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Association between Fetal Alcohol Spectrum Disorders and Asthma Diagnosis in Children

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Tulane University

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ABSTRACT

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By Katherine I. Foley

BACKGROUND: Prenatal alcohol exposure leads to a myriad of health outcomes that are known as Fetal Alcohol Spectrum Disorders (FASDs). In animal models, *in utero* ethanol exposure has been shown to be associated with diminished lung size and function as well as reduced immune strength. The current study attempts to provide further understanding of the relationship between prenatal alcohol exposure and lung development by hypothesizing that there is an association between having been diagnosed with FASD and having been diagnosed asthma.

METHODS: Information on asthma diagnoses in 619 children between the ages of 1 and 15 with a diagnosis of FASD and who attend the Emory Neurodevelopmental Exposure Clinic (ENEC) was compared with similar information collected about 708 children subjects who attend ENEC, but who do not have a diagnosis FASD and 23,889 children for whom information on asthma diagnoses was obtained through the National Health and Nutrition Examination Survey (NHANES). Logistic regression models were run to examine the association between FASD diagnosis and the cumulative incidence of asthma.

RESULTS: A similar proportion of children with FASD and those attending ENEC for other reasons had been diagnosed with asthma, even after adjusting for potential confounding factors (OR_{adj} = 0.96, 95% CI = 0.71, 1.29). In contrast, compared to participants in NHANES, children with FASD were 30% more likely to have been diagnosed with asthma (OR_{adj}= 1.29; 95% CI 1.03 to 1.61).

CONCLUSIONS: Depending on the comparison group, children with FASD were more likely than expected to have been diagnosed with asthma. However, there is significant concern about selection bias, residual confounding and differential misclassification, and these biases are likely to affect the two comparison groups differently. Therefore, there is insufficient evidence to support an association between FASD-exposure and asthma diagnosis. Future, prospective study that properly controls for confounding by several factors is needed.

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Table of Contents

INTRODUCTION

Fetal Alcohol Spectrum Disorders (FASDs) have been a focus of epidemiological and medical research since the syndrome was characterized in the early 1970s. Over the past several decades, animal models and observational studies have provided important information about both the clinical hallmarks and diagnostic criteria of the disorders. The clinical features include a distinct pattern of facial dysmorphology, as well as physical defects, socio-behavioral impairments, and intellectual deficits that persist throughout childhood. Much is also known about the types of care these children require as well as the fetal origins of the disorders. Recent literature has also suggested that prenatal alcohol exposure affects the development of the respiratory and immune systems (1-4). The connection between intrauterine alcohol exposure and fetal lung and immune development has been most notably demonstrated using animal models involving maternal administration of ethanol and direct observation of fetal outcomes. Because of the association between maternal ethanol exposure and fetal immune and lung development, we hypothesize that there may be an association between FASD diagnoses and asthma diagnoses in children.

BACKGROUND AND LITERATURE REVIEW

Fetal Alcohol Spectrum Disorders

The fetal alcohol syndrome was first documented by developmental pediatrician Dr. David Smith and his dysmorphology resident, Dr. Kenneth Jones in the early 1970s (5). Drs. Smith and Jones citied Paul Lemoine's 1967 study of anomalies in infants born to alcoholic mothers as the first of its kind in linking a pattern of birth outcomes to maternal alcohol abuse. This pattern was delineated by the following: growth deficiency both pre- and postnatal, small head size (i.e. microcephaly), mental abnormalities, and facial dysmorphia (6). These efforts were the first to attempt to define what would later develop into the clinical diagnostic criteria for the fetal alcohol syndrome.

Over the past several decades as the fetal alcohol syndrome (FAS) has been increasingly studied, a main goal of FAS research became defining and simplifying the clinical diagnosis of FAS (7). In 1996, the Institute of Medicine (IOM) published a report lead by Kathleen Stratton that outlined the criteria for the several disorders that fell into the broader diagnosis of FAS; this report includes five disorders associated with maternal alcohol consumption each with slightly different diagnostic criteria (8). These categories have since been adjusted by more recent research and eventually came to be known as a spectrum of illness known as Fetal Alcohol Spectrum Disorders, or FASD. The efforts of H. Eugene Hoyme and colleagues in publishing a clarification of the IOM criteria in 2005 sought to improve the clinical utility of these established criteria through the detailed definition of FASD (9). The accepted, standardized categories of FASD are as follows:

1) Fetal Alcohol Syndrome (FAS) with confirmed maternal alcohol use
2) Fetal Alcohol Syndrome (FAS) without confirmed maternal alcohol use
3) Partial FAS (pFAS) with confirmed maternal alcohol use

4) Partial FAS (pFAS) without confirmed maternal alcohol use

5) Alcohol-Related Birth Defects (ARBD)

6) Alcohol-Related Neurodevelopmental Disorder (ARND)

A diagnosis of FAS requires evidence of specific facial dysmorphia criteria, prenatal and/or postnatal growth deficiencies (i.e. being at or below the tenth percentile for age group in height or weight), and evidence of a brain growth deficiency (i.e. being at or below the tenth percentile for head circumference). Partial FAS (pFAS) requires a certain level of facial dysmorphia in combination with either physical growth retardation, brain deficiencies, or a "complex pattern of behavioral and cognitive abnormalities" that cannot be otherwise explained. This pattern is described in detail in Dr. Hoyme's report. In some cases, a child may meet all the diagnostic criteria for a certain category of FASD with the exception of documented and confirmed maternal alcohol abuse; therefore some clinicians may make a further distinction within a diagnosis of pFAS or FAS based on the documentation available to confirm this exposure. A diagnosis of Alcohol-Related Birth Defects (ARBD) requires confirmed maternal alcohol exposure and facial dysmorphia as well as evidence of a congenital structural defect such as a cardiac malformation or joint contractures; the IOM offers a list of congenital defects that satisfy these criteria. Lastly, a diagnosis of Alcohol-Related Neurodevelopmental Disorder (ARND) requires confirmed maternal alcohol exposure as well as either brain growth deficiency or a "complex pattern of behavioral or cognitive abnormalities" that cannot be otherwise explained.

