IS HEAVY 1st TRIMESTER PRENATAL ALCOHOL EXPOSURE ASSOCIATED WITH AN INCREASED INCIDENCE OF ONE OR MORE SUBTYPES OF OFFSPRING CONDUCT DISORDER?

by

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ABSTRACT

Children with prenatal alcohol exposure (PAE) tend to show higher rates of conduct disorder (CD), even after the effect of some potentially confounding factors, including parental alcoholism, parental drug abuse, and externalizing disorder, have been taken into account. It is clear that some subgroups of CD may show distinct developmental pathways; for instance, the use of construct of psychopath for subtyping CD children has grown and some research has highlighted a distinction between callous-unemotional traits and highly-impulsive traits. As more and more studies have examined the relationship between PAE and the occurrence of CD, some important questions have been raised. The objective of this study is to determine whether PAE is associated with a specific subtype of CD, or if it is equally associated with both highly impulsive and the callous-unemotional forms of diagnosis.

The National Institute of Mental Health Diagnostic Interview Schedule for Children- 4th Edition (DISC-IV) was used to assess the psychiatric disorders and symptoms of 572 children with PAE. Among these 572 children, 67 met the criteria for lifetime diagnosis of CD. We collapsed these children into three groups based on the levels of PAE (unexposed, lightly

exposed, heavy exposed). The analyses were conducted to examine the difference of each CD symptoms and clinical information of children.

The results suggest that while most of the CD symptoms and clinical information were similar among three groups, the differences of both domains of social impairment and psychiatric treatment in the twelve months preceding the diagnostic interview were statistically significant. Based on the outcome of the analyses, 1^{ST} trimester PAE is associated with an observable increase in the incidence of both callous-unemotional and highly-impulsive subtypes of children with CD, rather than being associated with one or the other of these two subtypes. We would conclude that the CD children with PAE or non-PAE show a similar range of clinical symptoms and subtypes. For public health significance, this might be helpful information for clinicians and public health officials when they discuss the diagnoses or issues about children with PAE. This information may also assist researchers to build an individual and comprehensive intervention for different subtypes of conduct disorder in children.

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1.0 INTRODUCTION

1.1 BACKGROUND

In a number of population-based epidemiological studies (Larkby and Day 1997; Hill, Lowers et al. 2000; Fryer, McGee et al. 2007; Disney, Iacono et al. 2008; Staroselsky, Fantus et al. 2009), researchers demonstrated that children or adolescents with prenatal alcohol exposure (PAE) have an elevated risk of conduct disorder (CD). The studies show that PAE is an important and independent risk factor for predicting CD, and that it has an association with CD diagnosis. According to previous studies (Fryer, McGee et al. 2007; Staroselsky, Fantus et al. 2009), about 90% of individuals with PAE have psychiatric problems, including Attention Deficit Hyperactivity Disorder (ADHD), depression, bipolar disorder or CD. Recent studies (Larkby and Day 1997; Disney, Iacono et al. 2008) further indicated that PAE had a direct effect on the rates of CD, even after the effect of some potentially confounding factors, including parental alcoholism, parental drug abuse, and externalizing disorder, have been taken into account.

1.2 CONDUCT DISORDER (CD)

CD is a form of childhood psychopathology in which the child repetitively and persistently violates the basic rights of other or major age-appropriate societal norms or rules (Frick 2006). Based on the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) diagnostic criteria for CD, children who meet the criteria for CD must demonstrate at least three of the following behaviors over the previous 12 months, with at least one criterion present in the past six months: (1) Aggression toward people and/or animals: often bullies, threatens, intimidates others, initiates physical flights, uses weapons to cause serious physical harm to others, shows physically cruelly toward people and animals, steals while confronting a victim, forces people into sexual activity. (2) Destruction of property: deliberately engages in fire to cause serious damage, deliberately destroys others' property. (3) Deceitfulness or theft: breaks into someone else's house, building or car, lies to obtain good or favor or to avoid obligations. (4) Serious violation of rules: stays out at night against parents wish before age 13, runs away from home overnight, often truants from school (Sterzer, Stadler et al. 2005; Frick 2006; Frick and Dickens 2006; Vloet, Konrad et al. 2008).

Studies show that there are several risk factors for CD. The risk factors include characteristics of the child (neuropsychological deficits, autonomic irregularities, and temperamental traits), family history of mental health disorders, low socioeconomic status, poor parenting, parental alcoholism, peer rejection and neighborhood disorganization (Frick and Dickens 2006; Frick and White 2008).

It has also became clear that there are subgroups of CD that may show distinct causal processes (Dandreaux and Frick 2009). Nowadays, the use of the construct of psychopathy for

subtyping CD children has grown, and some research has highlighted a useful distinction between callous-unemotional traits and highly-impulsive traits (Dolan 2008; Dandreaux and Frick 2009). Children with callous-unemotional traits are the main demographic of childhood-onset group (Langbehn and Cadoret 2001; Frick 2006), which had their first symptoms before age 10 and tend to show persistently higher rates of neuropsychological dysfunction (Moffitt 1993; Moffitt and Lynam 1994; Frick and Ellis 1999; Dandreaux and Frick 2009). Children in this subtype seem to show severe and aggressive patterns of behavior(Frick 2006), a lack of empathy and guilt, and are more persistent and less reactive to threatening and emotional stimuli (Vloet, Konrad et al. 2008). Children in the highly-impulsive subtype are more associated with adulthood-onset group, who had their first CD symptom after age 10 (Dolan 2008; Frick and White 2008). They often show a high level of impulsivity, rebelliousness, are highly reactive to emotional stimuli, and are more affiliated with delinquent peers (Frick and Ellis 1999; Frick and Dickens 2006). Children in this subtype are less likely to have persistent CD or to develop adult antisocial personality disorder (American Psychiatric Association 1994).

Both the callous-unemotional and highly-impulsive subtypes show impaired emotional regulation. According to the previous studies (Crowe and Blair 2008; Dolan 2008; Marsh, Finger et al. 2008; Yang, Glenn et al. 2008), amygdala-hippocampal and prefrontal cortex dysfunction may be linked to poor fear conditioning and impaired emotional regulation. These investigators suggest that the two subtypes are grounded in different types of structural and functional neurobiological disturbances affecting amygdala-ventromedial prefrontal cortex circuitry and parts of the limbic system (amygdale, hippocampus) (Vloet, Konrad et al. 2008; Yang, Glenn et al. 2008). When responding to threat-or fear related stimuli, the highly-impulsive CD subtype shows up-regulation of various components of the limbic system (amygdale, hippocampus) and

regulatory deficits in the prefrontal circuitry, while the callous-unemotional CD subtype shows down-regulation of the same limbic system and has fewer regulatory deficits in prefrontal circuitry.

1.3 PRENATAL ALCOHOL EXPOSURE (PAE)

Since the formal effects of prenatal alcohol exposure (PAE) were identified in the 1970s, it has been recognized that PAE is associated with a wide range of deleterious effects on offspring even for light maternal drinking (Jones and Smith 1973; Hill, Lowers et al. 2000; Kellerman 2008). Fetal Alcohol Syndrome (FAS), first defined by Jones and Smith (1973), denotes a triad of characteristics: (1) evidence of central nervous system (CNS) dysfunction; (2) facial abnormalities, including indistinct philtrum, thin upper vermilion border(lip) and small palpebral fissures (eye openings); and (3) pre-and/or postnatal growth retardation. FAS is not the only consequence of PAE. Other deficits include, cognitive dysfunction(Jones and Smith 1973; Streissguth 1989; Streissguth 1990; Russell, Czarnecki et al. 1991; Olson 1992), executive function deficits (Mattson, Goodman et al. 1999; Guerri, Bazinet et al. 2009), impairments in reaction time, attention and memory (Streissguth, Barr et al. 1986; Brown, Coles et al. 1991; Jacobson, Jacobson et al. 1993; Streissguth, Sampson et al. 1994; Streissguth 1995), verbal and visuospatial learning impairments(Willford, Richardson et al. 2004), behavioral disturbance (Nanson and Hiscock 1990; Olson 1992), difficulties in peer relationships (Steinhausen 1982) and social problems (Riley and McGee 2005). Fetal Alcohol Spectrum Disorders (FASD) includes a wide range of effects that are caused by PAE, including FAS, Alcohol Related

Neurodevelopmental Disorder (ARND) and other disorders (Clarke and Gibbard 2003; Riley and McGee 2005).

According to recent studies (Riley, McGee et al. 2004; Bookheimer and Sowell 2005; Barr, Bookstein et al. 2006; McGee and Riley 2006), the brain is the most vulnerable and sensitive organ to PAE. The dysfunctions in the brain include the functional and/or structural alteration on corpus callosum, basal ganglia, prefrontal cortex, and cerebellar anomalies (Clarren 1986; Riley and McGee 2005). These changes in the brain contribute the most significant impact on the lives of the children with PAE (Riley and McGee 2005) and can lead to damages including cognitive and behavioral deficits (Griesler and Kandel 1998; Spadoni, McGee et al. 2007).

