Pharmacology, Biochemistry and Behavior 93 (2009) 313–321

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Genetic and environmental influences on externalizing behavior and alcohol problems in adolescence: A female twin study☆

Valerie S. Knopik [a,*], Andrew C. Heath [b], Kathleen K. Bucholz [b], Pamela A.F. Madden [b], Mary Waldron [b]

[a] Center for Alcohol and Addiction Studies, Department of Community Health, Brown University Medical School, Box G-S121-4, Providence, RI 02912, United States
[b] Missouri Alcoholism Research Center, Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, United States

ARTICLE INFO

Available online 31 March 2009

Keywords:
ADHD
Alcoholism
Conduct disorder
Genetics
Twin studies
Prenatal substance exposure
Parental alcoholism

ABSTRACT

Genetic and environmental contributions to the observed correlations among DSM-IV ADHD problems [inattentive (INATT) and hyperactive/impulsive (HYP/IMP) behaviors], conduct problems (CDP) and alcohol problems (AlcProb) were examined by fitting multivariate structural equation models to data from the Missouri Adolescent Female Twin Study [$N = 2892$ twins (831 monozygotic pairs, 615 dizygotic pairs)]. Based on results of preliminary regression models, we modified the structural model to jointly estimate (i) the regression of each phenotype on significant familial/prenatal predictors, and (ii) genetic and environmental contributions to the residual variance and covariance. Results suggested that (i) parental risk factors, such as parental alcohol dependence and regular smoking, increase risk for externalizing behavior; (ii) prenatal exposures predicted increased symptomatology for HYP/IMP (smoking during pregnancy), INATT and CDP (prenatal alcohol exposure); (iii) after adjusting for measured familial/prenatal risk factors, genetic influences were significant for HYP/IMP, INATT, and CDP; however, similar to earlier reports, genetic effects on alcohol dependence symptoms were negligible; and (iv) in adolescence, correlated liabilities for conduct and alcohol problems are found in environmental factors common to both phenotypes, while covariation among impulsivity, inattention, and conduct problems is primarily due to genetic influences common to these three behaviors. Thus, while a variety of adolescent problem behaviors are significantly correlated, the structure of that association may differ as a function of phenotype (e.g., comorbid HYP/IMP and CDP vs. comorbid CDP and AlcProb), a finding that could inform different approaches to treatment and prevention.

1. Introduction

The relationship between childhood externalizing or disruptive behavior and substance use and dependence in adulthood has been well established (e.g., Robins, 1966, 1998; Caspi et al., 1996). Similar relationships have also been reported between childhood disruptive behavior and early alcohol use and alcohol dependence in adolescence (e.g., Disney et al., 1999; Kuperman et al., 2001). In particular, children with attention-deficit hyperactivity disorder (ADHD) appear to be at risk for substance use problems as they reach adolescence and adulthood (Flory et al., 2003). Several mechanisms have been postulated for this apparent association. First, children with ADHD are at risk for alcoholism because of their behavioral profiles in early childhood — profiles that include impulsivity, distractability, hyperactivity and, in general, cognitive and behavioral under-regulation (e.g., Smith et al., 2002). These symptoms not only describe ADHD, but also the larger construct of behavioral undercontrol implicated in alcoholism theory (Molina et al., 2007; Sher, 1991; Tarter et al., 1990; Zucker et al., 1995). Second, the association between ADHD and substance abuse may be merely an artifact of the overlap between ADHD and other behavioral problems, such as conduct disorder (CD) which has been shown, in both clinical and epidemiological samples, to co-occur with ADHD 30–50% (e.g., Szatmari et al., 1989; Biederman et al., 1987). In addition to its comorbidity with ADHD, CD has been implicated as a robust predictor of both concurrent and future alcohol problems (Rose et al., 2004), and evidence suggests that, among all childhood behavioral disorders, CD exhibits the strongest association with alcohol problems (Disney et al., 1999; Greenbaum et al., 1991; Molina et al., 2002; Moss and Lynch, 2001). Third, the co-occurrence of ADHD and CD represents a particularly severe form of CD that increases risk for later, adverse outcomes, such as substance use problems, and disorder (e.g., Disney et al., 1999; Fergusson et al., 1993; Flory et al., 2003; Molina et al., 1999).

In addition to the examination of the more direct observable relationships among these behaviors, there is also active research in the possible roles of familial and environmental factors in the etiology of childhood behavioral problems. For example, substance use problems and disorder in parents, which have been associated with ADHD (e.g., Knopik et al., 2005), can result in a variety of detrimental

☆ This work supported by NIH grants: DA17671, AA07728, AA09022, AA11998, HD049024.
* Corresponding author. Tel.: +1 401 863 6600; fax: +1 401 863 6647.
E-mail address: Valerie_Knopik@Brown.edu (V.S. Knopik).

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doi:10.1016/j.pbb.2009.03.011

rearing environments including, but not limited to, poor parenting, lack of parental discipline, and increased family conflict (e.g. Eliason and Skinstad, 1995; Ohannessian et al., 2004), all of which can contribute to child mis-behavior. Additional familial/environmental factors include pre- and perinatal risk factors such as low birth weight, prenatal substance exposure and secondary hand smoke exposure. Very low and low birth weights have been associated with ADHD symptoms in childhood (Botting et al., 1997; Breslau and Chilcoat, 2000; Mick et al., 2002b). Prenatal exposure to alcohol has been reported to be predictive of ADHD in childhood (Knopik et al., 2005; Streissguth et al., 1994; Coles et al., 1997) as well as earlier onset (e.g., Russell, 1991) and increased risk (Alati et al., 2006; Baer et al., 2003) of alcohol problems. Maternal smoking during pregnancy has also been shown to increase risk for ADHD (Knopik et al., 2006; Milberger et al., 1996; 1998; Mick et al., 2002a) as well as CD (Wakschlag et al., 2002).

