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PATERNAL ALCOHOLISM AND OFFSPRING ADHD PROBLEMS: A CHILDREN OF TWINS DESIGN

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Abstract

Objective—A recent Children-of-Female-Twin design suggests that the association between maternal alcohol use disorder and offspring ADHD is due to a combination of genetic and environmental factors, such as prenatal nicotine exposure. We present here a complementary analysis using a Children-of-Male-Twin design examining the association between *paternal* alcoholism and offspring attention deficit hyperactivity problems (ADHP).

Methods—Children-of-twins design: offspring were classified into 4 groups of varying genetic and environmental risk based on father and co-twin's alcohol dependence status.

Results—Univariate results are suggestive of a genetic association between paternal alcohol dependence and broadly defined offspring ADHP. Specifically, offspring of male twins with a history of DSM-III-R alcohol dependence, as well as offspring of non-alcohol dependent monozygotic twins whose cotwin was alcohol dependent, were significantly more likely to exhibit ADHP than control offspring. However, multivariate models show maternal variables independently predicting increased risk for offspring ADHP and significantly decreased support for a genetic mechanism of parent-to-child transmission.

Conclusions—In support of earlier work, maternal variables (i.e., maternal ADHD and prenatal exposure) were strongly associated with child ADHP; however, the role of paternal alcohol dependence influences was not definitive. While genetic transmission may be important, the association between paternal alcohol dependence and child ADHP is more likely to be indirect and a result of several pathways.

Keywords

ADHD; Alcohol dependence; Children-of-Alcoholics; Children-of-Twins; genetics

INTRODUCTION

Considerable evidence now exists that children-of-alcoholic parents (COAs) are at increased risk for various psychiatric, cognitive and interpersonal difficulties as well as developing alcohol use disorders (Johnson & Leff, 1999). Of particular relevance, significantly elevated rates of attention deficit-hyperactivity disorder (ADHD) have been reported in COAs

(Barkley, 1990; Knopik et al., 2005; Knopik et al., 2006; Roizen et al., 1996; Stewart et al., 1980). However, inconsistent findings have been reported (Reich et al., 1993; Schuckit et al., 1987). Thus, the underlying etiology of this phenotypic association is still not well understood. It is likely that differences in study outcomes are muddled by the very nature of the COA literature which has focused heavily either on children-of-male-alcoholics or on children exposed to significant amounts of prenatal alcohol (Knopik et al., 2006; Reich et al., 1993; Schuckit et al., 1987; Weinberg, 1997). Further, such inconsistent findings may be explained, in part, by (1) cross-study differences in controlling for potentially confounding variables; (2) cross-study differences in focus on maternal vs. paternal alcoholism; and (3) perhaps most importantly, cross-study differences in use of genetically informative designs.

Several mechanisms could account for apparent associations between parental alcoholism and child ADHD. First, alcoholism and ADHD may share common genetic variance (“common genes” hypothesis) whereby a parent might have pre-existing psychopathology (i.e., ADHD or conduct disorder [CD]) predisposing them to development of alcohol dependence. This is referred to as genetic covariation within individual. Alternatively, alcoholic parents may transmit genetic vulnerability to offspring not only for alcoholism but also for ADHD and other externalizing behaviors, a so-called cross-generation genetic covariation. In support of this “common genes” hypothesis, there is considerable evidence that a common genetic factor underlies much of the phenotypic association among alcoholism, drug abuse, antisocial personality and CD (Haber et al., 2005; Hicks et al., 2004; Krueger et al., 2002; Slutske et al., 1998). However, disorder-specific genetic variance also appears important (Blonigen et al., 2005; Krueger et al., 2002). On the other hand, genetically informative studies of specific relevance to the covariance between alcoholism and ADHD are surprisingly limited (Young et al., 2000); in spite of ample evidence that genetic influences underlie each disorder (e.g. Knopik et al., 2004; Knopik et al., 2005). Ultimately, failure to account/control for other possibly heritable conditions or behaviors exhibited by the index parent and/or spouse leaves open the possibility that the parental alcoholism/offspring ADHD association may be partly confounded by additional genetic influences not entirely related to parental alcoholism.

Second, the co-occurrence of parental alcoholism and child ADHD may result from teratogenic effects of substance use during pregnancy—influences that are primarily environmental in nature. The relationship between these teratogenic effects and genetic influences is likely complex. For example, two possible pathways contributing to offspring behavior are: (1) the birth mother meets criteria for a lifetime alcohol dependence, which is heritable, and engages in substance use during pregnancy or (2) the child’s father (but not the mother) meets lifetime criteria for alcohol dependence and the mother engages in substance use during pregnancy. In other words, prenatal exposure may correlate with parental behaviors that could act as key risk factors that are, in turn, transmitted to their offspring.

