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Family History Density Predicts Long Term Substance Use Outcomes in an Adolescent Treatment Sample

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Abstract

Aims—This study explored whether the density of family history (FH) of substance use disorders relates to post-treatment substance use outcomes in adolescents, with the primary aim of determining whether FH exerts a relatively stronger influence on longer-term outcomes.

Method—The present investigation examined adolescents (ages 12–18, $n = 366$) from two independent samples who were treated for alcohol/substance use disorder (ASUD) and re-assessed during the eight years following treatment with identical methodology. Primary substance use outcomes were assessed at 1, 2, 4, 6, and 8 years post-treatment and included total drinks, days using marijuana, and days using other drugs.

Results—In hierarchical linear models there were significant FH density X linear time interactions for total drinks ($z = 12.75, p < .001$) and marijuana use days ($z = 4.39, p < .001$); greater FH density predicted more total drinks and more marijuana use days, with both associations becoming stronger over time. The increasing linkage between FH and other drug use was not significant over time.

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Conflict of Interest

All of the authors declare that they have no conflicts of interest.

Contributors

Rubin Khoddam conducted literature searches, wrote the initial complete draft of the manuscript, and maintained contact between authors to bring the manuscript to fruition. Dr. Matthew Worley conducted statistical analyses, wrote the final results section, and edited drafts of the manuscript. Dr. Kendall C. Browne wrote the final methods section and edited drafts of the manuscript. Dr. Neal Doran helped with statistical analyses and edited drafts of the manuscript. Dr. Sandra A. Brown designed the study and wrote the protocol. All authors contributed to and have approved the final manuscript. We would all like to thank Dr. Marc A. Schuckit for his research, consultation, and support throughout this project.

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Conclusions—Findings are consistent with previous research indicating that the risk associated with FH increases over time, especially in relation to quantity/frequency measures of alcohol and marijuana use. By extending these findings to an adolescent clinical sample, the current study highlights that FH density of alcohol and drug dependence is a risk factor for poorer long-term outcomes for adolescent-onset ASUD youth as they transition into adulthood. Future work should explore the mechanisms underlying greater post-treatment substance use for adolescents/young adults with greater FH density.

Keywords

family history; alcohol and drug dependence; treatment outcome

1. INTRODUCTION

The development and long-term progression of alcohol and substance use disorders (ASUDs) is a complex process influenced by both biological and environmental variables. The specific contribution of risk conferred by genetic factors and environmental variables is complex (Liu et al., 2004; Prescott and Kendler, 1999), with effects varying over the course of development. In genetically-informative studies of substance use etiology, the role of genetic factors appear to increase over the course of development, while shared environmental factors diminish in importance (Koopmans et al., 1997; White et al., 2003; Viken et al., 1999). More specifically, initiation and early substance use patterns seem to be more strongly influenced by social and familial environments, with progression to more severe levels of use under relatively greater genetic influence (Kendler et al., 2008).

1.1. Family history as a risk factor

While there are many pathways toward developing ASUDs, one long-recognized common risk is a positive family history (FH), such as biological parent alcoholism (Cadoret et al., 1995; Heath et al., 1991; McGue, 1997). Approximately 40%-60% of the variance in alcohol use disorders (AUDs) may be explained by genetic influences (Heath et al., 1997; McGue, 1999; Prescott and Kendler, 1999), and estimates of genetic heritability may be up to 60%-80% for nicotine and cocaine (Kendler and Prescott, 1998; True et al., 1999).

1.2 Long-term influences of family history

Although FH is a commonly employed clinical indicator of genetic risk, its influence also includes environmental and social influences. Several mechanisms may underlay the means whereby risk conferred by FH changes over time. Research to date suggests FH may have a long-term influence on substance use severity and problems, including a more severe course and higher rates of ASUDs at long-term follow-up time points (Dawson et al., 1992; Chassin et al., 2004; Cloninger et al., 1981; Grant, 1998; Worobec et al., 1990). For instance, in community samples, individuals with positive FH consumed greater maximum drinks, met more dependence criteria, and had higher rates of marijuana use at an 8-year follow-up in one investigation (Schuckit and Smith, 1996).

FH impact may become stronger over time through cumulative effects of genetic and environmental components of risk (Jackson et al., 2000; Chassin et al., 2002). These longer-

term effects of FH are potentially partially mediated by lower subjective response to alcohol and subsequent consumption of greater quantities of drinks (e.g., Quinn and Fromme, 2011; Schuckit, 2002; Schuckit et al., 2004). Taken together, prior studies suggest positive FH should relate more strongly to long-term measures of substance use, but few studies have utilized frequent, repeated measures of substance use outcomes to closely examine whether the influence of FH on these outcomes changes over time.

1.3 The impact of family history on adolescents

The majority of studies examining the effects of FH on ASUDs have utilized community samples recruited according to FH status and followed over time. Few studies have examined the long-term effects of FH on those youth diagnosed and treated for ASUDs in adolescence. Late adolescence and young adulthood (i.e., age 18–22) is the highest risk developmental period for onset of alcohol and substance use related disorders (Johnston et al., 2011; Grant and Dawson, 1997; Substance Abuse and Mental Health Services Administration, 2009). Thus, this period may be particularly impactful for those with a history of early ASUDs. Given that the influence of genetic factors on substance use may increase over time (Kendler et al., 2008; Koopmans et al., 1997; White et al., 2003; Viken et al., 1999) and FH is thought to capture both genetic and environmental aspects of addiction that exert influence on outcomes once use has been initiated (e.g., Chassin et al., 2002, Jackson et al., 2000, Schuckit and Smith, 1996), the influence of FH could be more pronounced among those youth in substance use treatment.