Interestingly, despite interest in the phenotypic (or observed) relationship between childhood disruptive behavior and alcohol use, very little work has focused on subtypes of ADHD (i.e., inattention and hyperactivity/impulsivity) or the underlying genetic and environmental structures of the interrelationships among ADHD, CD, and alcohol problems, particularly in adolescence. Specifically, an additional mechanism could account for apparent associations between externalizing behavior and alcohol use in adolescence such that these phenotypes may share common genetic variance ("common genes" hypothesis) whereby comorbidity may be best explained by genes with pleiotropic effects (i.e., genes that influence more than one trait). In support of this "common genes" hypothesis, the covariation between hyperactivity and CD (Silberg et al., 1996) and CD, ADHD, and oppositional-defiant disorder (Dick et al., 2005; Nadder et al., 2002; Waldman et al., 2001) in adolescence was found to be largely attributable to genetic factors, and there is fairly strong evidence that a common genetic factor underlies much of the phenotypic association among alcoholism, drug abuse, antisocial personality and CD in late adolescence and adulthood (Hicks et al., 2004; Krueger et al., 2002; Slutske et al., 1998). However, disorder-specific genetic variance also appears important (Blonigen et al., 2005; Dick et al., 2005; Krueger et al., 2002). On the other hand, genetically informative studies of specific relevance to the covariance between alcohol problems and ADHD are surprisingly limited in spite of ample evidence that genetic influences underlie each disorder (e.g. Knopik et al., 2004; Knopik et al., 2005). For instance, Young et al. (2000) examined ADHD, CD, substance experimentation (including alcohol, nicotine, and illicit drug use) and novelty seeking in adolescents as indices of a latent behavioral disinhibition trait, which was found to be highly heritable. However, the lack of a direct assessment of alcohol and the additional variables contributing to the latent behavioral disinhibition trait make it difficult to extrapolate the magnitude of genetic influences to the covariation among ADHD and alcohol problems. Further, while some evidence for common genes exists, other studies have suggested that environmental influences, rather than genetic, underlie the co-occurrence of disruptive behaviors, particularly ADHD, CD, and oppositional-defiant disorder (Burt et al., 2001, 2005). Additionally, Rose et al. (2004) reported that, at age 14, genetic influences on alcohol dependence were negligible and that the covariation among symptoms of CD and alcohol dependence was due to environmental factors that are common to both phenotypes.

The aims of the present study focus on extending prior work by examining the relationships among ADHD, including Inattentive (INATT) and Hyperactive/Impulsive (HYP/IMP) subtypes, conduct problems (CDP), and alcohol problems (AlcProb) in adolescence and by addressing the following questions: First, are there associations between familial and environmental risk factors (i.e., parental alcoholism, parental smoking, maternal drinking/smoking during pregnancy, low birth weight) and our four defined phenotypes: inattention (INATT), hyperactivity/impulsivity (HYP/IMP), conduct problems (CDP) and alcohol problems (AlcProb) in adolescence? Second, after adjusting for pertinent familial risk factors, what proportion of the residual variance in each of these phenotypes is due to genetic and environmental factors? Finally, after adjusting for measured familial risk, what proportion of the comorbidity among these behavioral patterns is driven by biological risk, environmental risk, or both?

2. Methods

2.1. Participants and measures

Data were obtained from the Missouri Adolescent Female Twin Study cohort, a sample of female adolescent twin pairs and their parents participating in a longitudinal study of the development of alcohol problems and associated psychopathology in adolescent girls and women (MOAFTS; Heath et al., 2002). All twin pairs born in Missouri to Missouri-resident parents between July 1, 1975 and June 30, 1985, where both twins were still living, were identified from birth records. A cohort-sequential design was used with recruitment, over two years, of six-month cohorts of 13, 15, 17, and 19 year-olds. The third and fourth years of data collection added new cohorts of 11- and 13-year-old twins. Ascertainment of families began in January 1995 and continued through December 1998. After exclusion of those families with no maternal diagnostic interview and those with missing data, 1446 twin pairs (~65% of identified families; for details on nonparticipation see Heath et al., 2002) with complete data on all variables were included in the present analysis [831 monozygotic (MZ) pairs, 615 dizygotic (DZ) pairs]. 13% of the sample classified themselves as minority and almost exclusively as African-American, reflecting the minority composition of the Missouri population. Self-reported maternal education levels included 9.8% 'without high school diploma,' 39.5% 'high school diploma without any college education,' 29.2% 'some college education,' and 21.4% 'degree from 4-year college or more.'

2.2. Measures

A brief initial interview, using standard questions for zygosity assignment (Nichols and Bilbro, 1966), was conducted with a parent to determine zygosity of the twins. Comprehensive structured diagnostic telephone interviews were scheduled with parents of the twins and with the twin pairs. Verbal consent, or assent if minors, was obtained from all participants prior to their participation in the interview, as well as parental consent for the participation of their minor children in the study. All procedures were approved by the Institutional Review Board at Washington University, St Louis.

