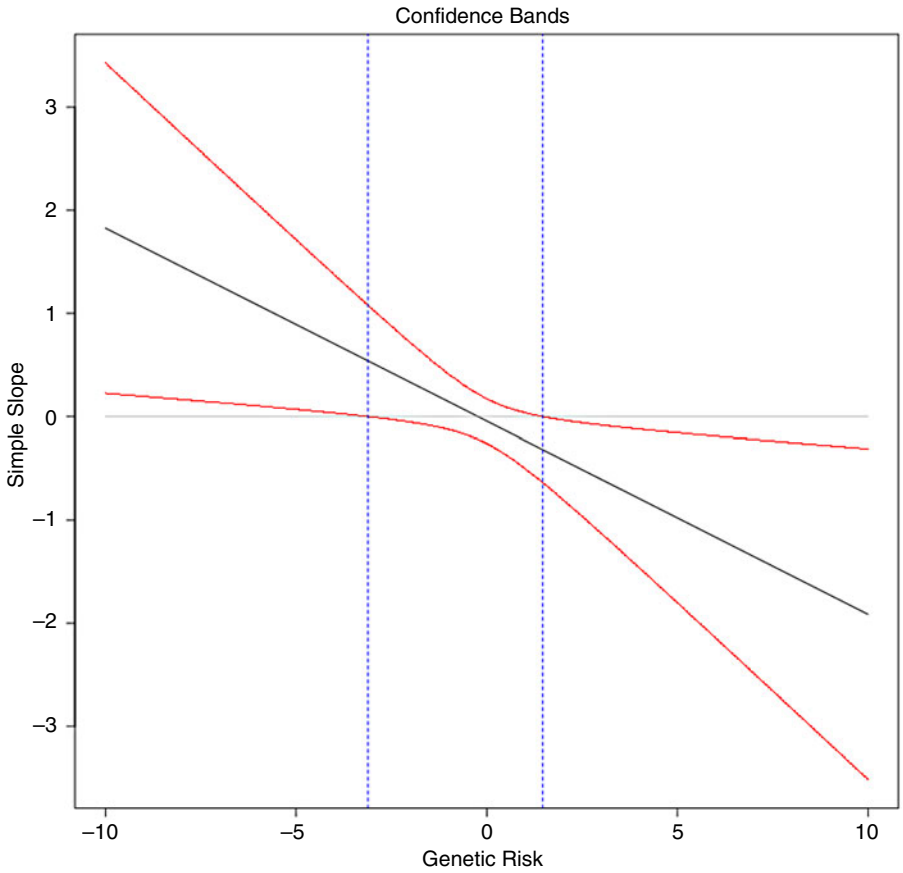

Figure 5. (Color online) Regions of significance ($p < .05$) for interaction between parental knowledge and genetic risk (adolescent report of knowledge model). Regression coefficients are nonsignificant at values of the moderator falling *within* the region (i.e., –3.11 to 1.47; gene score mean = 0, *SD* = 1.53). However, because very few individuals have gene scores below –3.11, it can be concluded that the simple slope of substance use disorder regressed on parental knowledge is significantly different from zero ($p < .05$) for values of genetic risk at or above 1.47, which is about 0.9 *SD* above the mean.

The fact that this relation between genetic risk and parental knowledge was significant even when parental AUD was in the model suggests that over and above parents' mental and physical presence in their children's lives, offspring risk for SUD influences the amount of knowledge that caregivers have. This suggests a unique role of adolescent self-disclosure on parental knowledge.

This trend of individuals at high genetic risk sharing less with their caregivers across adolescence likely does not describe those at medium and lower genetic risk, which may explain why mean levels of parental knowledge in this sample only decrease slightly across adolescence. The fact that this mediation effect (i.e., parental knowledge mediating the impact of polygenic risk on emerging adult SUD) was replicated across mother report and child report of knowledge suggests that it is robust. Although consistent with an evocative gene–environment effect, it should be noted that this finding could also be explained by passive gene–environment correlation. It may be that parents at higher genetic risk for SUDs have less knowledge about their children's lives, and are likely to have children who are also at higher risk for SUDs. Future research should examine whether this association between adolescents' genetic risk and parental knowledge is better explained by parents' genetic risk.

