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Fetal Alcohol Syndrome and Respiratory Symptoms Seen in Georgia Pre-adolescent Children

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B.S., University of California, Irvine, 2010

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ABSTRACT

FETAL ALCOHOL SYNDROME AND RESPIRATORY SYMPTOMS SEEN IN GEORGIA PRE-ADOLESCENT CHILDREN

By Lindsey M. Weiner

OBJECTIVES: Fetal Alcohol Syndrome is a collection of physical, mental, behavioral, and/or physiological symptoms that present in infants and young children exposed to alcohol during fetal development. In addition to the well-known medical problems associated with FAS, some observational studies and the results of animal research suggest that children with FAS may also be at greater risk of respiratory ailments such as lung infections and asthma. There is a need for diagnosticians and patients to fully understand the wide array of medical problems that may develop from fetal alcohol exposure, yet few studies have investigated whether children with FAS are more likely to develop respiratory symptoms than children without FAS.

METHODS: Medical chart data from 625 pre-adolescent patients of the Fetal Alcohol Clinic at the Marcus Autism Center were analyzed in a retrospective cross-sectional study comparing patients across three FAS diagnostic levels (full FAS, partial FAS, no FAS diagnosis). Logistic regression was used to fit a model to describe the association between FAS diagnoses and respiratory outcomes. Asthma-related symptoms were analyzed as a separate outcome.

RESULTS: The full logistic model included gender, insurance provider, maturity at birth, and race/ethnicity as covariates. In all comparisons, respiratory and asthma-like symptoms were less common among those children with an FAS diagnosis compared to those without an FAS diagnosis. No significant association between the prevalence of FAS diagnosis and the prevalence of respiratory symptoms (or asthma-related symptoms) could be detected ($P > 0.05$).

CONCLUSIONS: The low statistical power, misclassification, and lack of a proper control group hinder this study's ability to detect a significant association; however those without an FAS diagnosis may have other conditions that make them more susceptible to respiratory symptoms. Future studies should explore the use of a large and appropriately powered cohort or case-control study in order to further examine this possible association and to help uncover the extensive physiological effects that result from prenatal exposure to alcohol.

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INTRODUCTION

Fetal Alcohol Syndrome (FAS) is a permanent and potentially debilitating disorder that results from alcohol exposure during fetal development. In addition to an array of birth defects and developmental challenges, there is some evidence to support the notion that children with FAS are more likely to suffer asthma, wheezing, respiratory infections, and other lung problems compared to children with no prenatal alcohol exposure (4, 5, 8). While the correlation between prenatal alcohol exposure and respiratory symptoms has not been well described in newborns and young children with FAS, evidence from animal trials maintains that such a relationship between alcohol exposure and lung function should exist in FAS children.

Several studies using animal models have shown that animals exposed to ethanol in utero have lungs that are significantly less developed compared to ethanol-free controls (13, 15, 16, 17). Ethical considerations make it impossible to test this association in humans, and it is rare to find an observational study looking at this association. While adult alcoholics are at an increased risk of developing bacterial pneumonia, there has been no documentation of the extent of respiratory problems seen in alcoholics and whether such an association is present in children exposed to alcohol during fetal development (7). Thus, the goal of our study is to assess whether prenatal alcohol exposure is associated with the presence of respiratory problems including asthma-like symptoms and infections in pre-adolescent children living in Georgia.

Respiratory symptoms are a very common ailment for children, especially those under 5 years of age; most children will develop 3 to 8 respiratory illnesses each year for the first 5 years of life (11). Both the upper and lower respiratory systems can be affected

by bacteria, viruses, congenital deformities, environmental conditions, and allergies. The upper respiratory system includes the nose, mouth, and throat and is prone to common illnesses such as influenza and bacterial infections. More prone to severe assault, the lower respiratory tract is the site of viral and bacterial infections such as respiratory syncytial virus (RSV), asthma, and pneumonia. RSV affects 90% of all children in the United States by the age of 2, and asthma is the most common cause of emergency room visits in children under 5 years old (11). Asthma is characterized by inflamed and obstructed airways, chest constriction, wheezing, difficulty breathing, and coughing; while the exact cause of asthma is not known, researchers believe environmental and genetic factors, childhood infections, and over-active immune systems may contribute to its development (11). Furthermore, it is well established that parental smoking, recurrent chest infections, maternal or sibling asthma, male gender, preterm birth, Black or Hispanic race, and low socioeconomic status are additional significant risk factors for childhood asthma and wheezing (22-25, 27).