2.2.1. Parental, prenatal, and familial measures

The parent interview was a modified version of the SSAGA (Semi-Structured Assessment of the Genetics of Alcoholism; Bucholz et al., 1994), which was developed for the Collaborative Study of the Genetics of Alcoholism and is a comprehensive psychiatric interview used to assess physical, psychological, social, and psychiatric manifestations of alcohol abuse/dependence and related psychiatric disorders in adults. Modifications were made to the SSAGA to incorporate DSM-IV (APA, 2000) criteria as well as to adapt it for telephone use (see Bucholz et al., 1994; Hesselbrock et al., 1999 for reliability and validity data on the SSAGA). Parents (typically mothers) were asked to report about a wide range of behaviors in the twins, including ADHD, as well as about their own history of alcohol abuse/dependence and history of regular smoking. In addition, they provided information, using the Family History Assessment Module (FHAM; Rice et al., 1995), about their partner's history of alcohol problems. Mothers only were asked questions about their own smoking and drinking patterns during the pregnancy with the twins; hence,

analyses reported here are limited to families with maternal interview data. The diagnoses of DSM-IV alcohol abuse (mothers only) and dependence in the parents were assigned by computer algorithm.

2.2.1.1. Prenatal exposure to alcohol and smoking. Maternal drinking during pregnancy was divided into 5 exclusive categories: 1–10 days of use during the pregnancy, 11–35 days of use during the pregnancy, more than 35 days of use during the pregnancy, 'some heavy use' (i.e., at least 5–6 drinks on the days that they typically drank and having 5 or more drinks in a single day at least 1 day a month), and 'frequent heavy use' (i.e., 'some heavy use' plus having 5 or more drinks in a single day at least 2–3 days a month). Maternal smoking during pregnancy was first divided into two categories: light/moderate smoking (1–10 cigarettes per day) during the 1st trimester and beyond the first trimester, and heavy smoking (11+ cigarettes per day) during the 1st trimester and beyond the first trimester. If a mother stopped smoking at a certain point in her pregnancy, her data was included in the appropriate category. For example, if she quits after 1 month of the pregnancy, she would be counted as having smoked during the first trimester, and if she quits after 4 months, she would be counted as having smoked beyond the first trimester.

2.2.1.2. Birth weight. Mother's report of twins' birth weight was also obtained. Because twins are usually born 3–4 weeks premature and are, on average, 30% smaller than singleton births (Plomin, DeFries, McClearn, and Rutter, 1997), the established definitions of low birth weight (<2500 g) and very low birth weight (<1500 g) were not applied to this sample. Rather, low birth weight was defined by birth weights in the lowest 10th percentile of the distribution in this sample. This was equivalent to a birth weight of less than 1700 g (3.75 lb).

2.2.1.3. Parental regular smoking. The twin interview was based on the Diagnostic Interview for Children and Adolescents (DICA; Reich, 2000) and the C-SSAGA (Semi-Structured Assessment of the Genetics of Alcoholism-Child Version), and was adapted for telephone administration. In addition to covering their own histories of alcohol and smoking problems and various psychiatric disorders, twins were asked to report on smoking patterns of each parent (i.e., "Is your mother or father a current smoker?" and "If your mother or father has quit smoking, did they used to smoke at least 1 or 2 days a week?"). If either of these two questions were answered positively, the parent in question was considered to be a regular smoker.

2.2.1.4. Child ADHD symptoms. Assessment of child ADHD symptoms was based on items derived from the DICA (Reich, 2000) and the C-SSAGA. It has been suggested that measures of symptom count should be used rather than categorical diagnoses (Levy et al., 1997), and much research has been conducted using this strategy. For purposes of these analyses, DSM-IV ADHD symptom endorsement (see Table 1) was based solely on maternal report and defined as a sum total of items endorsed and required onset of each symptom prior to age 7. Separate summary scores were created for Inattentive (INATT) and Hyperactive/Impulsive (HYP/IMP) dimensions. Twins' self-report of ADHD data were not obtained.

Table 1
DSM-IV items for each child/adolescent outcome and mean scores prior to variable transformation.

INATT items	HYP/IMP items	CDP items	AlcProb items
Often fails to give close attention to details or makes careless mistakes	Often fidgets or squirms in seat	Often bullies, threatens or intimidates others	Tolerance: (a) need for markedly increased amounts of alcohol to achieve intoxication; or (b) markedly diminished effect with continued use of same amount of alcohol
Often has difficulty sustaining attention	Often leaves seat in situations where remaining seated is expected	Often initiates physical fights	Withdrawal: alcohol is taken to relieve or avoid withdrawal symptoms
Often does not seem to listen when spoken to directly	Often runs or climbs excessively in situations when it is inappropriate to do so	Has used a weapon that can cause serious physical harm to others	Alcohol is often taken in larger amounts or over a longer period of time than intended
Often does not follow through on instructions/tasks	Often has difficulty playing or engaging in leisure activities quietly	Has been physically cruel to people	Persistent desire or unsuccessful efforts to cut down or control alcohol use
Often has difficulty organizing tasks and activities	Often 'on the go' or acts as if 'driven by a motor'	Has been physically cruel to animals	Great deal of time spent in activities necessary to obtain alcohol, use alcohol, or recovers from its effects
Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort	Often talks excessively	Has stolen while confronting a victim (e.g., mugging, armed robbery)	Important social, occupations, or recreational activities given up because of alcohol use
Often loses things necessary for tasks or activities	Often blurts out answers before questions have been completed	Has forced someone into sexual activity	Continue to use alcohol despite heath or emotional problems likely to be caused or exacerbated by alcohol use
Often easily distracted	Often has difficulty awaiting turn	Has deliberately engaged in fire setting	
Often forgetful in daily activities	Often interrupts or intrudes on others	Has deliberately destroyed others' property	
		Has broken into someone else's house, building, or car	
		Often lies to obtain goods or favors or to avoid obligations (i.e., 'cons' others)	
		Has stolen items of nontrivial value without confrontation (e.g., forgery)	
		Often stays out at night despite parental prohibitions, beginning before age 13	
		Has run away from home overnight	
		Often truant from school	
Mean INATT (SD)	Mean HYP/IMP (SD)	Mean CDP (SD)	Mean AlcProb (SD)
1.55(2.42)	1.17 (1.96)	0.56 (1.05)	0.38 (0.99)

2.2.1.5. Child conduct problems (CDP). Assessment of lifetime child conduct problems (CDP) was based on items from the DICA for telephone administration (Reich, 2000). CDP was based on twin self-report and defined as a summary score of fifteen DSM-IV items endorsed (see Table 1).

