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Protective Effects Of The Alcohol Dehydrogenase-Adh1b Allele

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PROTECTIVE EFFECTS OF THE ALCOHOL DEHYDROGENASE-*ADH1B* ALLELE ON BEHAVIOR PROBLEMS IN ADOLESCENTS EXPOSED TO ALCOHOL DURING PREGNANCY

by

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CHAPTER 1 INTRODUCTION

Fetal alcohol spectrum disorder (FASD) refers to the broad range of physical and neurobehavioral outcomes associated with prenatal alcohol exposure (Hoyme et al, 2005). FASD ranges from non-syndromal individuals with known histories of prenatal exposure who exhibit subtle neurobehavioral impairment to the most severely affected individuals, who meet criteria for a diagnosis of fetal alcohol syndrome (FAS). FAS is characterized by pre- and/or postnatal growth restriction, microcephaly, and a distinctive set of craniofacial dysmorphic features. Neurobehavioral outcomes associated with prenatal alcohol exposure include lower IQ (Jacobson, Jacobson, Sokol, Chiodo, & Corobana, 2004; Mattson, Riley, Gramling, Delis, & Jones, 1997; Streissguth, Barr, Sampson, Darby, & Martin, 1989; Streissguth, Barr, & Sampson, 1990), slower information processing speed (Burden, Jacobson, & Jacobson, 2005a; Coles, Platzman, Lynch, & Freides, 2002; Jacobson, Jacobson, Sokol, & Ager, 1993; Streissguth et al., 1990), and poor attention and executive function (Burden, Jacobson, Sokol, & Jacobson, 2005b; Coles et al., 1997; Kodituwakku, Handmaker, Cutler, Weathersby, & Handmaker, 1995), verbal learning and memory (Mattson, Riley, Delis, Stern, & Jones, 1996; O'Leary, Thomas, Molteno, Jacobson, & Jacobson, 2011; Willford, Richardson, Leech, & Day, 2004) and arithmetic (Goldschmidt, Richardson, Stoffer, Geva, & Day, 1996; Howell, Lynch, Platzman, Smith, & Coles, 2006; Jacobson, Dodge, Burden, Klorman, & Jacobson, 2011; Meintjes et al., 2010; Streissguth et al., 1991; 1994).

Children and adolescents prenatally exposed to alcohol are also more likely to exhibit parent- and teacher-reported behavioral problems (Brown et al., 1991; Carmichael-Olson et al., 1997; Jacobson et al., 2006; Larkby, Goldschmidt, Hanusa, & Day, 2011) and problems in social functioning (Lynch, Coles, Corley, & Falek, 2003; Roebuck, Mattson, & Riley, 1999). Using the Child Behavior Checklist (CBCL; Achenbach, 1991) Mattson and Riley (2000) found that children (*M* age = 8.8 yr, range 4.0-16.5) with a history of prenatal alcohol exposure exhibited more problems in internalizing and externalizing problems than in non-exposed children. Within

the internalizing problems domain, these effects were seen on the withdrawn, anxious/depressed, social problems, and thought problems scales. For externalizing problems there were higher parent ratings on aggression and delinquency. Other studies have found similar results with prenatal alcohol exposure associated with more externalizing behavior problems in childhood (D'Onofrio et al., 2007; O'Leary et al., 2009) and adolescence (Disney, Iacono, McGue, Tully, & Legrand, 2008). Lower levels of prenatal alcohol exposure were also found to predict aggression and externalizing behavior problems on the CBCL in 6- to 7-year-old children (Sood et al., 2001). Larkby and colleagues (2011) found that one or more drinks per day during the first-trimester were associated with an increased rate of conduct disorder in adolescents. Thus, behavior problems during childhood and adolescence appear to be a consistent finding in those prenatally exposed to alcohol.

Although FASD is associated with a broad range of adverse outcomes, not all children born to mothers who drink during pregnancy are affected (Abel, 1995). Experimental studies with laboratory animals have demonstrated that dose and timing of exposure are among the factors that determine vulnerability or severity of outcome associated with prenatal alcohol exposure (Bonthius & West, 1991; Goodlett, Horn, & Zhou, 2005; Jacobson, Jacobson, Sokol, & Ager, 1998; Sood et al., 2001). In addition, three maternal factors have been identified as potentially significant moderators of severity of outcome—older maternal age at delivery (Abel & Dintcheff, 1985; Carter et al., 2005; Chiodo et al., 2010; Jacobson, Jacobson, & Sokol, 1996; Jacobson et al., 2004; May, 1991), home environment and 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 in 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 most common allele encoded at the *ADH1B* locus, *ADH1B*1*, is the most prevalent form found among Caucasians and African Americans (Brennan et al., 2004). Two other polymorphisms of *ADH1B* have also been identified, *ADH1B*2* and *ADH1B*3*. Alcohol is cleared much more rapidly in individuals who are homozygous or heterozygous for either of these variants due to greater enzymatic activity of ADH, compared with individuals who are homozygous for the *ADH1B*1* allele (Bosron & Li, 1987; Thomasson, Beard, & Li, 1995). The *ADH1B*2* allele is most prevalent in Asian populations (Bosron, Magnes, & Li, 1983; Brennan et al., 2004) and has been studied in the Cape Coloured (mixed ancestry) population in the Western Cape Province of South Africa (Viljoen et al., 2001), whereas the *ADH1B*3* allele has to date been identified only in African Americans and occurs at a rate of approximately 15-20% (Bosron & Li, 1987; Brennan et al., 2004). The *ADH1B* alleles are expressed in the fetal liver beginning in the second trimester (Smith, Hopkinson, & Harris, 1971).