A 2011 publication by Dr. Jones describes what several decades of research have shown to be maternal risk factors for Fetal Alcohol Syndrome in addition to ethanol exposure (10). These include maternal age greater than 30 years, lower socioeconomic status, ethnicity, having a previous child with an FASD diagnosis, maternal under-nutrition, and genetics relevant to liver enzymes. He did state, however, that there is no evidence to assume that the possible risk associated with maternal ethnicity or under-nutrition are not themselves attributable to socioeconomic status. In addition, sex is not known to be associated with FASD diagnosis. Some studies have suggested that children with FASD remain small (lower in height and underweight) for their age while other suggest that children with FASD may moving into higher height and weight categories and even develop obesity in various FASD groups (11).

Even though public health messages suggest that women should abstain from drinking when they are pregnant or contemplating pregnancy, many women drink during pregnancy, particularly before they are aware of the pregnancy (12). Even so, a sizable minority of women continues to drink during pregnancy; one in ten pregnant women reports alcohol use according to a 2013 CDC report. Further, drinking, and particularly heavy and binge drinking in pregnancy are more common in women who smoke and women with low incomes; in the same report, one in thirty-three pregnant women reported binge drinking within the last thirty days.

In Utero Alcohol Exposure and Fetal Development

Physiological mechanisms at work in the association between in utero alcohol exposure and fetal development and subsequent defects and/or deficiencies have been best studied using animal models. In 1983, Sulik et al reported facial dysmorphia typical of FAS in

offspring of mice whose mothers had been given ethanol early in embryonic development. These features were similar to those in children with FAS and included microcephaly, microphthalmia, short palpebral fissures, smooth philtrum, and long upper lip (13). Upon examination of the embryos via scanning electron microscopy, researchers also observed neural plate deficiencies, especially in the forebrain region. The consequences of such deficiencies include developmental abnormalities of the brain and eye, which are consistent with the diagnostic criteria for several of the FASD. Another important finding of this study was the fact that ethanol exposure in the gastrulation stage of embryonic development induced the abovementioned malformations; this is a stage of pregnancy prior to the time during which women know they are pregnant.

In 1989, Dr. Sant P. Singh and colleagues studied maternally-derived glucose in fetal tissue as a measure of nutrient uptake across the placenta of ethanol-exposed rats and non-ethanol exposed controls (14). Ethanol-exposed rat fetuses had reduced fetal brain and liver weights and lower maternally-derived glucose than rat fetuses who had not been exposed to alcohol. In addition, lungs and body size were reduced in ethanol-exposed rat pups. Dr. Singh and colleagues suggested that impaired placental transfer in ethanol-exposed rats may lead to nutrient deficiency and therefore intrauterine growth retardation when compared to control rats who were not exposed to ethanol in-utero.

Cynthia Driscoll and colleagues conducted comprehensive qualitative comparisons between reports of human behavior and cognitive deficits following prenatal alcohol exposure and animal models involving rats (15). Children and rat pups experienced

similar. Both groups experienced feeding difficulties and deficits in state regulation suggestive of central nervous system impairment, such as increased occurrence of tremors and jitters and poor thermoregulation. In addition, delayed motor function and balance were similar in rats and humans, as well as hyperactivity and deficits in attention span. Learning deficits common in children with FASDs manifested in rats as higher difficulty in associative learning and spatial learning. Driscoll et al concluded that there is overall a high level of congruency between the behavioral and neurodevelopmental consequences of ethanol exposure in rats and those in human children. In addition, they hypothesized the feasibility of a dose-response relationship between quantity and duration of ethanol exposure and degree of the abovementioned deficits.

Theresa Gauthier and colleagues have reported the effects of in utero alcohol exposure on lung development, and neonatal respiratory and immune. Their 2005 study demonstrated that fetal alcohol exposure results in oxidative stress experienced by the fetal lung using a guinea-pig model(1). In short, oxidative stress occurs as a result of the poor balance between antioxidants that destroys free radicals, preventing their harmful effects on the body, and free radicals themselves. The fetal lungs, in early stages of gestation, are deficient in glutathione, an important antioxidant. Ethanol intensifies this deficit and, because of this increased oxidative stress, alveolar macrophage function is inhibited. Alveolar macrophages are immune cells in the lung that are responsible for engulfing foreign materials through a process known as phagocytosis. They also found reduced levels of glutathione in ethanol-exposed alveolar macrophages in association with increased levels of oxidative stress. These macrophages demonstrated increased

apoptosis, or cell death, and diminished phagocytosis. They also suggest that glutathione supplementation of may reduce oxidative stress and might support alveolar macrophage function.

Theresa Gauthier and colleagues also studied the association between neonatal infection in term infants and maternal exposures such as alcohol and nicotine (2). Neonatal infections were more commonly diagnosed in infants whose mothers reported using that self alcohol or smoking in pregnancy. Further, the risk of neonatal infection was three or four times higher in neonates born to mothers reporting excessive alcohol consumption (≥7 drinks per week) compared those who were born to mothers who had not consumed any alcohol while pregnant. This study called for increased attention to and awareness of the association between maternal alcohol consumption and the developing immune system.

Dr. Xiangyuan Wang and colleagues conducted a mouse model trial in which maternal administration of ethanol took place in the second trimester of pregnancy (3). After ethanol administration, fetal lungs were examined histologically and seen to have experienced increased Hoxb5 gene expression, a gene responsible for the patterning of airway branches; its overexpression has been linked to lung malformations in humans. In addition, overall body size and the weight of lungs of fetal mice who had been exposed to ethanol were reduced relative to unexposed mice.

Childhood Asthma

The National Heart, Lung, and Blood Institute defines asthma as "a chronic lung disease that inflames and narrows the airways" (16).The narrowing of the airways leads to less opportunity for air flow into the lungs and causes episodes of wheezing. In 2015, the Centers for Disease Control and Prevention reported the prevalence of asthma in the United States is 8.4% in children and 13% overall, with male sex, non-white race, lower socioeconomic status, and younger age as notable risk factors (17). Asthma costs the United States tens of billions of dollars annually after accounting for associated medical costs, absenteeism from work and school, and years of life lost. Children with asthma may experience an asthma attack, characterized by acute onset of coughing/wheezing, chest tightness, and shortness of breath, which often leads to hospitalization, and occasionally death (AAAI). Fifty-seven percent of children with an asthma diagnosis had an asthma attack in 2007, according to that year's report by the Centers for Disease Control and Prevention. Almost 200 children died from an asthma-related death in the same year. Asthma symptoms can be exacerbated by environmental triggers or other conditions such as flu infection, respiratory syncytial virus (RSV), or sinus infections that are more common in children with weaker immune systems, making them more likely to experience an asthma attack (18).

