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Protective Effects of the Alcohol Dehydrogenase-*ADH1B**3 Allele on Attention and Behavior Problems in Adolescents Exposed to Alcohol during Pregnancy

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Abstract

Alcohol dehydrogenase is a critical enzyme in the metabolism of alcohol. Expression of three alleles at the *ADH1B* locus results in enzymes that differ in turnover rate and affinity for alcohol. The *ADH1B**3 allele, which appears to be unique to individuals of African descent, is associated with more rapid alcohol metabolism than the more prevalent *ADH1B**1 allele. It has been previously demonstrated that the presence of at least one maternal *ADH1B**3 allele confers a protective effect against alcohol teratogenicity in infants and children. This study was conducted to determine whether the presence of the *ADH1B**3 allele in the mother or child continues to be protective in alcohol-exposed individuals during adolescence. 186 adolescents and 167 mothers participating in a 14-year follow-up of the Detroit Longitudinal Cohort were genotyped for *ADH1B* alleles. Behavioral reports were obtained from classroom teachers. Frequencies of the *ADH1B**3 allele were 17.6% in the mothers and 21.0% in the adolescents, which are consistent with the 15-20% expected for African Americans. Prenatal alcohol exposure was associated with increased attention problems and externalizing behaviors in adolescents born to mothers with two *ADH1B**1 alleles but not in those whose mothers had at least one *ADH1B**3 allele. A similar pattern was seen in relation to the presence or absence of an *ADH1B**3 allele in the adolescent, which may have reflected the presence/absence of the maternal variant. This study is the first to demonstrate that the protective effects of the maternal *ADH1B**3 allele continue to be evident during adolescence. These persistent individual differences in vulnerability of offspring to the behavioral effects of fetal alcohol exposure are likely attributable to more rapid metabolism of alcohol that the *ADH1B**3 variant confers on the mother, leading to a reduction of the peak blood alcohol concentration to which the fetus is exposed during each drinking episode.

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Keywords

fetal alcohol spectrum disorders; prenatal alcohol exposure; alcohol dehydrogenase; *ADH1B**3 allele; adolescent externalizing behavior

1. Introduction

Fetal alcohol spectrum disorders (FASD) include the broad range of physical and neurobehavioral outcomes associated with prenatal alcohol exposure (Hoyme et al., 2005). Numerous alcohol-related neurocognitive deficits have been reported (e.g., Streissguth et al., 1990; Jacobson et al., 2004; 2008; 2011; Burden et al., 2005; Goldschmidt et al., 1996; Coles et al., 2010; J. Jacobson et al., 2011), but fewer studies have documented affective and behavioral problems. Children and adolescents prenatally exposed to alcohol exhibit parent- and teacher-reported behavioral problems (Brown et al., 1991; Carmichael-Olson et al., 1997; Jacobson et al., 2006), poorer social functioning (Roebuck et al., 1999), and more internalizing and externalizing problems (Mattson & Riley, 2000; D'Onofrio et al., 2007; O'Leary et al., 2009; Disney et al., 2008), even at relatively low levels of exposure (Sood et al., 2001). Larkby and colleagues (2011) found that one or more drinks/day during the first trimester were associated with an increased rate of conduct disorder in adolescents.

Although FASD are associated with a broad range of adverse outcomes, not all children born to mothers who drink during pregnancy are affected. Laboratory animal studies have demonstrated that dose and timing of exposure can determine vulnerability or severity of outcome (e.g., Goodlett et al., 2005). In addition, three maternal factors have been identified as moderators of severity of fetal alcohol-related outcomes—older maternal age at delivery (May, 1991; Jacobson et al., 1996), less stimulating home environment, and maternal alcohol abuse history (Jacobson et al., 2004).

The potential of genetic differences to moderate the risk of fetal alcohol related-impairment in humans has been examined for one class of polymorphisms, the *ADH1B* alleles. Alcohol is metabolized primarily in the liver by alcohol dehydrogenase (ADH), which oxidizes alcohol to acetaldehyde. Acetaldehyde is then oxidized to acetate by aldehyde dehydrogenase (ALDH) with ADH being the rate-limiting step. Functional polymorphisms in the locus encoding the beta subunit of the Class I ADH (*ADH1B*) have been found to alter rates of alcohol metabolism. The *ADH1B**1 allele, is the most prevalent form found among Caucasian and African Americans (Brennan et al., 2004). Alcohol is cleared more rapidly in individuals with either of this allele's variants—*ADH1B**2 and *ADH1B**3—due to greater enzymatic activity of ADH, compared with individuals homozygous for the *ADH1B**1 allele (Bosron and Li, 1987). The *ADH1B**2 allele is most prevalent in Asian populations (Brennan et al., 2004) and is seen in the Cape Coloured (mixed ancestry) population of South Africa (Viljoen et al., 2001). The *ADH1B**3 allele has been identified in Americans of African descent (Osier et al., 2002) and occurs at a rate of approximately 15-20% (Bosron and Li, 1987; Brennan et al., 2004).