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 as compared to the *ADH1B*1* allele. *ADH1B*3* has a much larger K_m for ethanol, such that at low ethanol concentrations, the *ADH1B*3* allele is slower than the *ADH1B*1 allele*, but at high concentrations it is greater than 10-fold faster (Lee, Hoog, & Yin, 2004) than the *ADH1B*1* allele. Numerous studies have shown that individuals with at least one *ADH1B*2* allele (Borras et al., 2000; Carr et al., 2002; Neumark et al., 2004; Pares et al., 1992; Shea, Wall, Carr, & Li, 2001; Thomasson et al., 1991; 1994; Wall, Shea, Luczak, Cook, & Carr, 2005) or ADH1B*3 (Edenberg et al., 2006; Ehlers et al., 2007; Wall, Carr, & Ehlers, 2003) are less likely to develop alcohol use disorders and consume less alcohol on average. To date there have been no alcohol challenge studies in individuals with the *ADH1B*3* allele.

McCarver, Thomasson, Martier, Sokol, & Li (1997) were the first to study the effects of the *ADH1B*3* allele on outcomes in African-American infants exposed to alcohol *in utero*. They

found that fetal alcohol exposure was associated with reduced birth weight and lower Bayley Mental Development Index (MDI) scores in the exposed 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,* whose birth weight and Bayley MDI performance were similar to the non-exposed infants. Das, Cronk, Martier, Simpson, & McCarver (2004) found protective effects of the *ADH1B*3* allele on alcohol-related facial dysmorphology when both the mother and child had at least one copy of the *ADH1B*3* allele.

In contrast, Stoler, Ryan, & Holmes (2002) found that affected infants, defined as infants with four of six FAS facial features and/or growth deficits greater than 2 SD below the mean, were more likely to have an *ADH1B*3* allele than non-affected infants. Additionally, the presence of a maternal *ADH1B*3* allele was associated with a greater risk of having an affected infant after controlling for cigarette and weight gain during pregnancy. Although alcohol consumption was not related to infant outcome after controlling for maternal genotype, cigarette use, and weight gain, there was some evidence that more women with the *ADH1B*3* allele reported heavy alcohol use ($\geq$ 1 drink per day) during pregnancy than those without the *ADH1B*3* allele (70% vs. 44%). These findings led the authors to conclude that the increased risk of having an alcohol affected infant may have been caused by heavier alcohol consumption in mothers with the *ADH1B*3* allele in their study. As noted by Warren and Li (2005), infant observations were limited to the neonatal period, possibly reducing the chance of detecting an effect of prenatal alcohol exposure, and very few of the mothers (10 out of 108) reported heavy alcohol use ($\geq$ 1 drink per day) during pregnancy; 80 women were abstainers. Thus, there were very few drinkers in this study and more of those women had the *ADH1B*3* allele.

In the most extensive investigation of the moderating effects of the *ADH1B*3* allele to date, 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 of alcohol exposure on infant head circumference, symbolic development assessed using the Belsky, Garduque, & Hrncir (1984) elicited play measure, and infant reaction time assessed in the Haith, Hazan, & Goodman (1988) visual expectancy paradigm. At 7.5 years, protective effects of the maternal *ADH1B*3* allele 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 as reported on the Achenbach Teacher Report Form (1991), effects that were 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. With regard to teacher-reported behavior problems, increased behavior problems were seen in relation to fetal alcohol exposure in children with both allele patterns on some endpoints (aggressive behavior and impulsivity), and the effects on others, particularly inattention and delinquency, were actually stronger in the children with at least one copy of the *ADH1B*3* allele.

Aims

1. To test the hypothesis that prenatal alcohol exposure is associated with increased behavior problems during adolescence: Teachers completed the Achenbach Teacher Report Form (TRF) and the Disruptive Behavior Disorders scales (DBD). Multiple regression analysis will be used to assess the relation between prenatal alcohol exposure and teacher-reported behavior problems. Logistic regression analyses will be performed to assess the relation between prenatal alcohol exposure and DBD-based diagnoses for ADHD, oppositional defiant disorder (ODD), and conduct disorder (CD). Based on previous findings, it is predicted that prenatal alcohol exposure will be positively associated with increased behavior problems in the domains of aggression and delinquency on the TRF. It is also predicted that prenatal alcohol exposure will be related to attention problems on the DBD. In addition, the effects of prenatal alcohol exposure on teacher

ratings of adolescent behavior will be determined for each gender separately. It is predicted that prenatal alcohol exposed boys will exhibit more teacher-reported problems in aggression and delinquency.

2. To test the hypothesis that the presence of the *ADH1B*3* allele in the mother mitigates the impact of prenatal alcohol exposure on teacher-reported behavior problems during adolescence: Previous studies have shown that the presence of the *ADH1B*3* allele in the mother protects against the impact of prenatal alcohol exposure during infancy (McCarver et al., 1997; Jacobson et al., 2006) and childhood (Jacobson et al., 2006). This study will seek to extend these findings to adolescence. It is predicted that prenatal alcohol exposure will be associated with more behavior problems in adolescents born to mothers lacking the *ADH1B*3* allele. In adolescents born to mothers with the *ADH1B*3* allele, it is expected that there will be no association between prenatal alcohol and teacher-reported behavior problems, demonstrating a protective effect of the maternal *ADH1B*3* allele.