1.4 Family history density

A comprehensive measure of FH computed according to the combination of familial relatedness and ASUD history (i.e. FH density score) may be the most comprehensive measure of FH (Dawson et al., 1992; Chassin et al., 1992; Harford et al., 1992; Schuckit and Smith, 1996; Stoltenberg et al., 1998). The FH density score considers the contribution of first- and second-degree relatives and has been considered a more appropriate clinical measure of biological risk than a single dichotomous variable (Zucker et al., 1994). Furthermore, a density score accounts for more variance in alcoholism severity and consequences of drinking when compared to a dichotomous FH score of first- and second-degree relatives (Turner et al., 1992), supporting the utility of FH density as a clinically-based measure of potential genetic risk for ASUDs.

1.5 Study aims

The primary aims of the present study were to examine whether FH density predicts post-treatment substance use outcomes in youth diagnosed with and treated for ASUDs in adolescence, and to explore whether FH density exerts relatively stronger influence on longer-term post-treatment outcomes. This is a qualitatively different group than examined prior community sample studies. Although prior literature has indicated FH does impact drinking outcomes, there are gaps in the literature regarding (1) the differential effects of FH density on short- compared to long-term outcomes and (2) its impact on a high-risk group of treatment-seeking adolescents. We hypothesized that greater FH density would predict greater levels of alcohol, marijuana, and other drug use, and that the effects of FH density would be relatively stronger for longer-term compared to shorter-term outcomes. To

examine the independent effects of FH density, we adjusted for other influences on adolescent treatment outcomes, which are associated with FH of ASUD. Specifically, conduct disorder, a risk factor previously associated with both ASUD, FH, and long-term substance use outcomes (Chassin et al., 1999; Chung et al., 2003; Sher, 1991; Zucker et al., 1994), and time-varying levels of depression and anxiety, were covaried to determine whether FH density was independently associated with adolescent ASUD treatment outcomes above and beyond the effects of these common prognostic indicators.

2. METHODS

2.1 Participants

The present research was conducted according to the guidelines and under the approval of the University of California, San Diego Human Research Protections Program. The current sample ($N = 366$) included youth selected from two previous studies of long-term alcohol/substance use treatment outcomes for adolescents (ages 12–18 at baseline), who were recruited at the onset of inpatient stays at alcohol and substance use treatment facilities in the San Diego area. The six treatment facilities were abstinence-focused and used a 12-step model of alcohol/substance abuse treatment as well as individual, family, and group psychotherapies drawing from cognitive-behavioral strategies. Length of inpatient treatment ranged from 5 days to 3 weeks. All participants in both studies met Diagnostic and Statistical Manual of Mental Disorders (*DSM-III-R*; American Psychiatric Association, 1987) criteria for alcohol and/or substance dependence. In the full combined sample utilized in the current study, 159 participants (43.4%) were adolescents who met no *DSM-III-R* Axis I disorders exclusive of conduct disorder (hereafter referred to as the ASUD-only group). The rest of the sample ($n = 207$, 56.6%) met criteria for an alcohol and/or substance use disorder and an additional non-conduct, *DSM-III-R* Axis I disorder (Comorbidity group). Axis I disorders were assessed with the Diagnostic Interview Schedule for Children—Computerized Version (*DISC-III-R*; McCarthy et al., 2005; Piancentini et al., 1993; Ramo et al., 2005; Tomlinson et al., 2004) administered separately with the adolescent and a collateral reporter (parent or custodial guardian). Additional eligibility criteria (across both studies) included 12–18 years of age, residence within 50 miles of the research site, participants' literate in English, and availability for one-year follow-up. Youth who did not have a collateral reporter (i.e., parent or guardian) to corroborate personal and FH information, had current psychotic symptoms, or had physical handicaps prohibiting participation were excluded from the study.

At intake participants averaged 16.12 ($SD = 1.30$) years of age; 51% were male, and 63% were Caucasian. Most of the sample (82%) met criteria for conduct disorder. All youth met *DSM-IV* criteria for lifetime alcohol dependence and 91% met criteria for drug dependence.

Further details regarding baseline alcohol and substance use of the treatment samples are reported elsewhere (Brown and D'Amico, 2001; Tomlinson et al., 2004).

2.2 Procedures

After obtaining parent/guardian consent, charts of consecutively admitted youth were screened for study inclusion, and trained research staff contacted eligible youth and parents

to explain the study and obtain informed assent/consent. Youth and parents completed baseline assessments within 3 weeks of admission. Following treatment, youth and a collateral reporter completed follow-up assessments were conducted at 1, 2, 4, 6, and 8 years after study entry. Follow-up assessments were arranged by phone, mail, and email. Participants were interviewed in person or by phone if necessary (e.g., out of 50 mile range) to minimize attrition, which did not exceed 11% in any year of follow-up (see Table 3). Adolescents and collateral reporters (e.g., parent/guardian, domestic partner) were interviewed separately. A significantly greater proportion ($\chi^2 = 6.37, p < .05$) of the comorbidity group (70%) was missing at least one outcome time point as compared to the ASUD-only group (53%), as rates of follow-up across time points were higher in the ASUD-only group (Mean = 97%) than in the comorbidity group (Mean = 91%). The likelihood of having any missing outcome data was not predicted by gender, intake age, ethnicity, conduct disorder, or FH density score.

2.3 Measures

2.3.1 Family History—For this study, we used a composite density score reflecting FH of either alcohol or drug dependence. A structured interview assessed objective problems of DSM-III-R alcohol or substance dependence criteria for all biological parents and grandparents. All reports of FH reflect consolidated information from both the participant and the collateral reporter. Any relative who met two or more alcohol or substance dependence criteria or received any alcohol or substance dependence treatment was coded as positive, with a score of .25 for each biological grandparent, and a score of .5 for each biological parent (Stoltenberg et al., 1998; Zucker et al., 1994). The composite FH density score was the sum of all scores and ranged from 0 to 2, with a score of 0 indicating absence of FH.