Small children under the age of 5 are more likely, in general, to suffer from nonspecific respiratory illnesses due to the constant exposures to bacteria and viruses in schools, daycares, and other social settings. If the child is less than 5 years old, his or her respiratory symptoms are more likely to be mistaken for asthma when in fact they are only the effects of a common allergy or virus. If the child is over the age of 5 and still experiencing asthma-related symptoms, there is a greater likelihood that this is a true presentation of asthma (11).

Especially in large cities, such as Atlanta, environmental triggers including smog, debris, and pollen are found at a heavy concentration in the air. In a 2011 study, the

American Lung Association ranked Atlanta as the 23rd worst city for high ozone levels and 30th worst city for particle pollution out of 277 metropolitan areas (21). It is therefore no surprise that a large proportion of Atlanta children suffer from illnesses such as asthma; in 2009, when the national asthma rate was 9.1%, Atlanta children were suffering asthma at a rate of 10% (20). Thus, we can not rule out that a high prevalence of asthma seen in the study population would only be the result of poor air quality and not the effect of alcohol exposure in utero.

This cross-sectional study will look at children evaluated by well-known professionals at a fetal alcohol clinic in Atlanta, Georgia and will evaluate whether the presence and degree of an FAS diagnosis is related to the prevalence of reported respiratory problems among pre-adolescent patients. The establishment of such a relationship could help physicians identify and treat the full extent of alcohol-related impairments in an exposed child, and may lead to further research on ways to circumvent and negate, if possible, the effects of alcohol on lung function.

LITERATURE REVIEW

Diagnosing FAS

Fetal Alcohol Syndrome (FAS) has been a widely recognized disease for decades; since its initial discovery in 1968, researchers and doctors have been encouraging pregnant women to refrain from the ingestion of alcohol due to the permanent and devastating health effects that alcohol exposure can cause to the developing fetus (1). FAS consists of a collection of reported symptoms presented by children exposed to alcohol during fetal development including physical birth defects, developmental problems, and behavioral irregularities (2). Nevertheless, the most commonly recognized effects of fetal alcohol exposure are growth deficiencies, central nervous system impairment, and characteristic facial dysmorphia (3). Each of these signs, if present, can be manifested with differing degrees of severity (ranging from negligible to severe) that depend largely on unknown individual characteristics and the amount and timing of alcohol exposure. As a result, the diagnostic techniques are variable and heavily reliant on experienced health professionals (2). Symptoms or a combination of symptoms described above may be present simultaneously or not at all in children with fetal alcohol exposure.

In 1996, the Institute of Medicine (IOM) became the first system to standardize the diagnosis of FAS by creating five diagnostic categories (1):

1. FAS with a history of maternal alcohol use
2. FAS without a history of maternal alcohol use
3. Partial FAS (pFAS) with a history of maternal alcohol use
4. Alcohol-related birth defects

5. Alcohol-related neurodevelopmental disorder

Category 1 consists of children with confirmed maternal use of alcohol, as well as evidence of facial abnormalities, growth retardation, and central nervous system (CNS) impairment. Category 2 has the same criteria for facial abnormalities, growth retardation, and CNS impairment as Category 1, however there is no requirement for confirmed maternal alcohol use. Category 3, or partial FAS, consists of confirmed maternal alcohol use, some degree of facial abnormalities, and *either* growth retardation, CNS abnormalities, or unexplained behavior/cognition irregularities. Categories 4 and 5 consist of separate criteria listing the possible birth defects and neurodevelopmental symptoms that can occur as a result of prenatal alcohol exposure; the IOM noted that these last two categories encompass some degree of uncertainty as to whether alcohol causes the adverse effects (1).