2.2.1.6. Child alcohol problems (AlcProb). Child alcohol problems were based on twin self-report of lifetime DSM-IV Alcohol Dependence criteria and were defined as the total summary score of seven items endorsed (see Table 1).

To improve the approximation to a normal distribution of these INATT, HYP/IMP, CDP, and AlcProb measures, a log transformation [log $(x+1)$] for each score was implemented preceding all analyses. Mean scores prior to variable transformation are shown in Table 1.

2.3. Data-analysis

2.3.1. Descriptive analyses

The associations between each child outcome (INATT, HYP/IMP, CDP, and AlcProb) and prenatal (e.g., prenatal substance exposure) and parental (e.g., alcohol dependence, smoking behavior outside of pregnancy) predictors were investigated using linear regression models. Both members of each twin pair were included in these regression analyses; therefore, confidence intervals were adjusted to allow for the non-independence of twin pairs using the Huber–White robust variance estimation option as implemented in STATA (StataCorp, 2003).

2.3.2. Genetic model fitting

In order to determine the extent of genetic and environmental influences on risk of INATT, HYP/IMP, CDP, and AlcProb, genetic structural equation models were fitted to the twin data using the Mx statistical modeling package (Neale and Cardon, 1992). In genetic twin analyses, models are tested that partition variance in a variable of interest into genetic [additive (A) and non-additive (D)] and environmental [shared (C) and non-shared (E)] components. Additive genetic influences (A) describe the effect of multiple genes that exert influence in a linear or additive fashion. In general, non-additive genetic effects describe interactive effects of different alleles and include genetic dominance (within locus interaction) and epistasis (across locus interaction). However, in most twin studies, non-additive effects are modeled as genetic dominance (Rettew et al., 2008). Shared or common environmental effects (C) are those influences that make members of a family more similar to one another. Non-shared or unique environmental effects (E) make members of twin pairs different. Important to note, E also includes measurement error. Considering proportions of variance, we denote the following: a^2 for the proportion of total variance due to additive genetic effects, d^2 for the proportion of total variance due to non-additivity, c^2 for shared environmental contributions, and e^2 for non-shared environmental variance.

Genetic modeling takes advantage of the differing degrees of genetic relatedness among MZ versus DZ twin pairs. MZ twins share all of their additive and non-additive genetic effects, while DZ pairs share, on average, 50% of the additive and 25% of their non-additive genetic effects. Shared environmental effects are assumed to correlate 1.0 between members of both MZ and DZ pairs. Consequently, the phenotypic correlation between MZ twin pairs is determined by $r_{MZ} = a^2 + d^2 + c^2$ and the phenotypic correlation between members of DZ pairs is determined by $r_{DZ} = .5a^2 + .25d^2 + c^2$. Examining the pattern of MZ and DZ correlations can provide guidance on model-fitting strategy, such that (a) $.5r_{MZ} = r_{DZ}$, suggests that the phenotype is due to additive genetic influences; (b) $.5r_{MZ} < r_{DZ}$, suggests that the phenotype is due to both additive genetic and shared environmental influences; or (c) $.5r_{MZ} > r_{DZ}$, suggests that the phenotype is due to additive and non-additive genetic influences.

The pattern of twin correlations (MZ vs. DZ) for the four outcomes of interest to this report is presented in Table 2. The correlations suggest that for INATT ($r_{MZ} = .79$; $r_{DZ} = .29$) and HYP/IMP ($r_{MZ} = .87$; $r_{DZ} = .36$) both additive and dominant genetic factors influence these outcomes and that shared environmental influences are not significant. However, for CDP ($r_{MZ} = .49$; $r_{DZ} = .32$) and AlcProb ($r_{MZ} = .58$; $r_{DZ} = .50$), it appears that additive genetic and shared environmental influences are important. These assumptions were confirmed by fitting univariate models that allowed for shared environmental influences (for INATT and HYP/IMP) or non-additive genetic effects (for CDP and AlcProb) to the symptom count measures. For INATT and HYP/IMP, shared environmental influences were estimated at zero (95% CI = 0.00–0.02 for INATT; 95% CI = 0.00–0.03 for HYP/IMP). For CDP and AlcProb, non-additive influences were estimated at zero (95% CI = 0.00–0.05 for CDP; 95% CI = 0.00–0.12 for AlcProb).