Third, parental alcoholism is associated with a less than optimal rearing environment. There is considerable evidence that alcoholic parents are characterized by higher family conflict, stress, ineffective parenting, and low parental warmth (e.g. Eliason & Skinstad, 1995; Ohannessian et al., 2004). These effects likely differ for paternal vs. maternal alcoholism to the extent that mothers are the primary caretakers of children (Chen & Weitzman, 2005). Also, alcohol-abusing individuals are more likely to have substance-abusing partners (e.g., Knopik et al., 2005), providing additional postnatal environmental risk (e.g., second-hand smoke exposure; Eskenazi & Castorina, 1999). These postnatal familial exposures, coupled with genetic and prenatal risk, create a complicated picture of apparent associations between parental alcoholism and child ADHD.

While genetically-informed designs could lend considerable information to the pathways and mechanisms underlying this complicated relationship (D'Onofrio et al., 2007; 2008; Knopik, in press), there is a surprising paucity of such research. Knopik and colleagues (2005) conducted analyses of adolescent female twin data, which suggested that prenatal and parental risk factors (including maternal and paternal alcohol dependence) combine additively with genetic risk of developing ADHD. In an attempt to further elucidate the relationship between maternal alcoholism and offspring ADHD, a subsequent analysis was undertaken utilizing the children-of-female-twins design which allows for control of genetic risk of parental alcohol dependence (Knopik et al., 2006). Results indicated (1) genetic transmission is an important determinant in the association between maternal alcohol use disorder and offspring ADHD, suggesting either (a) pleiotropic genetic effects, or (b) ADHD as a direct risk-factor for alcohol use disorder; and (2) prenatal risk factors contribute additively with genetic risk (rather than interactively), consistent with previous findings (Knopik et al., 2005).

Although this earlier work provided an important addition to the ADHD etiology literature, the relationship between genetic and teratogenic influences on child ADHD is still unclear as are cross-study inconsistencies regarding the teratogenic effects of prenatal substance exposure. Further, in Knopik et al. (2006), parental ADHD diagnoses were not available. Therefore, the potential confoundings of ADHD with parental alcoholism in determining offspring outcomes could not be assessed.

In light of these considerations and in an effort to continue identifying influences that might best account for the complicated cross-generational relationships, it is necessary to also consider the role of *paternal* rather than *maternal* alcoholism. Thus, the purpose of the present study is to conduct a complementary analysis to Knopik et al. (2006); examining the association between *paternal* alcohol dependence, prenatal substance exposure, and child attention deficit-hyperactivity-problems (ADHP) using a children-of-male-twins design, while also allowing for pertinent data on parental psychopathology, including lifetime history of maternal ADHD.

METHODS

Participants

Twin pairs from the Vietnam Era Twin Registry (VETR; Eisen et al., 1987; Goldberg et al., 2002) who participated in (i) a 1987 mail survey of general health (Henderson et al., 1990; Tsuang et al., 1996) and (ii) the 1992 Harvard Drug Study (HDS; Tsuang et al., 1996) formed the target sample from which we selected male twin pairs where (1) at least one twin has a history of DSM-III-R (APA, 1987) alcohol dependence, and (2) at least one twin had children born between 1974 and 1988. Randomly selected control pairs (concordant for no alcohol dependence) were also assessed. Analyses include 727 twin fathers, 732 mothers, and 1116 children (average age=19.1 yrs, SD=4.0) with complete data on all variables of interest (see Table 1 for sample characteristics). As reported in Scherrer et al. 2004, paternal alcohol status was not related to offspring participation in the study.

Measures

All male twin participants completed the VETR assessments, the 1987 mailed survey, and the HDS diagnostic interview. The 1987 survey assessed general health and obtained data on their biological offspring. The 1992 HDS interview was a telephone psychiatric diagnostic interview that assessed alcohol and substance-related disorders, mood disorders, anxiety disorders and personality disorders. Paternal ADHD was not assessed. Diagnoses of DSM-

III-R alcohol dependence and other diagnoses in the male twins were assigned by computer algorithm.

Male twins provided permission to contact biological mothers of their offspring. All participating mothers completed a computer-assisted telephone diagnostic interview based upon a modified version of the Semi-Structured Assessment of the Genetics of Alcoholism (SSAGA) (Bucholz et al., 1994; Hesselbrock et al., 1999), which is a comprehensive psychiatric interview that assesses physical, social, and psychiatric manifestations of alcohol use disorder and related disorders in adults. Modifications were made to the SSAGA to incorporate DSM-IV (APA, 1994) criteria. The maternal interview also assessed self-reported smoking and drinking during pregnancies, and offspring psychopathology and behavioral problems. Maternal DSM-IV psychiatric diagnoses (e.g., alcohol dependence, ADHD) were determined via computer algorithm. Maternal smoking during pregnancy (MSDP) was defined as a dichotomous variable indicating any smoking during the pregnancy of each child. Maternal drinking during pregnancy was defined as two dichotomous categories: (1) alcohol use during pregnancy before she knew she was pregnant and (2) alcohol use after she knew she was pregnant. The amount of drinking and smoking per trimester or over the course of the entire pregnancy was not determined. While these prenatal and offspring variables are retrospective, previous research assessing retrospective maternal reports of health behaviors during pregnancy (Jacobson et al., 2003; Heath, et al. 2003; Reich, et al., 2003) and of offspring ADHD (Faraone et al., 1995; Faraone & Doyle, 2001) have been found to be reliable and valid.