The three functional variants of the *ADH1B* gene have distinct pharmacokinetic properties. Both the *ADH1B**2 and *ADH1B**3 alleles have much larger maximal velocities than the *ADH1B**1 allele. *ADH1B**3 has a much larger K_m for ethanol, such that at low ethanol concentrations, it is slower than the *ADH1B**1 allele, but at high concentrations it is greater than 10-fold faster (Lee et al., 2004). Numerous studies have shown that individuals with at least one *ADH1B**2 (e.g., Carr et al., 2002) or *ADH1B**3 allele (e.g., Ehlers et al., 2007) are less likely to develop alcohol use disorders and consume less alcohol on average. Additionally, those with the *ADH1B**3 allele report higher sedation and a larger pulse-rate

increase than those without the allele in response to a moderate alcohol challenge (McCarthy et al., 2010).

McCarver et al. (1997) found that fetal alcohol exposure was associated with reduced birth weight and lower Bayley Mental Development Index (MDI) scores in exposed African American infants whose mothers were homozygous for the *ADH1B*1* allele. These effects were not seen in alcohol-exposed infants of mothers with at least one *ADH1B*3*. Das et al. (2004) found protective effects of the *ADH1B*3* allele on alcohol-related facial dysmorphology when both the mother and child had a copy of the *ADH1B*3* allele (but cf. Stoler et al., 2002).

In an extensive investigation of the moderating effects of the *ADH1B*3* allele, Jacobson and colleagues (2006) presented data from the Detroit Longitudinal Prenatal Alcohol Exposure Cohort during infancy and at 7.5 years. Confirming McCarver et al. (1997), the effects of prenatal alcohol exposure on Bayley MDI scores were markedly less severe in children born to mothers with at least one copy of the *ADH1B*3* allele. The presence of a maternal *ADH1B*3* allele was also protective against effects on infant head circumference, symbolic development, and reaction time. At 7.5 years, protective effects were seen on measures of attention, working memory, and executive function. In children whose mothers were homozygous for the *ADH1B*1* allele, prenatal alcohol exposure was associated with increased social problems, inattention, aggressive behaviors, and hyperactivity problems on the Achenbach (1991) Teacher Report Form (TRF), effects not seen in children born to mothers with at least one *ADH1B*3* allele. By contrast, there was no systematic pattern of protective effects relating to the presence of an *ADH1B*3* allele in the child.

The purpose of this study was to extend the findings seen in the Detroit cohort in infancy and at 7.5 years by determining whether the presence of an *ADH1B*3* allele continues to have an impact on prenatal alcohol-related behavior problems in adolescence. Teacher reports were used to assess behavior problems. We hypothesized that the presence of a maternal *ADH1B*3* allele would mitigate the effects of prenatal alcohol exposure on these outcomes. At 14 years we expected to see effects on delinquency and conduct disorder not seen at 7.5 years since these behaviors become more prevalent during adolescence. Given the higher incidence of externalizing problems and attention deficit hyperactivity disorder (ADHD) in males, (e.g., Biederman et al., 2002; Lahey et al., 2000), we also examined whether the effects of prenatal alcohol exposure on behavior problems in the more vulnerable adolescents lacking the *ADH1B*3* allele were stronger in males than females.

2. Methods

2.1 Participants

The sample consisted of 200 African American mother/child dyads from the Detroit Longitudinal Cohort assessed at 14 years for whom *ADH1B* allele data were available for mother and/or child. Mothers were recruited into the study between September 1986 and April 1989 during their first prenatal visit ($M=23.4$ weeks gestation) to a large inner-city maternity hospital. Moderate- and heavy-drinking women were over-represented by including all women reporting alcohol consumption at conception averaging at least 1 standard drink/day (0.5 oz absolute alcohol (AA)/day). A random sample of approximately 5% of the lower level drinkers and abstainers was also invited to participate. To reduce the risk that alcohol might be confounded with cocaine exposure, heavy cocaine (2 days/week) light alcohol (<7 drinks/week) users were included. Infant exclusionary criteria were birth weight <1500 g, gestational age <32 weeks, major chromosomal anomalies, neural tube defects, or multiple births.

2.2 Assessment of prenatal exposure

At each prenatal clinic visit ($M=5.3$ visits), the mother was interviewed using a timeline follow-back protocol to determine incidence and amount of drinking on a day-by-day basis during the preceding 2 weeks (Jacobson et al., 2002). Recall was linked to specific times of day and activities. Volume was recorded for each type of alcohol beverage consumed each day, converted to oz AA, and averaged across clinic visits. Each oz of AA is equivalent to 2 standard drinks. At the first visit, the mother was also asked to recall her day-by-day drinking during a typical week around time of conception. Smoking during pregnancy was reported as average number of cigarettes/day. Detailed drug use data were also obtained at each clinic visit.

2.3 ADH genotype determination

Five drops of blood were obtained by a phlebotomist from the mother by finger-stick puncture and from the child by finger-stick or venipuncture at 7.5 or 14 years and placed on diagnostic filter paper for ADH genotyping at the Indiana University School of Medicine. *ADH1B* genotypes were determined using enzymatic amplification of genomic DNA followed by hybridization with allele-specific oligonucleotides.