In order to examine the structure of the correlations among INATT, HYP/IMP, CDP, and AlcProb, a multivariate model (see Fig. 1) was fit to the data. This multivariate model simply extends the basic principles of the twin model and provides estimates of univariate parameters (i.e., a^2, c^2, d^2, and e^2 for each of the traits) in addition to cross-trait correlations, which can also be partitioned into genetic and environmental components. As evidenced in Table 2, the phenotypic correlations between the ADHD subtype scores (INATT and HYP/IMP) and AlcProb in these data were nonsignificant; however, it has been shown that the phenotypic correlational structure can be quite different from the underlying genetic and environmental structure (Cloninger, 1987; Heath and Martin, 1990; Stallings et al., 1996). Thus, the full model, guided by existing literature and the pattern of correlations in our data, allowed an ADE structure for INATT and HYP/IMP and an ACE structure for CDP and AlcProb and hypothesized one latent genetic factor (G) that influenced all four externalizing outcomes. The latent genetic factor was influenced by additive (A) and non-additive (D) genetic factors. In order for the model to be identified, we constrained the additive path, a, to 1, which forced the non-additive loading, d, to be a scalar proportion of the additive genetic effect on the latent G factor. One common latent non-shared environmental (E) factor was also allowed to influence all four outcomes. We also hypothesized one common shared environmental factor (C1) between CDP and AlcProb, with additional specific/independent shared environmental effects (C2) on AlcProb. The residuals for each outcome were partitioned into specific additive (A), specific non-additive (D; for

Table 2
Twin correlations of log-transformed variables for MZ and DZ female twin pairs (DZ correlations below the diagonal).

	T1HYP/IMP	T1INATT	T1CDP	T1AlcProb	T2HYP/IMP	T2INATT	T2CDP	T2AlcProb
T1HYP/IMP	**1.00**	0.44	0.22	0.02^{NS}	0.87	0.42	0.24	0.04^{NS}
T1INATT	0.45	**1.00**	0.21	0.02^{NS}	0.41	0.79	0.22	0.05^{NS}
T1CDP	0.19	0.15	**1.00**	0.21	0.19	0.20	0.49	0.20
T1AlcProb	−0.03^{NS}	−0.03^{NS}	0.25	**1.00**	0.03^{NS}	0.01^{NS}	0.13	0.58
T2HYP/IMP	0.36	0.21	0.16	0.03^{NS}	**1.00**	0.45	0.25	0.04^{NS}
T2INATT	0.20	0.29	0.13	0.04^{NS}	0.50	**1.00**	0.26	0.05^{NS}
T2CDP	0.12	0.13	0.32	0.08	0.22	0.19	**1.00**	0.19
T2AlcProb	0.10^{NS}	−0.05^{NS}	0.14	0.50	0.04^{NS}	0.04^{NS}	0.18	**1.00**

NS = nonsignificant.

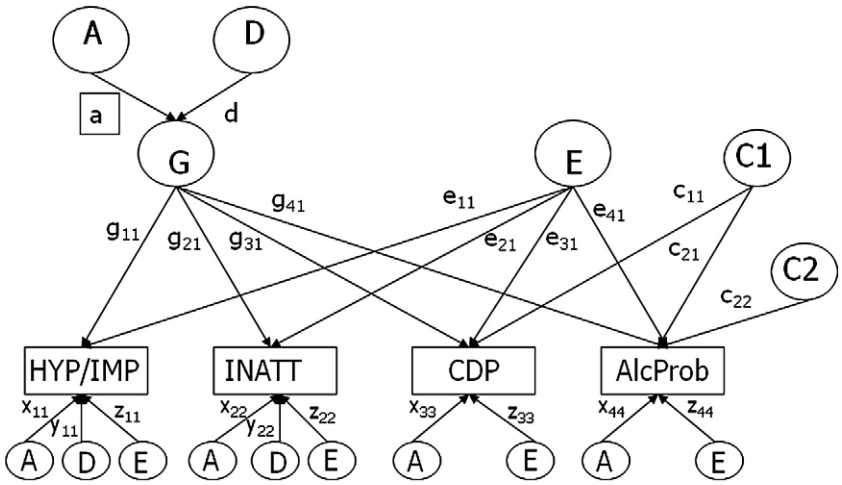

Fig. 1. Multivariate model, shown for one twin only. Allows for contrast effect for INATT and HYP/IMP (paths not shown). Parameters denoted with boxes indicate fixed paths: $a = 1$.

ADHD subtypes only), specific shared environmental (C; for CDP and AlcProb only), and specific non-shared environmental (E) components. Estimates of the proportion of the total variance that could be explained by additive genetic (a^2), dominance (d^2), shared (c^2) and non-shared environmental factors (e^2) were without covariate adjustment. This model also allowed for different mean values for each of the zygosity groups. 95% likelihood-based confidence intervals were also computed under this model.

Contrast effects or genetic dominance (non-additivity) pose alternative explanations for the very low DZ correlations relative to MZ correlations observed in the inattention and hyperactive/impulsive data. To account for this, an additional path between INATT scores of each twin and HYP/IMP scores of each of the twins, s, was also added to the model (not shown in Fig. 1). This path implies an interaction between phenotypes, and may be interpreted in two ways (Simonoff et al., 1998): (1) a social interaction between siblings (i.e., the behavior of one twin has an effect on the behavior of his/her cotwin) that can be either cooperative or competitive; or (2) a rater effect (i.e., parents stress the similarities or differences between the children). Following Rietveld et al. (2003), this will be referred to as a 'contrast effect' for the remainder of this article.