2.3.2 Demographics—The Structured Clinical Interview for Adolescents (SCI; Brown et al., 1989) was used to collect demographic and background information, information relating to participants' experiences with substance use, physical health, social and family relations, academic functioning, and related variables. Comparable interviews were conducted with parents to confirm historical and diagnostic information. Demographic variables were utilized as covariates in the current study and included age at intake, gender, and a dichotomous ethnicity indicator (Caucasian vs. other).

2.3.3 Substance Use—The well-standardized Customary Drinking and Drug Use Record (CDDR; Brown et al., 1998, 2001), a structured interview, was used to assess age of onset, quantity, frequency, and patterns of alcohol and substance use (i.e., marijuana, amphetamines, cocaine, barbiturates, hallucinogens, opiates, and other drugs) and DSM-III-R and DSM-IV alcohol/substance abuse and dependence symptoms. The lifetime version was used at intake and current (prior 90 days) CDDR was used at each follow-up assessment. Outcome variables examined in this study included measures of substance use in the past 90 days, including total drinks (typical quantity x frequency), days of marijuana use, and days of other drug use.

2.3.4 Conduct Disorder—The Conduct Disorder Questionnaire (CDQ; Brown et al., 1996) was used to assess conduct disorder behaviors derived from DSM-III-R and DSM-IV criteria. Importantly, this instrument differentiates behaviors that occur only in the context of substance use (e.g., during acquisition of alcohol/drugs, while intoxicated, during acute withdrawal) from those occurring independently of substance use. In this study a dichotomous variable reflected a diagnosis of conduct disorder based on behaviors that occurred independently of substance use on one more than one occasion.

2.3.5 Depression and anxiety—The Structured Clinical Interview for Adolescents (SCI; Brown et al., 1989) was used to collect information regarding anxiety and depression during each follow-up. The dichotomous diagnostic screening questions of standardized semi-structured interviews, including the Diagnostic Interview Schedule for Children (DISC-III-R; Piancentini et al., 1993) and Structured Clinical Interview for DSM-III-R (SCID; Spitzer et al., 1992), were used to reflect whether significant anxiety (“Have you been anxious so as to interfere with daily functioning?”) and depressive symptoms (“Have you been depressed continuously (for at least two weeks) so as to interfere with daily functioning?”) were present in the six months prior to each follow-up assessment.

2.4 Statistical Analysis

Hierarchical linear models (HLM) with random intercepts at the person level were used to examine the effects of FH density on long-term substance use outcomes. This statistical approach allows multiple time points nested within individuals, both static and time-varying predictors, and inclusion of all available data via maximum likelihood estimation, which is a preferred approach to missing data (Schafer and Graham, 2002). Among the study variables tested only conduct disorder and study group significantly predicted whether participants had missing outcome data. Consequently, conduct disorder and group (ASUD-only vs. comorbidity) were utilized as covariates in all models. All statistical analyses were performed in Stata 10.1 (StataCorp, 2007).

Preliminary models examined the effects of time (year of follow-up), demographics, and clinical covariates on substance use outcomes, to identify statistically significant covariates before testing the effects of FH density. Demographic variables and conduct disorder were treated as time-invariant covariates, while recent depression and anxiety were time-varying. Sequential HLMs then tested the main effect of FH density and the interactions of FH with linear and quadratic time. These models tested whether individuals with greater FH density had greater overall levels of substance use, and if the effects of FH density on substance use outcomes changed over time. The primary substance use variables were positively skewed, and thus Poisson distributions were utilized for these outcomes as recommended by Neal and Simons (2007).

3. RESULTS

3.1 Description of family history density and outcomes

Table 1 presents correlation among all key study variables. The distribution of FH density for the sample is displayed in Figure 1. Mean FH density across the sample was 0.64 ($SD =$

0.49). Approximately one-fifth of the sample (20%, $n = 78$) had no FH, while most of the sample (62%, $n = 240$) ranged from 0.25 to 1 and 18% ($n = 69$) reported high FH density from 1.25 to 2. A large majority of the sample (82%) met diagnostic criteria for conduct disorder independent of substance involvement, and conduct disorder was significantly more prevalent ($\chi^2 = 17.71, p < .001$) in males (89%) than in females (71%). Of note, mean levels of FH density were not significantly different ($t = -0.82, p = 0.41$) between youth with ($M = 0.66, SE = 0.03$) and without ($M = 0.61, SE = 0.05$) conduct disorder. As displayed in Table 2, descriptive statistics indicated all substance use outcomes were positively skewed. At the overall sample level, total drinks increased steadily over time, while marijuana and other drug use evinced nonlinear patterns of change, increasing until year 6 (mean age = 22 years) and decreasing thereafter.

3.2 Covariates of long-term treatment outcome

Prior to testing hypotheses related to FH density, preliminary models examined demographic and clinical covariates of substance use outcomes. In HLM the effects of time (in years), quadratic time, recent depression, and recent anxiety were estimated as time-varying covariates, while gender, ethnicity (white vs. nonwhite), study sample, baseline age, and conduct disorder were examined as time-invariant covariates. As shown in Table 3, gender, age, depression, and anxiety significantly predicted substance use outcomes. Males had greater levels of alcohol, marijuana, and other drug use. Participants who were younger at baseline had greater marijuana use. Depression and anxiety were both associated with greater total drinks, marijuana use, and other drug use. These significant covariate effects were included in all subsequent models, as were study sample and conduct disorder (to control for potential influences of group differences in missing data).