Assessment of child behavior was based on items derived from the Diagnostic Interview for Children and Adolescents (DICA; Herjanic & Reich, 1982) and the Semi-Structured Assessment of the Genetics of Alcoholism-Child Version (C-SSAGA). A range of DSM-IV-based attention deficit-hyperactivity problems (ADHP) were defined and were based on maternal report. Our earlier work (Knopik et al., 2005; Knopik et al., 2006) suggested associations between parental alcoholism and various measures of child ADHD, including narrow DSM-IV based ADHD diagnosis, broader DSM-IV diagnoses without clinical impairment, as well as DSM-IV symptom counts. In addition, the use of multiple thresholds (Levy et al., 1997) and recent work with latent classes of ADHD (e.g. Rasmussen et al., 2002) suggest that restricting the focus to narrowly defined measures of ADHD may exclude individuals exhibiting mild-but-meaningful subtypes (particularly among females). Thus, for the current study, offspring ADHD problems (ADHP) with onset prior to age 7 were characterized with two different symptom thresholds and also with Broad (B) or Narrow (N) classifications, corresponding to impairment criteria: (1) ADHP-4B: 4 or more symptoms on Inattentive or Hyperactive/Impulsive dimensions, no impairment criteria; (2) ADHP-6B: 6 or more symptoms on Inattentive or Hyperactive/Impulsive dimensions, no impairment criteria; (3) ADHP-4N: same as ADHP-4B but with impairment in 2 or more settings [school/work, home, or social settings]; (4) ADHP-6N: same as ADHP-6B but with impairment in 2 or more settings. By defining ADHP in this manner, we can begin to make predictions about those at more clinical risk (reaching narrow diagnosis) and those at more general risk (broad diagnosis), such that results can inform evidence-based approaches in child psychiatry. Consent was obtained from each parent for study participation and for permission to contact the offspring. Consent (or informed assent for minors) was also obtained from the participating offspring. All procedures were approved by the Institutional Review Boards of all participating institutions (Veteran Affairs Palo Alto Health Care System, Stanford University, Washington University, St. Louis).

Data Analyses

Our primary analyses incorporated a 4-group classification scheme based on DSM-III-R alcohol dependence histories of the twin parent (father) and his co-twin: (1) twin father (MZ

or DZ) with alcohol dependence and an MZ or DZ co-twin with any or no diagnosis (i.e., high genetic/high environmental risk); (2) unaffected twin father (non-alcohol dependent) and an alcohol dependent MZ co-twin (i.e., high genetic/low environmental risk); (3) unaffected twin father and an alcohol dependent DZ co-twin (i.e., intermediate genetic/low environmental risk); and (4) both twins unaffected (i.e., low genetic/low environmental risk).

We incorporated logistic regression techniques to model risk of ADHP, relative to no ADHP, as a function of 3 dummy variables corresponding to risk groups and using group 4 as the comparison group. This model also included child gender as a covariate (Table 3). This children-of-twins design is well suited for detecting genetic effects of paternal alcoholism [Odds Ratios (OR) for Groups 1,2 > 3 > 4], environmental consequences of paternal alcoholism (OR for Group 1 > 2,3,4), and gene \times environment interaction (G \times E; OR for Group 1 > 2,3 > 4). The model was then re-estimated after inclusion of potential environmental measures (i.e., prenatal exposure) and other parental psychopathology. This extension of the model allowed for the possibility that the association of ADHP with paternal alcohol dependence arises through confounding prenatal effects or through assortative mating, respectively. Variables were selected for the multivariate model by first entering dichotomous variables (i.e., divorce, psychiatric diagnosis, maternal alcohol dependence, maternal ADHD, prenatal variables) with each index of ADHP (4B, 6B, 4N, 6N) as a separate outcome measure. All covariates predicting outcome variables (p -values < 0.1, recommended by Hosmer & Lemeshow, 2000) were included in the multivariate logistic model. Multiple individuals from the same family (full or half siblings from the same father and the father's co-twin) were included in these regression analyses (as well as all sociodemographic comparisons); therefore, ORs and confidence intervals (CI) were adjusted for non-independence of observations using the Huber-White robust variance estimation option in STATA (StataCorp, 2003). Differences in ORs (risk group comparisons) were tested by Wald Chi-Square tests (adjusted for non-independence). Logistic regression models do not provide point estimates of genetic and environmental influences, but rather present estimates of risk through ORs.

RESULTS

As shown in Table 1, fathers in risk group 1–3 were significantly more likely to exhibit DSM-III-R nicotine dependence than controls (Group 4; $\chi^2=71.53$, $df=3$, $p<.0001$). Alcohol dependent fathers were also significantly more likely to have comorbid lifetime DSM-III-R psychiatric diagnosis and substance dependence compared to controls (OR=5.92, 95% CI=3.23–10.84 and OR=9.2, 95% CI=2.43–34.81, respectively). Interestingly, rates of maternal psychopathology (i.e., DSM-IV alcohol abuse, alcohol dependence, ADHD) did not differ across the 4 paternal risk groups (Table 1).

