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Measured Environmental Contributions to Cannabis Abuse/Dependence in an Offspring of Twins Design

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Abstract

Genetic and environmental factors are known to contribute to cannabis abuse/dependence (CAD). We sought to determine the magnitude of the contribution from measured environmental variables to offspring cannabis dependence in a design that controls for familial vulnerability. Data come from a study of 725 twin members of the Vietnam Era Twin Registry, 720 of their biological offspring (age 18–32 years) and 427 mothers. Data were obtained on offspring perception of family and peer support and substance use behaviors and offspring CAD. After adjusting for familial risk, and environmental covariates, CAD was significantly more likely among male offspring (OR=2.73; 95% CI: 1.69–4.41). Offspring CAD was associated with reporting: siblings used illicit drugs (OR=3.40; 95%CI:1.81–6.38), a few friends used drugs (OR=2.72; 95%CI: 1.04–7.09), a quarter or more friends used drugs (OR=8.30; 95% CI:3.09–22.33) and one-half or more 12th grade peers used drugs (OR=3.17; 95%CI: 1.42–7.08). Perceived sibling, friend and school peer substance use are strongly associated with CAD in young adults even after accounting for latent familial risk and for multiple measured intra-family and extra-family environmental influences.

Keywords

offspring; twin; cannabis abuse; cannabis dependence; parent; siblings; peers

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1. INTRODUCTION

Cannabis use, abuse and dependence in young persons remain an important public health issue. In their analyses of data from two population based surveys conducted approximately 10 years apart, (Compton, Grant, Colliver, Glantz, and Stinson, 2004) provide evidence that the prevalence of cannabis abuse/dependence (CAD) has increased among young adults (18–29 years of age). Problem cannabis use has been reported as a risk factor for progression to other illicit drugs (Agrawal, Neale, Prescott, and Kendler, 2004; Lynskey et al., 2003), is correlated with other psychiatric problems (Degenhardt, Hall, and Lynskey, 2001; Fergusson, Horwood, and Ridder, 2005) and has been implicated as a factor in the development and persistence of nicotine dependence (Patton, Coffey, Carlin, Sawyer, and Lynskey, 2005).

Twin studies in Australia (Lynskey et al., 2002) and the United States (Fu et al., 2002b; Kendler, Myers, and Prescott, 2007; Tsuang et al., 1996; Kendler, Karkowski, Neale, and Prescott, 2000) have found heritability estimates for cannabis dependence that range from 45%–58%. Lynskey and others (Lynskey and others, 2003) reported that genetic, shared environment and unique environment accounted for 45%, 20% and 35% of the total variance in liability for CAD, respectively, and these estimates were similar for adult men and women. In a test of genetic overlap among ASPD, depression, alcoholism and cannabis dependence in a sample of male twins from the Vietnam Era Twin Registry (VETR), Fu and colleagues (Fu et al., 2002a) observed genetic variance for CAD was due to 50% genetic, 13% shared environment and 36% unique environmental contributions (though confidence intervals included zero for shared environment). Also using VETR data, Tsuang and others (Tsuang and others, 1996) reported that the variance in CAD was due to 34% genetic factors, 28% shared environment and 38% unique environmental influences. Results of analyses from adult male-male twin pairs from the Virginia Twin Registry estimate genetic contribution to cannabis dependence at 58% without evidence for shared environmental factors (Kendler and others 2002). Kendler and colleagues (Kendler and others, 2007) suggest the males ascertained for the VETR and their unique historical exposure to cannabis may account for difference in estimates attributable to genetic and family environmental components reported for CAD in the VETR as compared to the Virginia Twin Registry. In general, data from twin samples that vary by gender and age and by a variety of cannabis abuse and dependence phenotypes suggests vulnerability is explained by approximately 40% of variance from genetic factors, 30% from shared and 30% from non-shared environmental influences (Rhee et al., 2003; True WR et al., 1999; Kendler et al., 2002; Karkowski, Prescott, and Kendler, 2000) .

A large portion of the psychosocial research on substance use disorders has been focused on family, friend and peer influences without incorporation of genetic factors (Hawkins, Catalano, and Miller, 1992). Numerous measured intra-family and extra-family variables are associated with CAD including race, gender, socioeconomic status, parenting styles, and sibling and peer drug use. The quality of parent-child relationships, including conflict and closeness, is also correlated with offspring substance use (Hopfer, Stallings, Hewitt, and Crowley, 2003; Hoffmann and Su, 1998; Walden B, McGue M, Iacono WG, Burt SA, and Elkins I, 2004). In a prospective offspring of alcoholic parents design, (King and Chassin, 2004) reported that appropriate and consistent parental discipline mediated the effect of paternal alcoholism on offspring substance use, and high parental support reduced the risk due to behavioral under-control unless behavioral problems were very severe. Several studies on parenting effects and offspring cannabis use indicate low parental discipline and low closeness as well as exposure to peer substance use are associated with initiation (Morojele and Brook, 2001) and transitions to cannabis use (Eitle, 2005; Morojele and Brook, 2001; Brook et al., 2002), while high parental warmth is a protective factor for cannabis use (Brook and others, 2002).