3.3 Family history density and long-term treatment outcomes

By testing the main effects of FH density and interactions with linear and quadratic time, we evaluated whether individuals with greater FH density had greater overall levels of alcohol, marijuana, and other drug use, and whether the relative effects of FH density on substance use outcomes changed during the eight years following treatment. Results of these models are displayed in Table 4. For alcohol use the interactions of FH density with linear ($b = 0.20, SE = 0.04, z = 12.75, p < .001$) and quadratic time ($b = -.02, SE = 0.004, z = -11.98, p < .001$) were statistically significant. Model estimates of simple effects indicated the FH density effect was small at Year 1 ($b = -0.73$) and peaked at year 6 ($b = -5.12$). As depicted in Figure 2 (with FH tri-chotomized for graphical purposes), the association between FH density and alcohol use increased significantly over time, such that individuals with greater FH density had relatively greater increases in total drinks that peaked around year 6. For example, individuals with FH density = 0 increased in total drinks from year 1 of follow-up ($M = 24.27$) to year 6 ($M = 43.18$), but those with FH density = 1 had larger increases over time from year 1 ($M = 28.25$) to year 6 ($M = 68.96$).

Results for marijuana use were similar, as FH density had statistically significant interactions with linear ($b = 0.16, SE = 0.04, z = 4.39, p < .001$) and quadratic time ($b = -.02, SE = 0.004, z = -3.77, p < .001$). The association between FH density and marijuana use increased across assessment waves, as model estimates of simple effects indicated *IRR* for

FH density was small at Year 1 ($b = -0.24$) and peaked at year 6 ($b = 0.43$). Youth with greater FH density were predicted to have greater increases in marijuana use than those with lower FH density. Individuals with FH density = 0 increased in days using marijuana from year 1 of follow-up ($M = 6.84$) to year 6 ($M = 7.90$), but those with FH density = 1 had larger increases over time from year 1 ($M = 5.43$) to year 6 ($M = 10.11$). For other drug use the main effects of FH density and interactions with time were not statistically significant, although the interaction with linear time was in the hypothesized direction and near alpha ($b = .05$, $SE = 0.003$, $p = .08$). Overall, the effects of FH density grew stronger over time for alcohol and marijuana and use, with greater FH density associated with accelerations in intensity of substance use at later follow-ups.

4. DISCUSSION

Given that multiple factors influence developmental changes in alcohol and drug use, it is important to understand how the magnitude and timing of these influences can shift over time. As a clinical indicator of biological predisposition to ASUDs, FH density would theoretically be a better predictor of chronic forms of ASUDs than of adolescence-limited patterns of use. Consistent with this theory are studies finding greater long-term quantity and frequency of use and greater dependence rates for those with positive FH (Jackson et al., 2000; Chassin et al., 2002). However, to our knowledge, no prior research has utilized frequent follow-up assessments to examine the emerging effects of FH density on short- and long-term substance use outcomes of youth following ASUD treatment during adolescence.

4.1 Interpretation of family history density and long-term treatment outcomes

We hypothesized that greater FH density would predict greater intensity (quantity and frequency) of alcohol and substance use, and that these effects would increase as youth progressed into their subsequent decade of life. In our clinical sample the risk associated with FH changed over time, such that FH influences increased during early adulthood, this peak risk period for onset of ASUDs. Specifically, those with greater FH density consumed more alcohol and used marijuana more frequently to a greater extent over eight years compared to the short-term outcomes following treatment. This is consistent with our hypothesis, and with the fact that social and environmental factors have been implicated more often in initial relapse among adolescents (Brown et al., 1989) while genetic indicators (i.e., FH and level of response to alcohol) have increasing influences on long-term drinking behavior (Rose et al., 2001).

These findings parallel those of prior studies of community youth where positive FH predicted greater alcohol and marijuana use at follow-up (Chassin et al., 1991; Schuckit and Smith, 1996) and more severe alcoholism, including quantity, frequency, and sustained use (Worobec et al., 1990). Of note, the Low Response Model (e.g., Schuckit et al., 2001), in which low response to alcohol is posited as a phenotypic risk factor related to FH (Erblich and Earleywine, 1999; Schuckit and Smith, 1996, 2000) that results in both greater quantity and frequency of alcohol use over time is consistent with the present findings (Schuckit and Smith, 1996). This study extends these findings to marijuana use and to treated ASUD youth as they mature into their mid-twenties. Future studies are needed to clarify the specific

genetic variations related to frequent use of specific substances, versus those related to engaging in greater use of all substances over time.

4.2 Interpretation of family history density and other drug use

Although we hypothesized that those with a greater FH density would report increased other drug use, our findings did not support this prediction. Other influences may dominate the risk for drug involvement and progression during this developmental period (Brown et al., 2008; Kendler et al., 2000, 2003). In a sample of twins and adoptive sibling pairs, higher heritability estimates were found for problematic alcohol use compared to initiation of use where there was a greater shared environmental component (Rhee et al., 2003; Rose et al., 2001). One possibility is that there may be greater heritability of this risk component impacting alcohol use with problem drinking groups. Conversely, there are individual environmental factors (i.e., incarceration), which dominate developmental transitions in this age range, such as specific peer groups, which impact the use and misuse of other drugs. These unique environmental factors may largely determine whether genetically predisposed individuals will use or misuse other types of drugs (Kendler et al., 2003). Of note, additional mechanisms (i.e. education, occupation, marriage and family status) have also been implicated in longitudinal trajectories of multiple substance use compared to alcohol use alone (Anderson et al., 2010).

4.3 Unique contributions of the present study

One methodological contribution of the present study to the current FH and treatment outcome literature is that the data were collected using a prospective, repeated measures design with high follow up-rates. Furthermore, this study utilized a continuous measure of FH density reflecting both parent and grandparent dependence history, which has been shown to better convey risk associated with genetic factors (Comtois et al., 2005). This more sensitive measure afforded us the opportunity to observe developmental trends through adolescence and into adulthood that would not have been possible using short-term or cross-sectional approaches.