While the three hallmark symptoms of FAS are strong indicators for the disorder, they are not the only medical problems that FAS patients experience. Additional symptoms of FAS include hearing loss, immune deficiencies, allergies, endocrine disruption, gastroenteritis, and respiratory infections (4, 5). Receiving heightened clinical interest, these concomitant medical problems have been the center of both human and animal-based studies as researchers attempt to fully uncover the spectrum of alcohol-related birth defects and abnormalities.

Alcohol Exposure and the Human Immune System

It is widely accepted that the over-consumption of alcohol substantially compromises the functionality of the adult immune system (6). The human immune system is composed of two components; the innate immune system including phagocytic

cells that provide a nonspecific response against all invading pathogens via cellular uptake (phagocytosis), and the adaptive immune system which encompasses T-cells and pathogen-specific antibodies (6). The coordination and normal function of both types of immune response systems are necessary for an individual to effectively fight infections, however both components are susceptible to damage from excessive alcohol use. Medical literature confirms that frequent and large quantity exposures to alcohol affect the cells and molecules that make-up the immune system; this includes abnormal production of antibodies, improper cytokine response to infection, and reduced functionality of several lymphocytes (6, 7). With deficient immune systems, regular alcohol abusers do not have the capacity to fight off common infections; it is thus no surprise that for more than half a century, physicians have been documenting high mortality and morbidity rates in alcoholics due to infectious diseases, particularly those of the respiratory system (6). Alcohol abusers have twice the risk of developing lethal bacterial pneumonia and other respiratory symptoms compared to non-alcoholics, and they are at a greater risk of developing tuberculosis, Hepatitis B and C, septicemia, urinary tract infections, lung abscess, and meningitis, among other infections (6, 7).

This known relationship has prompted researchers to investigate whether a similar association exists between alcohol exposure in utero and the risk of infections (and respiratory diseases) in children. Several observational studies have compared children with FAS to those without FAS. Johnson et al. documented a high prevalence of meningitis, sepsis, and pneumonia in a selected group of children with FAS (8). Fittingly, this research team also found diminished immune responses in children with FAS compared to an age-matched control population with growth retardation but without FAS

($P < 0.05$) (8). Additional evidence of an association between prenatal alcohol exposure and infections is shown by Gauthier et al. in an Atlanta-based study; results indicated that mothers who consumed large quantities of alcohol during the 3 months prior or during the 2nd or 3rd trimester of pregnancy delivered newborns who had a significantly increased risk of clinical sepsis and Group B *Streptococcus* infection compared to mothers who drank no alcohol during that same time frame ($P < 0.05$) (9).

Few studies have explored the relationship between fetal alcohol exposure and respiratory diseases. In one study, Yuan et al. showed that after controlling for maternal socioeconomic status, lifestyle factors, and diet, Danish children who were exposed to alcohol in utero were not any more likely to be hospitalized for asthma than unexposed children ($P > 0.05$) (10). While this might suggest that prenatal alcohol exposure does not play a significant role in the development of asthma, the study looked only at cases of asthma resulting in overnight hospitalization and did not account for the less severe, yet more common, episodes of asthma not needing hospitalization (11). Furthermore, over 80% of their study population self-reported alcohol use during pregnancy, which made for a very small control population (10). Caution should be used when drawing conclusions from this study; self-reported drinking patterns are likely to be under-reported, and Denmark's binge drinking pattern is likely to be less severe than that of the United States.

While a high incidence of infections in newborns and children suggests an impairment of the immune system in utero, there are a limited number of study designs that can be used to further evaluate this hypothesis. Thus, without clinical evidence, the

association between immune impairment, respiratory function, and alcohol exposure remains poorly defined in humans.