There is considerable literature on parenting, sibling and peer contributions to offspring cannabis use but not on CAD. Sibling modeling of drug use are significant predictors of adolescent drug use (Brook, Brook, and Whiteman, 1999; Brook JS, Brook DW, Gordon AS, Whiteman M, and Cohen P, 1990; Duncan, Duncan, and Hops, 1996), which some suggest is due to older siblings socializing younger brothers and sisters into substance use (Brook and others, 1999; Boyle, Sanford, Szatmari, Merikangas, and Offord, 2001). Sibling and peer substance use may be stronger predictors of adolescent and young adult drug involvement than parenting effects (Hoffmann and Su, 1998). Previous research comparing the relative impact of parent-offspring versus peer influences indicates peers have a greater influence than parents on substance use (Walden B and others, 2004). For example, data from the National Longitudinal Study of Adolescent Health provides convincing evidence that peer substance involvement and greater social independence (freedom to select own curfew, choose bedtime, select friends) are stronger predictors of progression from initiation to regular cannabis use when compared to the influence of parental warmth and communication (van den Bree and Pickworth, 2005). Though this is a strong body of literature on risk for cannabis use, the extant reports have not accounted for genetic vulnerability.

Existing studies of family and peer influences on CAD risk are limited by the possibility that environmental predictors of young adult drug problems are correlated with the genetic vulnerability. Thus, the observation that poor parenting is associated with cannabis use may be a result of a genetic correlation between poor parenting and drug dependence in the parents themselves. It is then impossible to conclude that parenting, sibling behavior, or peer contact contributes directly to offspring drug use outcomes because vulnerability genes are also higher among the offspring with the most at risk environments.

The classic twin design may overestimate the variance due to genes because gene x shared environment interactions are attributed to additive genetic variance unless specifically modeled (Heath and Nelson, 2002; Jacob et al., 2001). If there is not a main effect of the shared environment, it may appear that family resemblance is completely determined by genetic transmission. Also, in the case when a main effect of the shared environment is masked by genetic dominance (non-additive genetic factors) it may appear that family resemblance is determined only by genetic transmission. D'Onofrio and colleagues (D'Onofrio et al., 2003) demonstrate that the offspring of twins (OOT) design can address limitations of the classical twin design and can be used to quantify processes underlying intergenerational transmission of disease. The OOT design models measured family and non-family environmental contributions to CAD while accounting for the heritability of CAD. These strengths overcome some key limitations of the classic biometrical twin models.

Existing reports have not simultaneously modeled genetic and measured environmental contributions to young adult CAD. Because previous analyses from the twin fathers (Fu and others, 2002b; Tsuang and others, 1996) suggest significant shared and non-shared environmental contributions to CAD, as well as genetic influences, we hypothesized that measured environmental variables would significantly contribute to offspring CAD even after adjusting for familial vulnerability. Thus the present study utilizes an OOT design to: 1) test for bivariate associations between offspring CAD and measured parent, sibling and peer variables while controlling for latent familial influences and 2) fit a multivariate logistic regression model that estimates the association of parent, sibling and peer contributions to offspring CAD while adjusting for familial vulnerability.

2. Methods

2.1 Sample description

Participants were offspring of male twin members of the Vietnam Era Twin Registry (VETR). The VETR is a national registry of male-male twin pairs for whom both members served in the military during the Vietnam Era (1965– 1975). Construction of the registry and method of determining zygosity have been previously reported (Eisen, True, Goldberg, Henderson, and Robinette, 1987; Eisen, Neuman, Goldberg, Rice, and True, 1989; Henderson et al., 1990).

Data used to select families for the present project came from 1987 and 1992 surveys of the twin fathers. A mailed questionnaire sent to the twins in 1987 was used to verify family composition including number and birth dates of their children (Henderson and others, 1990). The twin fathers' DSM-III-R drug dependence and other psychiatric diagnoses were obtained from responses to a 1992 computer assisted telephone administration of the Diagnostic Interview Schedule (Robins LN, Helzer JE, Przybeck TR, and Regier DA, 1988; Robins, Helzer, Croughan, and Ratcliff, 1981).

In 2002, we began an offspring of twins (OOT) study focused on understanding genetic and environmental influences on the inter-generational transmission of illicit drug dependence. Criteria for selection into this OOT study included being a member of a twin pair where (i) both members completed the 1987 questionnaire and the 1992 interview; (ii) at least one member of the pair had a child born between 1973 and 1987, and (iii) at least one member met criteria for DSM-III-R lifetime drug dependence at the 1992 interview. In addition, control twins pairs were selected from those pairs in which neither cotwin met criteria for DSM-III-R lifetime drug dependence at the 1992 interview. After removing deceased individuals, those who had withdrawn from the Registry, and twins unavailable because of participation in other projects from the 527 twin pairs originally targeted, the VETR released 455 pairs to the study (910 individuals). Fifteen of the 910 fathers targeted for data collection were incarcerated, too ill to participate or deceased. Eighty-one percent (n=725) of the remaining 895 twins participated and completed interviews were obtained from 694 twins. In the paternal interview, permission was obtained to contact the biological mother of his offspring as well as the offspring themselves. Of the 604 mothers identified, 444 completed the eligibility screen and 427 mothers (71%) were interviewed. Only mothers who participated in rearing the offspring were included in the present analyses. Fathers gave consent to contact 950 offspring of whom 839 (88%) were interviewed.

2.2. Response rates and non-response bias

Using data from the 1992 diagnostic interview of the twin fathers, we were able to assess whether there were significant differences between the twin fathers targeted for the study and those who chose to participate. For this project, response bias was most important at the paternal level because fathers controlled access to offspring and their biological mothers. It is of note, however, that all twin pairs could be assigned a risk status even if the co-twin did not participate in the 2002 study because the relevant data for the fathers were available from the 1987 and 1992 surveys. We tested for an association between study participation and zygosity, race, education, service in Southeast Asia, nicotine dependence, alcohol dependence, any illicit drug dependence and cannabis dependence, (drug abuse without dependence in this sample of twins is negligible, <1%, (Tsuang and others, 1996)). Only two of these variables were associated with twin's participation: Fathers with less than a high school education had a lower response rate than those with only a high school education or more than a high school education ($p<0.001$), and fathers without history of any illicit drug dependence had a lower participation rate than those with such a history ($p<0.05$).