Rates of MSDP were high and did not differ between the two high genetic risk groups: offspring with a history of paternal alcohol dependence (Group 1) and offspring of non-dependent fathers with an alcohol dependent cotwin (Group 2; $\chi^2=0.58$, $df=1$, $p=0.45$). Further, MSDP rates were significantly elevated in the two high genetic risk-groups when compared to controls (Grps 1,2 vs 4: pooled OR=1.62, 95% CI=1.03–2.54). Thus, MSDP may be a potential confounding factor in interpreting elevated rates of offspring ADHP, most notably ADHP-4B [four or more symptoms broadly defined (i.e., no impairment criteria)], seen in risk-groups 1–2 (Table 3). The overall frequency of drinking during pregnancy ranged from 19%–29% for before mothers knew they were pregnant and decreased to a range of 9%–17% for drinking after confirming pregnancy. Consistent with expectation (Knopik et al., 2005), maternal drinking during pregnancy was significantly more common in mothers with alcohol dependent partners (Group 1) compared to controls

(OR=1.61, 95%CI=1.05–2.46 for drinking before knew pregnant; OR=2.05; 95%CI=1.16–3.62, for drinking after knew pregnant). Similar to MSDP, rates of prenatal alcohol were significantly higher in risk-groups 1 and 2 (high genetic risk) relative to controls (drinking before knew pregnant: pooled OR=1.64, 95%CI=1.09–2.46; drinking after confirmed pregnant: pooled OR=2.01, 95%CI=1.16–3.48). Sociodemographic differences between groups were minor and anticipated (e.g., higher divorce rate in Group 1), consistent with the known association between parental alcohol dependence and marital breakdown.

Univariate associations: Parental and prenatal risk factors and child ADHP (Table 2)

Offspring of alcohol dependent fathers are more likely to exhibit ADHP-4B in comparison to offspring of non-dependent fathers. Other definitions of ADHP (i.e., ADHP-6B, ADHP-4N, ADHP-6N) indicate trends toward increased rates in offspring of alcoholic fathers; however, these associations did not reach statistical significance (Table 2). Main effects did appear slightly more marked for offspring of fathers with severe DSM-III-R alcohol dependence. Other significant predictors of offspring ADHP were paternal DSM-III-R nicotine dependence, maternal ADHD, and consistent with earlier work (Knopik et al., 2005; Knopik et al., 2006), maternal DSM-IV alcohol dependence, prenatal exposure to alcohol (drinking after confirming pregnant) and MSDP.

Paternal alcohol dependence and Child ADHP – COT comparisons

While a trend for increased ADHP was found in offspring of alcohol dependent fathers, these findings only reached significance for a broadly defined measure of four or more inattention or hyperactive/impulsive symptoms, with no impairment criteria (i.e., ADHP-4B). Thus, power is low to confirm an independent relationship of paternal alcoholism and offspring ADHP. However, we performed the COT analyses in order to examine whether results would suggest genetic transmission, the importance of the environment, or G×E interplay. Table 3 presents ORs (controlling for gender and *before* parental and prenatal covariate adjustment), as a function of risk group. For ADHD-4B, we find a pattern consistent with a genetic explanation for the association between paternal alcohol dependence and increased offspring risk. Thus, relative to controls, rates of offspring ADHP-4B are significantly elevated not only in families where the father had a history of alcohol dependence (Group 1) but also in families where the father had no history of alcohol dependence but had an alcoholic monozygotic twin brother (Group 2). While similar patterns were found for other narrow and broad definitions of ADHP, they did not reach statistical significance.

For all ADHP measures, ORs for the first 2 groups (characterized by high genetic risk for offspring outcomes genetically correlated with paternal alcohol dependence) do not differ significantly (ADHP-4B: $\chi^2=0.29$, $df=1$, $p=0.59$; ADHP-6B: $\chi^2=2.05$, $df=1$, $p=0.15$; ADHP-4N: $\chi^2=0.61$, $df=1$, $p=0.43$; and ADHP-6N: $\chi^2=0.30$, $df=1$, $p=0.59$). Focusing on ADHP-4B, the combined OR (Groups 1,2 vs 4)=1.54, 95%CI=1.04–2.27, $p<0.05$. However, despite rates of offspring ADHP being lower in those at intermediate genetic risk (i.e., offspring of unaffected fathers with an alcoholic dizygotic twin brother [Group 3]), they were not significantly different than those with high genetic risk (in the case of unaffected fathers with an alcoholic monozygotic twin brother [Group 2]; $\chi^2=1.82$, $df=1$, $p=0.18$). Thus, while point estimates appear to support the possibility that genetic transmission may play a role in the association between broadly defined attention deficit hyperactivity problems and paternal alcohol dependence, a non-significant MZ vs DZ contrast decreases full support of the genetic transmission hypothesis. Results do not indicate significant evidence of G×E interaction effects since there is no evidence that a low risk environment (i.e., absence of paternal alcohol dependence) moderates the impact of high genetic risk for the development

of offspring ADHP. This is not to preclude the possibility that gene-environment interplay may be operating for variables not examined in this report.