3. Analyses will also be performed to assess whether the presence of the *ADH1B*3* allele in the adolescent conveys a protective effect against prenatal alcohol exposure on the same behavioral outcomes. Data from previous studies have produced conflicting evidence regarding whether offspring genotype is protective. McCarver et al. (1997) found that infants born to mothers who drank during pregnancy had higher Bayley Mental Development index scores when the infant had a copy of the *ADH1B*3* allele than infants without a copy. However, they did not find any protective effect of infant genotype on post-partum growth. In the Jacobson et al. (2006) childhood study, no discernible protective pattern was found with regard to the child's genotype. Given these data, it is predicted that the association between prenatal alcohol exposure and teacher-reported behavior problems will be similar in adolescents with or without the *ADH1B*3* allele.

4. Gender differences in susceptibility for different behavioral problems have been well documented. How gender differences affect the association of prenatal alcohol exposure and

behavioral problems is less well understood. A separate set of analyses will be performed that will examine the relation of prenatal alcohol to teacher-reported behavior problems for males and females separately. Within each gender, possible protective effects of the *ADH1B*3* allele will also be assessed. It is predicted that prenatal alcohol exposure will be more strongly related to inattention, hyperactivity, aggression, delinquency, and externalizing problems in boys. Gender differences in the protective effect of *ADH1B*3* on prenatal alcohol are not expected.

CHAPTER 2 METHODS

Participants

The 14-year sample consisted of 200 African American mother/child dyads 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 to a large maternity hospital in inner-city Detroit. Moderate- and heavy-drinking women were overrepresented in the sample by including all women reporting alcohol consumption at conception averaging at least 1 standard drink per 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 also included. Infant exclusionary criteria included birth weight <1500 g, gestational age <32 weeks, major chromosomal anomalies, neural tube defects, or multiple births.

Assessment of prenatal exposure

At each prenatal clinic visit, the mother was interviewed using a timeline follow-back protocol (Jacobson, Chiodo, Sokol, & Jacobson, 2002; Sokol, Martier, & Ernhart, 1985). Volume was recorded for each type of beverage consumed each day, converted to oz AA, and averaged across clinic visits. At the first visit, the mother was also asked to recall her day-by-day drinking during a typical week around the time of conception. Smoking during pregnancy was reported at the first antenatal and subsequent clinic visits as average number of cigarettes/day. Detailed drug use data were also obtained at each clinic visit.

ADH genotype determination

Five drops of blood were taken by a phlebotomist from the mother by finger-stick puncture and from the child by finger-stick or venipuncture at either the 7.5- or 14-year visit 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 (Xu, Carr, Bosron, Li, & Edenberg, 1988).

14-year procedure

Mothers and adolescents were transported to the Wayne State University Child Development Research Laboratory by a community-based outreach worker. Each adolescent received a gift and a small remuneration, and the mother received a small remuneration and a photo of her child. All maternal and adolescent assessments were conducted by a research team member blind with respect to maternal alcohol and drug use. Among the adolescents originally assessed in infancy, 61.3% were followed up at 14 years, and 89.8% of these provided genetic samples. No differences in amount or frequency of drinking at around the time of conception or across pregnancy were detected between those who participated in the 14-year follow-up and those who did not (all *p*s > .15). No differences in socioeconomic status or mother's education or marital status were found between those who participated in the 14-year follow-up and those who did not; 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/primary caregiver at recruitment and at the infant and 7.5-year and 14-year assessments, and oral assent from the children at 7.5 and 14 years.

The adolescent's classroom teacher completed the Achenbach Teacher Report Form (TRF; Achenbach, 1991), which assesses behavior problems on a 112-item rating scale. Teachers are asked to indicate how true each of the items are for the student. Each item is scored on a 3-point Likert scale: 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 generated by summing all items from each scale. Additionally, a second-order factor analysis has shown that the

Withdrawn, Somatic Complaints, and Anxious/Depressed subscales form one broad-band scale called Internalizing Problems and the Delinquent Behavior and Aggressive Behavior subscales form the Externalizing Problems scale (Achenbach, 1991).

At 7.5 years, the child was rated by his/her primary caregiver, classroom teacher, and study examiner on a check list of behavioral symptoms that provide the basis for a Diagnostic and Statistical Manual (DSM) diagnosis of ADHD, using the Barkley–DuPaul ADHD Rating Scale (Barkley, 1990). At 14 years, the adolescent was rated by his/her primary caregiver, classroom teacher, and study examiner, using the Disruptive Behavior Disorders scale (DBD; Pelham, Gnagy, Greenslade, & Milich, 1992), a 45-item scale on which they rate behaviors used to diagnose attention deficit hyperactivity disorder (ADHD), conduct disorder (CD), and oppositional defiant disorder (ODD), using items derived from the DSM-IV.