We also investigated response rates among biological mothers and offspring. Mothers not currently married to the biological father and those married to an ethnic minority were less likely to be interviewed ($p<0.001$). Offspring whose fathers were not currently married to their biological mothers were also less likely to be interviewed than those whose fathers were still married to their biological mothers ($p<0.001$). Additional detail on response rates among fathers, biological mothers and offspring have been previously reported (Duncan et al., 2008).

2.3 Sample selection for present analyses

For these analyses we limited the sample to the 720 offspring 18–32 years of age and their 456 fathers and 387 mothers. Offspring less than 18 years old (n=119) were excluded because they made up a relatively small portion of the sample (14%), very few had CAD (n=7) and were not through their age of greatest risk of CAD onset. The number of eligible fathers (n=456) was less than the total 725 interviewed because their child did not participate or they had no biological children (n=195) or had offspring out of the eligible age range (n=74). Fathers without offspring still informed the twin-family design because MZ or DZ uncles with previously characterized drug dependence status provide measures of genetic and family environmental vulnerability for CAD.

2.4 Data collection

Experienced staff from the Institute for Survey Research (ISR) at Temple University conducted data collection. Interviewers were blind to the prior substance use status of fathers and gave equal effort to recruitment of all respondents. All participants gave verbal consent prior to being interviewed, as approved by the Institutional Review Board at the participating universities. In addition, parents provided written consent for their minor offspring to be interviewed.

The maternal interview, conducted by telephone in 2003, covered the mother's DSM-IV history of drug abuse/dependence and non-substance use psychiatric disorders. The offspring interview, a modification of the SSAGA (Heath et al., 1999; Bucholz et al., 1994) as adapted for use by the Midwest Alcoholism Research Center, included items that operationalized DSM-IV lifetime criteria for CAD and contained non-diagnostic sections assessing school, work and family relationships. In addition, offspring were asked about the drinking, smoking and drug use behaviors of their siblings, high school peers and current same-sex and opposite sex friends. The outcome variable in these analyses was offspring lifetime DSM-IV cannabis abuse or dependence (CAD) derived from the offspring's own report.

2.4.1 The Four-Group Design—A four-group design variable accounted for the sample ascertainment strategy and was a measure of genetic and environmental risk for drug use disorders based on the father's and father's co-twin's drug dependence status. Offspring in Group 1, the high genetic-high environment (HG-HE) risk group, have fathers with a lifetime diagnosis of DSM-III-R illicit drug dependence (IDD with and without comorbid alcohol dependence (AD), not limited to cannabis) or fathers with DSM-III-R alcohol dependence whose cotwins had IDD, regardless of zygosity. Theoretically, these offspring are at high genetic risk because of their father's history of IDD/AD and at high environmental risk by virtue of being reared by an IDD/AD father. Offspring in Group 2, the high genetic-low environment (HG-LE) risk group, have MZ fathers without IDD or alcohol dependence but have uncles (who are their fathers' MZ co-twins) with IDD. Those in Group 3, the medium genetic-low environment (MG-LE) risk group, have DZ twin fathers without IDD but have uncles (who are their fathers' DZ co-twins) with IDD. Offspring in group 2, (HG-LE) are theoretically at high genetic risk because their fathers share 100% of their genes with their IDD MZ cotwin, while those in group 3, (MG-LE) are considered to be at moderate genetic risk because their fathers share an average of 50% of their segregating genes with their drug

dependent DZ cotwin. Both HG-LE and MG-LE offspring are postulated to be at low environmental risk because they are reared by an unaffected father. Finally, offspring in Group 4, the low genetic-low environment (LG-LE) risk group, have fathers and MZ or DZ uncles without IDD or alcohol dependence, and thus have neither the genetic vulnerability or environmental risks for IDD. Offspring response rate did not significantly vary across the 4 risk groups (p=0.09). Of the offspring in the HG-HE group 86.5% were interviewed, 94% of the HG-LE offspring, 89.6% of the MG-LE and 88.9% of LG-LE offspring were interviewed. Additional reports of the OOT design and paternal risk groups have been previously published (Volk et al., 2007; Jacob et al., 2003).

2.4.2—Maternal self-reported DSM-IV CAD was included in the analyses to account for the genetic and environmental contribution from mothers to offspring CAD. To adjust for potential non-response bias, a dummy variable reflecting whether or not the mother was interviewed was included in the bivariate and multivariate models.

2.4.3. Offspring perception of parental behaviors—Offspring reported on perceived parental problem drinking with interview items derived from the Family History of Alcoholism Module (FHAM) a reliable instrument utilized in the Collaborative Study on the Genetics of Alcohol (COGA) project (Rice et al., 1995). Offspring reporting that they thought their mother or father were ever excessive drinkers or that drinking ever caused their mother or father to have problems with health, school, family, police or other problems were coded as having a parent who was a problem/excessive drinker. Offspring were also asked if their mothers and fathers were never, past or current smokers. Perceived parental drug use was not assessed at baseline.