Ethanol Exposure Research in Animals

Nevertheless, great strides in fetal alcohol research have been made using animal models. These studies have uncovered evidence supporting a relationship between in utero ethanol exposure and a weakened immune system. Researchers have found that the non-human immune system is in fact compromised during ethanol-exposed fetal development; thus, many have proposed that this might explain the higher incidence of infections seen in children with FAS children compared to those without FAS. Experiments during the gestation of non-human primates revealed lower antibody titers in young primates exposed to ethanol compared to primates who underwent ethanol-free development (12). Sozo et al. demonstrated that daily ethanol exposure to in utero lambs resulted in a decreased mRNA expression of pro-inflammatory cytokines; these immune cells are crucial to effectively attack invading pathogens (13). Furthermore, the thymus, a specialized organ of the immune system, was found to have a lower weight, size, and cell count in ethanol-exposed mice compared to non-exposed mice (14). Thus, animal studies have accumulated evidence to support the hypothesis that prenatal alcohol exposure drastically alters the development of the immune system. Human studies support this finding, with several researchers documenting a weakened inflammatory response and a decreased production of critical immune cells including eosinophils, neutrophils, and macrophages in children with prenatal alcohol exposure (8, 15).

While the relationship between maternal alcohol use and decreased lung function has not been thoroughly described in humans, recent animal studies have found clinical

evidence to support the notion that alcohol exposure in utero has a negative effect on lung immunity and development. Histological experiments have shown that mice exposed to ethanol during mid-pregnancy, equivalent to the second trimester in humans, had pups with a significantly lower average lung weight compared to control mice (16). Two studies in lambs revealed that ethanol exposure during fetal development decreased the production of lung growth factors and the concentration of pro-inflammatory cytokines (13, 17). Furthermore, Gauthier et al. showed that alcohol exposure during murine development resulted in impaired interstitial and alveolar macrophage differentiation (15). Without proper macrophage activity in the lungs, the resulting ineffective phagocytosis provides an opportunity for bacterial colonization and infection in the respiratory system. Thus, evidence from animal experiments supports the conclusion that alcohol inhibits proper lung development and immune function, which provides a plausible mechanism for the altered lung function seen in children with FAS.

Despite the evidence presented here, the results of animal studies have generally been inconsistent and variable depending on the animal studied and trial methods. For example, a large study by Grossmann et al. on non-human primates showed no change in white blood cell count, monocyte production, or phagocytosis capacity after ethanol exposure during fetal development, and thus concluded that alcohol induces no effect to the innate immune system (12). There are also biological plausibility issues that surface when attempting to generalize the results of animal studies towards a human population. It will always be unclear as to the extent that animal trials are applicable to humans, and thus confirmatory studies with a human population are needed in order to further investigate the relationship between prenatal alcohol exposure and altered lung function.

While a strong association between fetal alcohol exposure and a challenged immune system and weakened lung capacity has been thoroughly documented in different species of animals, there are still limits in the current knowledge as to whether these studies have made conclusions applicable to humans. And without the ability to conduct controlled trials, the field relies solely on observational studies to identify such associations.

Conclusions

In their 1996 report, the IOM concluded that FAS is a "completely preventable set of birth defects and neurodevelopmental abnormalities" and is "arguably the most common non-genetic cause of mental retardation" (1). Despite the obvious and well-communicated risks, maternal alcohol use during pregnancy continues to be a major public health concern today; as many as 12.5% of all pregnant women report using alcohol during their pregnancy and the birth prevalence of FAS is estimated to be 2 per 1,000 births (18). Due to the often ambiguous nature in the diagnosis of Fetal Alcohol Syndrome, and in the absence of a maternal exposure report, physicians are called upon to identify prenatal alcohol exposure based on his or her observations of associated facial features and/or medical conditions. Research on the complete range of effects from prenatal alcohol exposure deserves attention in order to assist physicians in the accurate diagnosis and treatment of the disease, as well as to assist families in the understanding of the range of potential symptoms that may accompany FAS and affect the livelihoods of FAS children.

Cautions

While FAS is the most severe outcome that can result from alcohol exposure, it is not seen in every exposed child. The relationship between maternal and fetal

characteristics, the amount, timing, duration, and type of alcohol consumed during pregnancy, and the development of FAS has yet to be fully uncovered. Full or partial FAS diagnosis is to some extent a proxy for alcohol exposure in utero; there is evidence that children who were more heavily exposed to alcohol during pregnancy, such as recurrent episodes of binge drinking, are more likely to develop FAS or other alcohol-related health outcomes (19). But there are other unknown variables that influence the development of FAS such as maternal genetics, diet, and environmental factors. While those children with a full or partial FAS diagnosis likely have a report of maternal alcohol use, alcohol exposure during fetal development does not guarantee an FAS diagnosis; children with prenatal alcohol exposure may be born without any symptoms of FAS or with symptoms of a lesser degree of severity not warranting an FAS diagnosis [these less severe symptoms are classified as fetal-alcohol related spectrum disorders (FASD)] (19). Therefore, caution should be taken when using FAS diagnostic categories as an indicator for the extent of prenatal alcohol exposure.