About 80% of the children with PAE have behavioral and cognitive problems from infancy through adolescence (Olson, Streissguth et al. 1997; Guerri 1998; Pediatrics 2000 Aug; Bailey, Delaney-Black et al. 2004; O'Leary 2004; Riley, McGee et al. 2004; Green 2007; Spadoni, McGee et al. 2007). Studies have demonstrated that the children with PAE showed behavioral impairments include attention deficits (Streissguth, Barr et al. 1994; Baer, Barr et al. 1998; Mattson, Goodman et al. 1999; D'Onofrio, Van Hulle et al. 2007), social skill deficits (McGee, Fryer et al. 2008), emotional control problem (Coles, Kable et al. 2000), conduct problems (D'Onofrio, Van Hulle et al. 2007), depression, oppositional defiant disorder, hyperactivity disorder (Fryer, McGee et al. 2007; Guerri, Bazinet et al. 2009)**,** anxiety disorder, aggression, inappropriate sexual behavior (Green 2007), lying, stealing, and bullying (Clarke and Gibbard 2003).

1.4 HYPOTHESIS

As studies have examined the relationship between PAE and the occurrence of CD, some important questions have been raised. Is it not clear whether PAE is associated with a specific subtype of CD, or if it is equally associated with both highly-impulsive and the callous-unemotional forms of diagnosis.

In this study, we will compare the clinical symptoms and characteristics between CD children with and without PAE. The aim of this study is to explore whether different levels of PAE affect the pattern of symptoms, course, and outcome of the clinical information. We will distinguish whether the PAE and non-PAE children show different clinical symptoms and CD subtypes, or if both of PAE and non-PAE children show a similar range of clinical profiles and CD subtypes. Our specific null and alternative hypotheses are:

H_o: CD children in our sample are clinically heterogeneous between different levels of prenatal alcohol exposure groups and homogeneous within groups.

H_a: CD children in our sample are clinically homogeneous between different levels of prenatal alcohol exposure groups and heterogeneous within groups.

While different developmental pathways of CD have been discussed in previous research, it is important to note that the clear difference between the developmental pathways still has not been found (Dandreaux and Frick 2009). Children with PAE show higher rates of CD. Therefore, the understanding of the association between PAE and the increasing incidence of one or more subtypes of offspring CD is critical and can contribute to the development of intervention strategies for these children.

2.0 METHOD

2.1 STUDY DESIGN

The participants of this study are drawn from the Maternal Health Practices and Child Development Project (MHPCD), a prospective study of children and their mothers who have been observed over 20 years. The MHPCD project collects a wide range of information including demographic status, maternal psychosocial characteristics, lifestyle environment, and children's behavioral, neuropsychological growth and academic status to investigate the effects of prenatal exposure to alcohol, tobacco, marijuana and other drugs on the growth, behavioral and cognitive development of the offspring (Willford 2004).

This longitudinal study recruited women who attended the prenatal clinic at Magee Woman's Hospital in Pittsburgh, Pennsylvania between May 1982 and July 1985 (Day, Leech et al. 2002). Two study cohorts were selected from this group, based on the consumption of alcohol and marijuana in the first trimester: (a) Women who averaged three or more drinks per week in the first trimester and a random sample of one third of the women who drank alcohol less often or not at all were selected. (b) Women who used marijuana during the first trimester at the rate of two or more joints per months and a random sample of women who used less than this amount or none at all (Day, Leech et al. 2002). Women can be in either or both of the cohorts. Women

selected for the study were assessed for their substance use during each trimester (fourth, seventh prenatal month, and at delivery) of their pregnancies. Follow-up of the women and their offspring took place when the children were aged 8 and 18 months, and 3, 6, 10, 14 and 16 years. A 22-year follow-up is ongoing (Day and Richardson 2004; Willford, Richardson et al. 2004; Seto, Cornelius et al. 2005; Leech, Larkby et al. 2006; Cornelius, Goldschmidt et al. 2007; Rubio, Kraemer et al. 2008).

2.2 SUBJECT SELECTION

Initially, 829 women from two cohort groups were interviewed in their fourth month of pregnancy (Day and Richardson 2004). However, 763 women total were investigated at delivery. Some women dropped out before the delivery, including 16 women who were lost in the follow-up, 21 women who moved to other places, 8 who women refused the interview and examination at delivery, 2 women who had multiple-births, 1woman whose child was adopted and 18 women who had fetal deaths. During the ongoing follow-up, 51 women moved to other countries, 69 women were lost to follow-up, 3 women lost custody, 6 children were adopted, institutionalized or fostered and 4 children died. In this paper, 572 children who completed a DISC-IV structured clinical interview at the 16-year follow up will be used in the data analysis (Day and Richardson 2004; Willford, Richardson et al. 2004; Seto, Cornelius et al. 2005; Leech, Larkby et al. 2006; Cornelius, Goldschmidt et al. 2007; Rubio, Kraemer et al. 2008).

2.3 SUBJECT DESCRIPTION

Women who were at least 18 years old were recruited for the study. They were healthy and of lower socioeconomic status (Day and Richardson 2004). The average age of women was 23 years old (SD, 4.0 years, range 18 to 42 years) at recruitment, 60% of them had a high school diploma and 62% came from families had less than $400 income per month. Forty-three percent of the women were married. The mean alcohol consumed in the first trimester was 0.6 drinks per day (range from 0 to 20).

The 572 children in our sample consist of 303 (53%) females and 269 (47%) males, 45% Caucasian and 55% were African American. Based on the report of the DISC-IV, among these 572 offspring, 67 of them met the criteria for lifetime diagnosis of CD. Within the CD group, 40(60%) of them were male and 27 (40%) of them were female. The average age of the DISC-IV interviews was 16.9 years for males and 16.9 years for females.

2.4 MEASURE

For each interview at each phase, mothers' demographic characteristic and psychological status, current environment, medical history and used of alcohol, tobacco, marijuana and other drugs were collected. The growth, behavioral, psychological, physical and cognitive developments of children would also be assessed (Day, Leech et al. 2002; Day and Richardson 2004; Leech, Larkby et al. 2006).

Measurement of Clinical Information

DISC-IV. The National Institute of Mental Health Diagnostic Interview Schedule for Children – 4th Edition (" NIMH-DISC-IV" or "DISC-IV") was used to assess the clinical information for this study. DISC-IV is a highly structured diagnostic interview to assess more than 30 psychiatric disorders and symptoms in children and adolescents aged 6 to 18 years. DISC-IV is the most widely used and studied mental health interview that has been supported in both clinical and community population. The interview covers all common mental disorders of children and adolescent and is organized into six diagnostic sections: Anxiety Disorders, Mood Disorders, Disruptive Disorders, Substance-Use Disorders, Schizophrenia, and Miscellaneous Disorders.(David Shaffer; Association 1994; Schwab-Stone, Shaffer et al. 1996; Lahey, Loeber et al. 1998; Shaffer, Fisher et al. 2000; Roberts, Parker et al. 2005). All of the clinical information was drawn from the computerized DISC-IV records. The vast majority of variables (e.g., symptom counts, age at onset, duration of illness, lifetime and current diagnoses, treatment, co-morbid diagnoses, etc.) were taken from the Washington University SAS program used to interpret the raw data from DISC-IV interviews. In a small number of cases (e.g., lifetime and current impairment) we went back to the raw data recorded in the DISC-IV interview forms in order to obtain additional detail that was not available through the Washington University program.

Measurement of Alcohol Use

Substance use was assessed with an instrument developed for the MHPCD for each trimester of pregnancy (Day and Robles 1989). In the first trimester, marijuana and alcohol use were

examined for each month, while for second and third trimesters, assessment was over the entire trimester.

The alcohol use variable is Average Daily Volume (ADV) which measures the average number of drinks per day (dpd). The instrument created by Dr. Day and Dr. Robles (Day and Robles 1989) allows for the calculation of quantity, frequency, minimal and maximal intake on ADV. ADV is defined as

(number of drinks/week) × (4 weeks/month) / 31days/month

Subjects further can be categorized into four groups based on ADV: abstainer, no alcohol use during the trimester (ADV=0); light, fewer than 1.5 drinks per week (ADV>0, and ≤0.2); moderate, 1.5 drinks per week to less than one drink per day (ADV>.2, and ≤0.89); and heavy, one or more drink per day (ADV>0.89). The cut-point ADV>0.89 defines the level of one drink per day (Griesler and Kandel 1998; Schonfeld, Mattson et al. 2005; Rubio, Kraemer et al. 2008).

A prior study by Larkby et al.(Larkby and Day 1997) found that the incidence of CD was strongly associated with heavy prenatal drinking behavior (>.89 drinks per day, dpd) during the 1st trimester of pregnancy. Assuming a causal role for 1st trimester PAE, the data in Table 1 suggest an attributable risk proportion (or etiological fraction, Rothman 1986) of approximately 55% for both the male and female subjects with the highest PAE exposure (>.89 dpd) when compared to the rates observed in the unexposed group (0 dpd). Based on this finding, the clinical information in the *Result* section will be stratified into three 1st trimester PAE groups: Group0 (0 dpd), Group1 (>0 and ≤.89dpd) and Group2 (>.89 dpd). The sample size in Group0 is 22, Group1 is 21 and Group2 is 24.