Extended COT analyses: Paternal alcohol dependence, prenatal substance exposure, and parental psychopathology with child ADHP

To thoroughly examine the joint predictions of parental and prenatal risk factors on child ADHP and to investigate whether the role of paternal risk affected these predictions, we extended the COT model in a manner consistent with Knopik et al (2006). Table 4 summarizes results from this COT model predicting ADHP outcome simultaneously from family risk status and significant parental, prenatal, and sociodemographic covariates. It is notable that once paternal family risk of alcohol dependence is controlled for, maternal drinking after confirming pregnancy and maternal ADHD were the strongest predictors of child ADHP. Further, consistent with Knopik et al. (2006), MSDP remained a significant predictor of offspring risk for exhibiting four or more attention deficit hyperactivity symptoms, both broadly and narrowly defined (ADHP-4B and ADHP-4N). Controlling for other risk factors, increased risk for six or more symptoms (ADHP-6B and 6N) was not found in those exposed to MSDP. However, confidence intervals were broad, so possible important effects should not be excluded in this sample. Finally, the effects of maternal DSM-IV alcohol dependence on ADHP risk were markedly attenuated (although confidence intervals remain broad) once family risk, prenatal variables, and maternal ADHD were included in the model. This suggests that maternal ADHD (and other potential maternal psychopathology) may be important, albeit partial, confounders in the relationship between maternal alcoholism and offspring ADHP, a finding that builds upon earlier work that did not include such maternal data (e.g. Knopik et al., 2005; Knopik et al., 2006).

DISCUSSION

This study, complementary to our earlier children-of-female-twin study (Knopik et al., 2006), implemented a children-of-*male*-twin design that provided a genetically informative model of paternal alcohol dependence risk predicting child attention deficit hyperactivity problems (ADHP) in the context of prenatal substance exposure and other maternal influences. The COT design provides a powerful approach for attempting to clarify environmental consequences associated with paternal alcoholism. Major findings from these analyses were: (i) paternal alcohol dependence is associated with increased probability of high-risk environmental exposures, such as prenatal substance exposure, (ii) concerning offspring ADHP – conclusive evidence for genetic transmission (i.e. common genes hypothesis) was not found; however, maternal history of ADHD, and maternal drinking and MSDP significantly contributed to offspring risk both before and after controlling for the effects of paternal and maternal alcoholism; and (iii) maternal ADHD may be an important, albeit partial, confounder in the relationship between maternal alcoholism and offspring ADHP.

Results suggest a trend that children meeting narrow and broad definitions of ADHP are more likely in offspring in high genetic risk groups (indexed by paternal alcohol dependence). This trend reached significance only for ADHP-4B. Additionally, while maternal alcohol dependence was significantly predictive of ADHP at the univariate level (see also Knopik et al., 2005; Knopik et al., 2006), once we adjusted for genetic risk, prenatal variables, and parental psychopathology, the effect of maternal alcoholism was significantly attenuated, a finding that may be due, in part, to the relatively small number of mothers with diagnosis of alcohol dependence (10% of sample) and the large number of unaffected mothers with an alcohol dependent partner (Table 1), which reduced differences between offspring with an affected vs. an unaffected mother. Our failure to identify a robust relationship between parental alcoholism and offspring ADHP is not without precedent

(Reich, et al., 1993; Schuckit et al., 1987). Such inconsistency could, in part, be attributed to varying definitions of parental alcoholism and offspring ADHD. For the current report, paternal alcohol dependence is defined as DSM-III-R while maternal alcohol dependence uses DSM-IV criteria. In earlier work, we considered maternal DSM-IV alcohol abuse and dependence (Knopik et al., 2005; Knopik et al., 2006) and paternal alcohol problems defined as drinking that caused problems with health, family, job, police or other (Knopik et al., 2006). This latter definition of problem use was not significantly associated with offspring ADHD (Knopik et al., 2006). Concerning ADHD, earlier work defines it as narrow DSM-IV ADHD (Knopik et al., 2006), 'any ADHD,' symptom count, and ADHD with or without clinical impairment (Knopik et al., 2005). Considering the larger literature, other definitions such as dimensions of ADHD (Barnow et al., 2007), laboratory tasks (Corral et al., 1999), behavioral undercontrol (Sher, 1991), and attention and memory deficits (Tarter et al., 1989) have been used. Further, even when parental alcoholism has been found to predict ADHD, non-genetic and genetic explanations have often been difficult to untangle from one another since most studies in this literature have not used genetically informative design (Knopik et al., 2006). Importantly, while the current report did not yield significant associations between parental alcoholism and child ADHP, maternal ADHD was the strongest predictor of offspring ADHP, a finding consistent with ADHD being highly heritable ($h^2 \sim 75\text{--}80\%$) (e.g. Knopik et al., 2005; Spencer et al., 2002). Women with a lifetime history of ADHD may be more likely to develop alcohol dependence or abuse substances while pregnant. Further, most existing literature does not control for the fact that prenatal exposures may be confounded with parental behaviors (e.g., ADHD and/or alcohol dependence) that may be key transmittable risk factors. The inclusion of maternal ADHD [a variable unavailable in Knopik et al., 2006] in the multivariate model substantially reduced the importance of maternal alcohol dependence (although confidence intervals were broad); however, alongside maternal ADHD, prenatal exposure remained a significant predictor lending support to existing literature suggesting an association between offspring behavioral problems (including ADHD) and maternal smoking and drinking during pregnancy (e.g., Huizink & Mulder, 2006; Knopik, in press; Linnet et al., 2003). Thus, consistent with our earlier work (Knopik et al., 2005; Knopik et al., 2006) prenatal risk factors appear to combine additively with genetic risk (in this case maternal ADHD).