A case conference was conducted to arrive at ADHD diagnoses. Symptom counts were computed separately for inattention and hyperactivity at each age by totaling how many of the nine DSM-IV behavioral criteria for each ADHD subtype were endorsed as ''often'' or ''very often'' by parent, teacher, or examiner. Participants were assigned an ADHD diagnosis following procedures developed in collaboration with R. Klorman and J. Nigg, two licensed clinicians who are widely recognized for their expertise in ADHD research. An ADHD classification was assigned if (a) at least 6 of the 9 symptoms for inattention and/or 6 of the 9 symptoms for hyperactivity/impulsivity were endorsed (''pretty much'' or ''very much'' true of child) by one or more informants at either 7.5 or 14 years, (b) some impairment (± 2 ADHD symptoms) was reported in two or more settings (operationally defined in terms of reports from at least two informants—parent, teacher, examiner), and (c) some impairment (±2 symptoms) was documented at 7.5 years. An ODD diagnosis required four unique symptoms, and CD required three. Teachers were sent a small gift for mailing back the completed TRF and DBD forms.

Potential confounders

Fourteen control variables will be considered as potential confounders: demographic background—maternal age at delivery, socioeconomic status (Hollingshead, 1975), education, and marital status of the child's primary caregiver; other prenatal exposures—maternal smoking, cocaine, and marijuana use during pregnancy; child-rearing environment—caregiver's Peabody Picture Vocabulary Test-Revised (Dunn & Dunn, 1981); current use of alcohol, hard drugs, marijuana, and cigarettes by the caregiver, and adolescent's gender and age at the laboratory visit.

Data analysis

The alcohol and drug use measures was subjected to log X + 1 transformation to reduce the undue influence of extreme outliers. The relation between prenatal alcohol exposure and child outcomes was examined by multiple regression analysis. Because a control variable cannot be the true cause of an observed deficit unless it is related both to the exposure and outcome (Schlesselman, 1982), association with either exposure or outcome can be used as a criterion for identification of potential confounders. Selection in relation to outcome has the additional advantage of including covariates unrelated to exposure, which can increase precision (Kleinbaum, Kupper, & Muller, 1988). Any control variable that is related even weakly (at $p < .10$) to a given developmental outcome will be controlled statistically as a potential confounder in all analyses of effects on that outcome.

Each continuous outcome measure was examined in hierarchical multiple regression analyses in relation to maternal drinking averaged across pregnancy along with confounders that met the criteria described above. Diagnostic outcome measures were analyzed using logistic regression analysis, with confounders entered on the second step. A prenatal alcohol effect was inferred only if the relation of pregnancy drinking to developmental outcome is significant (at $p < .05$), after adjustment for the effects of the potential confounders. The mothers and the adolescents were each be divided into two groups on the basis of the presence or absence of at least one *ADH1B*3* allele. Regressions were run separately for each of these

subgroups using the covariates that were related to the outcomes at $p < .10$ for the entire sample of 200 participants for whom allele data were available at 14 years. Additionally, separate regressions were run for each gender.

CHAPTER 3 RESULTS

Sample characteristics are summarized in Table 1. The sample is composed of 200 economically disadvantaged African-Americans (117 males; 83 females). Adolescent WISC-IV IQ scores were in the moderate to low range, consistent with those commonly found in inner-city African-American populations. At the 14-year follow-up visit, 55% of the primary caregivers reported completing <12 years of education, and 48% were in tiers IV or V (semi-skilled or unskilled workers) on the Hollingshead (1975) SES scale. Eighty-three percent of the mothers reported some alcohol use during pregnancy, and of those reporting alcohol use, 14% reported moderate-heavy amounts of alcohol (on average at least 1 drink per day across pregnancy). Sixty-two percent reported smoking during pregnancy,14% of whom reported smoking one or more packs per day. Thirty-four percent reported using cocaine during pregnancy; 50% of the users reported using cocaine at least once per month across pregnancy. Twenty-seven percent reported smoking marijuana at least once during pregnancy; 75% of these mothers did so at a rate greater than once per month.

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 adolescent sample, which is consistent with what is expected in African American populations (Bosron et al., 1983). 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. As expected, when the mother had an *ADH1B*3* allele, the child was likely to have this allele as well. Only 14 adolescents who did have the *ADH1B*3* allele had mothers who lacked the allele, indicating that the *ADH1B*3* allele in these adolescents came from their fathers.

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		
WISC-IV IQ	78.9	12.4	51.0 - 112.0
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; N = 166)	0.3	0.7	0.001 - 6.5
Cigarettes (number/day; N = 121)	15.0	10.4	1.0 - 41.0
Marijuana (days/month; N = 55)	2.8	2.6	0.2 - 15.1
Cocaine (days/month; N = 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%)		

Table 2. Convergence of maternal and child presence or absence of the *ADH21B*3 allele*

	Mother		
	Absent	Present	Total
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

X^2 (1) = 47.45, p < .001

ADH genotype and maternal alcohol consumption during pregnancy and at 14 years

Table 3 shows the effects of maternal genotype on maternal alcohol consumption during pregnancy and at 14 years. The presence of the maternal allele did not affect alcohol consumption around time of conception or across pregnancy in this sample. Nor was current maternal alcohol consumption related to the mother's *ADH1B* genotype. Neither the maternal nor child *ADH1B* allele had an effect on alcohol use by the adolescent at 14 years.