Table 1. Conduct Disorder (CD) Incidence Rates in n=572 Offspring by Gender and Prenatal Alcohol Exposure (PAE) During the 1st Trimester of Pregnancy

PAE Group and Gender	CD/PAE Group	CD n	Person Years	Incidence per 1000 person years	Exact 95% CI
Males	Group 0: CD+non-PAE	13	1799	7.2	3.9-12.3
	Group 1: CD+≤.89 dpd	14	1736	8.1	4.4-13.5
	Group 2: CD+>.89 dpd	13	845	15.4	8.2-2.62
Females	Group 0: CD+non-PAE	9	1575	5.7	2.6-10.8
	Group 1: CD+≤.89 dpd	7	2580	2.7	1.0-5.6
	Group 2: CD+>.89 dpd	11	810	13.6	6.8-2.4
All	Group 0: CD+non-PAE	22	3374	6.5	4.1-9.9
	Group 1: CD+≤.89 dpd	21	4361	4.9	3.0-7.4
	Group 2: CD+>.89 dpd	24	1655	14.5	9.3-21.5

Child and Mother Characteristics

Children were assessed for psychosocial, behavioral and physical characteristics. The number of injuries, illness and hospitalizations were recorded by mothers for all the phases. Mothers reported their substance use at each phase, education, employment status, monthly household income and marital status at each interview.

Environment Characteristics

Current environment was measured using variables that covered multiple domains. Demographic variables included maternal age, work status, and income. In addition, to evaluate social support and environment, women were asked about the number of individuals available in their social network and about their recent life events. These instruments were adapted for the

study from an instrument used in the HUMAN Population Laboratory studies and from the PERI (Willford, Richardson et al. 2004).

2.5 DATA ANALYSIS

For this study, we paid more attention to exploration rather than testing hypothesis, meaning that the multiple tests of significance based on vaguely stated a priori hypotheses were carried out and PAE groups were combined or recombined in a number of ways in order to produce potentially informative results.

We used SAS and SPSS to perform the following analyses:

(1) For CD clinical information:

a. *Descriptive analysis*. We compared the mean, median and frequency for the clinical information variables among three groups.

b. *CD symptom severity rank.* We compared the mean and median of the severity rank of CD symptoms among three groups. CD symptoms were ranked according to the level of severity based on Gelhorn et al. (Gelhorn, Hartman et al. 2009). The Gelhorn et al. methodology (Item Response Theory analysis, Bock et al., 1988) uses symptom endorsement patterns as a way of modeling individual diagnostic criteria. It serves as a supplementary method of assessing illness severity, along with symptom counts and other variables (e.g., impairment levels and persistence).

Table 2. The Severity Rank of the Symptoms

Severity Rank	Symptom Description	Severity Rank	Symptom Description
1	Stealing: non-confront	9	Fights with others
2	Destruction of property	10	Out late at night
3	Lies	11	Cruel to people
4	Bullying others	12	Runs away
5	Breaking and Entering	13	Stealing: with confront
6	Cruel to animals	14	Setting fires
7	Used weapons		
8	Truant		

c. We clustered the DISC-IV data into these four clusters and compare the (occurrence) endorsement of each PAE groups in the four clusters.

Frick and Ellis (Frick and Ellis 1999; Loney, Frick et al. 2003) proposed four clusters of conduct problems based on a Meta-analysis of over 60 published factor analyses on approximately 28,401 children and adolescents. The cluster patterns are useful because the clusters can distinguish between children with only a single type of CD from those who show more than one pattern of CD and it is consistent with the distinctions for delineating types of delinquent behaviors.

The four clusters were: (1) Property Violations, including cruelty to animals, lying, arson, theft, vandalism; (2) Aggression, including assault, blaming others for mistakes, bullying others, cruelty to others, physical fighting, vindictiveness; (3) Covert Status Offenses, including rule breaking, running away from home, swearing, truancy; (4)

Oppositional Overt, including anger-resentment, annoying others, arguing with adults, defying adults' requests, stubborn, temper tantrums, touchiness/easily annoyed (Frick and Ellis 1999).

d. The chi-squared test or Fisher's exact test were used to evaluate the difference between two groups. We combined the non-PAE group and PAE≤.89 dpd group together and compared to the PAE>.89dpd groups. P-values were not adjusted for multiple comparisons, since it's not clear that the available procedures are particularly meaningful within this kind of analytic framework (Rothman 1990; Perneger 1998).
e. We performed ANOVA to test the difference of the clinical information if the variables meet the normal distribution. If they violate the normality assumption, Krusal-Wallis test was performed to test the differences among the three groups.
f. We also performed the logistic regression analyses to obtain odds ratio (OR), relative risk (RR) and the 95% confidence interval of OR and RR.

(2) Incidence rates were calculated of different levels for alcohol exposure for CD variables.

3.0 RESULTS

3.1 SYMPTOM FREQUENCY, COUNT AND MAXIMUM SEVERITY

Table 3 summarizes the frequency with which each of the 15 specific symptoms in the DISC-IV occur in children with lifetime diagnoses of conduct disorder in each of our three 1st trimesters PAE groups.

Table 3. Frequency (over the lifetime) of Symptom Endorsement among Conduct Disordered Children by Prenatal Alcohol Exposure (PAE) Group

Severity Rank	DISC-IV Symptom Description	Group 0 (CD+non-PAE)	Group 1 (CD +≤.89 dpd)	Group 2 (CD+ >.89 dpd)	Maximum Frequency Group
1	Stealing: non-confront	.773	.524	.792	Group2
2	Destruction of property	.455	.333	.583	Group2
3	Lies	.864	.857	.792	Group0
4	Bullying others	.182	.238	.167	Group2
5	Breaking and entering	.318	.286	.292	Group0
6	Cruel to animals	.000	.143	.125	Group2
7	Used weapons	.409	.619	.333	Group1
8	Truant	.227	.048	.083	Group0
9	Fights with others	.818	.619	.583	Group0
10	Out late at night	.136	.191	.083	Group1
11	Cruel to people	.318	.286	.375	Group2
12	Runs away	.046	.095	.167	Group2
13	Stealing: with confront	.091	.143	.083	Group1
14	Setting fires	.046	.048	.125	Group2
	Forced sex on others*	.000	.000	.000	

***Severity rank according to Gelhorn et.al (2009)**
***Gelhorn et.al (2009) did not rank the symptom forced sex on others.**

On Table 3, none of the three 1st trimester PAE groups show any of the 15 specific symptoms at a significantly higher frequency. When we collapse Groups 1 and 2 (any PAE exposure

groups) and compares these children to the unexposed offspring (Group 0) the results remain the same. Maximum endorsement frequency (MEF) is the PAE groups show the highest frequency in each CD symptoms. Table 4 shows the Group 0 had the maximum endorsement frequency (MEF) 29% (4/14) of the time, compared to 36% (5/14) of the time for both Groups 1 and 2. This distribution is not statistically different than chance (Fisher's exact test, p-value=1.00). When we collapse the MEF data into two groups, PAE (10/14, 71%) versus non-PAE (4/14, 29%), the p-value of the test is 0.5973 which is not statistically significant.

Table 4. Number of Maximum Endorsement Frequency (MEF) among Conduct Disordered Children by Prenatal Alcohol Exposure (PAE) Group

	Group 0 (CD+non-Pae)	Group 1 (CD +≤.89 dpd)	Group 2 (CD+ >.89 dpd)
Maximum Endorsement Frequency (MEF)	4/14	5/14	5/14

Table 5 summarizes both the mean and median symptom counts for the children in each one of the three study groups. Mean and median data are also shown for the symptoms having the maximum rank severity (Gelhorn, Hartman et al. 2009) reported by the children in each of the study groups. None of the differences shown on Table 5 is statistically significant.

Table 5. Distribution of Symptom Counts and Symptom with Maximum Severity among Conduct Disordered Children by Prenatal Alcohol Exposure (PAE) Group

Variables	CD/PAE Group	Mean (SE)	Median	Range
Symptom Count	Group 0: CD+non-PAE	4.68(.41)	4	3-9
	Group 1: CD+≤.89 dpd	4.43(.34)	4	3-8
	Group 2: CD+>.89 dpd	4.58(.43)	4	3-11
Symptom with Maximum Severity	Group 0: CD+non-PAE	10.10(.37)	9.5	7-14
	Group 1: CD+≤.89 dpd	9.91(.54)	10	5-14
	Group 2: CD+>.89 dpd	10.25(.54)	11	3-14

We also analyzed the symptom data using an approximate version of the cluster of conduct problems proposed by Frick and Ellis (1999, Frick et al. 1993). We used the DISC-IV data to construct three clusters of symptoms: property violations, aggression against persons, and covert status offenses. Our data showed that greater than 95% of the children in all three PAE exposure groups reported 2 or more clusters of symptoms. The PAE exposure groups did not differ with regard to the specific symptom clusters endorsed.

3.2 IMPAIRMENT

The raw data from the DISC-IV interview grade impairments based on self-reported difficulties occurring in four specific social domains: with the police, at school, at home, and with friends. Table 6 summarizes the mean and median numbers of impairment domains endorsed by our conduct disordered subjects.