METHODS

Hypothesis

Prenatal exposure to alcohol, as measured in this study by the proxy indicator of Fetal Alcohol Syndrome diagnoses, is associated with impaired lung function in pre-adolescent children.

Study Design

A cross-sectional study of patients seen at the Marcus Autism Center's Fetal Alcohol Clinic (hereafter referred to as "Marcus") was conducted on the 913 children diagnosed at the clinic between November 1990 and June 2008. By nature, the cross-sectional study will address whether the prevalence of respiratory symptoms (including infections and asthma-related symptoms) is higher in children diagnosed with full or partial FAS compared to other children seen in the clinic who did not receive such a diagnosis.

Data Collection

Marcus patients are referred to the clinic by social services agencies (i.e. adoption agency), school administrators, Division of Family and Children Services (DFCS), other medical professionals, or are self-referred; most often, the goal is to provide a differential diagnosis of FAS, however other services such as treatments, education, and social support services are available. Below average height or weight, developmental delays, learning difficulties, or facial disfigurement are all evidence of possible prenatal alcohol exposure and are the usual symptoms that justify an evaluation by the Marcus team. Patients' ages range from less than one year old to 29 years old; patient assent (or for

patients under 18, parental consent in addition) was required to include their data in this research study.

Marcus uses a multi-disciplined approach in order to comprehensively and accurately evaluate potential patients with FAS. Adapting the 1996 IOM guidelines for the diagnosis of FAS, Marcus has four diagnostic categories used to classify children with potential alcohol-related diseases; FAS (both with and without confirmed alcohol exposure), partial FAS (which implies confirmed alcohol exposure), alcohol-related neurodevelopmental disorder, and no related diagnosis. This study will compare children with full and partial FAS (1st and 2nd categories) to those without FAS (i.e., in the 4th diagnostic category). The 3rd category, neurodevelopmental disorder, is not explicitly used in this study due to the limited number of patients with this diagnosis; these patients are considered to be in the 'no related diagnosis' category for the purposes of our analyses.

Physicians at Marcus assess the degree of alcohol exposure, growth deficiency, dysmorphia, and CNS damage in each patient to arrive at a final "score" that will determine to which diagnostic category the patient belongs. Alcohol exposure is assessed by maternal report, social services reports, and alcohol-related medical or legal problems from the mother. Growth deficiency is measured by calculating the patient's height and weight percentiles (both currently and at birth), and a dysmorphia score is tallied based on facial and skeletal disfigurement in the face, chest, and hands. CNS damage is evaluated by head circumference percentile, CT/MRI exam, and the degree of cognitive, visual, motor, reading, spelling, and math skills (as appropriate depending on the age of the patient).

In this study, information on the presence of childhood respiratory symptoms was collected from patient charts. Asthma or wheezing may have been self-reported by the child's parent on the patient questionnaire, but in most cases, all other respiratory illnesses (infections, reactive airway disease, bronchiolitis, etc.) have been diagnosed by a medical professional either at Marcus or at another institution. The age of the child at the time of the diagnosis or report of respiratory symptoms is not known, other than the fact that these symptoms did not occur at birth; therefore, the outcome variable in this study is based on reported respiratory symptoms that occurred at any time during the child's life prior to their visit at Marcus.

Birth records, school records, prior medical records, laboratory reports, insurance claims, reports from DFCS, and notes by other medical evaluators, when available, were used to supplement the patient questionnaire and provided the majority of data for this study. All data were entered into Microsoft Access by medical abstractors employed by Marcus.