Based on the results of fitting linear regression models, we subsequently modified the multivariate variance components model to control for age as well as significant prenatal and parental predictors ($p<.05$). This was done by jointly modeling the linear regression of outcome (i.e., INATT, HYP/IMP, CDP, or AlcProb) on these covariates and the genetic and environmental contributions to the residual variance and covariance among outcome symptom count scores. In order to control for the age range in these data, we modeled age as a contrast coded covariate allowing for three groups: 11–14 years old, 15–18 years old, and 19+ years old. Models were fitted by maximum-likelihood using Mx (Neale and Cardon, 1992). Under this adjusted means model, genetic (additive and dominant) and environmental (shared and non-shared) parameter estimates were obtained after controlling for significant predictors of each outcome. By doing this, we tested for residual genetic and environmental contributions to variation in risk of INATT, HYP/IMP, CDP, and AlcProb, as well as residual genetic and environmental correlations among our four

Table 3
Prenatal and parental predictors of HYP/IMP, INATT, CDP, and AlcProb.

	Child/adolescent outcomes			
	HYP/IMP	INATT	CDP	AlcProb
	B (SE)	*B* (SE)	*B* (SE)	*B* (SE)
Low birth weight (<1700 g)	.043 (.053)	.092 (.059)	−.052 (.033)	−.077 (.027)**
Parental alcohol history				
Maternal AlcA/AlcD	.187 (.056)**	.063 (.059)	.152(.039)**	.084 (.036)*
Paternal AlcD	.058 (.046)	.149 (.051)**	.056 (.030)	.052 (.029)
Parental smoking history				
Mother — regular smoker	.118 (.051)*	.127 (.057)*	.077 (.034)*	.117 (.036)**
Father — regular smoker	.074 (.035)**	.031 (.039)	.082 (.023)**	.116 (.022)**
Maternal smoking during pregnancy^				
1st trimester				
Light/moderate: 1–10 cigs/day	.288 (.066)**	.165 (.069)*	.140 (.043)**	.031 (.037)
Heavy: 11+ cigs/day	.070 (.078)	.106 (.085)	.097 (.059)	−.001 (.050)
Beyond 1st trimester				
Light/moderate: 1–10 cigs/day	.199 (.063)**	.214 (.068)**	.110 (.038)**	−.016 (.033)
Heavy: 11+ cigs/day	.134(.059)*	.082 (.068)	.059 (.040)	.041 (.040)
Maternal alcohol use during pregnancy				
1–10 days	−.056 (.037)	−.063 (.042)	−.001 (.024)	.001 (.023)
11–35 days	−.082 (.107)	−.033(.120)	−.077 (.058)	−.005 (.065)
>35 days	.096(.149)	.216 (.201)	.095 (.132)	.436 (.197)*
Some heavy alcohol use	.027 (.115)	−.132 (.120)	−.053 (.093)	−.101 (.066)
Frequent heavy alcohol use	.031 (.173)	.533 (.258)*	.388 (.158)**	.133 (.117)

Adjusted regression coefficients estimated from multivariate linear regression models.
*$p<0.05$, **$p<0.01$.

phenotypes. These models allowed for a contrast effect for ADHD subtype scores (HYP/IMP and INATT).

3. Results

Twin pairs ranged in age from 11 to 23 years, with an average of 15.15 years. 4.6% of mothers met criteria for alcohol dependence (AlcD), 8.9% of mothers for alcohol abuse (AlcA), and based on maternal history report, 19.4% of fathers for AlcD. With regard to smoking, 37.1% of mothers and 40.1% of fathers were regular smokers (defined by twin report); moreover, 37% of mothers reported smoking during the 1st trimester and 21% continued to smoke beyond the 1st trimester. 24% of mothers reported drinking 1–10 days during pregnancy, 3% drank 11–35 days, less than 1% (0.7%) reported drinking on more than 35 days of the pregnancy. Further, some heavy use was reported by 2.5% of mothers and frequent heavy use was reported by 1% of the sample.

3.1. Parental alcoholism and smoking predicted increased risk of externalizing behavior and alcohol problems

Results indicated that parental alcoholism predicted increased risk of offspring HYP/IMP, CDP, and AlcProb. Significant associations were found between maternal AlcA/AlcD and child HYP/IMP [$B=.187$, 95% CI=.077–.297], child CDP [$B=.152$, 95% CI=.075–.230], and child AlcProb [$B=.084$, 95% CI=.013–.156], while paternal AlcD was significantly predictive of child INATT [$B=.084$, 95% CI=.048–.250]. Maternal regular smoking (outside of pregnancy) was also significantly predictive of all four phenotypes (B ranging from .077–.127), while paternal regular smoking predicted increased symptoms for HYP/IMP, CDP, and AlcProb (B ranging from .074–.116).

Substance use during pregnancy, particularly smoking during pregnancy, was also significantly associated with adolescent outcome. Light/moderate smoking (1–10 cigarettes/day) during the first trimester and beyond the first trimester was significantly associated with all externalizing behaviors (HYP/IMP, INATT, and CDP); however, was not predictive of adolescent alcohol problems. Frequent heavy alcohol use (5 or more drinks in a single day, 2–3 days a month) was associated with INATT and CDP.

After adjusting for all prenatal and parental risk factors, higher HYP/IMP scores were more likely in girls whose mothers met criteria for AlcA/AlcD, in girls whose parents were regular smokers, and in girls whose mothers reported smoking 1–10 cigarettes/day throughout pregnancy (Table 3). A similar pattern was seen for CDP and INATT; however, in the case of INATT, paternal AlcD was significantly predictive while maternal AlcA/AlcD was not. Higher symptom counts for both CDP and INATT were also found in girls who were exposed to frequent heavy alcohol use during pregnancy. Alcohol problems in these adolescent girls were increased in those with mothers who met criteria for AlcA/AlcD, parents who were regular smokers, and in girls with low birth weight.