Table 6. Number of Areas of Impairment among Conduct Disordered Children by Prenatal Alcohol Exposure (PAE) Group

Variables	CD/PAE Group	Mean (SE)	Median	Range
Number Areas of Impairment	Group 0: CD+non-PAE	2.96(.18)	3	2-4
	Group 1: CD+≤.89 dpd	2.81(.16)	3	1-4
	Group 2: CD+>.89 dpd	2.17(.23)	2	1-4

Figure 1 displays the proportion of subjects in the 1st trimester PAE groups endorsing difficulties in each of the four impairment domains. A statistical test of the impairment data indicates that the subjects from the heavy prenatal alcohol exposure group (Group 2), when compared to the subjects in both the unexposed (Group 0, *p=0.018*) and the light-to-moderately exposed (Group 1, *p=0.037*) groups, report difficulties in significantly fewer domains of social impairment. A comparison between Group 0+1 and Group 2 is statistically significant (*p=0.072*), heavy PAE group has fewer problems with social impairment.

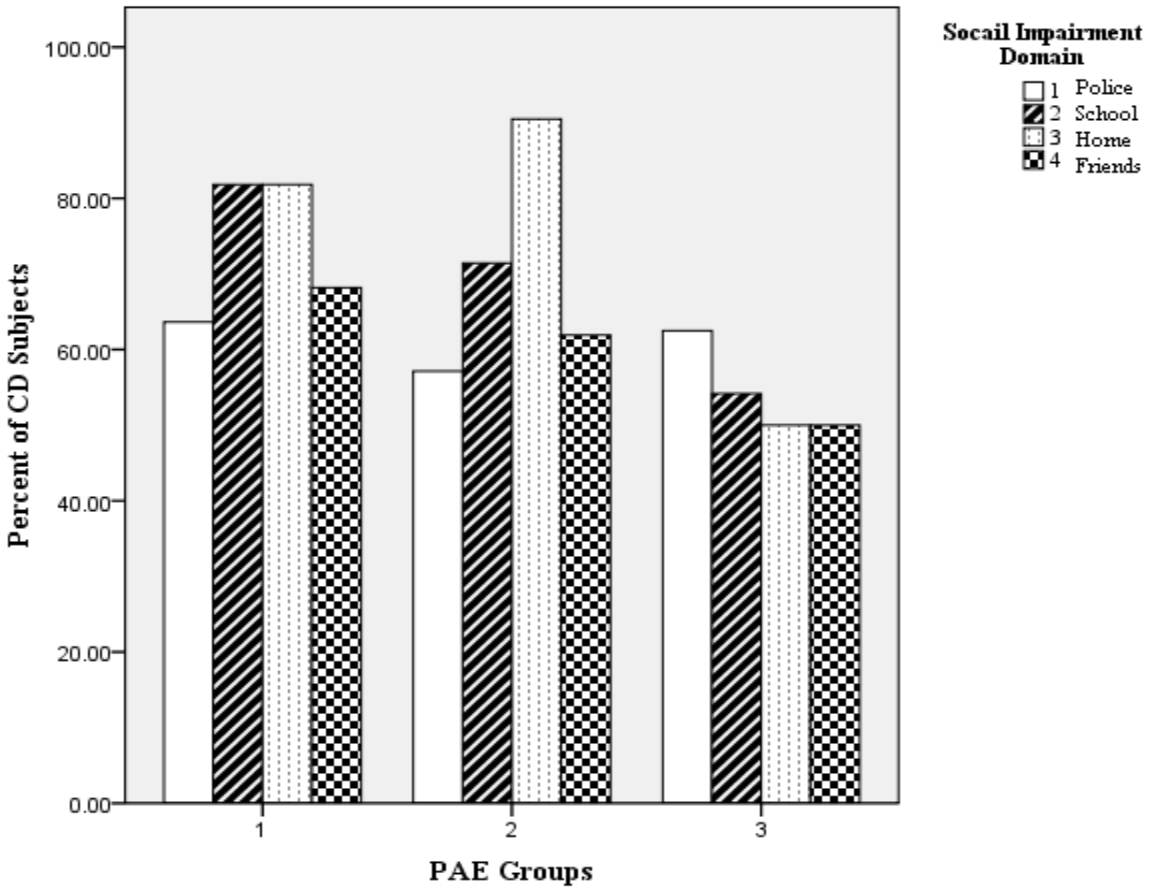

Figure 1. Proportion of Subjects in Each 1st Trimester Prenatal Alcohol Group Endorsing Different Domains of Social Impairment

3.3 AGE AT ONSET OF SYMPTOMS

Figure 2 displays the time to first onset of CD behavioral symptoms for the subjects in each of the three 1st trimester PAE groups using a Kaplan-Meier plot. The overall test of difference between the three curves is statistically non-significant (log rank test *p=0.67*). When we compare the unexposed alcohol group (Group 0) to light prenatal alcohol exposure (Group 1, log rank test *p*=0.48) and heavy prenatal alcohol exposure (Group 2, log rank test *p*= 0.39) individually, there are no statistically differences. But when we compare the curves immediately preceding childhood onset cut-off, the unexposed alcohol group (Group 0) show visibly increased frequency of childhood onset (symptoms onset before aged 10).

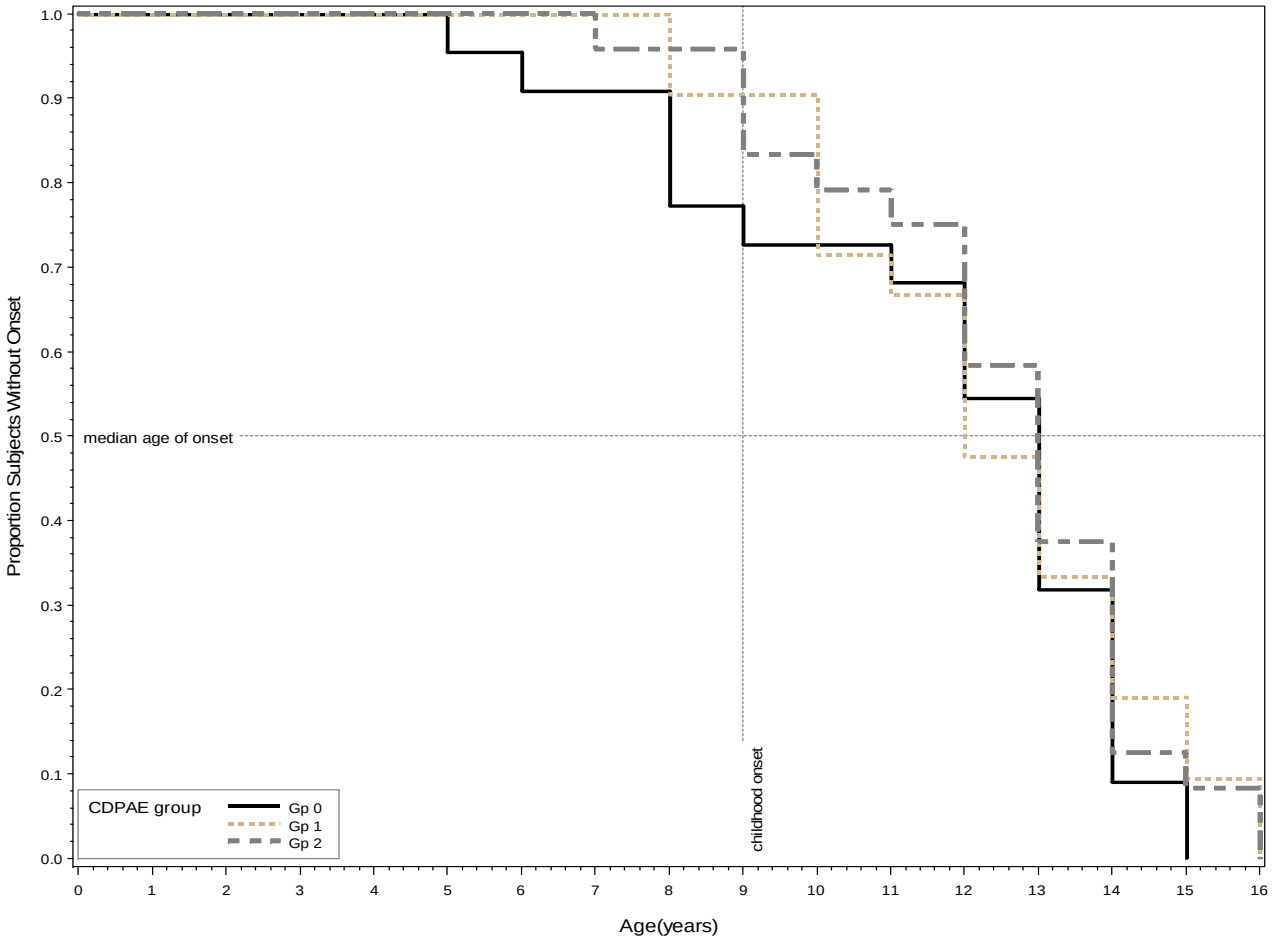

Figure 2. Proportion of Subject in Each Prenatal Alcohol Exposure Group Onset Illness

The mean and median ages of the first onset of behavioral symptoms for subjects with both childhood and adolescent forms of the disorder are summarized in Table 7. Although statistically non-significant (Group 0 vs Group 1 and Group 2, Chi-Square test, 1df, p =0.16), the data in Table 7 suggest a possible measure in childhood onsets in the alcohol non-exposed subjects (Group 0, OR=2.44).