Data Analysis

For this study, all patients were grouped into one of three FAS diagnostic categories (exposure groups); full FAS (with or without known alcohol exposure), partial FAS (with known exposure), and no FAS diagnosis (with or without exposure). To account for respiratory effects caused by other medically-relevant diseases, all patients with a congenital malformation or a diagnosed (either at Marcus or by a previous provider) neurological, vascular, or genetic disorder were excluded from analysis; this criteria excluded 76 observations from analysis. In addition, the 45 patients who were 13 years old or older at the time of their first visit to Marcus were not analyzed, along with

40 patients who could not be placed into a diagnostic category. Furthermore, 127 patients were missing information on potential confounders and were thus removed from further analysis. A total of 288 subjects were excluded and the remaining 625 subjects, ages less than 1 month old to 12.9 years old, were analyzed.

The frequencies of demographic characteristics in each exposure group were calculated. Statistical comparisons of these frequencies were calculated using chi-squared or ANOVA tests, and a p-value for each comparison was reported.

Next, prevalence odds ratios (referred to as 'odds ratios') and 95% confidence intervals describing the association between potential confounders and the presence of respiratory symptoms were calculated. Potential confounders were decided based upon previous literature, well-established risk factors for asthma/respiratory symptoms, and a significantly un-equal distribution of the covariate between exposure categories; the main covariates considered were gender, insurance provider (as a proxy measure for socio-economic status), maturity at birth, and race/ethnicity. The insurance variable was coded so that those with Medicaid were compared to those who self-paid, had private insurance (HMO, PPO, etc.), or had other means of payment. Maturity at birth refers to whether the patient was born full term or preterm and was controlled for using a dichotomous variable that was abstracted from patient records; full term births were defined as those births that occur at or after 37 completed gestational weeks. If the subject was missing this variable, we looked at birth weight data, if available; those who weighed 2.5 kilograms or more at birth were considered full term for the purpose of these analyses. The race/ethnicity variable compared self-identified 'White' to all other ethnicities

(African American, Native American/Alaskan Native, Asian, Pacific Islander, Hispanic, or other).

Additionally, we considered the effect of age and allergies. Age of the child, whether greater or less than 5 years old, was considered as a potential effect modifier due to the well-known differential expressional and risk of developing asthma-related symptoms before and after 5 years old. Furthermore, the prevalence of self-reported allergies was looked at in order to entertain the possibility that respiratory symptoms such as asthma might have been misclassified or over-reported. A subset of the outcome variable of respiratory symptoms was created to include only those with asthma-related symptoms (and excluding those with only respiratory infections). Asthma-related symptoms include asthma, wheezing, breathing treatments, and reactive airway disease. The appropriate odds ratios describing the crude relationships between each covariate and the outcome variable were reported.

Logistic regression was used to fit a model that described the relationship between FAS diagnostic categories and the presence of all respiratory symptoms (including asthma symptoms) and asthma-specific symptoms (evaluated separately). Because there were three exposure categories, all five two-way comparisons were assessed during the model building stage. Correlations between covariates were assessed using condition indices and variance decomposition proportions (VDPs). Co-linearity between two covariates was present if a condition index was greater than or equal to 30 and two corresponding VDPs were 0.05 or greater. Statistical interaction between covariates and the exposure variable were assessed using backwards elimination, as described by Kleinbaum and Klein, based on the Wald p-value for each interaction term (26). The

remaining model was considered the gold standard model. Covariates were assessed for confounding based on the change in odds ratio when each variable was removed; if, after removing a covariate from the model, the odds ratio describing the association between the exposure and the outcome meaningfully changed by more than 10%, that dropped covariate was a significant confounder and should remain in the model (26). The same assessment was performed for each pair of two and each unique group of three variables; each group was removed from the model individually to determine whether, as a whole, the removal of each group of variables changed the odds ratio by 10% or more and was thus needed in the model to control for confounding. If no significant confounding could be detected, then the final model would include the variables consistently used in modeling throughout the literature (gender, socioeconomic status (or insurance provider, in this case), maturity at birth, and race/ethnicity). The Hosmer-Lemeshow Goodness-of-fit test was used to assess the fit of the final chosen model to the data. Models with outcomes of all respiratory symptoms and asthma-related symptoms alone were stratified by age at less than or greater than 5 years old. To account for the probable effect that maternal smoking had on childhood respiratory symptoms, both currently and during pregnancy, a sensitivity analysis was performed for maternal smoking using the Monte-Carlo Simulation method.