The age period examined in the present study is particularly significant given the amount of developmental change occurring across neurologic, cognitive and social domains (e.g., Brown et al., 2008). Understanding the salience of important long-term risks is particularly significant for adolescents as they have yet to transition through the peak periods of alcohol and drug dependence and greater use can lead to more severe long-term trajectories and adverse consequences for the individual and society (Anderson et al., 2010; Brown and Ramo, 2006). Additionally, adolescents with a comorbid Axis I disorder have also been shown to have worse treatment outcomes, using substances more frequently (Tomlinson et al., 2004). Clinicians can use information from this developmental approach to inform treatment planning by identifying risk factors and critical opportunities for screening, assessment and supporting healthy development through non-substance using behaviors (Brown et al., 2008; Chung et al., 2005).

4.4 Limitations and future directions

Limitations of this study include the methods utilized for collecting FH density, as measures were collected via self-report of participants and parents/guardians without comprehensive diagnostic interviews of all parents and grandparents. This study utilized a summary measure of FH density that was compiled across alcohol, marijuana, and other drugs, which did not allow us to examine differences with FH density in alcohol vs. other drugs. Other forms of familial psychopathology, such as antisocial personality disorders or mood disorders, were not considered, but may also account for part of the association. The high rates of conduct disorder, while to be expected in clinical samples (e.g., Abrantes et al., 2005), makes it difficult to fully disentangle relations between conduct disorder and positive FH as noted in prior studies (Chassin et al., 1999; Sher, 1991; Zucker et al., 1994). Additionally, the present study was limited by a single dichotomous self-report item assessing for depression and anxiety that may not account for the full range of mood disorders. The time frame assessed for these items was past 6 months as opposed to past 90 days for substance use outcomes; thus, anxiety and depression may be reported outside the substance-using period.

It should also be noted that the sample from the current study was from inpatient facilities and may be qualitatively different from those in outpatient treatment programs. Thus, results may not generalize to other forms of less intensive treatment. The null finding for the FH main effect may be explained by the fact that this is a higher risk sample and that once patients are at the point of needing treatment, FH density alone has less of an effect on outcomes. Furthermore, the present study focused on FH as a genetically informative risk factor, but did not examine the extent to which environmental factors may contribute to long-term outcomes. Future studies should examine the extent to which peer use and individual environmental variables interact with genetically informative variables to predict post-treatment outcomes. Finally, because our latest time point of follow-up was eight years, this study was not able to examine whether these family history effects persist into later stages of life.

4.5 Conclusions

In this study of individuals treated for ASUDs in adolescence, we found that the risk conferred by greater FH density does increase over time for both alcohol and marijuana use. This finding contributes to the literature by demonstrating that the strength of the link between a genetically-determined risk factor (FH density) and severity of substance use increases over time among individuals who previously received treatment for ASUDs as they transition into young adulthood. Our findings indicate that adolescents with greater FH density scores who are receiving ASUD treatment are at greater risk for returning to increased levels of substance use in the long-term, and more tailored interventions may be needed for this higher-risk population.

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References

- Abrantes AM, Hoffman NG, Anton R. Prevalence of co-occurring disorders among juveniles committed to detention centers. *Int J Offender Ther Comp Criminol*. 2005; 49:179–293. [PubMed: 15746269]
- American Psychiatric Association. *Diagnostic And Statistical Manual Of Mental Disorders*. 3. APA; Washington, DC: 1987.
- Anderson KG, Ramo DE, Cummins KM, Brown SA. Alcohol and drug involvement after adolescent treatment and functioning during emerging adulthood. *Drug Alcohol Depend*. 2010; 107:171–181. [PubMed: 19926231]
- Brown SA, Vik PW, Creamer VA. Characteristics of relapse following adolescent substance abuse treatment. *Addict Behav*. 1989; 14:291–300. [PubMed: 2787585]
- Brown SA, Myers MG, Lippke L, Tapert SF, Stewart DG, Vik PW. Psychometric evaluation of the Customary Drinking and Drug Use Record (CDDR). A measure of adolescent alcohol and drug involvement. *J Stud Alcohol*. 1998; 59:427–438. [PubMed: 9647425]
- Brown SA, D'Amico EJ, McCarthy DM, Tapert SF. Four-year outcomes from adolescent alcohol and drug treatment. *J Stud Alcohol*. 2001; 62:381–388. [PubMed: 11414348]
- Brown, SA.; D'Amico, EJ. Outcomes for alcohol treatment for adolescents. In: Galanter, M., editor. *Recent Developments In Alcoholism: Vol. XVI. Selected Treatment Topics*. Plenum; New York: 2001. p. 307-327.
- Brown, SA.; Ramo, DE. Clinical course of youth following treatment for alcohol and drug problems. In: Liddle, HA.; Rowe, CL., editors. *Adolescent Substance Abuse: Research And Clinical Advances*. Cambridge University Press; New York: 2006. p. 79-103.
- Brown SA, McGue MK, Maggs J, Schulenberg JE, Hingson R, Swartzwelder HS, Martin CS, Chung T, Tapert SF, Sher KJ, Winters K, Lowman C, Murphy SA. A developmental perspective on alcohol and youth ages 16–20. *Pediatrics*. 2008; 121:S290–S310. [PubMed: 18381495]
- Cadoret RJ, Yates WR, Troughton E, Woodworth G, Stewart MA. Genetic-environmental interaction in the genesis of aggressivity and conduct disorders. *Arch Gen Psychiatry*. 1995; 52:916–924. [PubMed: 7487340]
- Chassin L, Pitts SC, DeLucia C, Todd M. A longitudinal study of children of alcoholics: predicting young adult substance use disorders, anxiety, and depression. *J Abnorm Psychol*. 1999; 108:106–119. [PubMed: 10066997]
- Chassin L, Prost J, Pitts SC. Binge drinking trajectories from adolescence to emerging adulthood in a high-risk sample: predictors and substance abuse outcomes. *J Consult Clin Psychol*. 2002; 70:67–78. [PubMed: 11860058]
- Chassin L, Flora D, King KM. Trajectories of alcohol and drug use and dependence from adolescence to adulthood: the effects of familial alcoholism and personality. *J Abnorm Psychol*. 2004; 113:483–498. [PubMed: 15535782]
- Chung T, Martin CS, Grella CE, Winters KC, Abrantes AM, Brown SA. Course of alcohol problems in treated adolescents. *Alcohol Clin Exp Res*. 2003; 27:253–261. [PubMed: 12605074]
- Chung T, Martin CS, Winters KC. Diagnosis, course, and assessment of alcohol abuse and dependence in adolescents. *Recent Dev Alcohol*. 2005; 17:5–27. [PubMed: 15789857]
- Cloninger C, Bohman M, Sigvardsson S. Inheritance of alcohol abuse: cross fostering analysis of adopted men. *Arch Gen Psychiatry*. 1981; 38:861–868. [PubMed: 7259422]
- Comtois KA, Tisdall A, Holdcraft LC, Simpson T. Dual diagnosis: impact of family history. *Am J Addict*. 2005; 14:291–299. [PubMed: 16019979]
- Conway KP, Swendsen JD, Merikangas KR. Alcohol expectancies, alcohol consumption, and problem drinking. The moderating role of family history. *Addict Behav*. 2003; 28:823–836. [PubMed: 12788259]