Table 7. Mean and median Age at Illness Onset for Childhood and Adolescent Onsets by 1ST Trimester Prenatal Alcohol Exposure Groups

Onset Type	CD/PAE Group	Counts	Percent of Total Group	Mean (SE)	Median
Childhood Onset (< 10 yrs.)	Group 0: CD+non-PAE	6	27.3%	7.3 (1.5)	8
	Group 1: CD+≤.89 dpd	2	9.5%	8 (0.0)	8
	Group 2: CD+>.89 dpd	4	16.7%	8.5(1.0)	9
Adolescent Onset (≥ 10 yrs.)	Group 0: CD+non-PAE	16	72.7%	13.25(1.1)	13
	Group 1: CD+≤.89 dpd	19	90.5%	12.7(2.0)	13
	Group 2: CD+>.89 dpd	20	83.3%	13.3(1.5)	13
All	Group 0: CD+non-PAE	22	100%	11.6(3.0)	13
	Group 1: CD+≤.89 dpd	21	100%	12.3(2.4)	12
	Group 2: CD+>.89 dpd	24	100%	12.5(2.3)	13

3.4 ILLNESS COURSE

Table 8 provides data on the numbers of episodes and remissions and Table 9 provides the means of the length of episodes (in years) and the proportion of time since first behavioral symptom onset spent in an episode. These data are markedly similar for all three study groups. The only exception is the longer mean length of illness episodes in the alcohol unexposed group (Group 0), which has larger proportion of early childhood onset subjects (see Table 7).

Table 8. Number of Episodes and Remission among Conduct Disordered Children by Prenatal Alcohol Exposure (PAE) Group

Course Variable	Numbers	CD/PAE Group	Counts	Percentage
Number of Episodes	**1**	Group 0: CD+non-PAE	21	95.5%
		Group 1: CD+≤.89 dpd	20	95.2%
		Group 2: CD+>.89 dpd	23	95.8%
	2	Group 0: CD+non-PAE	1	4.6%
		Group 1: CD+≤.89 dpd	1	4.8%
		Group 2: CD+>.89 dpd	1	4.2%
Number of Remission	**0**	Group 0: CD+non-PAE	15	68.2%
		Group 1: CD+≤.89 dpd	10	47.6%
		Group 2: CD+>.89 dpd	13	54.2%
	1	Group 0: CD+non-PAE	7	31.8%
		Group 1: CD+≤.89 dpd	11	52.4%
		Group 2: CD+>.89 dpd	11	45.8%

Table 9. Distribution of Illness Course Variable for Conduct Disorder Subjects by 1st Trimester Prenatal Alcohol Group

Course Variables	CD/PAE Group	Mean (SE)	Median	Range
Time in Episode (yrs)	Group 0: CD+non-PAE	3.68 (.59)	3	1-11
	Group 1: CD+≤.89 dpd	2.91 (.45)	2	1-8
	Group 2: CD+>.89 dpd	2.96(1.0)	2	1-8
Percent Time in Episode	Group 0: CD+non-PAE	0.77(.05)	.87	25-1.0
	Group 1: CD+≤.89 dpd	0.76(.06)	.92	13-1.0
	Group 2: CD+>.89 dpd	0.77(.05)	.81	.33-1.0

3.5 CURRENT STATE

Table 10 summarizes the clinical diagnostic state of the children with lifetime CD at the time of the MHPCD 16-year follow-up examination. This table suggests that a lager proportion (19/45, 42%) of the alcohol exposed children, Group 1 and Group 2, were fully remitted at the time of the 16-year follow-up compared to the unexposed group (Group 0, 5/22, 23%), a greater proportion of whom remained in a partial remission or an active episode. Although this difference is not statistically significant (*p=0.12*), the observed odds ratio (OR) is 2.48.

Table 10. Current Clinical State of Conduct Disordered Subjects at the 16 Year Follow-Up by 1st Trimester Prenatal Alcohol Group

Clinical State	CD/PAE Group	Counts	Percentage in each CD/PAE Group
Full Remission*	Group 0: CD+non-PAE	5	22.7%
	Group 1: CD+≤.89 dpd	9	42.9%
	Group 2: CD+>.89 dpd	10	41.7%
Partial Remission**	Group 0: CD+non-PAE	10	45.5%
	Group 1: CD+≤.89 dpd	2	9.5%
	Group 2: CD+>.89 dpd	4	16.7%
Active Episode	Group 0: CD+non-PAE	7	31.8%
	Group 1: CD+≤.89 dpd	10	47.6%
	Group 2: CD+>.89 dpd	10	41.6%

***no symptoms for last 12 months**
**** symptoms present, but does not meet full DSM-IV criteria**

3.6 TREATMENT

Table 11 summarizes treatment received for CD and/or some other psychiatric disorder during (a) the subjects' lifetimes and (b) the 12 month period preceding the DISC-IV interview. The lifetime data show that a greater proportion of the offspring (42%) in the more heavily exposed

alcohol group (Group 2) received treatment for a psychiatric disorder compared to the children in both the unexposed (18%, *p=0.08, OR=3.21*) and the light-to-moderately exposed alcohol groups (24%, *p=0.21, OR=2.29*), however both p-values are not statistically significant. For the data of the 12 month period preceding the DISC-IV interview, a greater proportion of treated subjects in the highly exposed alcohol group (Group 2, 36%) as compared to the non-exposed (Group 0, 0%, *exact p=0.012, OR=na*) and when we compare the highly alcohol exposed group (Group 2) to the light-to-moderately exposed alcohol groups (Group 1, 8.4%, *exact p=0.12, OR=6.1*) the odds ratio is relatively high but the p-value is not significant. When we combine Group 0 and Group 1 and compare to Group 2, the p-value is statistically significant and the odds ratio is 15 (combined Group 0 and Group 1vs Group 2, *exact p=0.01, OR=15*).

Table 11. Treatment for Conduct Disorder or Other DSM-IV Diagnosis (Lifetime and Last Year) by 1st Trimester Prenatal Alcohol Group

Course Variable		CD/PAE Group	Counts	Percentage in CD/PAE Group
		Group 0: CD+non-PAE	4	18.2%
		Group 1: CD+≤.89 dpd	5	23.8%
Ever Treated	Yes	Group 2: CD+>.89 dpd	10	41.7%
in life time		Group 0: CD+non-PAE	18	81.8%
		Group 1: CD+≤.89 dpd	16	76.2%
	No	Group 2: CD+>.89 dpd	14	58.3%
	Treated/Sought	Group 0: CD+non-PAE	0	0%
	treatment	Group 1: CD+≤.89 dpd	1	8.4%
Treated in		Group 2: CD+>.89 dpd	5	35.7%
last year*	Treatment not	Group 0: CD+non-PAE	17	100%
	wanted	Group 1: CD+≤.89 dpd	11	91.6%
		Group 2: CD+>.89 dpd	9	64.3%

***applies only to the 43 subjects in partial or active episode at 16 year follow-up (Table 9)**

3.7 CO-MORBID DIAGNOSES

In addition to CD, the data on eleven DSM-IV diagnoses were available for this analysis. The eleven diagnoses were collapsed into three groups for presentation: substance abuse diagnoses (alcohol abuse, dependence, and withdrawal; marijuana abuse and dependence), mood/anxiety disorders (major depressive disorder, general anxiety, PTSD, and separation anxiety), and other CD-associated diagnoses (anti-social personality, ADHD). These data are summarized on Table 12. Although none of the comparisons on Table 12 approaches statistical significance, a greater proportion of the subjects in the most highly exposed alcohol group (Group 2), compared to the children in either the unexposed (Group 0) or the light-to-moderately exposed alcohol group (Group 1), qualify for at least one of the candidate diagnosis in each one of our three diagnostic categories.

Table 12. Proportion of Conduct Disorder Subjects with Co-Morbid Diagnoses by Diagnostic Category and 1st Trimester Prenatal Alcohol Group

Diagnostic Categories	CD/PAE Group	Counts	Proportion
Substance Abuse*	Group 0: CD+non-PAE	10	54.5%
	Group 1: CD+≤.89 dpd	10	61.9%
	Group 2: CD+>.89 dpd	13	83.8%
Mood/Anxiety**	Group 0: CD+non-PAE	8	68.2%
	Group 1: CD+≤.89 dpd	5	28.6%
	Group 2: CD+>.89 dpd	9	70.8%
CD-Associated***	Group 0: CD+non-PAE	0	0.0%
	Group 1: CD+≤.89 dpd	1	4.8%
	Group 2: CD+>.89 dpd	4	16.7%

***alcohol abuse, dependence, and withdrawal; marijuana abuse and dependence,**
**** major depressive disorder, general anxiety, PTSD, separation anxiety**
***** anti-social personality, ADHD**

Figure 3 provides information on the frequency of multiple co-morbid diagnoses in each one of the study groups. This figure confirms that the children in the most highly exposed alcohol group (Group 2) show the greatest frequency of multiple (2+) co-morbid diagnoses, compared to the non-alcohol exposed (Group 0) and the less alcohol exposed (Group 1) children. The differences on Figure 3 are not statistically significant.