The American Academy of Allergy, Asthma, and Immunology (AAAI) defines several risk factors for developing asthma during childhood (19). These include allergies, family history of allergies and/or asthma, frequent respiratory infections, low birth weight, secondhand smoke before or after birth, and growing up in a low-income and/or urban environment. Preterm birth (birth prior to thirty-seven weeks gestation) is certainly

associated with FASD and has been known to be associated with asthma diagnoses in childhood (20); maternal smoking during pregnancy is also a known risk factor for asthma diagnoses in childhood (4). Race or ethnicity is known to be associated with asthma, but this could be explained by some interaction with socioeconomic status. Studies assessing childhood BMI in children with asthma are unclear and there is evidence showing that asthma is associated with both overweight and underweight status in children (21).

Fletcher et al studied the long-term effects of childhood asthma and several outcomes in adulthood, such as obesity and absenteeism from school and/or work (22). They found that children with asthma were more likely to be obese in adulthood, have overall reduced health status, and much higher cumulative absenteeism from school and work than children without an asthma diagnosis. They mention strong immune function as an important consideration in managing asthma and suggest that interventions targeted at preventing asthma development in utero and in early childhood would be beneficial to the individual lifetime health of these children and also less costly overall.

After accounting for socio-demographic factors, prematurity and/or low birth weight have been established as risk factors for an asthma diagnosis during childhood. In a 2006 study, Nepomnyaschy and colleagues observed that children born at less than 2500 grams had a two-fold greater risk of being diagnosed with asthma by age three than children not born at low birth weights (23).

Summary

Prenatal alcohol exposure has the potential to affect both human immune function and lung development. As asthma is believed to be an immune condition and is a respiratory condition with a high morbidity in children, we therefore sought to understand the link between FASD and asthma. The American Lung Association has funded research that seeks to improve an understanding of the link between the immune system and asthma. In short, asthma is considered a Type 2 immune response, meaning it is the result of inflammation of monocytes and macrophages that are a critical part of the human immune system (24). This link between immune development and asthma during childhood has implications for an association between restricted fetal development and childhood asthma diagnosis. Evaluating a possible association between FASDs and asthma may lead to further characterization of health outcomes associated with FASD.

METHODS

Study Question

Is there a higher cumulative incidence of asthma among children diagnosed with Fetal Alcohol Spectrum Disorders (FASDs) in a Neurodevelopmental Exposure Clinic than among control children without an FASD diagnosis, selected from National Health and Nutrition Examination Survey (NHANES)?

Hypothesis

After adjusting for sex, age, race, body mass index, maternal smoking, and low birth weight, children with a diagnosis of Fetal Alcohol Spectrum Disorders (FASDs) who are seen in a Neurodevelopmental Exposure Clinic will have higher rates of asthma than the control children who participated in the National Health and Nutrition Examination Survey (NHANES).

Study Design

This study is a cross-sectional study assessing a history of asthma diagnoses in two populations. Therefore we will estimate the cumulative incidence of having a had a diagnosis of asthma using odds ratios to estimate the relative incidence of asthma diagnoses in children with and without FASD diagnoses. Because the clinic is a referral-based population, unexposed participants were selected from an external data source due to the potential for a relationship to exist between the FASD-unexposed from the Emory

Neurodevelopmental Exposure Clinic (ENEC), who likely have other diagnoses, which might also be associated with the risk of having been diagnosed with asthma, and the outcome of asthma. Unexposed subjects from NHANES were chosen because NHANES is a nationally representative sample and is more representative of the general population as a comparison group. This allows us to examine the potential for the FASD-asthma relationship to be biased by referral to the clinic rather than FASD itself; therefore these unexposed subjects from the ENEC data were retained in the study population for use as a secondary, internal unexposed group.

Participants

The data for the exposed subjects with an FASD (n=619) came from ENEC; it is previously collected data and has been utilized in previous studies conducted by the clinic staff. Prenatal alcohol exposure to ethanol is documented and confirmed by the ENEC team using court reports, medical records, and family interviews. Before each child visits the clinic, his or her birth records and previous medical records are requested and examined. Important information from these records includes birth weight, length, and head circumference, as well as any medication and information about previous diagnoses. On the day of each child's visit to the clinic, a full day of evaluations takes place. In no particular order, each child undergoes a medical visit with a registered nurse, a psycho-behavioral evaluation performed by clinical psychologist, as well as an educational evaluation by a specialist. Following each patient's visit, the ENEC staff creates an interdisciplinary team report summarizing the child's visit and diagnoses. The only data extracted from the ENEC data for the purposes of this study were those collected in the medical visit. These data are recorded in the patients' files, which was later extracted and

input into a database. The data includes all children ages six months to eighteen years who were seen at ENEC between 1995 and 2011 whose parent or legal guardian signed an informed consent prior to the start of the clinic visit day. The exposed subjects are those whose clinic visits terminated with a diagnosis of FASD, according to specific International Classification of Diseases code 760.1. The specific level of FASD diagnosis is recorded in the child's report and the database as well.

Children are referred to ENEC in a number of ways; for example, referral from the Department of Family and Children's Services if they are in the foster system, or referral from a primary care physician. Because of the capability of the clinic to administer psychological and educational testing as well to make diagnoses and recommendations in their comprehensive final interdisciplinary reports, they receive referrals for children who exhibit social behaviors and intellectual challenges that are often associated with or included as diagnostic criteria for FASDs.

The study population included only children ages 1-15 seen at ENEC between 1995 and 2011. This particular age cutoff was made due to a large amount of missing relevant covariates in the NHANES data for children age 16-18 (99% of subjects in this age range had missing data for maternal smoking and low birth weight). For the current study we limited the study sample to children over the age of 1 to ensure that diagnoses of asthma were not temporary wheezing that is common in infants because of their small lung size.

Based on these restrictions there were a total of of 1,453 children seen at ENEC. We then excluded those subjects who had missing data for either FASD diagnosis (n=0), prior history of asthma (n=88). Because of the indefinite status of those as deferred and how few there were in the population (n=35), these subjects were also excluded from analysis along with the subjects who were categorized under "unknown" FASD status (n=3). After these exclusions were made, 1,327 subjects remained (97.2%), 619 of whom were diagnosed with an FASD after a full evaluation by the ENEC team. The remaining 708 unexposed subjects in the ENEC data were retained as a secondary, internal comparison group. These exclusions are shown in Figure 1.