2.4 14-year assessments

Among the adolescents originally assessed in infancy, 61.3% were seen at 14 years, 89.8% of whom provided genetic samples. No differences in amount or frequency of drinking at time of conception or across pregnancy were detected between those who participated in the 14-year follow-up and those who did not (all $ps>.15$). Nor did the 14-year participants differ in socioeconomic status, maternal education, or marital status from those not followed up (all $ps>.20$); however, those who participated were born to slightly older mothers ($M=27.0$) than those who did not ($M=25.3$; $t(478)=3.13$; $p<.01$). Procedures were approved by the Wayne State University Human Investigation Committee. Written informed consent was obtained from the mother at recruitment and the mother/primary caregiver at the follow-up assessments; oral assent was obtained from the children at 7.5 and 14 years. The mother and child each received a small remuneration; and the mother, child, and teacher also received a small gift. All assessments were conducted by a research assistant blind regarding maternal alcohol and drug use; teachers were also blind regarding adolescent exposure history.

Each mother/caregiver was interviewed about her current use over the past year using a timeline follow-back interview, and oz AA/day, drinks/occasion, and frequency of drinking (days/week) were calculated. For the adolescents, among whom alcohol use was generally sporadic, total number of drinks consumed over the past year was calculated.

The adolescent's classroom teacher completed the Achenbach (1991) TRF, which assesses behavior problems on a 112-item rating scale. Teachers are asked to indicate how true each of the items is for the student (0=Not True, 1=Somewhat or Sometimes True, 2=Very True or Often True). Items are summed to generate eight subscales: Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, and Aggressive Behavior. The Total Problems score is the sum of all items from each scale. The Withdrawn, Somatic Complaints, and Anxious/Depressed subscales are summed to measure Internalizing Problems; Delinquent and Aggressive Behavior, to measure Externalizing Problems (Achenbach, 1991).

2.5 Potential confounders

Fourteen control variables were considered as potential confounders: maternal age at delivery, socioeconomic status (Hollingshead, 1975), education, and marital status of the

child's primary caregiver; maternal smoking, cocaine, and marijuana use during pregnancy; maternal/caregiver's Peabody Picture Vocabulary Test-Revised (Dunn and Dunn, 1981); current use of alcohol, hard drugs, marijuana, and cigarettes by the caregiver; and adolescent's gender and age at the laboratory visit.

2.6 Data analysis

Alcohol use across pregnancy was highly skewed (skew=6.34) and was, therefore, transformed by recoding the four cases with values >3 SD above the mean to the highest observed value (Winer, 1971), reducing skew to 2.5. Prenatal exposure to marijuana (skew=4.1) and cocaine (skew=2.9) were log transformed, reducing both skews to <2.0. All continuous outcome variables were also examined for potential outliers, and any cases with values >3 SD above (or below) the mean were recoded to 1 value greater (or less) than the next most extreme observed value. Any control variable that was related even weakly (at $p < .10$) to a given outcome was controlled statistically as a potential confounder in all analyses of effects on that outcome.

Each continuous outcome measure was examined in multiple regression analyses in relation to maternal drinking averaged across pregnancy together with the potential confounders that met the criterion noted above. A prenatal alcohol effect was inferred only if the relation of pregnancy drinking to developmental outcome was significant (at $p < .05$), after adjustment for the effects of the potential confounders.

Because interaction terms have very low power in most non-experimental field studies (McClelland and Judd, 1993), the mothers and the adolescents were each divided into two groups on the basis of the presence or absence of at least one *ADH1B*3* allele. The regressions were then run separately for each of these subgroups using the same covariates used in the regression analyses run for the sample as a whole. These regressions were also run separately for each gender.

3. Results

Eighty-three percent of the mothers reported alcohol use during pregnancy (Table 1), of whom 14% reported moderate-heavy use (1 drink/day on average across pregnancy). Sixty-two percent smoked during pregnancy (14% of whom smoked 1 pack/day), 34% used cocaine (50%, at least once/month), 27% smoked marijuana at least once during pregnancy (75%, more than once/month).

3.1 ADH genotype

As in previous studies, the *ADH1B*1/*1* genotype was the most common among both the mothers and adolescents (Table 1). Frequencies of the *ADH1B*3* allele were 17.6% in the maternal sample and 21.0% in the adolescent sample, consistent with rates expected in African Americans. Table 2 presents the convergence of the *ADH1B*3* allele in the subset of 153 mother-child dyads for whom we have genotypes for both.

3.2 ADH genotype and alcohol consumption by the mother and adolescent

The presence of the maternal allele was not related to maternal alcohol consumption around time of conception or across pregnancy in this sample (Table 3). Nor was current maternal alcohol consumption related to maternal genotype. The proportion of adolescents that reported having ever consumed alcohol did not differ by maternal genotype (allele absent=42.0% vs. present=42.9%, $\chi^2=0.01$) or adolescent genotype (absent=41.0% vs. present=41.9%, $\chi^2=0.01$). Among adolescent consumers, no differences were found in alcohol consumption in the past year when comparing maternal genotype (absent=11.2

drinks vs. present=14.2, $t=0.37$) or adolescent genotype (absent=10.0 drinks vs. present=11.2, $t=0.15$).