Several important limitations should be considered. First, fathers were drawn from the Vietnam Era Twin Registry, which included several selection criteria that affected the final sample. The twin father's selection process ensured that both members of each twin pair were accepted into the US military; significant psychopathology (including early-onset alcohol dependence), behavioral disorders associated with overt impairment, and/or insufficient educational attainment would have precluded entry into the armed services. These selection criteria may have contributed to a sample containing a broad, highly prevalent, and considerably heterogeneous alcohol dependence phenotype (Sartor et al., 2003) and relatively few severely-affected cases (7% of sample). Thus, if the sample includes, on average, less severe cases of paternal alcohol dependence, we would expect lower levels of genetic risk in the offspring (e.g. Cadoret et al., 1994; Cloninger et al., 1981). In contrast, our earlier COT study involving female alcoholics defined by DSM-IV criteria (Knopik et al., 2006) most likely represented more severely affected cases. This is likely due, at least in part, to sample selection differences but also to differences between DSM-IV and DSM-III-R criteria. DSM-III-R dependence is more inclusive than DSM-IV criteria (e.g. Grant, 1996). Given the relatively lower prevalence of alcoholism among females, the more stringent criteria of DSM-IV, and the greater impairment that may be evidenced, the offspring of alcoholic mothers would reflect a higher genetic liability than would the current sample of offspring of male alcoholics. If true, some of the differences between these two studies can be attributed to differences in genetic risk in the offspring for various outcomes, including ADHD.

Second, we are dependent on retrospectively-reported broadly-defined measures of substance use during pregnancy. This could have caused us to overestimate the importance of these risk factors. While considerable research supports reliability and validity of retrospective reporting of pregnancy variables (e.g. Christensen et al., 2004; Heath et al., 2003; Reich et al., 2003), this does not preclude further investigation using more detailed assessments, including frequency, timing, and duration of exposure. Third, offspring ADHP was determined only via maternal report rather than by direct clinical evaluation. Although maternal report has been shown to be reliable for ADHD (Faraone et al., 1995) and our goal was to examine a range of ADHD problems, a clinically defined sample and the addition of multiple raters of ADHD (e.g., parents and teachers and/or clinicians) may offer additional information. Relatedly, the child assessments and some of the parent measures were assessed by one rater – the mother -- who supplied information on her own as well as her children’s psychopathology. Given that maternal ADHD was the strongest predictor of child ADHP data, the possibility of reporter bias may have caused us to overestimate the risk attributed to maternal ADHD. Finally, paternal alcohol dependence may be influenced by maternal psychopathology. Across all ADHP variables, the inclusion of maternal measures affected the magnitude of the associations with paternal genetic risk variables. This would suggest the possibility of assortative mating (Eaves et al., 2005). However, given the fairly small magnitude of the unadjusted associations between paternal risk and offspring ADHP, these results should be interpreted cautiously and warrant further investigation.

In general, despite limited evidence for a genetic association between paternal alcoholism and child ADHP, results are supportive of earlier work. Namely, children at high genetic risk for ADHP may also be at high environmental risk for ADHP, primarily from maternal influences (maternal ADHD and substance use during pregnancy). Although our male COT design could not be used to assess alcohol dependence or ADHD twin mothers, the association between maternal ADHD and offspring attention deficit hyperactivity problems (ADHP) can be reasonably interpreted in terms of a genetic transmission model. Future follow-up assessments, incorporating additional and more detailed assessments of paternal alcohol dependence, paternal ADHD, maternal ADHD, maternal nicotine dependence, maternal substance use during and outside of pregnancy, as well as multiple ratings and assessments offspring behavior across development, are warranted in order to further elucidate these complex relationships.

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Table 1

Sample characteristics (means or percent endorsement) as a function of family risk status for DSM-III-R alcohol dependence (AD).