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

	Mother		
	Absent	Present	*t*
At conception	*N* = 105	*N* = 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	*N* = 105	*N* = 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	*N* = 103	*N* = 60	
Oz AA per day	0.9	1.0	0.65
Drinks/occasion	4.4	4.2	0.50
Frequency (days/week)	1.7	1.9	0.94

Effects of prenatal alcohol exposure on adolescent behavior for the total sample

Table 4 presents the analyses relating ounces of AA/day across pregnancy to teacher-reported behavior problems. Prenatal alcohol exposure was associated with increased attention problems, hyperactivity, aggression, delinquency, social problems, externalizing problems, and total problems on the Achenbach Teacher Report Form. However, after controlling for potential confounders, only externalizing problems and its two subscales, aggression and delinquency, were related to prenatal alcohol exposure for the sample as a whole. On the Disruptive Behavior

Table 4. Moderating effects of the *ADH1B*3* allele on the relation between prenatal alcohol exposure and adolescent outcome

			Maternal *ADH1B*3*						Adolescent *ADH1B*3*					
	Total sample		Absent			Present			Absent			Present		
	r	β	*N*	*r*	β	*N*	*r*	β	*N*	*r*	β	*N*	*r*	β
Achenbach Teacher Report Form (*N* = 135)														
Attention problems[a]	.17*	.09	65	.30**	.22†	47	.03	-.09	78	.18†	.18	47	.16	.04
Inattention[a]	.14†	.08	65	.26*	.20†	47	.05	-.05	78	.12	.13	47	.19	.06
Hyperactivity[a]	.19*	.10	65	.36**	.26*	47	-.02	-.15	78	.25*	.23†	47	.12	.01
Social problems[b]	.15*	.09	65	.22*	.12	47	.11	-.02	78	.19†	.18	47	.16	.07
Thought problems[c]	.01	-.004	65	.13	.13	47	-.04	-.06	78	-.02	-.01	47	.19	.16
Anxious/Depressed[d]	.03	-.001	65	.16	.12	47	-.06	-.16	78	.06	.04	47	.05	-.01
Somatic complaints[e]	.11	.03	65	.08	-.04	47	.12	.18	78	.21*	.10	47	.05	.04
Withdrawn[f]	.07	.07	65	-.06	-.06	47	.05	.05	78	.09	.09	47	.05	.05
Aggression[a]	.23**	.18*	65	.37***	.35**	47	.06	-.02	78	.30**	.30*	47	.22†	.14
Delinquency[g]	.21**	.17*	65	.17†	.11	47	.21†	.17	78	.22*	.20†	47	.28*	.17
Internalizing problems[h]	.07	.05	65	.04	.05	47	.03	.07	78	.11	.10	47	.07	.05
Externalizing problems[i]	.23**	.20*	65	.33**	.30*	47	.09	.08	78	.29**	.27*	47	.24†	.19
TRF total[a]	.20*	.14	65	.29**	.24†	47	.07	-.03	78	.25*	.24*	47	.21†	.11
Disruptive Behavior Disorders Rating Scale (*N* = 132)														
Inattention[j]	.17*	.15†	66	.29**	.27*	45	.09	.08	79	.18†	.17	43	.16	.12
Hyperactivity[j]	.16*	.11	66	.33**	.26*	45	-.02	.10	79	.26*	.22†	43	.04	.07
Oppositional defiant disorder[f]	.05	.05	66	.09	.09	45	.06	.06	79	.07	.07	43	.07	.07
Conduct disorder[k]	.03	.03	66	.17†	.14	45	-.08	-.09	79	.08	.08	43	-.11	-.15

† $p < .10$. * $p < .05$. ** $p < .01$. $^{***}p < .001$

[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

Disorders Rating Scale, prenatal alcohol exposure was associated with increased teacher-reported symptoms of inattention and hyperactivity, but only inattention was marginally associated with prenatal alcohol after control for confounders.

Table 5 presents the results of logistic regression analyses between prenatal alcohol exposure and ADHD, ODD, and CD diagnoses made from combined teacher and parent report. Prenatal alcohol exposure was associated with greater risk of positive diagnosis of ADHD-Hyperactivity subtype based on the combined parent and teacher reports. After controlling for confounders, logistic regression analysis revealed that for each 1 ounce increase in oz AA per day that the child was exposed to *in utero,* there was a greater than two-fold increase in the risk of being diagnosed with ADHD-hyperactive subtype. Prenatal alcohol exposure was not associated with risk for ADHD-inattention subtype or ODD in this cohort. After controlling for confounders, prenatal alcohol exposure was also associated with increased risk for conduct disorder.

Moderating effects of the maternal ADH1B*3 allele

Among adolescents with mothers homozygous for the *ADH1B*1* allele, prenatal alcohol exposure was associated with an increased number of total behavioral problems on the TRF; however this relation fell short of statistical significance after control for gender and prenatal cocaine exposure (Table 4). By contrast, externalizing problems on the TRF was related to prenatal alcohol exposure in those offspring whose mothers were homozygous for the *ADH1B*1* allele, even after controlling for gender. Of the externalizing problem subscales, higher ratings on the aggression scale were associated with prenatal alcohol exposure after control for confounders in those whose mothers lacked an *ADH1B*3* allele. The effects of alcohol on hyperactivity/impulsivity also persisted after control for confounders in those lacking the *ADH1B*3* allele. On the attention problems and inattention subscales, prenatal alcohol was associated with higher ratings in those born to mothers lacking the *ADH1B*3* allele, but after