3.2. Genetic influence on the risk for externalizing behavior and alcohol problems

The parameter estimates and subsequent variance components obtained from fitting the covariate-adjusted multivariate model to the symptom count data (Fig. 2, Table 4) confirm significant total genetic influences on HYP/IMP ($a^2+d^2=0.87$), INATT ($a^2+d^2=0.82$), and CDP ($a^2=0.29$) after controlling for the effects of prenatal and childhood risk factors. Consistent with other reports of alcohol use in adolescence (Rhee et al., 2003; Rose et al., 2004), heritability for AlcProb was estimated at 13% and was nonsignificant. Shared environmental factors were important for CDP ($c^2=.14$) and even more so for AlcProb ($c^2=.34$). Non-shared environmental factors, while small, were significant and accounted for between 14 and 18% of the total variance in HYP/IMP and INATT risk after controlling for prenatal and parental predictors. Larger non-shared environmental effects were found for CDP and AlcProb ($e^2=.57$ and $e^2=.53$, respectively). A significant contrast effect, in the form of sibling cooperation or maternal bias, was seen for HYP/IMP ($s=.0737$). Contrast effects for INATT were nonsignificant ($s=-.0360$).

3.3. Genetic and environmental contributions to the comorbidity of externalizing behaviors and alcohol problems

Genetic and environmental covariance and correlation matrices are shown in Table 5. Significant genetic correlations were found between the three externalizing behaviors ($r_{G(HYP/IMP\text{-}INATT)}=0.5257$; $r_{G(HYP/IMP\text{-}CDP)}=0.3145$; $r_{G(INATT\text{-}CDP)}=0.3039$), suggesting that these behaviors are due, in part, to the same genetic influences. However, in these adolescent females, there was no significant correlation between ADHD behaviors (HYP/IMP and INATT) and alcohol problems. Conduct problems were significantly correlated with AlcProb; however, this association was not due to genetic factors ($r_G=.0030$), but rather to environmental contributions ($r_C=.4904$ and $r_E=.1235$). This finding is consistent with Rose et al. (2004) and suggests that, in adolescence, correlated liabilities for conduct and

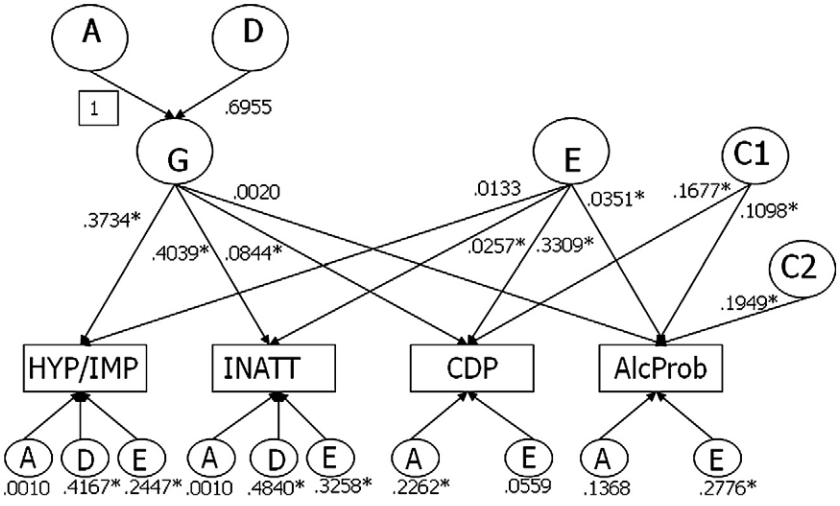

Fig. 2. Parameter estimates from the multivariate model. Significant paths denoted with *. Model allows for sibling interaction for INATT ($s=-.0360$) and HYP/IMP ($s=.0737$*; paths not shown). Parameters denoted with boxes indicate fixed paths.

Table 4
Raw and standardized variance parameters attributed to additive genetics, non-additive genetics, shared environment, and non-shared environment after covariate adjustment.

	A	*D*	*C*	*E*	Total	%*a*	%*d*	%*c*	%*e*
HYP/IMP	0.1394	0.2411	–	0.0601	0.4406	0.32	0.55	–	0.14
INATT	0.1631	0.3132	–	0.1068	0.5831	0.28	0.54	–	0.18
CDP	0.0582	–	0.0281	0.1126	0.1989	0.29	–	0.14	0.57
AlcProb	0.0187	–	0.0501	0.0783	0.1471	0.13	–	0.34	0.53

Estimated from multivariate model.
A = additive genetic variance; *D* = non-additive genetic variance; *C* = shared environmental variance; *E* = non-shared environmental variance.

alcohol problems are found in environmental factors common to both phenotypes.

4. Discussion

This investigation sought to determine the structure of the comorbidity among four adolescent phenotypes indexing externalizing behaviors: hyperactivity/impulsivity, inattention, conduct problems, and alcohol problems. Specifically, we sought to examine measured familial/environmental risk factors and their associations with externalizing behavior and alcohol problems and, once taking those measured risks into account, to determine what proportion of the variance and covariance among these phenotypes was due to biological risk, environmental risk, or both.

Major findings from these analyses include: (i) parental risk factors, such as parental alcohol dependence and regular smoking, increase risk for externalizing behavior; (ii) prenatal exposures predicted increased symptomatology for HYP/IMP (smoking during pregnancy), INATT and CDP (prenatal alcohol exposure); (iii) after adjusting for measured familial/prenatal risk factors, genetic influences were significant for HYP/IMP, INATT, and CDP; however, similar to earlier reports (Rhee et al., 2003; Rose et al., 2004), genetic effects on alcohol dependence symptoms were negligible, a finding consistent with the fact that, in adolescence, drinking tends to be exploratory and episodic with alcohol dependence symptoms being rarely endorsed (Rose et al., 2004); and (iv) in adolescence, correlated liabilities for conduct and alcohol problems are found in environmental factors common to both phenotypes, while covariation among impulsivity, inattention, and conduct problems is primarily due to genetic influences common to these three behaviors.