Data regarding parenting, early rearing environment and quality of relationships were obtained by offspring report to several questions based on Sarason and colleagues' (Sarason BR et al., 1991) constructs for perceived support in social relationships and from Robins and colleagues' (Robins et al., 1985) scale for assessing early home environmental correlates of psychopathology. Offspring were asked separately about mothers' and fathers' strictness, rule consistency, closeness and pressure to perform well in school for when they were 6–13 years of age. Strictness was measured on a 5-point scale ranging from a lot more (compared to other parents) to a lot less strict. Due to the small number of subjects at the ends of the scale, we modeled strictness as a 3 level variable, a lot more/little more; same; little less/lot less. Rule consistency was measured with a binary response to the question, 'Was your mother/father pretty consistent about rules or would she/he insist upon a rule one day and forget about it the next'? Closeness was measured on a 4-point scale ranging from very close, somewhat close, not very close, to not at all close. Because few respondents reported that they were not at all close to their mother/father, we modeled closeness as a 3-level variable; very close, somewhat close and not very/not at all close. Pressure to perform well in school was measured by first asking if 'it was important to mother/father that you did well in school.' If respondents said yes, then they were asked to rate how much pressure parents put on doing well in school on a 4 point scale ranging from a lot to none. This latter category included respondents who said it was not important to parents that they do well in school.

2.4.4. Offspring perception of sibling behaviors—Using the excessive and problem use questions from the FHAM, offspring who reported siblings were ever excessive drinkers or that drinking ever caused their siblings problems with health, school, family, police or other problems were coded as having a sibling who was a problem/excessive drinker. Offspring also reported if any siblings had ever used marijuana, cocaine, stimulants, opiates, hallucinogens, PCP, sedatives, solvents or inhalants. From these questions, we created a three level sibling drug use variable: sibling never used any drug, used only marijuana, or used other drugs alone

or with marijuana. This variable was included in the model as a set of dummy variables with individuals whose siblings never used drugs comprising the reference category.

Sibling relationships were measured by offspring reports on how much they could discuss worries with any sibling, how much they thought any sibling would help with problems and how much they thought a sibling would understand them. Responses to each question were on a 4 level scale ranging from 'a lot' to 'not at all'. Because the sibling support variables were highly correlated, we created a 10 level ordinal sibling support variable by summing the responses to each 4 point scale which produced a range of values from 3 to 12 that we re-scaled to values 1 to 10.

2.4.5. Offspring perception of peer behaviors—included perceived smoking, alcohol and drug use among current same sex and opposite sex friends and a separate series of questions about substance use among students in their high school during 12^{th} grade. For the current friends question, offspring reported the number of current male/female friends that used drugs such as marijuana, the number that used alcohol at least once a week, and the number that smoked cigarettes. For the 12^{th} grade school peer questions, offspring were asked how many students used any drugs including marijuana, how many used alcohol and how many smoked cigarettes. Response options for both the friends and school peer questions were on a 6 point scale from 'none', 'just a few', 'a quarter', 'three-quarters', 'almost all' to 'all'.

We did not model effects of friend's gender because we found little difference in the effect of substance use in same sex as compared to opposite sex friends.

2.5 Analyses

Descriptive analyses of all independent and outcome variables are expressed as percentages for categorical variables. Cross-tabulations and chi-square tests of significance were used to examine simple associations among each predictor variable and CAD. The multivariate logistic regression model included the 4 group paternal risk variable, maternal CAD, maternal participation and all sociodemographic, parent, sibling and peer variables found to be significant ($p<0.05$) in the chi-square tests of the bivariable association with CAD.

Inspection of the full tetrachoric correlation matrix revealed correlations that ranged from −0.0005 to 0.6977. The full correlation matrix is available upon request. To avoid effects of multicollinearity, we did not include sibling problem drinking in the model because it was correlated 0.6977 with sibling drug use. Chi-square tests of significance were computed using STATA version 8.2 (Stata Corporation, 2005) and the multivariate logistic regression was computed using the SURVEYLOGISTC procedure in SAS v.9.0 which adjusts error variance in non-independent observations.

3. Results

3.1. Bivariate associations with CAD

Among the 720 offspring, 13.7% had never used and had never had a chance to use cannabis, 24.5% had a chance but never used cannabis and 61.8% had used cannabis. Among those who used cannabis 31.3% had abuse only and 9.3% had CAD.

Table 1 displays the association of predictor variables among offspring with and without CAD. The paternal 4-group design variable was significantly ($p=0.01$) associated with offspring CAD. Seventy-two percent of offspring with CAD were in group 1 whereas only 58% of offspring without CAD were in group 1. The distribution of CAD and non-CAD offspring was similar in groups 2 and 3. Fewer CAD offspring were in group 4 (13%) as compared to non-CAD offspring (24%).

There was no significant association between offspring CAD and maternal CAD or with maternal interview completion. Offspring with CAD were more likely to be male (63% vs. 47%), but there was no differences in race or age.

Among parent sociodemographic variables, CAD offspring were more likely to report biological parents were divorced/separated/widowed or never married compared to non-CAD offspring (46% vs 35%). Parent household income, and father's and mother's education were not significantly associated with offspring CAD.

Among offspring perceived parent behaviors, a higher proportion of CAD offspring reported that their mother (p=0.01) and father (p=0.0003) were problem or excessive drinkers as compared to non-CAD offspring. More CAD offspring reported having a father who smoked at time of interview as compared to non-CAD offspring (p=0.0017), but no differences were observed for maternal smoking.

Among the parenting variables examined, a significantly higher proportion of offspring with CAD compared to those without CAD reported that their mother (p=0.018) and/or father (p=0.027) were a little/lot less strict than other parents. A higher proportion of offspring with CAD than those without CAD reported that their mother (p=0.029) and father (p=0.0001) were not consistent about rules. A higher proportion of CAD offspring were not very/not at all close to fathers as compared to non-CAD offspring (p=0.016). There were no differences observed for ratings of closeness to mothers, or on amount of pressure to do well in school among CAD and non-CAD offspring.