Table 5. Moderating effects of the *ADH1B*3* allele on the relation between prenatal alcohol exposure and risk for behavioral disorder

	Total sample *N* = 200		Maternal *ADH1B*3*				Child *ADH1B*3*			
			Absent *N* = 105		Present *N* = 62		Absent *N* = 117		Present *N* = 69	
	OR_1	OR_2	OR_1	OR_2	OR_1	OR_2	OR_1	OR_2	OR_1	OR_2
ADHD-Inattentive[a]	1.45	1.29	2.11†	1.68	1.52	1.38	1.49†	1.33	1.40	1.36
ADHD-Hyperactive[b]	2.60**	2.29*	5.21*	3.90*	0.72	0.72	3.76**	3.10*	0.63	0.56
Oppositional Defiant Disorder[c]	1.34	1.46	1.72	1.56	0.98	1.34	1.41	1.40	1.29	2.86
Conduct Disorder[d]	1.76*	1.69*	2.69*	2.79*	1.02	0.72	1.89*	1.78*	0.45	0.40

$^{\dagger}p < .10$ $^{*}p < .05$

OR_1 = Unadjusted odds ratio OR_2 = Odds ratio adjusted for confounders

[a]Confounders: gender, socioeconomic status [b]Confounders: gender [c]Confounders: gender, cigarettes/day during pregnancy, prenatal marijuana exposure, socioeconomic status [d]Confounders: mother's age at delivery, prenatal marijuana exposure

control for gender and prenatal cocaine exposure, these associations also fell just short of statistical significance. Prenatal alcohol exposure was not related to any of the TRF measures in those whose mothers had the *ADH1B*3* allele, which is consistent with previous findings that the presence of the maternal *ADH1B*3* allele appears to protect against the effects of prenatal alcohol exposure on teacher-reported behavioral problems in children at 7.5 years (Jacobson et al., 2006).

On the Disruptive Behavior Disorders (DBD) Ratings Scale, prenatal alcohol exposure was also related to increased teacher-reported symptoms of inattention and hyperactivity only in those born to mothers homozygous for the *ADH1B*1* allele (Table 4). By contrast, in children born to mothers who had at least one *ADH1B*3* allele, prenatal alcohol exposure was not related to these teacher-reported symptoms of ADHD on the DBD.

Among those born to mothers lacking the *ADH1B*3* allele, prenatal alcohol exposure was associated with increased risk for ADHD-hyperactivity and conduct disorder, even after control for confounders (Table 5). This association between prenatal alcohol exposure and ADHD-Hyperactivity was particularly strong, with each 1 ounce increase in AA/day across pregnancy corresponding to an almost 5-fold increase in the risk for ADHD-Hyperactivity. In children born to mothers with the *ADH1B*3* allele, alcohol exposure was no longer associated with risk for behavioral disorders, suggesting a protective effect of the allele on adolescent behavioral disorders.

Moderating effects of the child ADH1B allele on the relation between prenatal alcohol exposure and adolescent behavior

Among adolescents lacking the *ADH1B*3* allele, prenatal alcohol exposure was associated with hyperactivity, aggression, externalizing problems, and total problems on the TRF, after controlling for confounders. In adolescents with the *ADH1B*3* allele, these effects were reduced, indicating that similar to the pattern of moderating effects of the maternal genotype, presence of the *ADH1B*3* allele in the adolescent appeared to convey a protective

effect against prenatal alcohol exposure on teacher-reported behavioral problem in hyperactivity, aggression, and externalizing problems, although this effect was less pronounced (Table 4). Risk for ADHD-Hyperactivity and conduct disorder diagnosis were related to prenatal alcohol exposure in adolescents lacking the *ADH1B*3* allele, but the presence of the allele only appeared to convey a protective effect on risk for ADHD-Hyperactivity (Table 5).

Moderating effects of gender

Because there are gender differences in the incidence of certain behavior problems during adolescence, the effects of prenatal alcohol exposure on teacher-reported behavior problems was assessed separately for boys and girls (Table 6-7). Among boys, prenatal alcohol exposure was associated with hyperactivity, social problems, aggression, delinquency, externalizing problems and total problems after control for confounders (Table 6). For girls only, prenatal alcohol exposure was associated with more somatic complaints after controlling for confounders (Table 7).

Among boys, the presence of a maternal *ADH1B*3* allele conveyed a protective effect of prenatal alcohol exposure on teacher-reported problems in the domains of attention, hyperactivity, aggression, externalizing problems and total problems (Table 6). Among girls, the presence of a maternal *ADH1B*3* allele conveyed a protective effect of prenatal alcohol exposure on inattention symptoms from the DBD (Table 7).