- Dawson DA, Harford TC, Grant BF. Family history as a predictor of alcohol dependence. *Alcohol Clin Exp Res*. 1992; 16:572–575. [PubMed: 1626658]
- Erblich J, Earleywine M. Children of alcoholics exhibit attenuated cognitive impairment during an ethanol challenge. *Alcohol Clin Exp Res*. 1999; 23:476–482. [PubMed: 10195821]
- Grant BF. The impact of a family history of alcoholism on the relationship between age at onset of alcohol use and DSM-IV alcohol dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. *Alcohol Health Res World*. 1998; 22:144–147. [PubMed: 15706789]
- Harford TC, Parker DA, Grant BF. Family history, alcohol use and dependence symptoms among young adults in the United States. *Alcohol Clin Exp Res*. 1992; 16:1042–1046. [PubMed: 1471758]
- Heath AC, Bucholz KK, Madden PAF, Dinwiddie SH, Slutske WS, Bierut LJ, Statham DJ, Dunne MP, Whitfield JB, Martin NG. Genetic and environmental contributions to alcohol dependence risk in a nation twin sample: consistency of findings in women and men. *Psychol Med*. 1997; 27:1381–1396. [PubMed: 9403910]
- Jackson KM, Sher KJ, Wood PK. Trajectories of concurrent substance use disorders: a developmental, typological, approach to comorbidity. *Alcohol Clin Exp Res*. 2000; 24:902–913. [PubMed: 10888081]
- Johnston, LD.; O'Malley, PM.; Bachman, JG.; Schulenberg, JE. Monitoring The Future National Survey Results On Adolescent Drug Use: Overview Of Key Findings 2010. National Institute on Drug Abuse; Bethesda, MD: 2011.
- Kendler, KS.; Prescott, CA. Genes, Environment, and Psychopathology. Guilford; New York: 2006.
- Kendler KS, Karkowsk LM, Neale MC, Prescott CA. Illicit psychoactive substance use, heavy use, abuse, and dependence in a US population-based sample of male twins. *Arch Gen Psychiatry*. 2000; 57:261–269. [PubMed: 10711912]
- Kendler KS, Jacobson KC, Prescott CA, Neale MC. Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. *Am J Psychiatry*. 2003; 160:687–695. [PubMed: 12668357]
- Kendler KS, Schmitt E, Aggen SH, Prescott CA. Genetic and environmental influences on alcohol, caffeine, cannabis, and nicotine use from early adolescence to middle adulthood. *Arch Gen Psychiatry*. 2008; 65:674–682. [PubMed: 18519825]
- Koopmans JR, van Doornen LJ, Boomsma DI. Association between alcohol use and smoking in adolescent and young adult twins: a bivariate genetic analysis. *Alcohol Clin Exp Res*. 1997; 21:537–546. [PubMed: 9161615]
- Liu I, Blacker DL, Xu R, Fitzmaurice G, Lyons MJ, Tsuang MT. Genetic and environmental contributions to the development of alcohol dependence in male twins. *Arch Gen Psychiatry*. 2004; 61:897–903. [PubMed: 15351768]
- McCarthy DM, Tomlinson KL, Anderson KG, Marlatt GA, Brown SA. Relapse in alcohol- and drug-disordered adolescents with comorbid psychopathology: changes in psychiatric symptoms. *Psychol Addict Behav*. 2005; 19:28–34. [PubMed: 15783275]
- McGue M. A behavioral-genetic perspective on children of alcoholics. *Alcohol Health Res World*. 1997; 21:210–217. [PubMed: 15706771]
- McGue M. The behavioral genetics of alcoholism. *Curr Dir Psychol Sci*. 1999; 8:109–115.
- Neal DJ, Simons JS. Inference in regression models of heavily skewed alcohol use data: a comparison of ordinary least squares, generalized linear models, and bootstrap resampling. *Psychol Addict Behav*. 2007; 23:441–452. [PubMed: 18072826]
- Piancentini J, Shaffer D, Fisher PW, Schwab-Stone M, Davies M, Gioia P. The Diagnostic Interview Schedule for Children – Revised Version (DISC-R): III. Concurrent criterion validity. *J Am Acad Child Adolesc Psychiatry*. 1993; 32:658–665. [PubMed: 8496130]
- Prescott CA, Kendler KS. Genetic and environmental contributions to alcohol abuse and dependence in a population-based sample of male twins. *Am J Psychiatry*. 1999; 156:34–40. [PubMed: 9892295]
- Quinn PD, Fromme K. Subjective response to alcohol challenge: a quantitative review. *Alcohol Clin Exp Res*. 2011; 35:1759–1770. [PubMed: 21777258]