NHANES data are available through the Centers of Disease Control and Prevention (CDC) in two-year increments. The unexposed subjects (those without an FASD diagnosis) were obtained using NHANES from the 1999-2000 report through the 2011-2012 report. There was no missing asthma data in the NHANES datasets. The total unexposed population using this data was 23,889.

Variable and Data Measures

FASD was diagnosed by the ENEC Interdisciplinary Team in the manner discussed above; the specific diagnosis was based on the availability of the diagnostic criteria for each level of FASD in the child's medical and social history, as well as the results of his or her psychological and educational testing. The categories of FASD exposure assigned by the clinic staff are as follows: ethanol-exposed (meaning the subject was confirmed to have been exposed prenatally to alcohol but does not meet the other diagnostic for FASDs), Alcohol-Related Birth Neurodevelopmental Disorder (ARND), Partial FAS

(pFAS), FAS, deferred diagnosis (in which indicators of an FASD are observed but more information is needed to make a final diagnosis) and other, non-FASD diagnoses. Those diagnosed with "other", meaning they were not diagnosed with an FASD, constituted the secondary, internal unexposed group.

Asthma status was assessed for both cases and controls as having ever been diagnosed with asthma by a medical professional. For the ENEC subjects, this information could have been gathered by pediatrician records or caregiver self-report, and for the NHANES unexposed group, this information is gathered solely by caregiver self-report. It is coded as a dichotomous variable.

In addition to the outcome and exposure variables for asthma and FASD diagnoses, several covariates were included in the analysis: sex, age, race, current body mass index, low birth weight, and maternal smoking during pregnancy. Sex of each child was coded as male or female in both ENEC and NHANES data. Age range was 1 through 15, inclusive, and was coded continuously in one-year increments. The race variables in the NHANES and ENEC data were recoded so that race could be included as a covariate. In both data, there were equivalent categories for both non-Hispanic White and non-Hispanic Black races, so these categories were included in the final coding for race. There was also an "Other, including mixed race" category in each data source, which was also retained in the final coding. In the NHANES data, Mexican-American race and non-Mexican-American Hispanic race were coded separately, but were combined into a single Hispanic-race category for the purposes of this analysis. In the ENEC data, there were

separate categories for Native American race, as well as Asian or Pacific Islander race; however, these categories did not exist in the NHANES data. These were added to the "Other, including mixed race" category in the ENEC data. The final race categories were as follows: non-Hispanic White (reference), non-Hispanic Black, Hispanic, and Other, including mixed race. We created indicator variables to represent these categories in the logistic model. Because the NHANES methodology involves oversampling Hispanic subjects, two indicator other variables were created to identify each subject as white or non-white and Hispanic or non-Hispanic, and these two covariates were used in place of the multi-level race variables in sensitivity analyses. Body mass index (BMI) was not previously calculated in the data, but was calculated prior to analysis using each subject's weight (in kilograms) and height (in centimeters) using the following formula:

$$BMI = (weight/height/height)*10{,}000$$

Body mass indices were set to missing if their values were less than ten or greater than sixty. Values were recoded into four categories: underweight (<18.5) , normal weight (18.5 to 24.9), overweight (25 to 29.9), and obese (≥30). We created indicator variables to represent these categories in the logistic model. The NHANES data does not include a variable for weeks gestation at birth; our analysis includes birth weight rather than weeks gestation or size for gestational age. Instead, birth weight is dichotomized into low-birth-weight or non-low-birth-weight, with a cutoff of 2500 grams, the standard cutoff in the U.S. for a neonate to be considered low-birth-weight. Infants born below 2500 grams are coded as being low birth weight infants, and those at or above the cutoff of 2500 grams are considered non-low birth weight infants. Maternal smoking in pregnancy was coded dichotomously in both ENEC and NHANES data where an answer of "Yes" signifies that

the mother smoked while she was pregnant with the subject. This data is collected through self-report in the NHANES data and is collected through self-report and birth records for the ENEC subjects. Because there was a substantial amount of data missing for this variable (32% of FASD-exposed, 37% of other ENEC subjects, 1% of NHANES subjects) and because many children with FASD have been adopted and/or in foster care, we considered that a child without documentation of maternal smoking in pregnancy is likely to have been unexposed.

Analytic Methods

All analyses were performed using SAS version 9.4.

We assessed the distribution of covariates through univariate analyses; categorical covariates were analyzed using frequency tables. The distribution of age, the only continuous variable included in the analyses, was examined through its mean and standard deviation in each exposure group.

We performed bivariate analyses using chi-square tests of independence to assess whether the categorical covariates of interest (all but age) were independently associated with the outcome of asthma diagnosis. We used the NHANES data in these analyses as this is an estimate of the true distribution of these covariates in the population. For the multi-level covariates for race and BMI, a referent category was chosen; white was the referent racial group and normal was the referent BMI group. Odds ratios were obtained to determine which characteristics that are shown to be associated with an asthma diagnoses.

We ran logistic regression models to assess the association between FASD exposure and the outcome of asthma diagnosis, controlling for the covariates of interest, using the ENEC unexposed subjects as the comparison group in the first comparison, and the NHANES unexposed subjects as the comparison group in the second comparison. This allowed us to examine the association between any FASD diagnosis and asthma. After crude models were run for both of these comparisons, we stratified the exposure status into the four levels of FASD diagnosis and ran each one through the model individually. We ran both unadjusted and fully-adjusted models for each comparison. Only seven children had an ARND diagnosis and only one of these had been diagnosed with asthma diagnosis. These children were retained in the study population and included in the pooled analysis but there are no reported results for this individual level because of the absence of a meaningful effect measure due to small cell sizes.

RESULTS

Univariate Analyses of Covariates

The univariate distributions of the covariates of interest for the exposed group and each of the unexposed groups are shown in Table 1. The ENEC data, both for exposed and unexposed is about 60% male, while the NHANES data is more evenly distributed, about 50% male. The mean age is lowest in the FASD-exposed subjects, at 5.6 ± 3.7 years, and is highest in the NHANES unexposed group, at 7.8 ± 4.6 years. Distribution of race is notably different across exposure groups. For the FASD-exposed children, 49% are non-Hispanic Black, and only 2.3% identify as primarily Hispanic race; however, for the NHANES unexposed group, 37% of subjects are Hispanic and only 28% non-Hispanic Black. This is largely due to the oversampling of Hispanics in the NHANES data collection process. Individuals with FASD were more likely than either NHANES subjects or non-FASD children from ENEC to be born with low birth weight. Forty-eight percent of individuals with an FASD diagnosis were born low birth weight, whereas 23% of the other children seen at the clinic and only 9% of NHANES subjects were born low birth weight. A higher proportion of children with FASD (48%) were known to have a mother who smoked during pregnancy than other children in either the ENEC (39%) or the NHANES (14%) comparison groups. A body mass index that is considered underweight (<18.5) was the most common categorization of BMI across all exposure groups, but was highest among the FASD-exposed individuals (81%).