Table 6. The relation of prenatal alcohol exposure to teacher-reported behavior problems among boys

	Total sample (Boys only)		Maternal allele				Child allele			
			Absent		Present		Absent		Present	
	r	β	*r*	β	*r*	β	*r*	β	*r*	β
Achenbach Teacher Report Form	*N* = 79		*N* = 38		*N* = 27		*N* = 47		*N* = 26	
Attention problems	.16†	.13	.31*	.28	-.03	-.12	.17	.23	.25.	.21
Inattention	.12	.11	.27†	.27	-.04	-.13	.10	.18	.29†	.17
Hyperactivity	.20*	.16	.36*	.30†	-.01	-.12	.25*	.28†	.22	.17
Social problems	.17†	.19	.28*	.23	.09	.07	.17	.23	.31†	.45†
Thought problems	-.02	.002	.09	.13	-.01	-.02	-.08	-.01	.27†	.27
Anxious/Depressed	.04	.04	.21	.26	-.02	-.02	.04	.02	.12	.15
Somatic complaints	.07	-.03	.04	-.10	-.03	.01	.16	.05	-.01	-.08
Withdrawn	.07	.07	-.12	-.12	-.002	-.002	.07	.07	.09	.09
Aggression	.30**	.28*	.44**	.46**	.18	.16	.37**	.40*	.38*	.35†
Delinquency	.19*	.18	.18	.11	.12	.09	.21†	.21	.28†	.24
Internalizing problems	.06	-.01	.05	.11	-.01	.09	.09	.01	.11	.002
Externalizing problems	.29**	.29*	.39**	.39*	.17	.17	.34**	.34*	.38*	.38†
TRF total	.22*	.20†	.31*	.30†	.08	.02	.27*	.31†	.34*	.31
DBD Rating Scale	*N* = 77		*N* = 38		*N* = 27		*N* = 47		*N* = 26	
Inattention	.15†	.15	.26†	.26	.09	.09	.14	.14	.30†	.30
Hyperactivity	.22*	.19	.39**	.34†	.10	.12	.32*	.30†	.12	.11
Oppositional defiant disorder	.11	.11	.14	.14	.26†	.26	.13	.13	.22	.22
Conduct disorder	.11	.10	.27†	.20	.10	.10	.14	.14	-.02	-.08

† $p < .10$. * $p < .05$. ** $p < .01$. *** $p < .001$

Table 7. The relation of prenatal alcohol exposure to teacher-reported behavior problems among girls only

	Total sample (Girls only)		Maternal allele				Child allele			
			Absent		Present		Absent		Present	
	r	β	*r*	β	*r*	β	*r*	β	*r*	β
Achenbach Teacher Report Form	*N* = 56		*N* = 27		*N* = 20		*N* = 31		*N* = 21	
Attention problems	.04	.02	.17	.15	.02	-.03	.14	.12	-.22	-.31
Inattention	.06	.05	.15	.14	.12	.10	.13	.12	-.21	-.26
Hyperactivity	-.02	-.05	.18	.17	-.15	-.23	.13	.11	-.22	-.36†
Social problems	-.003	-.06	.02	.05	.10	.03	.13	.14	-.08	-.13
Thought problems	.03	-.01	.26†	.23	-.28	-.19	.18	.15	-.20	-.22
Anxious/Depressed	-.06	-.17	-.02	-.12	-.13	-.18	.03	-.08	-.11	-.19
Somatic complaints	.28*	.29*	.20	.21	.36†	.37	.45**	.44*	.16	.22
Withdrawn	.05	.05	.06	.06	.15	.15	.15	.15	-.21	-.21
Aggression	-.15	-.18	-.11	-.11	-.20	-.29	-.18	-.19	-.17	-.33†
Delinquency	.17	.17	.04	.06	.34†	.34	.21	.21	.10	.07
Internalizing problems	.04	.02	.03	.000	.06	.10	.15	.11	-.10	-.04
Externalizing problems	-.09	-.09	-.07	-.07	-.11	-.11	-.07	-.07	-.14	-.14
TRF total	-.01	-.03	.06	.05	-.04	-.10	.09	.07	-.18	-.30
DBD Rating Scale	*N* = 55		*N* = 28		*N* = 20		*N* = 32		*N* = 19	
Inattention	.14	.14	.31†	.31†	.06	.06	.30*	.30†	-.26	-.26
Hyperactivity	-.17	-.19	-.04	-.08	-.30	-.14	-.20	-.24	-.19	-.20
Oppositional defiant disorder	-.15	-.15	-.07	-.07	-.23	-.23	-.16	-.16	-.17	-.17
Conduct disorder	-.10	-.09	-.003	.05	-.19	-.18	-.05	-.04	-.17	-.23

† $p < .10$. * $p < .05$. ** $p < .01$. *** $p < .001$

CHAPTER 4 DISCUSSION

This is the first study to examine the moderating effects of the *ADH1B* genotype on the relation between prenatal alcohol exposure and behavioral outcomes during adolescence. In the sample as a whole, prenatal alcohol exposure was related to teacher-reported behavior problems in aggression, delinquency, and externalizing behaviors. These findings are consistent with a previous study that found that even low levels of prenatal alcohol exposure are associated with increases in aggression and externalizing problems in adolescents on the parent-reported CBCL (Sood et al., 2001). The presence of the *ADH1B*3* allele in the mother conveyed a consistent protective effect against prenatal alcohol exposure during adolescence on all those endpoints affected by alcohol, especially among boys. These findings are consistent with our previous report showing that the presence of the maternal *ADH1B*3* allele protected against fetal alcohol-related impairments in infancy and at 7.5 year (Jacobson et al., 2006) and with previous infant studies examining this allele (Das et al., 2004; McCarver et al., 1997).