A similar proportion of CAD and non-CAD offspring reported they had no biological siblings. A higher proportion of CAD offspring than non-CAD offspring reported sibling(s) were problem/excessive drinkers (p=0.008). A substantially higher proportion of CAD offspring as compared to non-CAD offspring reported siblings used illicit drugs with or without cannabis (p<0.00001). The mean sibling support measure was similar for non-CAD and CAD offspring.

A significantly higher proportion of offspring with CAD, compared to those without CAD, reported a quarter or more current friends smoked (p<0.00001), used alcohol at least once per week (p<0.00001) and used drugs (p<0.00001).

A significantly lower proportion of offspring with, as compared to those without, CAD reported that none or a few of their school peers in their last year of high school smoked (p=0.0052). Substantially higher proportions of CAD offspring compared to non-CAD offspring reported one-half or more of their school peers in senior high drank alcohol (p<0.00001) and used drugs (p<0.00001).

3.2. Logistic regression results

Table 2 shows the results of multivariate modeling of familial risk factors and all covariates that were significant in the bivariate comparisons reported in Table 1. The regression model provided a good fit to the data (likelihood ratio χ^2=183.28, 34 d.f. p<0001, ROC=0.82). In the multivariate model, high genetic and high environmental risk for CAD was not significantly associated with offspring CAD after other variables were taken into account. Male gender was positively associated with CAD (OR=2.73; 95% CI:1.69–4.41). There was a non-significant trend for association between report of maternal problem drinking and offspring CAD (OR=1.66; 95% CI: 0.89–3.10). No other perceived parent behavior variables approached significance. Having one or more full siblings was marginally associated with reduced likelihood of offspring CAD (OR=0.50; 95% CI: 0.24–1.04). Sibling use of illicit drugs with or without cannabis, but not cannabis only, was significantly associated with offspring CAD (OR=3.40; 95% CI: 1.81–6.38). Offspring report that a quarter or more friends smoke

(OR=1.94; 95%CI: 0.94–4.00) approached a significant association with offspring CAD. Offspring with CAD were more likely to report a few friends used drugs and a quarter or more friends used drugs (OR=2.72; 95%CI: 1.04–7.09 and OR=8.30; 95%CI: 3.09–22.33). Those who reported a quarter or more were at significantly greater risk than those reporting a few friends used drugs. Offspring who reported one-half or more peers from high school used drugs were more likely to have CAD (OR=3.17; 95%CI: 1.42–7.08).

4. Discussion

Multivariable analyses indicated offspring CAD was significantly associated with being male, perceived sibling illicit drug use, and reporting most peers in high school used drugs and a few and a quarter or more close friends use drugs. The magnitude of the association between CAD and friends drug use was greater for offspring who reported a quarter or more friends used drugs as compared to those who reported just a few used drugs. These associations remained after accounting for genetic and shared environmental risk for CAD in the OOT design and after adjusting for other sociodemographic, parental substance use, parenting and parent-offspring closeness, sibling drug use and support, and smoking and alcohol use in friends and school peers.

Our results expand the literature on the transmission of CAD across generations. Although previous research suggests genetic and shared environment contribute to problem cannabis use (Fu and others, 2002a; Karkowski and others, 2000; Kendler and others, 2002; Lynskey and others, 2002; Rhee and others, 2003; True et al., 1999) we found high genetic risk and high shared environmental influences were not significantly associated with CAD in a multivariate model that accounted for the variance due to measured environmental variables such as sibling and peer influences. We are not aware of other studies that have tested for an association between measured environmental influences and offspring CAD while accounting for genetic liability. These analyses inform existing twin research by identifying pathways in which genetic influences and high risk environments may contribute to offspring CAD. Genetic and family environmental vulnerability may influence offspring drug use outcomes because offspring at genetic and environmental risk may select drug using peers, and be exposed to high risk environments such as sibling drug use.

Maternal CAD, income, marital status, paternal problem drinking, paternal smoking, paternal closeness, maternal strictness, having full siblings and sibling drug use, friends drug use and school peer drug use were correlated with the paternal 4-group drug risk design. Thus the significant bivariate association between CAD and these intra and extra-family environmental variables may indicate the presence of a gene-environment correlation. Modeling gene-environment correlations and interactions will be conducted with a-priori hypotheses in future analyses of these data.

Our observation that female gender is associated with reduced risk of young adult CAD is consistent with existing research (Young et al., 2002). A higher prevalence of CAD in men has been reported in large epidemiological studies, such as the 2002 National Survey on Drug Use and Health (Office of Applied Studies, 2003). The association between gender and CAD in our sample is unlikely due to differences in opportunities to use cannabis. Analyses of data from offspring who never used cannabis indicated that self reported opportunity to use the drug was nearly equal in both genders (52% of males and 48% of females had been offered cannabis).

Perceived parent smoking and drinking and offspring report of parenting variables (e.g. closeness to parents, strictness, rule consistency) were not significantly associated with offspring CAD after simultaneous adjustment for familial effects, sibling and peer influences. This finding is supported by (Hoffmann and Su, 1998) prospective study of offspring of parents

with a history of psychoactive substance use disorder. Their results suggest offspring drug use is not mediated by parent-offspring relationships but rather by peer drug use and offspring deviant behavior.

Offspring perception of sibling drug use was associated with increased odds of CAD. Significant sibling effects, a measure of shared environmental influences and genetic correlation for substance use disorder, have been previously reported for CAD among adolescents in treatment (Hopfer and others, 2003), and sibling modeling of drug use has been reported to be a significant predictor of adolescent drug use (Brook JS and others, 1990; Duncan and others, 1996). Others have found that the sibling effect is largely explained by older siblings increasing the risk for younger sibling drug involvement (Brook and others, 1999; Boyle and others, 2001). Examining the influence of younger as compared to older sibling is beyond the scope of the present report.