Bivariate Analyses

Table 2 shows the results for bivariate analyses considering an association between the categorical covariates of interest (all covariates with the exception of age) and the dichotomous outcome of asthma diagnosis for the NHANES unexposed group, chosen because it is the most representative of the general population. Using chi-square tests of independence, we estimated the proportion of the NHANES subjects in each stratum of covariates who had an asthma diagnosis. Gender, race, ethnicity, birth weight, maternal smoking, and current BMI were all associated with the likelihood of having been diagnosed with asthma, with the exception of the "Other, including multiracial" group. According to this analysis, these include male sex (OR=1.5, 95% CI 1.4 to 1.6), non-Hispanic Black race (OR=1.6, 95% CI 1.5 to 1.8), low birth weight (OR=1.5, 95% CI 1.3 to 1.7), maternal smoking during pregnancy (OR=1.4, 95% CI 1.3 to 1.6), and a BMI classified as overweight (OR=1.3, 95% CI 1.2 to 1.5), or obese (OR=1.6, 95% CI 1.3 to 1.8). Protective effects were seen for Hispanic race (OR=0.90, 95% CI 0.82, 0.99) and BMI classified as underweight (OR=0.74, 95% CI 0.68, 0.80).

Logistic Regression

Table 3 contains the results of the logistic regression. We did not see an association between FASD and asthma diagnoses when the FASD-exposed subjects were compared to the other ENEC subjects (OR= 1.02, 95% CI 0.77 to 1.35). In contrast, having an asthma diagnosis was more common among children diagnosed with FASD in comparison to NHANES data (OR=1.65 95% CI 1.33, 2.03). However, controlling for potentially confounding variables attenuated the observed association (OR=1.29, 95% CI = 1.03,1.61). Asthma was more commonly diagnosed in children with FASD than the

comparison population in all diagnostic subgroups, but was statistically significant only for the subgroup knows to have been exposed to alcohol in utero (OR=1.56, 95% CI 1.04, 2.34) (Table 3).

DISCUSSION

Interpretation of Results

This study provides an important contribution the association between FASDs and long-term physical outcomes has not been extensively studied. Because a myriad of intellectual and socio-behavioral outcomes, the extent of which can be quite severe, are associated with FASDs, these are often the focus of long-term FASD studies. An attempt to elucidate the relationship between in utero ethanol exposure and physical development and immune health in human children is important to supplement the existing animal studies and physiological links that have been hypothesized. Unfortunately, the results in Table 3 do not provide conclusive evidence regarding the hypothesized association between FASD diagnoses and asthma diagnosis during childhood. The fully-adjusted pooled odds ratio using an external comparison group is 1.29 (95% CI 1.03, 1.61), which implies that those children with any FASD diagnosis are about 30% more likely to have asthma than children without an FASD diagnosis. However, the odds ratio for the comparison using ENEC unexposed subjects is 0.96 (95% CI 0.71, 1.29), suggesting that there is no association between FASD and asthma when considering only the clinic subjects. The accuracy of the results reported here are subject to a number of limitations, discussed in the following subsection.

Strengths and Limitations

Strengths

A strength of this study is the use of two unexposed comparison groups in order to assess how well confounding may be controlled for, and how much selection bias and

information bias, specifically misclassification, may contribute to the measures of association obtained in the results. Using both an internal and external comparison groups allowed for consideration of the potential for an association between FASD and asthma to be a result of referral to the clinic rather than FASD itself. Because the ENEC subjects, both FASD-exposed and unexposed, are referred to the clinic for assessment, it is likely that even those children without exposure to FASD are suffering from another developmental disorder with some similar diagnostic criteria to FASD that may be associated with an asthma diagnosis during childhood. Therefore, the ENEC comparison group may have a higher proportion of asthma diagnoses than the general population. The use of the second comparison group using NHANES data was an attempt to see how the unexposed ENEC subjects compare to the general population and assess the possibility of yielding different effects based on populations with different distributions of covariates as well as unknown confounding factors.

Additionally this study is large relative to most other studies of FASD. There were 619 children with FASD included in this study. Additionally, we had data on 708 children with other neurodevelopmental conditions and 23,889 subjects using the NHANES data. Having such a large sample size makes it more likely that the group of FASD-exposed subjects does in fact represent those diagnosed with FASD in the general population, and the large size of the NHANES comparison group provides strength in the sense that these individuals represent the non-FASD general population well. The study power may also be more limited in the ENEC comparison group as there are so many fewer subjects than in the NHANES group. This may contribute to the lack of association between the

exposed group and ENEC unexposed group; however, it is more likely that although the ENEC comparison group also has a high number of subjects, they are subject to selection bias, an issue discussed in the limitations below.

Limitations & Sensitivity Analyses

A primary limitation of this study is selection bias. If the true association is null, as the ENEC comparison suggests, there may be a diagnostic selection bias because children with FASD are more likely to receive medical attention, even for conditions thought to be unrelated to their developmental disability. Thus, FASD may truly be unrelated to the risk of developing asthma and the observed association using the NHANES comparison group may represent diagnostic bias. Alternatively, it may be inappropriate to considering that the children referred to ENEC for other conditions as representative of the general population if these conditions are also associated with the risk of developing asthma. Thus, a truly non-null association may be masked by selection bias when using this comparison population. Through performing basic sensitivity analyses using estimates of selection probabilities, we sought to assess how much this issue could impact the measures of association in the results. Because there was no missing asthma data for the NHANES comparison group, we set the selection probabilities equal to 100% for the unexposed subjects both with and without asthma. When the selection probabilities were equal among those FASD-exposed individuals both with and without asthma (set at values of 50%, 75% and 90%), the corrected OR was 1.73, higher than our crude OR of 1.65 from Table 3. When selection was 10% higher for FASD-exposed subjects with the outcome compared to FASD-exposed subjects without the outcome, the OR was 1.54, slightly lower than our unadjusted OR in Table 3. When the difference was 15% higher

for those with the outcome, the OR was 1.44, suggesting that the more likely the exposed subjects with the outcome are to be selected into the study population, the closer to the null the true association may be. This likely does affect the measures of association shown in Table 3.