- Ramo DE, Anderson KG, Tate SR, Brown SA. Characteristics of relapse to substance use in comorbid adolescence. *Addict Behav.* 2005; 30:1811–1823. [PubMed: 16139961]
- Rhee SH, Hewitt JK, Young SE, Corley RP, Crowley TJ, Stallings MC. Genetic and environmental influences on substance initiation, use, and problem use in adolescents. *Arch Gen Psychiatry.* 2003; 60:1256–1264. [PubMed: 14662558]
- Rose RJ, Dick DM, Viken RJ, Kaprio J. Gene-environment interaction in patterns of adolescent drinking: regional residency moderates longitudinal influences on alcohol use. *Alcohol Clin Exp Res.* 2001; 25:637–643. [PubMed: 11371711]
- Schuckit MA, Gold EO. A simultaneous evaluation of multiple markers of ethanol/placebo challenges in sons of alcoholics and controls. *Arch Gen Psychiatry.* 1988; 45:211–216. [PubMed: 3422553]
- Schuckit MA, Smith TL. An 8-year follow-up of 450 sons of alcoholic and control subjects. *Arch Gen Psychiatry.* 1996; 53:202–210. [PubMed: 8611056]
- Schuckit MA, Mazzanti C, Smith TL, Ahmed U, Radel M, Iwata N, Goldman D. Selective genotyping for the role of 5-HT_{2A}, 5-HT_{2C}, and GABA_A receptors and the serotonin transporter in the level of response to alcohol: a pilot study. *Biol Psychiatry.* 1999; 45:647–651. [PubMed: 10088053]
- Schuckit MA, Smith TL. The relationships of a family history of alcohol dependence, a low level of response to alcohol and six domains of life functioning to the development of alcohol use disorders. *J Stud Alcohol.* 2000; 61:827–835. [PubMed: 11188488]
- Schuckit MA, Smith TL. The clinical course of alcohol dependence associated with a low level of response to alcohol. *Addiction.* 2001; 96:903–910. [PubMed: 11399221]
- Schuckit, MA. Vulnerability factors for alcoholism. In: Davis, KL.; Charney, D.; Coyle, JT.; Nemeroff, C., editors. *Neuropsychopharmacology: The Fifth Generation of Progress*. Lippincott Williams & Wilkins; Baltimore: 2002. p. 1399-1411.
- Schuckit MA, Smith TL, Anderson KG, Brown SA. Testing the level of response to alcohol: social information processing model of alcoholism risk – A 20-year prospective study. *Alcohol Clin Exp Res.* 2004; 28:1881–1889. [PubMed: 15608605]
- Schuckit MA. An overview of genetic influences in alcoholism. *J Subst Abuse Treat.* 2009; 36:S5–S14. [PubMed: 19062348]
- Sher, KJ. *Children Of Alcoholics: A Critical Appraisal Of Theory And Research*. University of Chicago Press; Chicago: 1991.
- Spitzer RL, Williams JBW, Gibbon M, First MB. The structured clinical interview for DSM-III-R (SCID): history, rationale, and description. *Arch Gen Psychiatry.* 1992; 49:624–629. [PubMed: 1637252]
- Stoltenberg SF, Mudd SA, Blow FC, Hill EM. Evaluating measures of FH of alcoholism: density versus dichotomy. *Addiction.* 1998; 93:1511–1520. [PubMed: 9926555]
- Substance Abuse and Mental Health Services Administration. Results from the 2008 National Survey on Drug Use and Health: National Findings (Office of Applied Studies, NSDUH Series H-36). Rockville, MD: 2009. HHS Publication No. SMA 09-4434
- Tomlinson KL, Abrantes A, Brown SA. Psychiatric comorbidity and substance use treatment outcomes of adolescents. *Psychol Addict Behav.* 2004; 18:160–169. [PubMed: 15238058]
- True WR, Xian H, Scherrer JF, Madden PAF, Bucholz KK, Heath AC, Eisen SA, Lyons MJ, Goldberg J, Tsuang M. Common genetic vulnerability for nicotine and alcohol dependence in men. *Arch Gen Psychiatry.* 1999; 56:655–661. [PubMed: 10401514]
- Turner WM, Cutter HSG, Worobec TG, O'Farrell TJ, Bayog RD, Tsuang MT. Family history models of alcoholism: age of onset, consequences and dependence. *J Stud Alcohol.* 1993; 54:167–171.
- Viken RJ, Kaprio J, Koskenvuo M, Rose RJ. Longitudinal analyses of the determinants of drinking and of drinking to intoxication in adolescent twins. *Behav Genet.* 1999; 29:455–461. [PubMed: 10857250]
- White VM, Hopper JL, Wearing AJ, Hill DJ. The role of genes in tobacco smoking during adolescence and young adulthood: a multivariate behaviour genetic investigation. *Addiction.* 2003; 98:1087–1100. [PubMed: 12873243]
- Worobec TG, Turner WM, O'Farrell TJ, Cutter HS, Bayog RD, Tsuang MT. Alcohol use by alcoholics with and without a history of parental alcoholism. *Alcohol Clin Exp Res.* 1990; 14:887–892. [PubMed: 2088125]

Zucker RA, Ellis DA, Fitzgerald HE. Developmental evidence for at least two alcoholisms. *Ann N Y Acad Sci.* 1994; 708:134–146. [PubMed: 8154674]

Highlights

- Family history density predicted more total drinks and more marijuana use days.
- The risk associated with family history increases over time.
- Family history is a risk factor for poorer long-term treatment outcomes.