In adjusted analyses, offspring who perceived that a few and a quarter or more friends used drugs were more likely to have CAD. Post-hoc analyses of age of cannabis initiation and perception of the number of 12^{th} grade drug users suggested peer selection may contribute to CAD. Offspring who perceived none or just a few peers in 12^{th} grade used drugs had a mean age onset of 16.3 years, those who reported one-quarter to one-half used cannabis had a mean age onset of 15.8 years and those who perceived one-half or more 12^{th} grade peers used drugs had a mean age onset of 14.8 years. Thus, on average, offspring presumably were using cannabis prior to selecting their social network in the 12^{th} grade. We recognize that our analyses do not comprise a conclusive test of peer selection versus deviant socialization. Nonetheless, current peer's drug use had the strongest association with offspring CAD.

We are unable to conclude whether peer influence or peer selection best explains offspring CAD; however, we can conclude that perceived peer drug use is strongly associated with offspring CAD. This is consistent with previous research comparing the relative impact of parent-offspring versus peer influences (Walden B and others, 2004). Our analyses expand on the well established role of peer drug use in adolescent drug problems (Hoffmann and Su, 1998; McCabe and Boyd, 2005) by demonstrating that the effect remains after controlling for familial influences and measured parental and sibling environmental factors. We are currently in the process of collecting longitudinal data which will elucidate the predictive power of parent, sibling and peer influences on CAD trajectories.

4.1. Strengths

A principal strength of the present work is the use of the twin-offspring design which permits a sensitive test for measured environmental influences while accounting for known familial contributions to CAD. Substance dependence in the fathers was associated with *increased* participation which increased the power to detect the effect of paternal drug use on offspring cannabis abuse/dependence. Therefore, lack of significance in our familial effect in adjusted models is not an artifact due to non-response. Additional strengths include the large sample size and non-clinical sample that enhance generalizability while avoiding bias inherent to clinical samples. The structured method of data collection reduces interviewer bias. Last the unique age range of the offspring captures a cross-section of development referred to as emerging adulthood, a period of life between 18 and the mid-30s (Arnett, 2000; Arnett JJ, 2005), which is a relatively new and growing field in developmental psychology.

4.2. Limitations

Sample size limitations may have reduced our statistical power to detect differences in the risk for CAD between Group 2 (HG-HE) and Group 3 (MG-LE) effects. It is possible that only very large genetic effects would result in detection of differences between Group 2 and Group

3. From bivariate analyses, we are able to conclude that high genetic and high environment as compared to low genetic and low environmental risk is associated with offspring CAD. Present results apply to the combined diagnosis of cannabis abuse and dependence, but the genetic and environmental risk to sub-clinical criteria or dependence alone may not be the same.

Retrospective reports of school peer substance use in 12th grade may suffer from recall bias. We consider the school peer influence to be a gross measure of exposure to substance use sensitive to measuring the effect of normative vs. deviant levels of substance use. As described above, our data suggest peer selection may explain the perception of the number of students using drugs in the 12th grade.

It is not possible to measure all environmental influences on offspring. Expansion of the shared environment assessment may reveal key parent, sibling and peer level variables that have not been adequately measured. The distribution of recency of drug use may influence interactions with siblings, parents and peers. For instance longitudinal data will help clarify the direction of effect for peer substance use. A recent report from Poelen and colleagues (Poelen EAP, Engles CMER, Van Der Vorst H, Scholte RHJ, and Vermulst AA, 2007) indicates limited long-term influence of peer drinking on alcohol consumption. Follow-up is necessary to collect more detailed assessment of the parent-offspring environment, to better assess sibling substance use and drug problems and the impact of older as compared to younger siblings on offspring CAD, to better characterize romantic relationships and their impact on offspring drug involvement and to allow for changes in CAD as a function of emerging adulthood for the entire cohort. Longitudinal data collection is warranted to measure the trajectory of key constructs in young adulthood transitions (e.g. college graduation, marriage, birth of a child, death of parents) and their association with drug dependence development, persistence or cessation.

4.3. Conclusions

Prior to adjusting for measured environmental covariates, these data indicated that latent genetic and environmental factors contributed to adolescent and young adult CAD, but sibling and peer drug use contributed to offspring CAD over and above the effect of genetic and environmental effects.

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Table 1

Prevalence of predictor variables in offspring with and without history of lifetime DSM-IV cannabis abuse/ dependence