3.3 Effects of prenatal alcohol exposure on adolescent attention and behavior

Prenatal alcohol exposure was associated with increased externalizing problems and higher ratings on two teacher-reported subscales, aggression and delinquency, after control for confounders (Table 4). On the DBD scale, prenatal alcohol was related to more teacher-reported symptoms of inattention after control for confounders.

3.4 Effects of prenatal alcohol exposure on adolescent attention and behavior in adolescents with and without the maternal and/or child *ADH1B*3* alleles

We evaluated the hypothesized protective effects of the *ADH1B*3* allele by examining the pattern of significant standardized regression coefficients in regressions run separately for adolescents born to mothers with and without the *ADH1B*3* allele. Effects of prenatal alcohol exposure on TRF attention problems, hyperactivity, aggression, externalizing problems, and total problems were significant among adolescents with mothers lacking the *ADH1B*3* allele and were not seen in those with mothers who had that allele (Table 4). On the inattention and social problems subscales, prenatal alcohol was associated with higher ratings in those born to mothers lacking the *ADH1B*3* allele, but after control for confounders, these effects fell just short of statistical significance. On the DBD, prenatal alcohol exposure was related to increased inattention and hyperactivity symptoms only in those born to mothers without the *ADH1B*3* allele. Prenatal alcohol was not related to *any* of the TRF or DBD measures in those whose mothers had the *ADH1B*3* allele.¹

Among adolescents who themselves lacked the *ADH1B*3* allele, prenatal exposure was associated with TRF hyperactivity, aggression, delinquency, externalizing and total problems and DBD inattention and hyperactivity symptoms (Table 4). These effects were not significant after control for confounders in adolescents with the *ADH1B*3* allele, suggesting that as with maternal genotype, presence of the *ADH1B*3* allele in the adolescent may convey some protection against the effects of prenatal alcohol on these outcomes.²

3.5 Gender differences in effects on behavior problems

Consistent with previous studies, boys showed higher levels of attention problems (both inattention and hyperactivity), social problems, aggression, delinquency, and externalizing and total problems on the TRF; inattention and hyperactivity on the DBD than girls (Table 5). Given these differences, the effects of prenatal alcohol were assessed separately for boys

¹The multiple regressions presented in Table 4 for the sample as a whole were each re-run adding an interaction term for AA/day during pregnancy by presence/absence of at least one *ADH1B*3* allele. Among the analyses examining the exposure by maternal allele interactions, only the interaction term for TRF Hyperactivity was significant ($\beta = -.24, p = .03$) and only the interaction terms for TRF Aggression and DBD Hyperactivity fell short of statistical significance ($\beta = -.19, p = .10$, and $\beta = -.19, p = .075$, respectively). These analyses confirm our expectation that interaction terms would have very low power to detect effects in this non-experimental field study (see McClelland and Judd, 1993).

²Given that many of the outcomes are correlated, we performed a factor analysis to reduce the number of outcome variables being tested as an additional check that observed group differences are not attributable to multiple comparisons. This factor analysis included the 12 primary outcomes; TRF Inattention and Hyperactivity were omitted because they are components of TRF Attention, and TRF Externalizing, Internalizing, and Total problems were omitted because they are derived from the primary TRF scales. Two factors emerged: Internalizing, which was comprised of the three TRF Internalizing scales, and Externalizing, which was comprised of the two TRF Externalizing scales, TRF Attention, Social Problems, and Thought Problems, and the four DBD measures. We constructed composite scores for each of these factors by transforming the raw scores to standard scores and averaging them. When each of these composites was examined in relation to prenatal alcohol exposure and potential confounders, prenatal alcohol was not related to the Internalizing composite for the total sample or any of the allele groups (all p s > .20). The prenatal alcohol effect on the new Externalizing composite for the sample as a whole after control for confounders fell just short of statistical significance ($\beta = .16, p = .067$). This effect was significant for both the allele absent groups ($\beta = .28, p < .05$ for maternal; $\beta = .25, p < .05$, for adolescent) but not for either of the allele absent groups (β s = .03 and .09 for the maternal and adolescent alleles, respectively).

and girls. Among boys, prenatal exposure was associated with increased social problems, aggression, and externalizing and total problems (Table 6). For girls, prenatal alcohol was associated with more somatic complaints (Table 7). Among boys whose mothers lacked an *ADH1B*3* allele, prenatal alcohol exposure was related to increased TRF hyperactivity, aggression, externalizing and total problems, and DBD hyperactivity (Table 6). Prenatal alcohol was related to the same outcomes in the boys who themselves lacked the *ADH1B*3* allele. Among girls who lacked the *ADH1B*3* allele, prenatal alcohol exposure was associated with increased somatic complaints (Table 7).