The fact that polygenic risk was related to older adolescent (but not younger adolescent) parental knowledge, whereas parental AUD was related to younger adolescent mother-reported knowledge, suggests that there are multiple mechanisms that influence parental knowledge. It may be that in the beginning of adolescence, the extent to which mothers try to know about their offspring's lives is important. Parents with an AUD may engage in less monitoring, have less positive relationships with their children, and therefore be less aware of their adolescents' activities. In later adolescence, however, adolescents at higher genetic risk may make risky decisions consistent with their genotypes, and may disclose less to their caregivers (Haworth et al., 2009; Scarr & McCartney, 1983). In this way, older adolescents may exert more control over how much information their parents have. Although much work has been done examining how parents obtain information about their offspring's lives (e.g., Stattin & Kerr, 2000), less research has examined how these mechanisms change across development.

In examining the fourth study hypothesis, we tested whether older adolescent peer substance use mediated the effect of poly-

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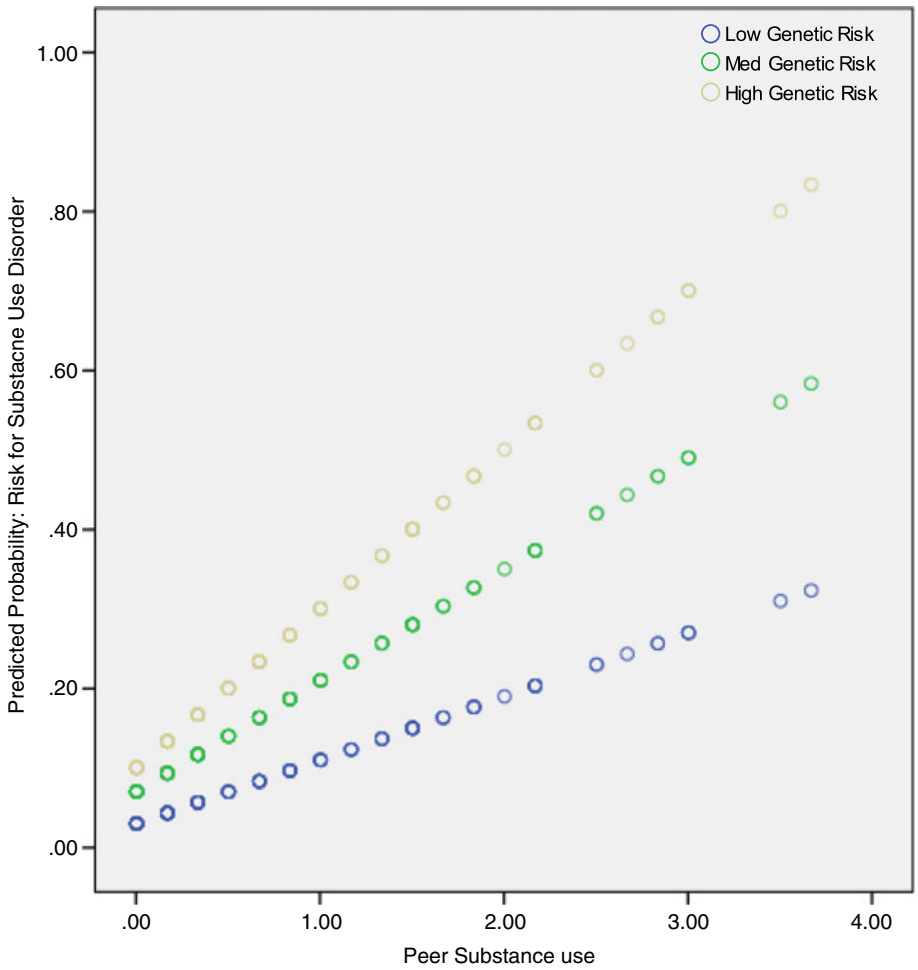

Figure 6. (Color online) Interaction between peer substance use and genetic risk to predict substance use disorder (coefficients from mother report of parenting model; $N = 254$).