Characteristic	1. Father AD (n = 334)	2. Father unaffected; MZ Co-twin AD (n = 111)	3. Father unaffected; DZ Co-twin AD (n = 89)	4. Father unaffected; Co-twin unaffected (n = 193)
# offspring, total	505	162	145	304
# siblings, mean (SD)	1.64 (1.00)	1.72 (1.11)	1.79 (1.11)	1.55 (0.94)
Child sex, % male	49.7	46.9	49.7	44.1
Child age, mean (SD)	19.91 (3.94) ^{NS}	19.98 (3.86) ^{NS}	19.25 (3.81) ^{NS}	19.62 (3.95)
Paternal age, mean (SD)	50.36 (2.61) ^{NS}	51.10 (2.68) ^{NS}	50.76 (2.60) ^{NS}	50.86 (2.65)
Maternal age, mean (SD)	47.36 (3.82) ^{NS}	47.40 (4.30) ^{NS}	47.18 (3.64) ^{NS}	48.31 (3.59)
<i>Pregnancy risk factors:</i>				
Mother smoked during pregnancy	27.7 [*]	24.1 ^{NS}	20.0 ^{NS}	18.4
Mother drank before knew pregnant	27.9 [*]	29.0 [*]	23.4 ^{NS}	19.4
Mother drank after knew pregnant	16.6 [*]	14.2 ^{NS}	14.5 ^{NS}	8.9
<i>Sociodemographic risk/protective factors:</i>				
Paternal university education, %	58.2 ^{NS}	63.6 ^{NS}	71.7 ^{NS}	65.1
Family income < \$35,000, %	17.3 [*]	19.8 [*]	20.7 [*]	10.5
Parental marital status: divorced, %	21.9 [*]	15.4 ^{NS}	15.2 ^{NS}	12.2
<i>Parental psychiatric and substance abuse histories[#]:</i>				
Paternal DSM-III-R substance abuse/dependence, %	17.8 [*]	10.5 [*]	4.8 ^{NS}	2.3
Paternal DSM-III-R nicotine dependence, %	65.5 [*]	47.5 [*]	47.6 [*]	22.7
Paternal any DSM-III-R psychiatric diagnosis, %	34.7 [*]	18.5 [*]	18.6 [*]	8.2
Maternal DSM-IV alcohol abuse %	10.9 ^{NS}	6.2 ^{NS}	9.0 ^{NS}	7.2
Maternal DSM-IV AD, %	11.7 ^{NS}	12.3 ^{NS}	6.9 ^{NS}	6.9
Maternal history of DSM-IV ADHD, %	8.5 ^{NS}	7.4 ^{NS}	7.6 ^{NS}	4.3

* $p < 0.05$ for comparison with control group (father unaffected, cotwin unaffected).

^{NS} Non-significant for comparison with control group (father unaffected, cotwin unaffected); all comparisons adjusted for non-independence of observations (multiple siblings per family).

[#] Maternal diagnosis of nicotine dependence and paternal ADHD were not available.

Table 2

Univariate associations of ADHD problems in offspring with parental, prenatal, and sociodemographic variables[^].

	ADHP-4B	ADHP-6B	ADHP-4N	ADHP-6N
Paternal DSM-III-R AD	1.28 (1.01–1.75) [*]	1.15 (0.74–1.78)	1.26 (0.81–1.97)	1.23 (0.76–1.99)
Paternal DSM-III-R severe AD	1.40 (1.02–1.93) [*]	1.34 (0.86–2.10)	1.28 (0.80–2.05)	1.31 (0.79–2.16)
Paternal DSM-III-R psychiatric diagnosis	1.13 (0.78–1.64)	1.37 (0.83–2.25)	1.55 (0.94–2.54)	1.58 (0.92–2.72)
Paternal DSM-III-R substance abuse/dependence	1.31 (0.79–2.21)	1.70 (0.91–3.18)	1.48 (0.76–2.88)	1.59 (0.79–3.19)
Paternal DSM-III-R nicotine dependence	1.40 (1.03–1.91) [*]	1.46 (0.92–2.30)	1.66 (1.04–2.65) [*]	1.83 (1.10–3.07) [*]
Maternal DSM-IV alcohol abuse	1.54 (0.94–2.52)	1.58 (0.82–3.04)	1.48 (0.74–2.94)	1.55 (0.75–3.22)
Maternal DSM-IV AD	2.09 (1.30–3.37) ^{**}	2.08 (1.15–3.74) [*]	2.47 (1.40–4.35) ^{**}	2.73 (1.51–4.94) ^{**}
Maternal DSM-IV ADHD	4.05 (2.53–6.49) ^{**}	4.92 (2.78–8.73) ^{**}	3.80 (2.08–6.95) ^{**}	3.77 (1.99–7.16) ^{**}
Mother drank before knew pregnant	1.30 (0.93–1.83)	1.49 (0.92–2.41)	1.54 (0.93–2.54)	1.71 (1.01–2.91)
Mother drank after knew pregnant	1.71 (1.14–2.56) ^{**}	2.50 (1.49–4.21) ^{**}	2.71 (1.60–4.60) ^{**}	3.15 (1.82–5.45) ^{**}
Mother smoked during pregnancy	1.89 (1.35–2.64) ^{**}	1.52 (0.93–2.50)	2.01 (1.25–3.25) ^{**}	1.64 (0.96–2.80)
Male gender	1.68 (1.24–2.28) ^{**}	2.10 (1.35–3.29) ^{**}	2.19 (1.37–3.51) ^{**}	2.20 (1.34–3.62) ^{**}
Divorce	1.53 (1.03–2.27) [*]	1.82 (1.08–3.07) [*]	2.00 (1.19–3.37) ^{**}	2.33 (1.35–4.03) ^{**}
Overall prevalence	17.6%	7.8%	7.2%	6.3%