4. Discussion

This is the first study to examine the effects of prenatal alcohol exposure on behavior problems in adolescents with and without the maternal and/or child *ADH1B*3* allele. In the sample as a whole, prenatal alcohol was related to teacher-reported behavior problems on measures of aggression and externalizing behaviors. These findings are consistent with numerous studies linking prenatal alcohol to increases in aggression and externalizing problems in adolescents on the parent-reported Child Behavior Check List (Mattson and Riley, 2000; Sood et al., 2001; D'Onofrio et al., 2007; Disney et al., 2008; O'Leary et al., 2009). When children born to mothers lacking the *ADH1B*3* allele were examined separately, the effects on aggression and externalizing behaviors were significant, and effects were seen on hyperactivity and inattention that were not seen in the sample as a whole. By contrast, *no* adverse effects were seen in adolescents born to mothers with at least one *ADH1B*3* allele. Thus, the presence of the maternal *ADH1B*3* allele appeared to convey a consistent and enduring protective effect during adolescence against adverse effects on all the endpoints affected by prenatal alcohol, especially among boys.

These findings are consistent with previous reports showing that the presence of the maternal variant protected against fetal alcohol-related impairments in infancy and at 7.5 years (McCarver et al., 1997; Das et al., 2004; Jacobson et al., 2006). Moreover, these data extend the findings from the 7.5-year follow-up of this cohort to show that the maternal *ADH1B*3* allele continues to protect against prenatal alcohol-related problems in social, attention, aggression, and externalizing behaviors in adolescence.

The mechanism by which this maternal allele conveys this protective effect against prenatal alcohol exposure is not clearly understood (see Warren and Li, 2005). One possible explanation is that the presence of the *ADH1B*3* allele may cause mothers to drink less due to higher acetaldehyde concentrations that result from more rapid alcohol metabolism. However, we did not detect any differences in the amount or frequency of alcohol consumption during pregnancy in mothers with or without the *ADH1B*3* allele, suggesting that the protective effects of the *ADH1B*3* allele are likely not due to reductions in pregnancy drinking. Alternatively, although the amount of alcohol consumed is similar, peak blood alcohol concentrations are reduced in those with the *ADH1B*3* allele as compared to those homozygous for the *ADH1B*1* allele due to the more rapid metabolism of alcohol caused by the *ADH1B*3* allele. When peak blood alcohol levels are lower, lower concentrations of alcohol will reach the fetus, thereby reducing the fetal exposure to alcohol.

When the subgroup of adolescents who were homozygous for the *ADH1B*1* allele were examined separately, adverse effects of prenatal alcohol exposure were seen on most of the same outcomes as in those whose mothers were homozygous for that allele, and no adverse effects were related to prenatal alcohol exposure in the adolescents who themselves had at least one *ADH1B*3* allele. Because 70% of adolescents with the *ADH1B*3* allele in this sample also had mothers with the allele (Table 2), it is possible that this protective effect was actually due to the maternal protective allele. Unlike the maternal *ADH1B*3* allele,

which is expressed throughout the pregnancy, the fetal *ADH1B* genes are not expressed until the second trimester (Smith et al., 1971). Previous research on this cohort indicated that mothers reported drinking on average about 1 oz AA or the equivalent of 2 standard drinks/day around time of conception but that their drinking declined to <0.3 AA/day across pregnancy (Jacobson et al., 2002). Thus, the fetal *ADH1B* allele may not have the full opportunity to convey a protective effect on outcome since it is expressed only later in the pregnancy when alcohol consumption has decreased.

Thus, these data suggest that presence of the more efficient *ADH1B**3 allele conveys a protective effect against prenatal alcohol exposure that persists well into adolescence. As indicated above, the presence of a maternal *ADH1B**3 allele may limit the amount of alcohol that enters the fetal blood stream. Studies are needed to determine clearance rates in humans with and without this allele. Because this sample consisted mainly of low-to-moderately-exposed adolescents, it is not clear whether the presence of this allele is protective in the presence of heavier exposure. However, the findings of Viljoen et al. (2001) regarding a related version of the polymorphism in the Cape Coloured (mixed ancestry) population in South Africa, the *ADH1B**2 allele, suggest that the variant also plays a protective role in heavily exposed mother-infant dyads.

Our data are consistent with previous reports that boys are more likely than girls to exhibit externalizing problems, such as aggression (e.g., Lahey et al., 2000), and that boys are at greater risk for ADHD symptomatology (Biederman et al., 2002). When the effects of prenatal alcohol exposure on these outcomes were examined separately by gender, most of the effects on adolescent behavior problems in the boys lacking the *ADH1B**3 allele were notably stronger than when both genders were analyzed together. The magnitude of the effects is weaker when the girls are included presumably because girls are less likely to express behavioral problems in these domains or may exhibit these symptoms in a less disruptive manner that may not be noted or reported by teachers.

One limitation of this study is that, because most of the adolescents with the *ADH1B**3 allele were born to mothers who also had the allele, the effects associated with adolescent allele status may actually be attributable to the presence of the protective allele in the mother. In addition, pharmacological data suggest that this allele is most active at higher concentrations of alcohol. Because this sample was primarily comprised of moderately exposed adolescents, the protective effects of the allele may actually be stronger in samples with heavier exposure. Future studies including larger numbers of individuals with fetal alcohol syndrome (FAS) or partial FAS are needed to determine whether this allele can protect against structural and morphological abnormalities in FASD.