The mechanism by which this maternal allele conveys this protective effect against prenatal alcohol exposure is not clearly understood. One possible explanation is that the presence of the *ADH1B*3* allele may cause mothers to drink less due to higher levels of acetaldehyde that build-up. 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 in our sample the protective effects of the *ADH1B*3* allele are likely not due to reductions in pregnancy drinking. Alternatively, although the amount of alcohol consumed may be similar, peak blood alcohol concentrations may be blunted in those with the *ADH1B*3* allele as compared to those homozygous for the *ADH1B*1* allele due to the rapid metabolism of alcohol conveyed by the *ADH1B*3* allele. This mechanism would lead to lower concentrations of alcohol reaching the fetus in mothers with the *ADH1B*3* allele, thus reducing the impact of 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 hyperactivity that were not evident in the initial analysis of the data for the sample as a whole. A similar, but less pronounced pattern of protective effects on teacher-reported behavioral problems were also seen in adolescents with the *ADH1B*3* allele. It is unclear, however, whether this protective effect may have been due to the maternal protective allele, which these adolescents would have inherited (Table 2), since 70% of adolescents with the *ADH1B*3* allele also had mothers with the allele.

As with previous studies (Jacobson et al., 2006; McCarver et al., 1997), a less consistent pattern was found between adolescents with or without the *ADH1B*3* allele. This lack of a clear moderating effect from the adolescent *ADH1B* genotype could be due to a number of factors. Unlike the maternal *ADH1B*3* allele which would be expressed throughout the pregnancy, the fetal *ADH1B* genes are not expressed until the second trimester (Smith et al., 1971). Thus, these alleles in the fetus may only exert their metabolic effects on alcohol consumption from the second trimester onward. Previous research on this cohort indicated that mothers reported drinking 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). These data suggest that the fetal *ADH1B* alleles may not have the full opportunity to convey an effect on outcome since they are only expressed later on in the pregnancy when alcohol consumption has decreased.

The presence of a more efficient *ADH1B* allele conveys a protective effect against prenatal alcohol exposure that persists well into adolescence. While the mechanism for this protection may not be clearly understood, one possibility is that the presence of a maternal *ADH1B*3* allele may limit the amount of alcohol that enters the fetal blood stream. Further 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 suggest that the variant also plays a protective role in heavily exposed mother-infant dyads.

When gender was included as a moderator, the majority of alcohol-related effects on teacher reports of adolescent behavior were seen in boys in the domains of externalizing behaviors. These findings are consistent with previous studies that found that boys are more likely than girls to exhibit externalizing problems, such as aggression and delinquency, (Lahey et al., 2000; Zahn-Waxler, 1993) and that boys are generally at greater risk for ADHD, ODD and CD (Biederman et al., 2002; Faraone et al., 1995; Maughan, Rowe, Messer, Goodman, & Meltzer, 2004; Wakschlag et al 1997). Similar to the analyses including both genders, the presence of a maternal *ADH1B*3* allele conveyed a protective effect on teacher-reported behavior problems among boys.

The impact of alcohol exposure on externalizing behaviors and the protective effect of the maternal *ADH1B*3* allele emerged substantially more strongly when moderating effects of gender were considered. The magnitude of the effects is relatively weak for the whole cohort, presumably because those analyses included girls who were exposed but either unaffected, less likely to express behavioral problems in this domain, or exhibit these symptoms in a less disruptive manner, which may not be noted or reported by teachers. By contrast, the modest effects seen on these behaviors in the cohort as a whole emerged as a strong effect in boys. From both a clinical and scientific point of view, the examination of these and other important moderators may help to better identify which children are affected and understand the nature of their disability more clearly.

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ABSTRACT

PROTECTIVE EFFECTS OF THE ALCOHOL DEHYDROGENASE-*ADH1B* ALLELE ON BEHAVIOR PROBLEMS IN ADOLESCENTS EXPOSED TO ALCOHOL DURING PREGNANCY

by

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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 African Americans, 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 African American infants and children. This study was conducted to determine whether the presence of the *ADH1B*3* allele in the mother or fetus continues to be protective in alcohol-exposed individuals during adolescence. 186 adolescents and 167 mothers participating in the 14-year follow-up of the Detroit Longitudinal Cohort had been genotyped for *ADH1B* alleles. The frequencies of the *ADH1B*3* allele were 17.6% in the mothers and 21.0% in the adolescents, which are consistent with the 22% expected for the African American population. Confirming previous studies, 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. The presence of an *ADH1B*3* allele in the adolescent conveyed a less pronounced protective effect against fetal alcohol-related deficits at this age. This study is the first to demonstrate that the protective effects of the maternal *ADH1B*3* allele continue to be

evident during adolescence and suggests that differences in alcohol metabolism genes may help account for individual differences in the vulnerability of offspring to the effects of fetal alcohol exposure. The protective effect of the maternal *ADH1B*3* allele may be due to the more rapid metabolism of alcohol that it confers on the mother, which presumably results in a reduction of the peak blood alcohol concentration to which the fetus is exposed during each drinking episode.

AUTOBIOGRAPHICAL STATEMENT

Neil C. Dodge was born in Grosse Pointe, MI on October 10, 1981. He is married to the most beautiful woman in the world, Kathryn Dodge. Rumor has it that Neil C. Dodge reached the South Pole two days before Roald Amundsen did on December 14, 1911 but promptly decided to leave before planting his flag pole because it was “pretty cold”. Neil C. Dodge enjoys many things including life, liberty, the pursuit of happiness, and tacos.