genic risk on emerging adult SUD. The polygenic risk score was unrelated to peer substance use, although peer substance use conferred risk for emerging adult SUD (for those at all levels of genetic risk). Therefore, older adolescent peer substance use did not mediate this effect. The finding that polygenic risk was not associated with peer substance use is inconsistent with active and evocative gene–environment correlation. 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 age trend may appear because as individuals age, they gain freedom to associate with those whose behaviors are more consistent with their genotypes. A post hoc analysis of the current data showed that the correlation between polygenic risk and emerging adult peer substance use was significant (zero-order correlation $r = .157$, $p < .05$). As individuals move out of adolescence and into emerging adulthood, they may have greater control over the people with whom they socialize (active gene–environment correlation) and/or may be more vulnerable to deviant peer groups (evocative gene–environment correlation).

In examining the fifth and final study hypothesis, we did find evidence for genetic risk moderating the effects of older adolescent parental knowledge as well as older adolescent peer substance use, on emerging adult SUD. In terms of the interaction between parental knowledge and genetic risk, for those at highest levels of genetic risk, less parental knowledge was associated with higher risk of SUD. For those at medium and low levels of genetic risk, there was no relation between parental knowledge and SUD.

Many genetically informed studies have found evidence for a fan-shaped interaction, in which genetic influences are stronger at higher levels of environmental risk and environmental influences are stronger at higher levels of genetic risk (for a review, see Dick, 2011). Specifically, interactions between parental knowledge and genetic risk have predicted alcohol use and misuse, such that the genotype exerts a stronger influence in environments with less parental knowledge (Miranda et al., 2012; Salvatore et al., 2014). These studies suggest that risky environments are most predictive of adverse outcomes for those who are most genetically vulnerable. The fact that this interaction effect is consistent with previous research and was obtained over and above gene–environment

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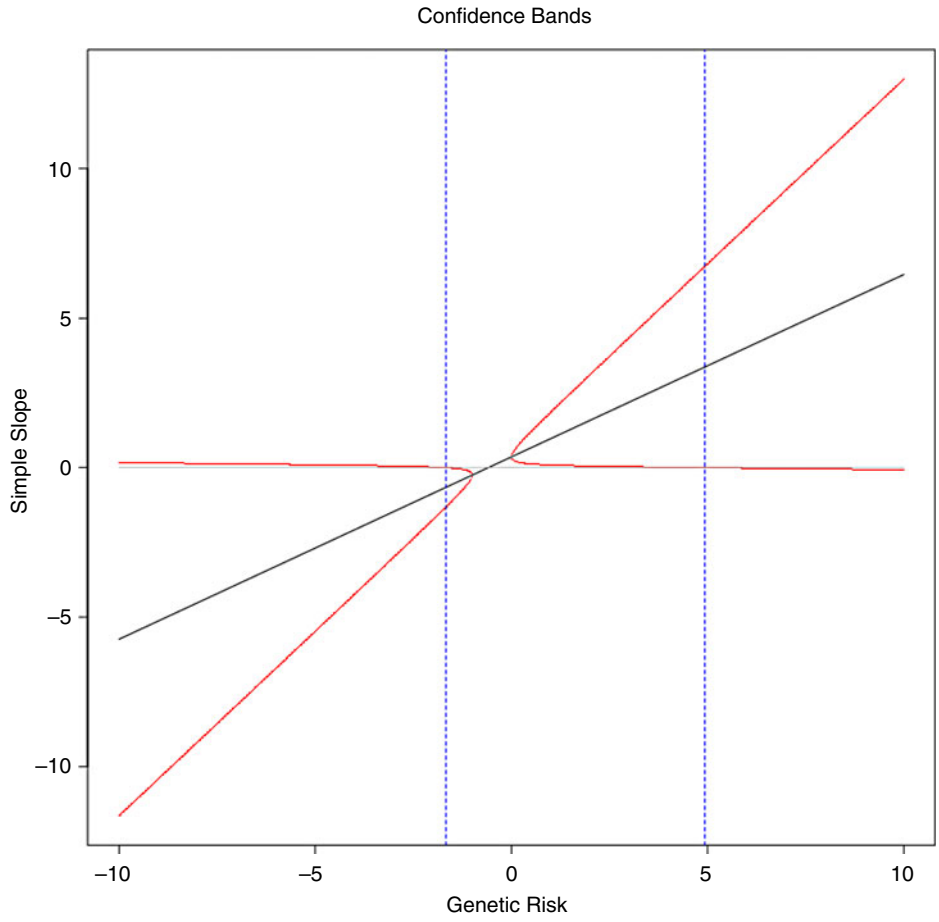