	Offspring cannabis abuse/ dependence % (*n*)	No cannabis abuse/ dependence % (*n*)	Design Based *P*-value
Familial vulnerability	(*n*=180)	(*n*=540)	
Twin fathers 4-group design [1]			
GRP 1 MZ and DZ fathers (HG, HE)	71.7 (129)	58.0 (313)	F=3.64
GRP 2 MZ index unaffected, co-twin affected (HG, LE)	8.3 (15)	8.5 (46)	(*p*=0.012)
GRP 3 DZ index unaffected, co-twin affected (MG, LE)	7.2 (13)	9.8 (53)	
GRP 4 MZ and DZ twins unaffected (LE, LE)	12.8 (23)	23.7 (128)	
Maternal self report cannabis abuse/dependence			
No	71.7 (129)	71.1 (384)	F=3.64
Yes	10.0 (18)	6.7 (36)	(*p*=0.012)
No maternal data	18.3 (33)	22.2 (120)	
Mother completed interview			
No	18.3 (33)	22.2 (120)	F=1.07
Yes	81.7 (147)	77.7 (420)	(*p*=0.30)
Socio-demographics of offspring			
Female	37.2 (67)	52.6 (284)	F=14.70
Male	62.8 (113)	47.4 (256)	(*p*=0.002)
Age			
18–23 yrs of age	48.9 (88)	45.9 (248)	F=0.42
24–32 yrs of age	51.1 (92)	54.1 (292)	(*p*=0.518)
Caucasian	90 (162)	85.9 (464)	F=1.54
Non-Caucasian	10 (18)	14.1 (76)	(*p*=0.216)
Paternal sociodemographics			
Father's reported yearly household income (2003)			
1–$40,000	16.1 (29)	18.4 (98)	F=0.21
$40,001–$60,000	29.4 (53)	30.2 (161)	(*p*=0.887)
$60,001–$90,000	27.2 (49)	26.6 (142)	
$90,001 or more	27.2 (49)	24.7 (132)	
Father's education			
≤ high school	28.3(51)	34.6 (186)	F=1.96
> high school	71.7 (129)	65.4 (351)	(*p*=0.163)
Mother's education[2]			
≤ high school	31.9 (47)	33.3 (140)	F=0.077
> high school	68.1 (100)	66.7 (280)	(*p*=0.782)
Biological parents marital status (paternal report)			
Married	54.2 (97)	64.6 (343)	F=5.05
Divorced/separated/widowed/never married	45.8 (82)	35.4 (188)	(*p*=0.025)
Offspring perceived parent behaviors			

	Offspring cannabis abuse/ dependence % (*n*)	No cannabis abuse/ dependence % (*n*)	Design Based *P*-value
Mother not problem/excessive drinker	86.1 (155)	92.4 (499)	F=6.51
Mother problem/excessive drinker	13.9 (25)	7.6 (41)	(*p*=0.011)
Father not problem/excessive drinker	63.9 (115)	77.8 (420)	F=13.36
Father problem/excessive drinker	36.1 (65)	22.2 (120)	(*p*=0.0003)
Mother never smoker	43.9 (79)	47.0 (252)	F=0.38
Mother past smoker	26.7 (48)	27.0 (146)	(*p*=0.682)
Mother current smoker	29.4 (53)	26.0 (140)	
Father never smoker	19.6 (35)	32.9 (177)	F=6.44
Father past smoker	38 (68)	36.7 (197)	(*p*=0.0017)
Father current smoker	42.5 (76)	30.3 (163)	
Mother strictness			
A lot more/little more	39.7 (71)	46.6 (251)	F=3.66
Same	31.3 (56)	34.7 (187)	(*p*=0.018)
Little less/lot less	29.1 (52)	18.7 (101)	
Father strictness			
A lot more/little more	33.7 (59)	41.4 (220)	F=10.84
Same	30.9 (54)	33.8 (180)	(*p*=0.027)
Little less/lot less	35.4 (62)	24.8 (132)	
Mother consistent about rules	72.1 (129)	83.3 (448)	F=4.79
Mother not consistent about rules	27.9 (50)	16.7 (90)	(*p*=0.001)
Father consistent about rules	75.4 (129)	82.6 (440)	F=2.12
Father not consistent about rules	24.6 (42)	17.5 (93)	(*p*=0.029)
Mother closeness			
Very close	64.4 (116)	66.1 (356)	F=2.12
Somewhat close	25.0 (45)	27.8 (150)	(*p*=0.121)
Not very/not at all close	10.6 (19)	6.1(33)	
Father closeness			
Very close	40.7 (72)	48.0 (258)	F=4.15
Somewhat close	37.3 (66)	38.7 (208)	(*p*=0.016)
Not very/not at all close	22.0 (39)	13.2 (71)	
Mother pressure to do well in school			
A lot	32.8 (59)	36.0 (194)	F=0.67
Some	48.9 (88)	42.9 (231)	(*p*=0.570)
A little	11.7 (21)	13.2 (71)	
None	7.7 (12)	8.0 (43)	
Father pressure to do well in school			
A lot	32 (56)	31.3 (167)	F=0.28
Some	42.3 (74)	43.0 (229)	(*p*=0.839)
A little	19.4 (34)	17.6 (94)	
None	6.3 (11)	8.1 (43)	

	Offspring cannabis abuse/ dependence % (*n*)	No cannabis abuse/ dependence % (*n*)	Design Based *P*-value
Offspring perceived sibling behaviors			
No full biological siblings	16.7 (30)	16.1 (87)	F=0.029
Any full biological siblings	83.3 (150)	83.9 (453)	(*p*=0.87)
Any sibling problem/excessive drinker[3]			
No	64.7 (97)	77.7 (352)	F=9.82
Yes	35.3 (53)	22.3 (101)	(*p*=0.0019)
No siblings use illicit drugs[3]	20.6 (30)	48.4 (214)	F=33.31
Any sibling(s) use cannabis only	19.2 (28)	27.8 (123)	*p*<0.0001
Any sibling(s) use illicit drugs w/w.o. cannabis	60.3 (88)	23.8 (105)	*t*=0.12, *p*=0.90
Sibling support[3] (mean; s.d.)	7.65 (±2.5)	7.63 (±2.5)	
Offspring perceived peer behaviors			
Number of current friends who smoke			
None	19.0 (33)	46.9 (247)	F=31.42
Few	28.7 (50)	31.5 (168)	*p*<0.00001
Quarter or more	52.3 (91)	22.3 (119)	
Number of current friends who use alcohol at least 1 time/ week			
None	12.1 (21)	22.3 (119)	F=12.01
Few	24.7 (43)	34.5 (184)	(*p*<0.00001)
Quarter or more	63.2 (110)	43.3 (231)	
Number of current friends who use drugs			
None	4.6 (8)	29.6 (158)	F=56.78
Few	20.7 (36)	39.9 (213)	(*p*<0.00001)
Quarter or more	74.7 (130)	30.5 (163)	
Number of peers in 12th grade who smoked			
None/few	11.7 (21)	22.6 (120)	F=5.32
Quarter to one-half	68.7 (123)	62.5 (331)	(*p*=0.005)
> one-half	19.6 (35)	14.9 (79)	
Number of peers in 12th grade who drank alcohol			
None/few	7.3 (13)	14.7 (78)	F=10.72
Quarter to one-half	34.1 (61)	45.6 (241)	(*p*=0.00001)
> one-half	58.7 (105)	39.7 (210)	
Number of peers in 12th grade who used drugs			
None/few	12.9 (23)	32.9 (174)	F=27.66
Quarter to one-half	50.8 (91)	53.3 (282)	(*p*<0.00001)
> one-half	36.3 (65)	13.8 (73)	