In addition, NHANES oversamples for Hispanic individuals, so it is not necessarily a sample representative of the population in terms of racial distribution. If Hispanic race is a true risk factor for asthma diagnosis, and more Hispanics were selected to be in the sample, this may lead to an underestimate of the FASD-asthma association as shown in Table 3. The fully-adjusted model was run again for all comparisons with the pair of dichotomous indicator variables of white/non-white and Hispanic/non-Hispanic in place of the three indicator variables that were included in the main model. Due to the NHANES method of oversampling Hispanic subjects, this secondary model was run in order to assess the effect, if any, the coding of race had on the results of the main analysis. The recoding of race had a negligible effect on the odds ratios for all comparisons made. For example, the odds ratio for the fully-adjusted effect of FASD on asthma diagnosis using the ENEC unexposed group with the white/non-white and Hispanic/non-Hispanic indicator variables was 0.95 (95% CI 0.72 to 1.25) when it had been 0.96 (95% CI 0.71, 1.29) using the indicator variables representing four categories of race. The odds ratio for the fully-adjusted effect of FASD on asthma diagnosis using the NHANES unexposed group with the white/non-white and Hispanic/non-Hispanic indicator variables was 1.27 (95% CI 1.03, 1.56) whereas it was 1.29 (95% CI 1.03, 1.61) using the four categories of race in the model. We decided that this sampling bias was sufficiently controlled for by including race in the model.

An additional potential source of selection bias is that logistic regression excludes any observations for which one or more of the predictor variables is missing, the crude models were run using only the observations that were included in the fully-adjusted models. After analysis was complete, the crude models were run again including all of the observations that had been excluded from the main analysis due to missing covariates; the difference in effect measures was negligible.

There is also likely some residual confounding due to limitations in what we were capable of controlling for in this study population. It is likely that the differences can be attributed to the effect of both the referral bias as well as some residual confounding. The lack of ability to control for certain important covariates, such as socioeconomic status (SES) and geographic region was a major limitation of this study. First, SES was not included as a covariate in the analysis due to the complexity of controlling for such a characteristic in this specific study population. Common proxies of socioeconomic status, such as parental education and insurance status, were not available or had high proportions of missing data for the ENEC population. Income was considered as a proxy to control for socioeconomic status and was available in the NHANES data; however, the only option to assign income data to the ENEC subjects was to match the subjects' zip codes from intake to the median family income from the U.S. Census from the year they visited the clinic. This was carried out, but the distribution of income in this population was particularly unevenly distributed when categorized to match the NHANES data and again when the variable was recoded into different categorical breakdowns. Another problem with using income information is the fact that many of the children in the ENEC

sample were in foster care or had been adopted, so even if family income was collected accurately at intake, the child's home situation would likely not be equivalent to that which his mother had experienced during pregnancy or that the child experienced during previous years when exposures associated with asthma might be more common. For these reasons, no proxy for socioeconomic status was included in the model. However, it is likely that SES confounds the association between FASD and asthma diagnosis; therefore some residual confounding due to lack of controlling for SES may be present in the reported effects.

In addition, we were not able to control for geographic region in this study. The Emory Neurodevelopmental Exposure Clinic is located in Atlanta, Georgia, and most of the patients referred for evaluation are from Atlanta or the state of Georgia. Children who are not from Georgia are often from neighboring states in the southeast U.S. In contrast, NHANES data is a national sample. In collecting data for the NHANES, geographic information is recorded for subjects, but census tract, current state of residence, and other geographically relevant information is restricted by the CDC and was not available for the purposes of this study. Ideally, a geographic restriction would have been made in the NHANES unexposed group to only the southeast region of the U.S. where there is a more uniform underlying distribution of baseline risk of asthma.

In addition, the distribution of current BMI among the NHANEs population was 48% underweight, 26.5% normal weight, with the rest being overweight (7%), obese (4%), or missing (14.5%). This is not representative of the general population as we expect it to be.

The complexity of diagnosing asthma at young ages is another limitation of this study. Cumulative diagnosis of asthma increases with age as children have more opportunity to encounter exposures associated with asthma, and more opportunity to be diagnosed with asthma as well. Because very young children experiencing asthma-like symptoms are sometimes known to "grow out" of an early asthma diagnosis, some physicians will not diagnose asthma until the child is older. Some younger children may in fact have asthma, but no formal diagnosis at the point during which they were assessed at ENEC or surveyed through NHANES. This lack of specificity has implications for misclassification of the outcome, and may be differential if FASD-exposed subjects were more or less likely than children in the general population to have had regular pediatrician visits. If the NHANES unexposed subjects tend to be older than the exposed subjects, this could also contribute to differential misclassification; in this study population, the NHANES unexposed subjects have a slightly higher average age than the FASD-exposed subjects. We performed sensitivity analyses using specific misclassification bias parameters to assess the impact of misclassification of asthma on the observed associations. We set the specificity and sensitivity of asthma diagnoses for the NHANES unexposed group equal to 100%. We assumed that overall, children diagnosed with FASD are not likely to have been misdiagnosed due to the very specific criteria for diagnosis; however, it is likely that many children who truly do have FASD are not diagnosed as such; therefore we set the sensitivity to 75% and the specificity to 90% for the exposed group. The corrected odds ratio we obtained was 1.46, which is weaker and closer to the null than the association we obtained through the unadjusted logistic model, 1.65. It's possible that misclassification of outcome does affect the

measures of association presented in Table 3, specifically through overestimation of the association.

It is also possible that the specific diagnoses of FASD do not represent etiologically distinct groups. We do not consider analyses of the various levels of FASD diagnosis (ethanol-exposed, pFAS, and FAS) to be increasingly related to strength of association with an asthma diagnosis simply because they are relevant to the severity of disease. Rather, this stratification by specific level of FASD diagnosis acknowledges the varying specificities of the FASD diagnosis for each particular level, rather than an etiologic relationship between level of FASD diagnosis and likelihood of prior history of asthma. Because the "ethanol-exposed" category only has only one criterion required to satisfy the diagnosis (that is, confirmed in utero ethanol exposure), it is likely that this category is fairly specific; however there are likely many truly exposed children who are not considered as such, and therefore the sensitivity is low for this diagnosis. On the other end of the spectrum, there is full FAS diagnosis, which requires several criteria to be met for diagnosis, as described in the background literature. This definition is less sensitive due to the increased potential for misclassification of exposure; however, we do not think this likely affected the overall pooled association between FASD and asthma.