Figure 1.
Distribution of family history density scores and ASUD treated youth.

Figure 2. Association between family history density and substance use outcomes increases over time for youth treated for alcohol and drug problems.

Table 1

Correlation matrix of all study variables.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1. Comorbidity																				
2. Male	-.15																			
3. Age	-.23	.19																		
4. White	.19	-.03	.09																	
5. Conduct	.18	.22	-.11	.03																
6. FH density	-.08	-.13	-.13	.02	.05															
7. Total drinks Y1	.08	.13	.12	.08	.09	-.02														
8. Total drinks Y2	.04	.15	.09	.05	.09	.01	.29													
9. Total drinks Y4	.01	.29	-.06	-.01	.05	.02	.17	.33												
10. Total drinks Y6	.04	.21	-.04	-.01	.08	.11	.02	.19	.27											
11. Total drinks Y8	.09	.09	-.08	-.01	.02	.05	.13	.23	.23	.45										
12. Marijuana Y1	.05	.16	.06	.03	.11	-.08	.48	.14	.22	.12	.18									
13. Marijuana Y2	.15	.14	.03	.03	.05	-.04	.15	.33	.16	.12	.08	.41								
14. Marijuana Y4	.15	.14	-.10	-.07	.09	-.04	.12	.09	.31	.17	.14	.34	.40							
15. Marijuana Y6	.10	.19	-.09	.05	.14	.09	.15	.07	.07	.27	.31	.22	.27	.48						
16. Marijuana Y8	.09	.18	-.04	.08	.15	.02	.13	.15	.13	.19	.37	.22	.34	.40	.75					
17. Other drugs Y1	.01	.15	.04	-.01	.03	-.06	.47	.12	.23	.13	.18	.87	.35	.31	.18	.16				
18. Other drugs Y2	.12	.15	.03	.02	.04	-.02	.17	.44	.16	.09	.07	.22	.85	.33	.19	.26	.37			
19. Other drugs Y4	.17	.14	-.10	-.03	.07	-.08	.06	.17	.36	.10	.13	.26	.30	.75	.28	.23	.31	.35		
20. Other drugs Y6	.18	.10	-.05	.14	.13	.05	.05	.11	.01	.27	.19	.15	.25	.31	.75	.54	.15	.26	.34	
21. Other drugs Y8	.14	.09	-.01	.12	.12	.03	.06	.17	.09	.18	.41	.18	.31	.24	.56	.73	.16	.33	.32	.67

Note. Shaded cells indicate statistically significant correlations at $p < .05$.

Coefficients are Pearson correlations between two continuous variables, point-biserial correlations between a dichotomous and continuous variable, and Phi correlation between two dichotomous variable.

Table 2

Descriptive data on substance use outcomes at each long-term follow-up in adolescents treated for alcohol or substance dependence.

	Retention rate	Total drinks	Days of marijuana use	Days of other drug use
Year of follow-up	%	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>
Year 1	96	25.65 (58.02)	5.77 (10.01)	8.07 (14.46)
Year 2	96	35.00 (72.37)	6.97 (10.70)	9.45 (15.49)
Year 4	93	46.93 (81.87)	8.38 (11.99)	12.34 (18.46)
Year 6	95	52.50 (86.35)	9.02 (12.62)	13.89 (20.64)
Year 8	89	58.53 (100.82)	8.08 (12.21)	12.63 (20.85)

Table 3

Statistically significant covariates of past-90 day substance use outcomes assessed at long-term follow-ups in adolescents treated for alcohol or substance dependence.

Covariates	Total drinks <i>b</i> (SE)	Days of marijuana use <i>b</i> (SE)	Days of other drug use <i>b</i> (SE)
Time	0.26 (.007) ***	0.20 (.01) ***	0.21 (.01) ***
Time ²	− 0.02 (.001) ***	− 0.01 (.002) ***	− 0.02 (.002) ***
Gender (male)	1.14 (.22) ***	1.19 (.24) ***	0.98 (.24) ***
Age	− 0.05 (.09)	− 0.18 (.09) *	− 0.13 (.09)
Depression	0.14 (.01) ***	0.08 (.03) **	0.23 (.02) ***
Anxiety	0.40 (.01) ***	0.13 (.03) ***	0.22 (.02) ***

*
p < .05,

**
p < .01,

***
p < .001.

Table 4

Results of hierarchical linear models examining main effects of family history density and interactions with time in adolescents treated for alcohol or substance dependence.

Covariates	Total drinks	Days of marijuana use	Days of other drug use
	<i>b</i> (<i>SE</i>)	<i>b</i> (<i>SE</i>)	<i>b</i> (<i>SE</i>)
Year	0.12 (.01)***	0.11 (.03)***	0.18 (.02)***
Year ²	− 0.004 (.001)**	− 0.01 (.003)**	− 0.02 (.002)***
Study sample	0.34 (.22)	0.41 (.24)	0.46 (.24)
Conduct disorder	0.32 (.29)	0.21 (.32)	0.25 (.31)
Gender (male)	1.14 (.22)***	1.19 (.24)***	0.97 (.24)***
Baseline age	− 0.04 (.09)	− 0.18 (.09)	− 0.11 (.09)
Depression	0.14 (.01)***	0.08 (.03)**	0.24 (.02)***
Anxiety	0.40 (.01)***	0.13 (.03)***	0.22 (.02)***
FH density	− 0.25 (.22)	− 0.28 (.24)	− 0.19 (.24)
FH x year	0.20 (.02)***	0.16 (.04)***	0.05 (.03)
FH x year ²	− 0.02 (.002)***	− 0.02 (.004)***	− 0.001 (.003)

*
p < .05,

**
p < .01,

***
p < .001.