Figure 7. (Color online) Regions of significance ($p < .05$) for interaction between peer substance use and genetic risk (mother report of knowledge model). Regression coefficients are nonsignificant at values of the moderator falling *outside* the region (–1.89 to 4.93; gene score mean = 0, $SD = 1.53$). However, because very few individuals have gene scores above 4.93, it can be concluded that the simple slope of substance use disorder regressed on peer substance use is significantly different from zero ($p < .05$) for values of genetic risk at or below –1.89, which is about 1.25 *SD* below the mean.

correlation increases confidence in its validity. It also extends the evidence to clinical SUD outcomes and makes it less likely that parental knowledge is simply a marker of genetic risk for SUDs in the prediction of SUD.

Similar to the case of parental knowledge, genetic risk and older adolescent peer substance use interacted to predict emerging adult SUD. Although the simple slopes for peer substance use on emerging adult SUD were significant at all levels of genetic risk, this effect was more pronounced at highest and medium levels of genetic risk. This finding is consistent with literature finding stronger effects of deviant peer affiliations on substance use phenotypes for those at higher levels of genetic risk (Miranda et al., 2012; Salvatore et al., 2014). As with the interaction between parental knowledge and genetic risk, this finding suggests that adverse environments have the most negative effects for those most vulnerable individuals. The fact that this interaction holds over and above gene–environment correlation increases confidence in its validity. This finding also adds to existing literature by establishing that peer substance use exerts a prospective effect on emerging adult clinical SUD outcomes, with this effect increasing for those at highest levels of genetic risk for SUD.

It is important to consider these findings in the context of prevention and intervention. First, because polygenic risk predicted older adolescent but not younger adolescent parental knowledge, parenting programs may think about educating caregivers about increasing offspring effects on their parenting behaviors as their adolescents age. Parenting programs might also continue to encourage parents to take active steps to learn about their adolescents' lives. Although it is recognized that many adolescents thrive on increasing autonomy during this time, it is important for parents of older adolescents to engage with their adolescents and solicit information from them in order to decrease the likelihood of later SUD. Some researchers have found that parental knowledge and accessibility during adolescence prospectively predicted quantity and frequency of drinking during the first year of college (Abar & Turrisi, 2008; Turrisi & Ray, 2010).

Second, the finding that, together, younger and older peer substance use mediated the effect of parent AUD on SUD