Power calculations for each diagnostic comparison, and for both outcome measures, were completed using OpenEpi Version 2.3.1. For all types of respiratory symptoms, the highest statistical power to detect any significant difference in the prevalence of respiratory symptoms was 14.8% when comparing any FAS diagnosis (full and partial) to no FAS diagnosis. The lowest statistical power of 2.6% was seen in the

comparison between full FAS and partial FAS diagnoses. For asthma-related symptoms only, the highest power was 16.9%; this power corresponds to the comparison between any FAS diagnosis (full FAS and partial FAS) and no FAS diagnosis. The weakest comparison was between full FAS and partial FAS diagnosis, with a statistical power of 2.7% to detect any significant difference in the prevalence of respiratory symptoms. With 80% power, the minimum detectable odds ratio comparing the prevalence of asthma between those with any FAS diagnosis and those with no FAS diagnosis was 1.66.

SAS version 9.3 (SAS Institute) and an alpha of 0.05 were used for all analyses. This study was approved by Emory University's Institutional Review Board.

RESULTS

The database from Marcus contained medical information on 913 patients seen between November 1990 and June 2008; after exclusions, we analyzed data from 625 patients who were less than 1 month to 12.9 years old at the time of their evaluation by Marcus. All subjects reported living in one of 65 counties in Georgia at the time of their visit, with the largest proportion (25%) residing in Fulton County.

Demographic characteristics of the study population were reported (Table 1). From the population we analyzed, 27% had full FAS, 18.4% were found to have partial FAS, and 54.6% had a non-FAS diagnosis. There were slightly less females than males (40.5%), with the majority of the population being non-Hispanic African-American (51.7%) and with an average age in each exposure group of around 5 years old. A significantly different distribution of full term births was seen across the three exposure groups, with subjects in the full FAS category having the smallest proportion of full term births ($P = 0.02$). Birth weight and the presence of any reported medical problems also differed across the exposure groups significantly, with full FAS subjects having the smallest birth weight and the largest proportion with medical problems ($P < 0.001$, $P = .01$, respectively). Furthermore, almost all subjects were covered by Medicaid and about 20% reported having asthma or asthma-like symptoms (Table 1).

Birth weight was used to classify 27 (4%) subjects as either full term or preterm; 20 of these were considered to be full term. There was a minor difference in the distribution of FAS diagnostic categories among these subjects; of the 20 subjects who were classified as full term, 15% had a full FAS diagnosis, 30% had partial FAS, and

55% had no FAS diagnosis. Of the 7 subjects classified as preterm, 28.6% had full FAS, 14.3% had partial FAS, and about 57.1% had no FAS diagnosis.

Univariate analyses revealed that male gender, being less than 5 years old, and having allergies were significant predictors of respiratory symptoms (Table 2). Allergies had the strongest association with respiratory symptoms; those with allergies were more than twice as likely to have reported any respiratory symptoms compared to those without allergies (odds ratio = 2.08, 95% confidence interval (CI): 1.23, 3.51). When looking at asthma symptoms alone, gender and allergies had the only significant associations; females were 44% less likely to have reported asthma compared to males (odds ratio = 0.56, 95% CI: 0.37, 0.86), and those with allergies were significantly more likely to report asthma-related symptoms (odds ratios = 2.02, 95% CI: 1.18, 3.45). The majority of all subjects both with and without asthma were covered by Medicaid; we thus assume that subjects were from a similar social class (Table 2).

Logistic models were then created in order to assess the association between the prevalence of FAS or partial FAS diagnoses and having ever experienced any respiratory symptoms (Table 3). The crude odds ratios and the fully-adjusted odds ratios are shown in Table 3; the gold standard model included gender, insurance provider, maturity at birth, and race/ethnicity.

Starting with the gold standard model, each covariate was removed individually and the change in odds ratios for each of the five diagnostic comparisons was observed (Table 3). As seen in the table, removal of each of the four potential confounders resulted in non-meaningful changes in the odds ratios for all five diagnostic comparisons. While this implies that none of the covariates were statistically significant confounders,

the final chosen model retained all four covariates to remain consistent with published literature; regardless, a Hosmer-Lemeshow p-value of 0.53 for this model suggests that the model did fit the data appropriately.