Low birth weight, as described in the section on the sensitivity analyses, is not an ideal covariate for which to account for preterm birth in examining the association between FASD and asthma diagnosis due to its potential position on the causal pathway between the exposure and outcome. Ideally, preterm birth status (i.e. gestational age) would have been a better covariate; however, NHANES data does not include information on

gestational age. Because FASD leads to prenatal growth restriction, it is probable that considering low birth weight as a proxy for preterm birth introduces differential misclassification of this covariate, as some neonates born at low birth weight may also have been small for gestational age which may be on the causal pathway between FASD and asthma. In the study population, FASD-exposed children are more likely to be born at low birth weight than unexposed NHANES subjects (49% vs. 9% respectively).

As low birth weight is associated with the exposure of FASD and could be considered a risk factor for the outcome of asthma diagnosis, it was considered a potential confounder and included in the main model. However, because birth weight percentile (weight for gestational age) is a diagnostic criteria for several levels of FASD, birth weight may lie on the supposed causal path between FASD and asthma, and therefore controlling for it may introduce some confounding. The adjusted model was run without the dichotomous low birth weight variable but retaining all others from the main model. For the FASD-exposed subjects compared to the ENEC unexposed group in the main model that included the low birth weight variable, the odds ratio was 0.96 (95% CI 0.71, 1.29); after regression without the low birth weight covariate it was 0.94 (0.72, 1.23), a negligible difference. However, the adjusted odds ratio using the NHANES unexposed group without the low birth weight variable was 1.42 (95% CI 1.16, 1.74), which is just about 10% more than that seen in the model that did include the low birth weight variable (OR=1.29, 95% CI 1.03, 1.61). From this secondary analysis, it appears that including the low birth weight variable might in fact introduce some confounding to the measured effect, specifically bias toward from the null.

The maternal smoking variable is another potential source for misclassification bias, which is common in analyses utilizing data collected through self- report, especially that of drug and alcohol use; social desirability bias may have played a role in the effects seen in these analyses. For example, mothers may not have been inclined to report whether or not they smoked while they were pregnant because it is known to not be a socially acceptable behavior in many settings. The ENEC data for this variable was collected using self-report, medical records, and court reports, so may have been able to eliminate some potential for misclassification in this way; however, the collection of this variable for NHANES relied solely on self-report so misclassification may have been differential. In contrast, upon recoding the missing maternal smoking data as undocumented maternal smoking, this could have introduced a different source of differential misclassification for this variable. This covariate was missing 32% and 37% of the time for the FASD-exposed and FASD-unexposed at ENEC, respectively; however, only about 1% of this data was missing in the NHANES sample. Considering the exposed and both unexposed groups, if subjects with missing data for maternal smoking were in fact more likely to have mothers who truly had smoked during pregnancy, this would differentially impact the ENEC data. We performed sensitivity analyses to assess the effect of the different sensitivities of the maternal smoking covariate under the assumption that true non-smokers are very rarely misclassified as smokers in both outcome strata; their specificities were set to 100%. The sensitivity of maternal smoking data from ENEC is likely impacted by the 30-40% missing data in each group sampled from ENEC as described here; the sensitivity of this group was set to 60%. Because of the NHANES comparison group being subject to bias due to self-report

of a socially undesirable characteristic, we set the sensitivity for this group to 75%. The resulting Mantel-Haenszel odds ratio was 0.88 compared to the crude odds ratio of 1.20 produced in this analysis. This suggests that differential misclassification of smoking may, in fact, have produced the observed relationship between FASD and asthma in comparison to the NHANES population. When the sensitivities were set to 75% for the ENEC group and 85% for the NHANES group, this MHOR was 1.03. As it seems that the measure of association is susceptible to changes in sensitivity for this covariate, it is possible misclassification of maternal smoking impacted our results.

Children with FAS are often not living with a biologic parent. This leads to the possibility of differential misclassification of covariates because their current caregivers may not be aware of prior exposures and/or diagnoses. Additionally, these children may be more likely to have been placed in high income homes and thereby receive better than average healthcare. Current caregivers may not be aware of a prior asthma diagnosis, or they may not have knowledge of maternal smoking on the part of the biological mother; which is a likely explanation for anywhere there is missing data in the ENEC sample.

FUTURE DIRECTIONS AND CONCLUSIONS

Suggestions for Future Research

There are a number of important considerations for future studies involving asthma and other long-term physical outcomes of FASDs. First, a study to most effectively assess this relationship would be able to measure asthma status in a standardized manner to better estimate the true risk of asthma among those children diagnosed with an FASD compared to those with no FASD diagnosis. This might be accomplished by examining children with and without FASD and assessing asthma status equivalently for all subjects as part of the study, perhaps through spirometry, methacholine challenges, and/or use of asthma medication. Future studies should attempt to collect data regarding important covariates as accurately as possible across both exposure strata. Ideally, the study population would be very large such that each recognized level of FASD diagnosis could be considered on its own. In addition, this would be a longitudinal-type study that begins at or before birth, so as to accurately measures competing risks in each child's environment as well as utilize the element of time in the most practical way- from exposure to outcome.

Another consideration for future research is continued efforts in animal studies, especially those that seek to analyze the link between in utero alcohol exposure and immune function, as the immune system has a role in asthma development and respiratory outcomes in childhood and adulthood. It is known that immune function and asthma are related physiologically; however, it is important to further extend this link to fetal development and teratogenic disruption of the human immune system.

Conclusions

Regarding the original hypothesis, due to the limitations associated with the main analyses, this study does not provide sufficient evidence of an association between FASD as an exposure and the outcome of asthma diagnosis. However, this study does provide support for efforts to understand the long-term implications of FASD and prenatal alcohol exposure on a variety of clinical outcomes, including asthma.

As Fetal Alcohol Spectrum Disorders have various diagnostic criteria ranging from intellectual deficiencies to cardiac malformations, this is a complex condition from which to attempt to predict a child's risk of certain outcomes such as childhood asthma. The treatment of each child with an FASD diagnosis must be tailored to address that child's specific socio-behavioral, intellectual, and physical capabilities and limitations. This requirement for multi-faceted, individualized treatment is a challenge for researchers and professionals in this field. For this reason, as well as the fact that one hundred percent of FASD cases are preventable, it is important to continue prevention efforts; however children who currently suffer from an FASD require continued research efforts that seek to identify most accurately what difficulties they may face and how those in the field can best address the needs of these children.