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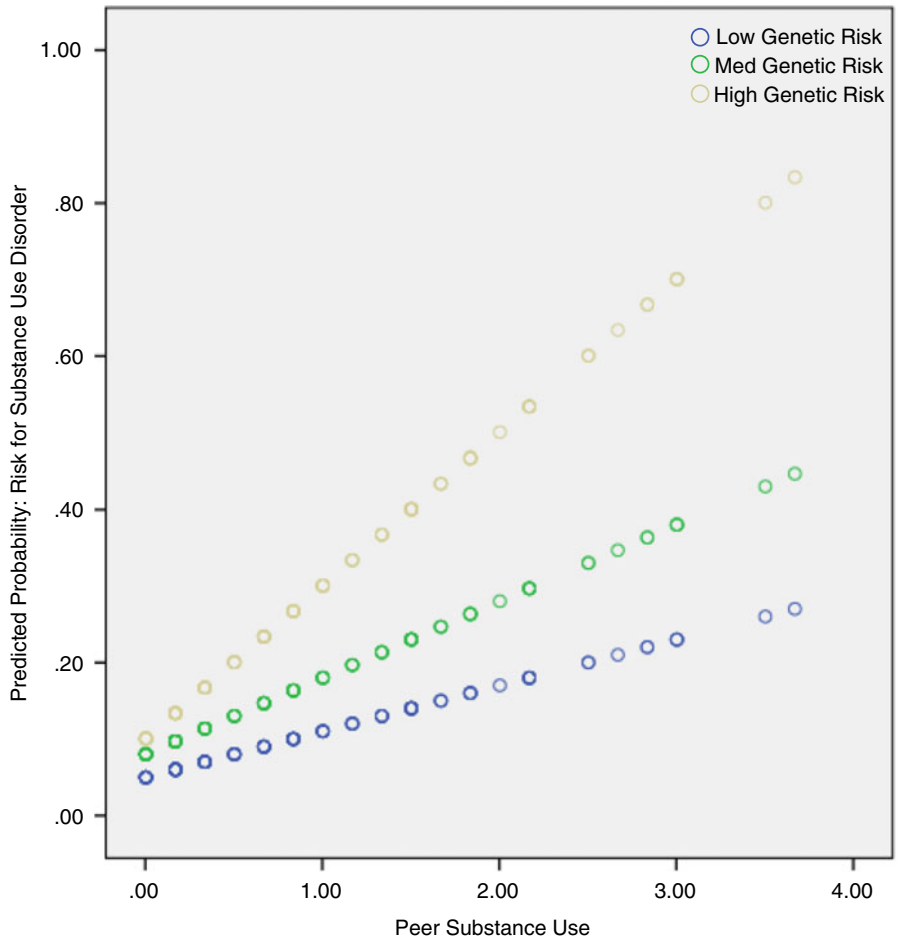

Figure 8. (Color online) Interaction between peer substance use and genetic risk to predict substance use disorder (coefficients from adolescent report of parenting model; $N = 254$).

suggests that peers uniquely influence risk for SUD. Intervention work should emphasize to parents with AUDs the importance of peer relationships for their adolescents. These interventions should target counteracting the harmful, normalizing messages that substance-using peers communicate to adolescents about alcohol and drugs.

Third, the findings that late adolescent parental knowledge and peer substance use exerted stronger prospective effects on emerging adult SUD for those at higher levels of genetic risk are also noteworthy. These findings suggest that intervention efforts that increase parental solicitation of information and counteract the harmful messages that substance-using peers communicate in late adolescence may be especially important in reducing risk for emerging adult SUD among those at greater propensity for alcohol and drug misuse.

Although the current findings contribute to the literature by delineating the roles of parental knowledge and peer substance use in the development of clinical SUD while considering gene–environment correlation, there are also limitations to consider. First, parent genotype was not measured, so the extent to which parents' genetic risk influences parenting could not be tested. Prior research has found evidence for significant passive gene–environment effects (Rice, Lewis, Harold, & Thapar, 2013). Second, in creating the polygenic risk score, we 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, which some have previously found (Salvatore & Dick, 2015). Third, the effect of this polygenic risk score, as well as other effects of measured genes on outcomes, is typically small (Bierut, 2011) and the sample included relatively few participants. Therefore, the current study may have been underpowered to detect main effects, and even more underpowered to detect interaction effects (Dick et al., 2015). Fourth, a three-item measure of parental knowledge may be less stable and reliable than a measure including more items. Study findings would have also been strengthened by the use of observational measures of parenting and/or defiant peer affiliation (e.g., Granic, Dishion, Hollenstein, & Patterson, 2003), instead of relying on self-report of these constructs. In addition, we only included mother report and child report of knowledge, so these findings may not generalize to findings using father report of parenting. These findings may also not generalize to families who are not of Caucasian or Hispanic ethnicity. The current