Another possible limitation of this study is that the lack of effects found in the adolescents born to mothers with the *ADH1B**3 allele could be partly due to reduced statistical power in that group. There is sufficient power to detect an r of .33 in the maternal allele absent group (2-tail $\alpha = .05$, $\beta = .20$) and an r of .39 in the allele present group. Whereas the significant effects in the allele absent group range from $r = .22$ to .41 (median = .29), the effects on those outcomes in the allele present group range from $r = .01$ to .20 (median = .06). Given the lack of overlap between the groups and the fact that the largest r observed in the allele present group is only .20, lack of power is not likely preventing the detection of effects in that group.

These findings demonstrate that the behavioral manifestations of prenatal alcohol exposure clearly persist into adolescence, even at low to moderate levels of exposure, particularly in those who are more vulnerable to the exposure. The strikingly consistent pattern of decreased vulnerability associated with at least one *ADH1B**3 allele is impressive given that

none of the adverse effects were seen in the groups with that allele. From both a clinical and scientific point of view, the examination of genetic and other important factors that can influence the impact of fetal alcohol exposure can lead to improved identification of affected children.

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Abbreviations

AA	Absolute alcohol
ADH	Alcohol dehydrogenase
ADH1B	Beta subunit of class I alcohol dehydrogenase
ADHD	Attention deficit/hyperactivity disorder
ALDH	Aldehyde dehydrogenase
CD	Conduct disorder
DBD	Disruptive Behavior Disorders
DSM-IV	Diagnostic and Statistical Manual-IV
MDI	Mental Development Index
ODD	Oppositional defiant disorder
TRF	Teacher Report Form

Highlights

- Fetal alcohol exposure related to attention and behavior problems in adolescents.
- Maternal *ADH1B**3 allele protects against fetal alcohol teenage behavior problems.
- Protective effects of *ADH1B**3 allele not due to less maternal alcohol consumption.
- First study to show protective effects of maternal *ADH1B**3 allele in adolescence.

Table 1
Sample characteristics (*N* = 200)

	Mean or %	SD	Range
Child characteristics			
Age at testing	14.4	0.6	13.3 - 16.5
Grade	8.4	1.0	5.0 - 11.0
Gender (% male)	58.5		
Caregiver characteristics			
Mother's age at delivery	27.6	6.1	14.2 - 43.9
Primary caregiver's education (yr)	12.5	1.9	6.0 - 21.5
Socioeconomic status	30.0	10.3	8.0 - 66.0
Marital status (% married)	25.0		
Prenatal exposure (consumers only)			
Alcohol (oz AA/day; <i>N</i> = 166)	0.3	0.7	0.001 - 6.5
Cigarettes (number/day; <i>N</i> = 121)	15.0	10.4	1.0 - 41.0
Marijuana (days/month; <i>N</i> = 55)	2.8	2.6	0.2 - 15.1
Cocaine (days/month; <i>N</i> = 70)	4.1	4.0	0.1 - 17.0
Maternal genotype			
*1/*1	105 (62.9%)		
*1/*3	60 (35.9%)		
*3/*3	2 (1.2%)		
Adolescent genotype			
*1/*1	117 (62.9%)		
*1/*3	60 (32.3%)		
*3/*3	9 (4.8%)		

AA = absolute alcohol

Table 2
Convergence of maternal and child presence or absence of the *ADH1B*3* allele

	Mother		Total
	Absent	Present	
Child			
Absent	79 (84.9%)	18 (30.0%)	97 (63.4%)
Present	14 (15.1%)	42 (70.0%)	56 (36.6%)
Total	93	60	153

$\chi^2 (1) = 47.45, p < .001$

Table 3
Pregnancy and current drinking patterns by presence of the *ADH1B*3* allele

	Mother		<i>t</i>
	Absent	Present	
At conception	<i>N</i> = 105	<i>N</i> = 62	
Oz AA per day	1.0	0.7	1.20
Drinks/occasion	3.8	3.6	0.28
Frequency (days/week)	2.5	2.0	1.28
During pregnancy	<i>N</i> = 105	<i>N</i> = 62	
Oz AA per day	0.3	0.2	0.76
Drinks/occasion	3.0	2.7	0.39
Frequency (days/week)	0.9	0.8	0.85
Current	<i>N</i> = 96	<i>N</i> = 58	
Oz AA per day	1.0	1.0	0.16
Drinks/occasion	4.6	4.1	0.56
Frequency (days/week)	1.8	2.0	0.69

AA = absolute alcohol

All *ps* > .10.