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TABLES

Table 1. Distribution of Covariates in Children with Fetal Alcohol Spectrum Disorders and Comparison Populations.

Variable (n, %)	ENEC[a] FASD-Exposed (n=619)	ENEC FASD-Unexposed (n=708)	NHANES FASD-Unexposed (n=23,889)
Age in years (mean ± std dev)	5.6 ± 3.7	6.2 ± 3.5	7.8 ± 4.6
Sex			
Male	369 (59.6)*	425 (60.0)*	12,018 (50.3)
Female	250 (40.4)	283 (40.0)	11,871 (49.7)
Race			
Non-Hisp White	238 (38.5*)	301 (42.5)*	6,653 (27.9)*
Non-Hisp Black	301 (48.6)	306 (43.2)	6,684 (27.9)
Hispanic	14 (2.3)	12 (1.7)	8,890 (37.2)
Other, including multiracial	60 (7)	80 (11.3)	1662 (7.0)
Missing		9 (1.3)	
Low Birth Weight[b]			
Yes	302 (48.8)	161 (22.7)*	2,116 (8.9)*
No	317 (51.2)	547 (77.3)	21,624 (90.5)
Missing			149 (0.6)
Maternal Smoking			
Yes	296 (47.8)	279 (39.4)*	3264 (13.7)*
No	323 (52.2)	429 (60.6)	20,625 (86.3)
BMI Class			
Underweight	498 (80.5)*	533 (75.3)*	11,511 (48.2)*
Normal	96 (15.5)	534 (75.3)	6,337 (26.5)
Overweight	4 (0.7)	535 (75.3)	1,632 (6.8)
Obese	7 (1.1)	536 (75.3)	957 (4.0)
Missing	14 (2.3)	537 (75.3)	3,452 (14.5)

[a]ENEC=Emory Neurodevelopmental Exposure Clinic, FASD=Fetal Alcohol Spectrum Disorders, NHANES=National Health and Nutrition Examination Survey, BMI=Body Mass Index, World Health Organization classifications

[b]Subject considered low birth weight if born below 2500g

**Indicates statistically significant difference across strata of covariate*

Table 2. Relationship between Covariates and Asthma Diagnosis in NHANES[a] Comparison Group.

Variable		n (%)[b]	OR, 95% CI	$\chi^2_{df=1}$[c]	p-value
Sex			1.5 (1.4, 1.6)	106.3	<0.001
	Male	2,080 (17.3)			
	Female	1,490 (12.6)			
Race					
	Non-Hisp White (ref[d])	884 (13.3)	1.0 (ref)	210.3[e]	<0.001
	Non-Hisp Black	1,345 (20.1)			
	Hispanic	1,075 (12.1)			
	Other, including multiracial	266 (16.0)			
White Race			0.83 (0.76, 0.90)	19.7	<0.001
	Yes	884 (13.3)			
	No	2,686 (15.6)			
Hispanic Race			0.69 (0.64, 0.74)	90.6	<0.001
	Yes	1,075 (12.1)			
	No	1,495 (16.6)			
Low Birth Weight[e]			1.5 (1.3, 1.7)	52.1	<0.001
	Yes	430 (20.3)			
	No	3,126 (14.5)			
Maternal Smoking			1.4 (1.3, 1.6)	47.3	<0.001
	Yes	618 (18.9)			
	No	2,952 (14.3)			
BMI Class					
	Underweight	1,563 (13.6)			
	Normal (ref)	1,111 (17.5)	1.0 (ref)	110.6	<0.001
	Overweight	323 (19.8)			
	Obese	218 (22.8)			

[a]*NHANES: National Health and Nutrition Examination Survey, OR= odds ratio with 95% confidence interval BMI= Body Mass Index, World Health Organization classifications*

[b]*Number (%) of subjects in that strata with an asthma outcome*

[c]*Wald chi-square test statistic values*

[d]*Reference category*

[e]*Degrees of freedom for Race and BMI chi-square test = 3*

[f]*Subject considered low birth weight if born below 2500g*

Table 3. Association between Diagnosis of Fetal Alcohol Spectrum Disorders and Asthma Diagnosis in Children.

	Unadjusted			Fully adjusted[c]		
Comparison	OR[a] (95% CI)	$\chi^2_{df=1}$[b]	p-value	OR (95% CI)	$\chi^2_{df=10}$	p-value
All FASD vs. ENEC[d]	1.02 (0.77, 1.35)	0.01	0.91	0.96 (0.71, 1.29)	18.42	0.07
EtOH-exposed[e] vs. ENEC	1.22 (0.79, 1.88)	1.17	0.28	1.14 (0.73, 1.79)	0.98	0.32
pFAS vs. ENEC	0.93 (0.07, 4.54)	0.01	0.93	0.83 (0.53, 1.31)	0.02	0.89
FAS vs. ENEC	0.98 (0.68, 1.42)	0.11	0.74	0.96 (0.64, 1.42)	0.14	0.7
All FASD vs. NHANES[f]	1.65 (1.33, 2.03)	21.523	<0.001	1.29 (1.03, 1.61)	403.41	<0.001
EtOH-exposed vs. NHANES	1.97 (1.3, 2.9)	2.06	0.15	1.56 (1.04, 2.34)	1.54	0.21
pFAS vs. NHANES	1.50 (1.00, 2.24)	0.19	0.66	1.17 (0.78, 1.76)	1.05	0.83
FAS vs. NHANES	1.59 (1.16, 2.18)	1	0.48	1.24 (0.89, 1.71)	0.19	0.66

[a] *OR=odds ratio and 95% confidence interval, FASD=Fetal Alcohol Spectrum Disorders, ENEC=Emory Neurodevelopmental Exposure Clinic, pFAS=Partial Fetal Alcohol Syndrome, FAS=Fetal Alcohol Syndrome, NHANES=National Health and Nutrition Examination Survey*

[b] *Wald chi-sqare test statistic values*

[c] *Adjusted for age, sex, race, low birth weight, maternal smoking, BMI*

[d] *ENEC group: the unexposed (non-FASD) subjects from Emory Neurodevelopmental Exposure Clinic*

[e] *EtOH-exposed are subjects with an FASD diagnosis who satisfy only the criterion of having been exposed to ethanol in utero*

[f] *NHANES group: the unexposed (non-FASD) subjects from the National Health and Nutrition Examination Survey*

FIGURES

Figure 1. Study Population Exclusions for Emory Neurodevelopmental Exposure Clinic Subjects