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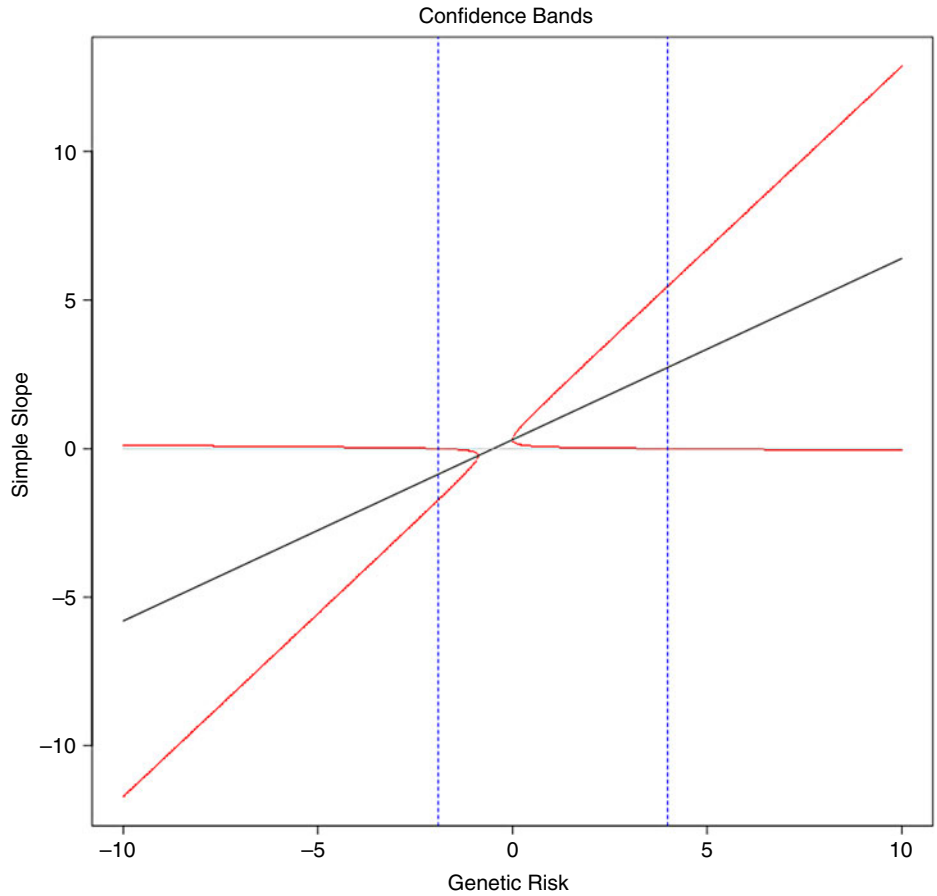

Figure 9. (Color online) Regions of significance ($p < .05$) for interaction between peer substance use and genetic risk (adolescent report of knowledge model). Regression coefficients are nonsignificant at values of the moderator falling *outside* the region (–1.91 to 3.99; gene score mean = 0, *SD* = 1.53). However, because very few individuals have gene scores above 3.99, it can be concluded that the simple slope of substance use disorder regressed on peer substance use is significantly different from zero ($p < .05$) for values of genetic risk at or below –1.91, which is about 1.25 *SD* below the mean.

subsample ($N = 254$) is also at lower risk (i.e., less likely to be male, have a parent with an AUD, and meet criteria for a SUD) compared to those who were excluded from the current study analyses ($N = 200$). Although these differences were small in magnitude, current study findings should be interpreted with caution. Fifth, there are major biological and social differences between 11- and 14-year-olds and between 18- and 25-year-olds (including exposure to substance-using peers), yet individuals within these two age bands were grouped together, potentially obscuring some of the relations among constructs.

In summary, the current study found that parental AUD predicted younger adolescent parental knowledge using mother report, and genetic risk predicted older adolescent parental knowledge, suggesting that there are multiple pathways that influence parental knowledge about their offspring's lives. Moreover, over and above gene–environment correlation, less parental knowledge and more peer substance use predicted greater risk for SUDs, with these effects being stronger for those at higher levels of genetic risk. Finally, this study replicated previous research in finding that peer substance use mediated the effect of parental AUD on SUD and extends this literature by demonstrating this effect over and above polygenic risk. Taken together, these findings support the ideas that evocative gene–environment effects increase with age across adolescence and that some of the most important environmental risk factors for SUDs exert nonuniform effects that vary across level of genetic propensity.

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