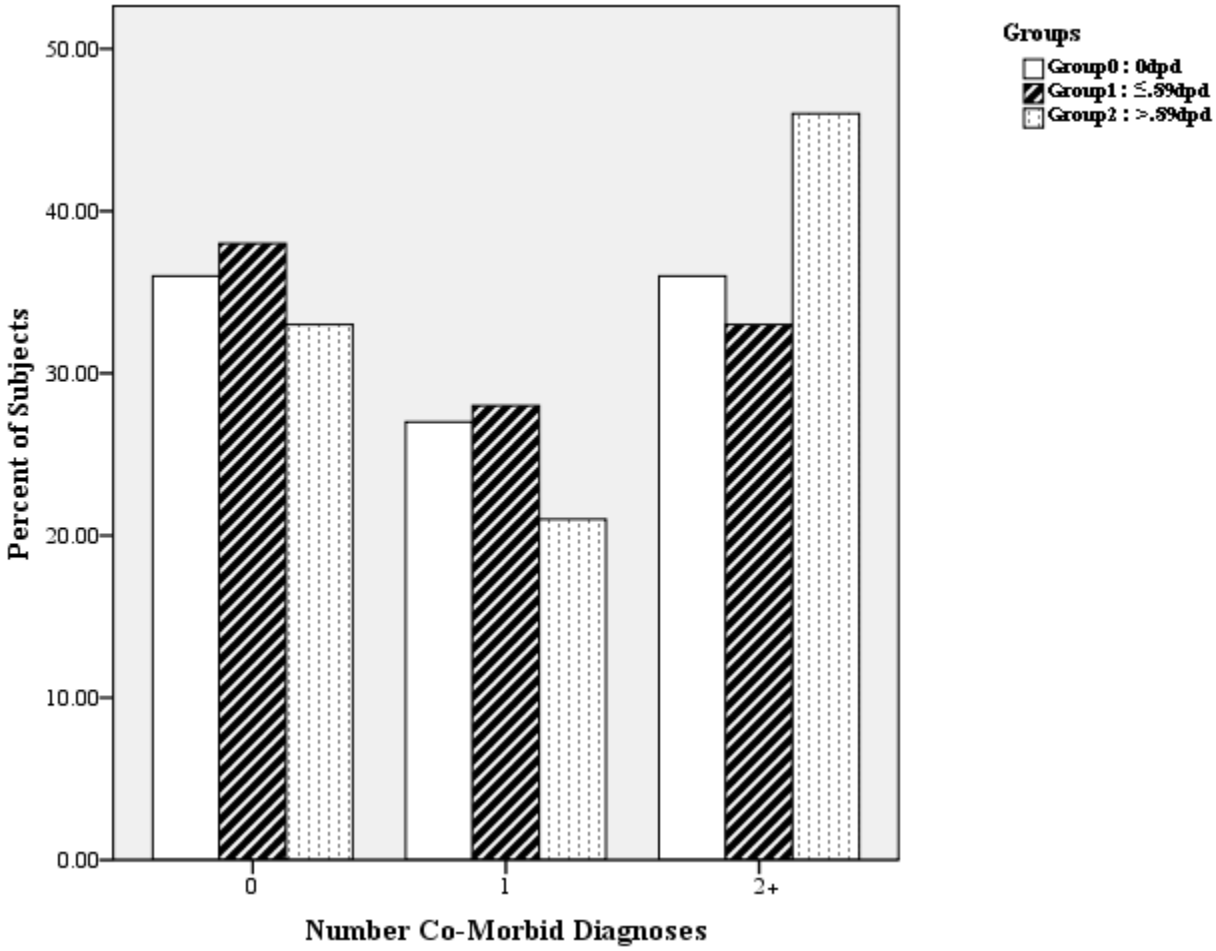

Figure 3. Number Co-Morbid Diagnoses among Conduct Disordered Children by Prenatal Alcohol Exposure Groups

4.0 DISCUSSION

The *Results* section of this study reviewed the clinical profiles of CD children with differential levels of PAE found in the 16-year follow-up DISC-IV interview data. In the *Data Analysis* section, we argued that these clinical self-report data could be usefully summarized using two primary criteria: (a) significant statistical differences between the PAE groups; and (b) statistically non-significant but *potentially informative* measures of association (i.e., odds ratios and relative risks).

Significant statistical differences were observed in two features of these clinical profiles: (a) domains of social impairment and (b) psychiatric treatment in the twelve months preceding the diagnostic interview. In both cases, the heavily exposed alcohol group (Group 2) compared favorably with the unexposed (Group 0), and when combined the unexposed and the light-to-moderately exposed alcohol groups (Group 0 + Group 1) compared with heavily exposed alcohol group (Group 2), the differences are statistically significant. It is possible that these two clinical features of our subjects are related – i.e., more frequent treatment leads to few impairments. However, the data indicate that children receiving treatment in the 12 months preceding their interview reported a similar number of domains of social impairment (mean: 2.4, se: 0.6) compared to those who did not receive any treatment (mean 1.8, se: 0.2, Kruskal-Wallis test p=0.29) in the 12-month period preceding their interview. The findings are also negative when we compare mean reported impairment domains between children with and without lifetime

treatment (mean: 2.5 vs. 2.7). The increased frequency of treatment in the heavily exposed alcohol group might appear to be a negative clinical feature suggesting, perhaps, more severe symptoms or impairment. However, this factor can also be interpreted as a measure of comparative treatment resistance and the possibly greater openness of the highly alcohol exposed children to external intervention.

Turning to non-significant but potentially informative measures of association, the most robust odds ratios occur for the lifetime treatment data. These data are similar to the 12-months treatment data and show a favorable odds ratio of 2.70 (*p=0.07*) for the highly exposed alcohol group versus the combined unexposed and light-to-moderately exposed children (Group 0+1). Another area showing a potentially informative odds ratio was the current clinical state at the 16-year follow-up. Here we found that the combined group of children with PAE (Group 1+2) was 2.48 times more likely to be in a state of complete remission compared the alcohol unexposed children (Group 0). We also found that the alcohol unexposed children (Group 0) were 2.44 times more likely than the combined group of PAE children (Group 1+2) to show an onset of behavioral occurring before 10 years of age (*p=0.16*). Childhood versus adolescent onset is an important marker of disease severity and the best single predictor of a poor adult outcome in the DISC-IV interview data. The data on the distribution of childhood and adolescent onsets are potentially quite important and will be discussed in greater detail shortly.

Compared to the preceding features of the children's clinical profiles, we found little to differentiate our three 1st trimester PAE groups with regard to the number, severity, and kind of behavioral symptoms, the overall mean age at onset, the numbers of episodes and remissions, the percentage of time spent in an episode since symptomatic onset, or the distribution of co-morbid diagnoses. Overall, the differences found between the clinical profiles of our 1st trimester PAE

groups seem relatively meager in terms of number and significance. We also failed to uncover a consistent relationship between any two of the exposure groups (e.g., Groups 0 and 1 or Groups 1 and 2) that would suggest they are clinically more similar to one another as compared to the third group and, therefore, that they can be collapsed together. Recalling the alternative hypothesis described in the *Introduction*, these data suggest that o*ur samples of children are, for the most part, homogeneous between groups and heterogeneous within groups – i.e., the PAE and non-PAE children show a similar range of clinical symptoms and subtypes*.

The preceding summary of the DISC-IV data would seem to imply that 1st trimester prenatal alcohol exposures are not directly associated with either of the recognized subtypes of conduct disorder and may give rise to either the impulsive or the callous-unemotional form of the diagnosis. However, there is one more epidemiological approach to the data that can be pursued. If we look at the data from prior investigations with these children (Larkby and Day 1997) and the overall incidence rates reported on Table 1, it would appear that PAE has a ***direct threshold*** effect in the offspring of mothers who consumed about a drink a day during the earliest phase of gestation. As a consequence of this alcohol consumption, the incidence of conduct disorder amongst the offspring of these women is estimated to increase approximately 2.5 times over the expected baseline rate (5.6 per 100) observed in the combined alcohol unexposed and light-to-moderately exposed children (Group 0+1). This difference in rates gives an attributable risk (or etiological fraction) of approximately 60% which suggests that about 14 of the 24 conduct disordered children in the heavily exposed group (Group 2) are causally associated with their mother's prenatal drinking behavior. The next question involves how to identify the relevant clinical characteristics of these hypothesized *alcohol-related* conduct disordered children? As noted earlier, investigators have identified two basic subtypes of the disorder: a highly impulsive

subtype characterized by a *later adolescent onset* (≥10 years old) and a fluctuating, less severe course versus a callous-unemotional subtype characterized by an *earlier childhood onset* (<10 years old) and a more persistent, severe course. If it is the case that a heavy 1st trimester PAE is associated with ***both*** subtypes of the disorder, we would expect to see an approximate doubling of the incidence of ***both*** childhood and adolescent onsets among the most highly alcohol exposed children (i.e., Group 2) when compared to the unexposed and light-to-moderately alcohol exposed children (Group 0+1). If a heavy 1st trimester PAE is associated with ***either*** subtype of the disorder, we would expect to see an excess of either childhood or adolescent onsets among the most highly alcohol exposed children (i.e., Group 2) when compared to the unexposed and light-to-moderately alcohol exposed children (Group 0+1).