[^] AD=alcohol dependence

^{*} $p < .05$

^{**} $p < .01$

Table 3

Odds ratios for ADHP problems in groups of offspring differing in paternal zygosity, paternal alcohol dependence, and cotwin alcohol dependence (AD)[^]

Risk status	ADHP-4B		ADHP-6B		ADHP-4N		ADHP-6N	
	Prev (%)	OR (95% CI)	Prev (%)	OR (95% CI)	Prev (%)	OR (95% CI)	Prev (%)	OR (95% CI)
1. Dad AD	19.6	1.52* (1.02–2.28)	8.7	1.38 (0.78–2.44)	8.1	1.33 (0.75–2.36)	6.9	1.26 (0.68–2.32)
2. Dad UN – MZ Cotwin AD	21.6	1.72* (1.03–2.88)	12.3	2.03* (1.03–4.01)	9.9	1.64 (0.83–3.26)	8.0	1.47 (0.70–3.10)
3. Dad UN – DZ cotwin AD	14.5	1.06 (0.59–1.89)	5.0	0.77 (0.32–1.86)	3.5	0.54 (0.20–1.45)	3.5	0.60 (0.22–1.66)
4. UN/UN	13.8	1.00	6.4	1.00	6.3	1.00	5.6	1.00

[^] Child gender (male) was a significant covariate ($p < .01$) for all ADHP categories.

* $p < .05$

Table 4

Multivariate associations between ADHP measures, family risk status, prenatal exposure variables, and parental psychopathology[^].

Risk status	ADHP-4B		ADHP-6B		ADHP-4N		ADHP-6N	
	Prev (%)	OR (95% CI)	Prev (%)	OR (95% CI)	Prev (%)	OR (95% CI)	Prev (%)	OR (95% CI)
1. Dad AD	19.6	1.10 (0.70–1.72)	8.7	0.88 (0.46–1.70)	8.1	0.78 (0.41–1.50)	6.9	0.67 (0.33–1.34)
2. Dad UN – MZ Cotwin AD	21.6	1.42 (0.81–2.51)	12.3	1.57 (0.74–3.34)	9.9	1.25 (0.57–2.72)	8.0	1.04 (0.44–2.43)
3. Dad UN – DZ cotwin AD	14.5	0.88 (0.48–1.61)	5.0	0.58 (0.23–1.47)	3.5	0.40 (0.14–1.13)	3.5	0.43 (0.15–1.24)
4. UN/UN	13.8	1.00	6.4	1.00	6.3	1.00	5.6	1.00
Prenatal risk								
Smoked during pregnancy	25.4	1.69** (1.19–2.40)	10.7	1.32 (0.78–2.23)	11.4	1.72* (1.03–2.88)	8.7	1.30 (0.74–2.31)
Drank before knew pregnant	20.6	0.84 (0.55–1.26)	10.5	0.74 (0.40–1.34)	9.6	0.67 (0.36–1.24)	8.9	0.71 (0.36–1.36)
Drank after knew pregnant	25.2	1.64* (1.07–2.51)	15.7	3.16*** (1.67–5.99)	14.8	3.39*** (1.80–6.37)	14.2	3.74*** (1.90–7.34)
Parental psychopathology								
Paternal DSM-III-R nicotine dependence	20.2	1.19 (0.86–1.68)	9.5	1.30 (0.77–2.19)	9.0	1.39 (0.81–2.39)	8.1	1.59 (0.87–2.91)
Maternal DSM-IV alcohol dependence	29.1	1.62 (0.95–2.76)	14.3	1.56 (0.73–3.34)	14.6	1.71 (0.85–3.43)	13.6	1.92 (0.90–4.10)
Maternal DSM-IV ADHD	43.0	4.31*** (2.57–7.23)	26.4	5.71*** (2.98–10.93)	20.3	4.27*** (2.21–8.23)	17.7	4.21*** (2.08–8.49)

[^] AD=alcohol dependence. Multivariate model covariates included based on Hosmer & Lemeshow³⁹ criteria.

Adjusted multivariate model covariates (not in table): Child gender (male) remained significant ($p < 0.01$) for all ADHP categories. Divorce was non-significant for ADHP-4B ($p = .25$), ADHP-6B ($p = .23$), or ADHP-4N ($p = .09$) in the multivariate model; however it remained significant for the multivariate model of ADHP-6B ($p = .04$).

* $p < .05$

*** $p < .01$