Table 4
Effects of prenatal alcohol exposure on attention and behavior in adolescents with and without maternal and adolescent *ADHIB3 allele**

	Total sample			Maternal <i>ADHIB</i> *3						Adolescent <i>ADHIB</i> *3					
	<i>r</i>	β	<i>N</i>	Absent	<i>r</i>	β	<i>N</i>	Present	<i>r</i>	β	<i>N</i>	Absent	<i>r</i>	β	<i>N</i>
Achenbach Teacher Report Form (<i>N</i> = 135)															
Attention problems ^a	.20*	.13	65	.33**	.25*	.47	78	.23*	.22†	.47	78	.23*	.22†	.47	78
Inattention ^a	.17*	.12	65	.29*	.23†	.47	78	.17	.18	.47	78	.17	.18	.47	78
Hyperactivity ^a	.22**	.14	65	.39**	.30*	.47	78	.30**	.27*	.47	78	.30**	.27*	.47	78
Social problems ^b	.17*	.11	65	.25*	.15	.47	78	.23*	.21†	.47	78	.23*	.21†	.47	78
Thought problems ^c	.02	.01	65	.13	.15	.47	78	-.04	-.01	.47	78	-.01	.01	.47	78
Anxious/depressed ^d	.06	.03	65	.19	.16	.47	78	-.15	-.10	.47	78	.11	.10	.47	78
Somatic complaints ^e	.11	.03	65	.09	-.01	.47	78	.21	.11	.47	78	.20†	.11	.47	78
Withdrawn ^f	.07	.07	65	-.06	-.06	.47	78	.07	.09	.47	78	.09	.09	.47	78
Aggression ^a	.25**	.20*	65	.41***	.39**	.47	78	.06	-.02	.47	78	.34**	.33**	.47	78
Delinquency ^g	.23**	.18*	65	.22†	.15	.47	78	.20	.17	.47	78	.25*	.22*	.47	78
Internalizing problems ^h	.08	.06	65	.06	.07	.47	78	.05	.09	.47	78	.13	.12	.47	78
Externalizing problems ⁱ	.25**	.23**	65	.38**	.35**	.47	78	.09	.08	.47	78	.33**	.31**	.47	78
TRF total ^a	.22**	.16†	65	.23**	.29*	.47	78	.07	-.02	.47	78	.29**	.28*	.47	78
Disruptive Behavior Disorders Rating Scale (<i>N</i> = 132)															
Inattention ⁱ	.21*	.19*	66	.33**	.31*	.45	79	.10	.09	.45	79	.24*	.23*	.43	79
Hyperactivity ^j	.17*	.13	66	.39**	.33**	.45	79	-.04	.08	.45	79	.30**	.27*	.43	79
Oppositional defiant disorder ^f	.06	.06	66	.12	.12	.45	79	.05	.05	.45	79	.10	.10	.43	79
Conduct disorder ^k	.06	.05	66	.20†	.17	.45	79	-.08	-.09	.45	79	.13	.13	.43	79

Regression analyses show the relation of prenatal alcohol exposure to the outcomes listed after control for confounders.

† $p < .10$.

* $p < .05$.

**
 $p < .01$

 $p < .001$

^a Confounders: gender, prenatal cocaine exposure

^b Confounders: gender, mother's age at delivery, socioeconomic status, prenatal cocaine exposure, prenatal marijuana exposure, age

^c Confounders: gender, prenatal marijuana exposure

^d Confounders: gender, prenatal marijuana exposure, mother's age at delivery, age

^e Confounders: gender, prenatal cocaine exposure, age

^f Confounders: none

^g Confounders: gender, socioeconomic status

^h Confounders: gender, primary caregiver's PPVT score, age

ⁱ Confounders: gender

^j Confounders: gender, prenatal cocaine exposure, primary caregiver's marital status

^k Confounders: socioeconomic status

Table 5
Effects of gender on teacher-reported behavior problems

	Total sample		Boys		Girls		<i>t</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
Achenbach Teacher Report Form	(N = 135)		(N = 79)		(N = 56)		
Attention problems	10.0	8.8	12.9	8.7	5.9	7.4	4.87***
Inattention	7.9	6.9	10.0	6.4	4.9	6.3	4.59***
Hyperactivity	4.4	4.7	5.9	4.9	2.3	3.2	5.17***
Social problems	1.7	2.4	2.1	2.5	1.1	2.1	2.44*
Thought problems	0.5	1.1	0.7	1.3	0.3	0.7	1.89†
Anxious/Depressed	1.8	2.7	2.1	3.0	1.4	2.2	1.55
Somatic complaints	0.4	1.0	0.5	1.2	0.2	0.5	1.94†
Withdrawn	2.1	3.0	2.3	3.1	1.9	2.9	0.84
Aggression	7.1	9.1	8.8	10.0	4.6	6.9	2.90***
Delinquency	2.2	2.6	2.8	2.9	1.4	1.9	3.53***
Internalizing problems	4.0	5.2	4.6	5.8	3.2	4.3	1.56
Externalizing problems	9.3	11.2	11.7	12.4	6.0	8.3	3.19**
TRF total	26.2	25.1	32.8	26.7	16.9	19.3	4.00***
Disruptive Behavior Disorders Rating Scale	(N = 132)		(N = 77)		(N = 55)		
Inattention	2.1	2.9	2.6	3.2	1.3	2.3	2.68**
Hyperactivity	1.3	2.2	1.6	2.5	0.8	1.6	2.39*
Oppositional defiant disorder	0.8	1.8	0.9	1.9	0.6	1.7	0.73
Conduct disorder	0.2	0.7	0.2	0.6	0.2	0.9	0.12

* $p < .05$ ** $p < .01$ *** $p < .001$

Table 6
Relation of prenatal alcohol exposure (oz AA/day) to teacher-reported behavior problems among boys