When we actually calculate the stratified onset rates for Group 2 versus Group 0 and Group 1 we observe an unambiguous doubling of the incidence of ***both*** subtypes of the disorder in the most highly exposed alcohol group. The incidence rate for childhood onsets is 3.9 per 1000 at-risk years for the heavily exposed children (Group 2) versus 1.72 per 1000 at-risk years for the combined groups 0 and 1. Stratified incidence rates for adolescent onsets are 27.7 per 1000 at-risk years for the heavily exposed children compared to 12.0 per 1000 at-risk years for the combined unexposed and light-to-moderately exposed children. These comparative incidence data would seem to provide additional, very strong evidence supporting the above conclusion that heavy (>.89 dpd) 1st trimester PAE is associated with an observable increase in the incidence of ***both*** of the currently recognized subtypes of childhood conduct disorder, rather than being associated with one or the other of these two clinical phenotypes.

It is important to clearly understand the differences in the developmental pathways of different subtyping groups of CD. In our study, the clinical information for CD children did not show

much difference between different levels of PAE groups, and also the comparisons of incidence rates in childhood-onset and adolescent-onsets groups show that PAE cannot distinguish the two different subtyping groups. However, in our study the incidence rates for both males and females with heavy PAE are significantly higher than the light-to-moderate PAE groups. This finding supports with the previous studies that PAE plays a significant role in predicting the risk of CD. Therefore, enhancing the understanding of the role of prenatal alcohol exposure in the development of conduct disorder is a critical issue and also leads to building the interventions comprehensively and individually.

This analysis has a number of clear limitations. First, we are restricted to the clinical features indentified as part of conduct disorders by the DSM-IV and included in the DISC-IV interview. A number of authors have suggested that these clinical features are distinctly behavioral in nature and fail to take into account other import aspects of conduct disorders such as emotional functioning (Blair et al. 2005) or empathic capabilities (Decety et al. 2008). A second limitation of our data stems from the self-report nature of the DISC-IV interview and the possibility of certain features of children's behavior being underreported; for instance it may be difficult to achieve an accurate assessment of diagnoses such as ADHD without secondary information from parental and/or other sources. Despite such limitations, an in depth comparison of the behavioral and clinical information available through the DISC-IV interview may serve as an important starting point for indentifying clinical profiles of conduct disordered children that may be associated with the occurrence of prenatal alcohol exposures. Third, the sample size in each PAE group is small, which limits to statistical power to detect the association. We need to carefully interpret the negative findings in this study. Fourth, the mothers were quite homogeneous. They

were selected according to the consumption of alcohol and marijuana during pregnancy and were generally light to moderate users.

Public Health Significance

About 1 in 4 American women consumes alcohol during pregnancy (Disney, Iacono et al. 2008) and CDC studies show that approximately between 0.2 to 1.5 per 1,000 live births in the U.S have a wide range of deficits caused by prenatal alcohol exposure. The effects of PAE not only impact on child's life but also affect their family, education and even society as a whole. Data from CDC showed that the lifetime medical and social costs of each child with fetal alcohol syndrome (FAS) are estimated to be as high as US$800,000. It is critical to build an intervention for children with PAE deficits to decrease the serious impact on their lives. However, few studies focus on discussing the association between PAE and subtypes of conduct disorder. Our study used the clinical information of conduct disorder children to analyze the difference between prenatal alcohol exposure and non-exposure groups. The findings of this study provide future studies a brief background on the association between PAE and different subtypes of conduct disorder. This might be helpful information for clinician and public health official when they discuss the diagnoses or issues about children with PAE. This information may also assist researchers to build an individual and comprehensive intervention for different subtypes of conduct disorder children.

BIBLIOGRAPHY

Association, A. P. (1994). "Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)".

Baer, J. S., H. M. Barr, et al. (1998). "Prenatal alcohol exposure and family history of alcoholism in the etiology of adolescent alcohol problems." J Stud Alcohol **59**(5): 533-43.

Bailey, B. N., V. Delaney-Black, et al. (2004). "Prenatal exposure to binge drinking and cognitive and behavioral outcomes at age 7 years." Am J Obstet Gynecol **191**(3): 1037-43.

Barr, H. M., F. L. Bookstein, et al. (2006). "Binge drinking during pregnancy as a predictor of psychiatric disorders on the Structured Clinical Interview for DSM-IV in young adult offspring." Am J Psychiatry **163**(6): 1061-5.

Bookheimer, S. Y. and E. R. Sowell (2005). "Brain imaging in FAS: commentary on the article by Malisza et al." Pediatr Res **58**(6): 1148-9.

Brown, R. T., C. D. Coles, et al. (1991). "Effects of prenatal alcohol exposure at school age. II. Attention and behavior." Neurotoxicol Teratol **13**(4): 369-76.

Clarke, M. E. and W. B. Gibbard (2003). "Overview of fetal alcohol spectrum disorders for mental health professionals." Can Child Adolesc Psychiatr Rev **12**(3): 57-63.

Clarren, S. K. (1986). "Neuropathology in fetal alcohol syndrome." in: West JR Ed. Alcohol and Brain Development. New York: Oxford University Press: 158-166.

Coles, C. D., J. A. Kable, et al. (2000). "Early identification of risk for effects of prenatal alcohol exposure." J Stud Alcohol **61**(4): 607-16.

Cornelius, M. D., L. Goldschmidt, et al. (2007). "Smoking during teenage pregnancies: effects on behavioral problems in offspring." Nicotine Tob Res **9**(7): 739-50.

Crowe, S. L. and R. J. Blair (2008). "The development of antisocial behavior: what can we learn from functional neuroimaging studies?" Dev Psychopathol **20**(4): 1145-59.

D'Onofrio, B. M., C. A. Van Hulle, et al. (2007). "Causal inferences regarding prenatal alcohol exposure and childhood externalizing problems." Arch Gen Psychiatry **64**(11): 1296-304.

Dandreaux, D. M. and P. J. Frick (2009). "Developmental pathways to conduct problems: a further test of the childhood and adolescent-onset distinction." J Abnorm Child Psychol **37**(3): 375-85.

David Shaffer, C. L., Prudence Fisher, "Diagnostic Interview Schedule for Children."

Day, N. L., S. L. Leech, et al. (2002). "Prenatal alcohol exposure predicts continued deficits in offspring size at 14 years of age." Alcohol Clin Exp Res **26**(10): 1584-91.

Day, N. L. and G. A. Richardson (2004). "An analysis of the effects of prenatal alcohol exposure on growth: a teratologic model." Am J Med Genet C Semin Med Genet **127C**(1): 28-34.

Day, N. L. and N. Robles (1989). "Methodological issues in the measurement of substance use." Ann N Y Acad Sci **562**: 8-13.