Interestingly, while conduct problems were significantly associated with alcohol problems, there was no significant relationship between alcohol use symptomatology and both dimensions of ADHD (hyperactivity/impulsivity and inattention) in this adolescent female sample. This finding is not without precedent and is entirely consistent with earlier work by Moss and Lynch (2001) who examined the relationships between conduct disorder, ADHD, and oppositional-defiant disorder on subsequent alcohol use disorder. They found that, while male adolescents demonstrated direct effects of CD and ADHD on alcohol use disorder, female adolescent data only indicated a robust direct effect of CD on alcohol use disorder. Thus, findings stress the importance of considering gender effects, an issue that many studies in this area have been underpowered to detect (e.g., Molina et al., 2007).

The present work should be interpreted in the context of its strengths and limitations. First, we are reliant on maternal report of ADHD symptoms and twins' self-report for conduct and alcohol problems. Although maternal report has been shown to be reliable for ADHD (Faraone et al., 1995) and other behavioral problems (e.g., Cronk et al., 2002), the addition of multiple raters (i.e., direct clinical evaluation or teacher reports) of behavior may offer additional information. Second, while not a main outcome in the study, 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 thorough timing and duration of exposure. Third, as with any cross-sectional study, the results are limited to a particular developmental period, in this case early to late adolescence. Further investigations are needed to determine whether the same relationships hold at both earlier (childhood) and later (adulthood) developmental periods. This is particularly important given recent work by Molina et al. (2007) who demonstrated that childhood ADHD predicted heavy drinking, drunkenness, alcohol use disorder symptoms and alcohol use disorder for late adolescence but not for early adolescence. Further evidence for considering additional developmental stages, can be found in a genetic association study by Dick et al. (2006) who show that the GABRA2 gene is significantly associated with childhood CD symptoms but not with childhood alcohol dependence symptoms. However, they do show a consistent elevation in risk for alcohol dependence that is associated with GABRA2, but this association only becomes evident in the mid-20s and then remains throughout adulthood (Dick et al., 2006).

Regarding its strengths, this study is the first genetically informative design to consider the specific relationships between dimensions of ADHD (i.e., hyperactive/impulsivity and inattention), conduct problems and alcohol use problems in adolescence. Also, families were recruited from the community rather than through a clinically referred proband, thus the results are likely to generalize to the population; although this also likely resulted in lower symptom endorsement and possibly less power to detect associations.

In summary, results of the present investigation indicate that, after controlling for prenatal and familial risk factors shown to increase risk for ADHD subtypes, conduct problems, and alcohol dependence symptomatology, most of the covariance among impulsivity, inattention, and conduct problems is due to common genetic influences; however, the observed comorbidity between conduct and alcohol problems is driven primarily by environmental influences common to both behaviors. Each phenotype is also under the influence of additional, unique genetic and/or environmental factors, suggesting that these externalizing disorders, while sharing some genetic and/or environmental influences, are not simply manifestations of the same underlying biological or environmental predisposition. Consistent with earlier reports, dimensions of ADHD were not significantly associated with alcohol problems in this adolescent female sample, and similar to earlier work (Knopik et al., 2005, 2006, 2009), prenatal

Table 5
Genetic and environmental covariance (above diagonal) and correlations (below diagonal) estimated from multivariate model.

	HYP/IMP	INATT	CDP	AlcProb
Genetic[a]				
HYP/IMP	–	0.2238	0.0468	0.0011
INATT	0.5257	–	0.0506	0.0012
CDP	0.3145	0.3039	–	0.0001
AlcProb	0.0130	0.0127	0.0030	–
Shared *E*				
HYP/IMP	–	NE	NE	NE
INATT	NE	–	NE	NE
CDP	NE	NE	–	0.0184
AlcProb	NE	NE	0.4904	–
Non-shared *E*				
HYP/IMP	–	0.0003	0.0044	0.0005
INATT	0.0037	–	0.0085	0.0009
CDP	0.0535	0.0775	–	0.0116
AlcProb	0.0073	0.0082	0.1235	–

[a] Genetic correlations include both additive and non-additive genetic contributions, when applicable. NE = not estimated.

and familial predictors of behavior, while significant, did not mediate genetic risk on externalizing behavior. Thus, while a variety of adolescent problem behaviors are significantly correlated, the structure of that association may differ as a function of phenotype (e.g., comorbid HYP/IMP and CDP vs. comorbid CDP and AlcProb) and developmental course (childhood, adolescence and adulthood), a finding that could inform different approaches to research, treatment, and prevention. For example, when considering risk for alcohol problems in adolescence, early identification efforts might focus on conduct problems and environmental factors common to both. Additionally, focusing on shared genetic factors that influence a spectrum of externalizing behaviors, may aid in identifying susceptibility genes and understanding the biological pathways that affect vulnerability for a variety of poor outcomes (Dick et al., 2008). To conclude, a greater understanding of the structure of comorbidity can have an important impact on public health and remediation efforts of the deleterious effects of behavioral disorders such that information on the underlying covariance structure can provide information on (i) putative risk factors (biological and/or environmental) for disorders, and (ii) clinical treatment, including medication (e.g., treatments efficacious for one disorder should be investigated as a potential treatment for the other disorder).

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