	Total sample (Boys only)			Maternal allele			Child allele		
	<i>r</i>	<i>β</i>	<i>N</i>	Absent	Present	<i>r</i>	Absent	Present	<i>β</i>
Achenbach TRF			<i>N</i> = 79	<i>N</i> = 38	<i>N</i> = 27	<i>N</i> = 47	<i>N</i> = 26		
Attention problems	.20[†]	.18	.35[*]	.32[†]	-.01	.23	.29[†]	.26	.20
Inattention	.17	.17	.31[†]	.31[†]	-.02	.16	.23	.30	.25
Hyperactivity	.24[*]	.20[†]	.39[*]	.34[*]	-.01	.30[*]	.33[*]	.21	.15
Social problems	.20[†]	.23[*]	.31[*]	.28[†]	.11	.22	.26[†]	.30	.45[†]
Thought problems	-.01	.02	.11	.15	-.01	-.06	.01	.26	.27
Anxious/Depressed	.07	.09	.25	.31[†]	.02	.11	.11	.10	.14
Somatic complaints	.06	-.03	.06	-.05	-.02	.15	.06	-.02	-.10
Withdrawn	.06	.06	-.09	-.09	.03	.07	.07	.09	.09
Aggression	.33^{**}	.31^{**}	.48^{**}	.49^{**}	.18	.41^{**}	.44^{**}	.36[†]	.32
Delinquency	.21[†]	.18[†]	.23	.16	.12	.24	.22	.26	.22
Internalizing problems	.07	-.003	.09	.13	.03	.12	.03	.09	-.01
Externalizing problems	.31^{**}	.31^{**}	.43^{**}	.43^{**}	.17	.38^{**}	.38^{**}	.36[†]	.36[†]
TRF total	.25[*]	.23[*]	.36[*]	.35[*]	.09	.31[*]	.35[*]	.32	.29
DBD Rating Scale			<i>N</i> = 77	<i>N</i> = 38	<i>N</i> = 27	<i>N</i> = 47	<i>N</i> = 26		
Inattention	.20[†]	.20[†]	.31[†]	.31[†]	.09	.21	.21	.29	.29
Hyperactivity	.24[*]	.21[†]	.44^{**}	.40[*]	.07	.37^{**}	.35[*]	.08	.09
Oppositional defiant disorder	.13	.13	.17	.17	.25	.17	.17	.19	.19
Conduct disorder	.17	.14	.31[†]	.24	.09	.21	.20	-.03	-.08

Regression analyses show the relation of prenatal alcohol exposure to the outcomes listed after control for confounders.

[†]
p < .10.

^{*}
p < .05.

Confounders are the same as in Table 4.

 $p < .01$.

 $p < .001$

Table 7
Relation of prenatal alcohol exposure (oz AA/day) to teacher-reported behavior problems among girls

	Total sample (Girls only)			Maternal allele			Child allele		
	<i>r</i>	β		Absent	Present		Absent	Present	
Achenbach TRF	<i>N</i> = 56			<i>N</i> = 27	<i>N</i> = 20		<i>N</i> = 31	<i>N</i> = 21	
Attention problems	.04	.02		.16	.15	.02	.15	.14	-.31
Inattention	.06	.05		.15	.13	.12	.15	.13	-.25
Hyperactivity	-.02	-.05		.18	.17	-.14	.14	.12	-.37 [†]
Social problems	.001	-.05		.02	.05	.10	.17	.17	-.13
Thought problems	.02	-.01		.25	.22	-.25	.16	.14	-.21
Anxious/Depressed	-.06	-.16		-.03	-.12	-.16	.03	-.07	-.18
Somatic complaints	.29*	.30*		.17	.19	.40*	.45**	.44*	.25
Withdrawn	.05	.05		.05	.05	.15	.16	.16	-.20
Aggression	-.15	-.17		-.10	-.11	-.19	-.16	-.17	-.34 [†]
Delinquency	.18	.18		.04	.05	.35 [†]	.24	.24	.06
Internalizing problems	.03	.02		.02	-.02	.07	.15	.10	-.05
Externalizing problems	-.08	-.08		-.07	-.07	-.10	-.05	-.05	-.14
TRF total	-.01	-.03		.05	.05	-.03	.10	.10	-.30
DBD Rating Scale	<i>N</i> = 55			<i>N</i> = 28	<i>N</i> = 20		<i>N</i> = 32	<i>N</i> = 19	
Inattention	.16	.16		.32 [†]	.32	.08	.33*	.33 [†]	-.23
Hyperactivity	-.16	-.17		-.01	-.06	-.28	-.16	-.19	-.22
Oppositional defiant disorder	-.14	-.14		-.06	-.06	-.21	-.14	-.14	-.16
Conduct disorder	-.09	-.08		-.001	.05	-.17	-.05	-.02	-.22

Regression analyses show the relation of prenatal alcohol exposure to the outcomes listed after control for confounders.

[†] $p < .10$.

* $p < .05$.

** $p < .01$.

100

 $p < .0001$

Confounders are the same as in Table 4.