Disney, E. R., W. Iacono, et al. (2008). "Strengthening the case: prenatal alcohol exposure is associated with increased risk for conduct disorder." Pediatrics **122**(6): e1225-30.
Dolan, M. (2008). "Neurobiological disturbances in callous-unemotional youths." Am J Psychiatry **165**(6): 668-70.
Frick, P. J. (2006). "Developmental pathways to conduct disorder." Child Adolesc Psychiatry Clin N Am **15**(2): 311-31, vii.
Frick, P. J. and C. Dickens (2006). "Current perspectives on conduct disorder." Curr Psychiatry Rep **8**(1): 59-72.
Frick, P. J. and M. Ellis (1999). "Callous-unemotional traits and subtypes of conduct disorder." Clin Child Fam Psychol Rev **2**(3): 149-68.
Frick, P. J. and S. F. White (2008). "Research review: the importance of callous-unemotional traits for developmental models of aggressive and antisocial behavior." J Child Psychol Psychiatry **49**(4): 359-75.
Fryer, S. L., C. L. McGee, et al. (2007). "Evaluation of psychopathological conditions in children with heavy prenatal alcohol exposure." Pediatrics **119**(3): e733-41.
Gelhorn, H., C. Hartman, et al. (2009). "An item response theory analysis of DSM-IV conduct disorder." J Am Acad Child Adolesc Psychiatry **48**(1): 42-50.
Green, J. H. (2007). "Fetal Alcohol Spectrum Disorders: understanding the effects of prenatal alcohol exposure and supporting students." J Sch Health **77**(3): 103-8.
Griesler, P. C. and D. B. Kandel (1998). "The impact of maternal drinking during and after pregnancy on the drinking of adolescent offspring." J Stud Alcohol **59**(3): 292-304.
Guerri, C. (1998). "Neuroanatomical and neurophysiological mechanisms involved in central nervous system dysfunctions induced by prenatal alcohol exposure." Alcohol Clin Exp Res **22**(2): 304-12.
Guerri, C., A. Bazinet, et al. (2009). "Foetal Alcohol Spectrum Disorders and alterations in brain and behaviour." Alcohol Alcohol **44**(2): 108-14.
Hill, S. Y., L. Lowers, et al. (2000). "Maternal smoking and drinking during pregnancy and the risk for child and adolescent psychiatric disorders." J Stud Alcohol **61**(5): 661-8.
Jacobson, S. W., J. L. Jacobson, et al. (1993). "Prenatal alcohol exposure and infant information processing ability." Child Dev **64**(6): 1706-21.
Jones, K. L. and D. W. Smith (1973). "Recognition of the fetal alcohol syndrome in early infancy." Lancet **302**(7836): 999-1001.
Kellerman, T. (2008). "Prenatal Alcohol Exposure and the Brain. Assessed on April 2009. http://www.come-over.to/FAS/FASbrain.htm"
Lahey, B. B., R. Loeber, et al. (1998). "Validity of DSM-IV subtypes of conduct disorder based on age of onset." J Am Acad Child Adolesc Psychiatry **37**(4): 435-42.
Langbehn, D. R. and R. J. Cadoret (2001). "The adult antisocial syndrome with and without antecedent conduct disorder: comparisons from an adoption study." Compr Psychiatry **42**(4): 272-82.
Larkby, C. and N. Day (1997). "The effects of prenatal alcohol exposure." Alcohol Health Res World **21**(3): 192-8.
Leech, S. L., C. A. Larkby, et al. (2006). "Predictors and correlates of high levels of depression and anxiety symptoms among children at age 10." J Am Acad Child Adolesc Psychiatry **45**(2): 223-30.

Loney, B. R., P. J. Frick, et al. (2003). "Callous-unemotional traits, impulsivity, and emotional processing in adolescents with antisocial behavior problems." J Clin Child Adolesc Psychol **32**(1): 66-80.
Marsh, A. A., E. C. Finger, et al. (2008). "Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders." Am J Psychiatry **165**(6): 712-20.
Mattson, S. N., A. M. Goodman, et al. (1999). "Executive functioning in children with heavy prenatal alcohol exposure." Alcohol Clin Exp Res **23**(11): 1808-15.
McGee, C. L., S. L. Fryer, et al. (2008). "Deficits in social problem solving in adolescents with prenatal exposure to alcohol." Am J Drug Alcohol Abuse **34**(4): 423-31.
McGee, C. L. and E. P. Riley (2006). "Brain imaging and fetal alcohol spectrum disorders." Ann Ist Super Sanita **42**(1): 46-52.
Moffitt, T. E. (1993). "Adolescence-limited and life-course-persistent antisocial behavior: a developmental taxonomy." Psychol Rev **100**(4): 674-701.
Moffitt, T. E. and D. Lynam, Jr. (1994). "The neuropsychology of conduct disorder and delinquency: implications for understanding antisocial behavior." Prog Exp Pers Psychopathol Res: 233-62.
Nanson, J. L. and M. Hiscock (1990). "Attention deficits in children exposed to alcohol prenatally." Alcohol Clin Exp Res **14**(5): 656-61.
O'Leary, C. M. (2004). "Fetal alcohol syndrome: diagnosis, epidemiology, and developmental outcomes." J Paediatr Child Health **40**(1-2): 2-7.
Olson, H. C., Sampson, P.D., Barr, H.. Streissguth, A.P. Bookstein, F.L., (1992). "Prenatal Exposure to Alcohol and School Problems in Late Childhood: A Longitudinal Prospective Study." Devel. Psychopathol **4**: 341-359.
Olson, H. C., A. P. Streissguth, et al. (1997). "Association of prenatal alcohol exposure with behavioral and learning problems in early adolescence." J Am Acad Child Adolesc Psychiatry **36**(9): 1187-94.
Pediatrics, A. A. o. (2000 Aug). "Fetal alcohol syndrome and alcohol-related neurodevelopmental disorders." Pediatrics. **106(2 Pt 1)**: 358-61.
Perneger, T. V. (1998). "What's wrong with Bonferroni adjustments." BMJ **316**(7139): 1236-8.
Riley, E. P. and C. L. McGee (2005). "Fetal alcohol spectrum disorders: an overview with emphasis on changes in brain and behavior." Exp Biol Med (Maywood) **230**(6): 357-65.
Riley, E. P., C. L. McGee, et al. (2004). "Teratogenic effects of alcohol: a decade of brain imaging." Am J Med Genet C Semin Med Genet **127C**(1): 35-41.
Roberts, N., K. C. Parker, et al. (2005). "Comparison of Clinical Diagnoses, NIMH-DISC-IV Diagnoses and SCL-90-R Ratings in an Adolescent Psychiatric Inpatient Unit: A Brief Report." Can Child Adolesc Psychiatr Rev **14**(4): 103-5.
Rothman, K. J. (1990). "No adjustments are needed for multiple comparisons." Epidemiology **1**(1): 43-6.
Rubio, D. M., K. L. Kraemer, et al. (2008). "Factors associated with alcohol use, depression, and their co-occurrence during pregnancy." Alcohol Clin Exp Res **32**(9): 1543-51.
Russell, M., D. M. Czarnecki, et al. (1991). "Measures of maternal alcohol use as predictors of development in early childhood." Alcohol Clin Exp Res **15**(6): 991-1000.
Schonfeld, A. M., S. N. Mattson, et al. (2005). "Moral maturity and delinquency after prenatal alcohol exposure." J Stud Alcohol **66**(4): 545-54.

Schwab-Stone, M. E., D. Shaffer, et al. (1996). "Criterion validity of the NIMH Diagnostic Interview Schedule for Children Version 2.3 (DISC-2.3)." J Am Acad Child Adolesc Psychiatry **35**(7): 878-88.
Seto, M., M. D. Cornelius, et al. (2005). "Long-term effects of chronic depressive symptoms among low-income childrearing mothers." Matern Child Health J **9**(3): 263-71.
Shaffer, D., P. Fisher, et al. (2000). "NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses." J Am Acad Child Adolesc Psychiatry **39**(1): 28-38.
Spadoni, A. D., C. L. McGee, et al. (2007). "Neuroimaging and fetal alcohol spectrum disorders." Neurosci Biobehav Rev **31**(2): 239-45.
Staroselsky, A., E. Fantus, et al. (2009). "Both parental psychopathology and prenatal maternal alcohol dependency can predict the behavioral phenotype in children." Paediatr Drugs **11**(1): 22-5.
Steinhausen, H. C., Hesteler,V., and Spohr, H.L. (1982). "Development and Psychopathology of Children with the Fetal Alcohol Syndrome." J.Devel.Behav.Pediat. **3**: 49-54.
Sterzer, P., C. Stadler, et al. (2005). "Abnormal neural responses to emotional visual stimuli in adolescents with conduct disorder." Biol Psychiatry **57**(1): 7-15.
Streissguth, A. P. (1990). "Prenatal alcohol-induced brain damage and long-term postnatal consequences: introduction to the symposium." Alcohol Clin Exp Res **14**(5): 648-9.
Streissguth, A. P., H. M. Barr, et al. (1994). "Prenatal alcohol and offspring development: the first fourteen years." Drug Alcohol Depend **36**(2): 89-99.
Streissguth, A. P., H. M. Barr, et al. (1986). "Attention, distraction and reaction time at age 7 years and prenatal alcohol exposure." Neurobehav Toxicol Teratol **8**(6): 717-25.
Streissguth, A. P., Barr, H.M., Sampson,P.D., Darby, B.L., and Martin, D.C (1989). "IQ at age 4 in relation to maternal alcohol use and smoking during pregnancy." Devel. Psychopathol **25**: 3-11.
Streissguth, A. P., Booksterin,F.L., Sampson, P.D., and Barr, H.M. (1995). "Attention: Prenatal Alcohol and continuities of viglance and attentional problems from 4 through 14 years." Devel. Psychopathol **7**: 419-446.
Streissguth, A. P., P. D. Sampson, et al. (1994). "Maternal drinking during pregnancy: attention and short-term memory in 14-year-old offspring--a longitudinal prospective study." Alcohol Clin Exp Res **18**(1): 202-18.
Vloet, T. D., K. Konrad, et al. (2008). "Structural and functional MRI- findings in children and adolescents with antisocial behavior." Behav Sci Law **26**(1): 99-111.
Willford, J. (2004). "Light to Moderate Drinking During Pregnancy May Lead to Learning and Memory Deficits in Adolescents." Alcoholism: Clinical & Experimental Research.
Willford, J. A., G. A. Richardson, et al. (2004). "Verbal and visuospatial learning and memory function in children with moderate prenatal alcohol exposure." Alcohol Clin Exp Res **28**(3): 497-507.
Yang, Y., A. L. Glenn, et al. (2008). "Brain abnormalities in antisocial individuals: implications for the law." Behav Sci Law **26**(1): 65-83.