1) 4-group design: Group 1 – Offspring at high genetic (HG) and high environmental (HE) risk because fathers are MZ and DZ twins with DSM-III-R illicit drug dependence , Group 2 – Offspring at high genetic (HG) and low environmental (LE) risk because fathers are unaffected MZ twins with DSM-III-R illicit drug dependent co-twins, Group 3 – Offspring at medium genetic (MG) and LE risk because fathers are unaffected DZ with DSM-III-R illicit drug dependent co-twins, Group 4 – offspring at low genetic and LE because fathers are unaffected MZ and DZ control pairs.

[2] Among mothers with survey data

[3] among offspring with full siblings

Table 2

Logistic regression model for risk of lifetime CAD in 720 young adults as a function of familial risk and significant covariates

Full Model	Odds Ratio	95% Confidence Interval
familial vulnerability		
4-group design[1]		
GRP 1 (HG, HE)	1.19	(0.63–2.22)
GRP 2 (HG, LE)	0.95	(0.42–2.13)
GRP 3 (MG, LE)	1.22	(0.44–3.41)
GRP 4 (LE, LE)	1.00	--
Mother DSM-IV cannabis abuse/ dependence		
YES	0.88	(0.35–2.23)
Mother interviewed:		
YES	1.25	(0.71–2.17)
Socio-demographics of offspring		
male	**2.73**	**(1.69–4.41)**
female	**1.00**	--
Parental sociodemographics		
bio. parents divorced/separated/widowed/never married	0.86	(0.50–1.48)
biological parents married	1.00	--
Offspring perceived parent behaviors		
Mother problem/excessive drinker:		
YES	1.66	(0.89–3.10)
Father problem/excessive drinker:		
YES	1.12	(0.67–1.86)
Father never smoker	1.00	--
Father past smoker	1.19	(0.66–2.14)
Father current smoker	1.15	(0.61–2.14)
Mother a lot more/little more strict	1.01	(0.57–1.78)
Mother same strictness	1.00	--
Mother little less/lot less strict	1.19	(0.73–1.95)
Father a lot more/little more strict	1.38	(0.76–2.52)
Father same strictness	1.00	-
Father little less/lot less strict	1.04	(0.59–1.84)
Mother consistent about rules		
NO	1.00	--
YES	0.74	(0.42–1.32)
Father consistent about rules		
NO	1.00	--
YES	0.77	(0.44–1.35)
Very close to father	1.00	--
Somewhat close to father	1.23	(0.80–1.89)
Not very/not at all close to father	1.70	(0.87–3.35)
Offspring perceived sibling behaviors		

Full Model	Odds Ratio	95% Confidence Interval
No full siblings	1.00	--
One or more full siblings	0.50	(0.24–1.04)
Any sibling problem/excessive drinker:		
NO	1.00	--
YES	1.28	(0.72–2.25)
No siblings use drugs	1.00	--
Siblings use cannabis only	1.24	(0.59–2.59)
Siblings use illicit drugs w/w.o. cannabis	**3.40**	**(1.81–6.38)** *
Offspring perception of peer behavior		
Current friends smoking:		
none	1.00	--
a few	1.47	(0.76–2.87)
a quarter or more	1.94	(0.94–4.00)
Current friends drink at least 1/week:		
none	1.00	--
a few	0.97	(0.47–2.02)
quarter or more	0.64	(0.31–1.33)
Current friends use drugs:		
none	1.00	--
a few	**2.72**	**(1.04–7.09)**
quarter or more	**8.30**	**(3.09–22.33)** *
12th grade high school peer smoking:		
none/few	1.00	--
quarter to one-half	1.02	(0.49–2.14)
more than one–half	0.72	(0.29–1.76)
12th grade high school peer drinking:		
none/few	1.00	--
quarter to one-half	0.76	(0.36–1.60)
more than one-half	0.72	(0.33–1.62)
12th grade high school peer drug use:		
none/few	1.00	--
quarter to one-half	1.40	(0.79–2.61)
one-half or more	**3.17**	**(1.42–7.08)** *

1) 4-group design: Group 1 - Offspring at high genetic (HG) and high environmental (HE) risk because fathers are MZ and DZ twins with DSM-III-R illicit drug dependence , Group 2- Offspring at high genetic (HG) and low environmental (LE) risk because fathers are unaffected MZ twins with DSM-III-R illicit drug dependent co-twins, Group 3- Offspring at medium genetic (MG) and LE risk because fathers are unaffected DZ with DSM-III-R illicit drug dependent co-twins, Group 4- offspring at low genetic and LE because fathers are unaffected MZ and DZ control pairs.

* Odds ratios are significantly different ($p<0.05$).

Bold text indicates statistically significant odds ratio.