In each of the five diagnostic comparisons, respiratory symptoms were less common among those with a full FAS diagnosis compared to children with a partial FAS or no related diagnosis (Table 3). The gold standard model was then stratified by age at children greater than or less than 5 years old (Table 4). Models including only children less than 5 years old (n= 349) and models with children greater than or equal to 5 years old (n= 276) showed a similar association between FAS and respiratory symptoms, with almost all odds ratios being less than, but not significantly different from, 1. The strongest association for children less than 5 years old was seen when comparing partial FAS to no FAS diagnosis (odds ratio = 0.68), and the strongest odds ratio for children 5 years old and older was seen when comparing full FAS diagnosis to partial FAS diagnosis (odds ratio = 0.54).

The gold standard model was then used to look at the prevalence of asthma-related symptoms, both for all subjects and stratified around the age of 5 (Table 5). No significant associations were seen in any of these models, and almost all comparisons implied a protective effect of an FAS or partial FAS diagnosis against the development of asthma-related symptoms.

Using the Monte-Carlo simulation method, a sensitivity analysis was performed to account for the information bias that resulted from not controlling for maternal smoking status. With an odds ratio between smoking and respiratory outcomes as high as 2.45, the model-adjusted odds ratio between FAS diagnosis and respiratory problems was

still found to be protective; although not significantly different from 1, the simulation placed the odds ratio between 0.77 and 0.83.

DISCUSSION

In contrast to our hypothesis, respiratory symptoms were not more common among children with FAS compared to those without FAS. In most analyses, the prevalence of respiratory symptoms was in fact lower in those with a full or partial FAS diagnosis compared to children without such a diagnosis. The odds ratios, while not significant, were less than 1 in all comparisons, implying a protective effect of an FAS diagnosis against the development of respiratory symptoms.

Those without an FAS-related diagnosis had a higher prevalence of respiratory symptoms; these children might have had other diagnoses (such as another developmental or physical disorder) that made them more prone to respiratory diseases compared to those with an FAS or partial FAS diagnosis. This could explain why in general, FAS diagnoses appeared to be protective. In addition, there was no true control population; those without any type of FAS diagnosis were still likely to have been exposed to some alcohol or drugs in utero (i.e. the suspected reason they were being evaluated by Marcus), and therefore lung function could have been altered in all diagnostic groups, biasing the results towards the null. Furthermore, it is also possible that this is just a chance finding; the scientific understanding and the large body of literature on the toxicity of alcohol to the fetus does not support the notion that alcohol exposure in utero would provide protection against damage to the respiratory system.

As expected based on medical knowledge of FAS, those with a full FAS diagnosis were significantly more likely to be born prematurely, have a lower birth weight, and present with other medical problems compared to those without an FAS diagnosis. Our analyses are consistent with prior literature on respiratory illnesses; males and children

under the age of 5 were significantly more likely to experience respiratory problems in our study population. Males were also significantly more likely to have asthma-related symptoms, and the same association with children under the age of 5 was seen, although not to a significant level, when looking at asthma symptoms alone as the outcome. These findings validate our data and provide support to our observed results by confirming that our study population experienced the same trends that have been well-established in the literature.

The overall rate of asthma in this study population was 20.6%, more than twice as high as the average asthma rate in Atlanta (24). Thus, our study population was more likely to be exposed to asthma risk factors than the average Atlanta child (i.e., poor air quality in Atlanta cannot explain the higher rate). Children exposed to toxic substances during fetal development (the majority of this study population) are logically at a higher risk of being born into a less nurturing environment than children without toxic exposures. Especially given the high correlation between smoking and alcohol consumption, children in this study were more likely than the average child to have parents that were smoking at the time of pregnancy, thus increasing their risk of developing lung problems. Furthermore, a large proportion of children diagnosed at Marcus have been in and out of foster homes and other social services, which likely contributed to a stressful living environment; psychological and emotional stress has been found to be a causal factor in the development of asthma symptoms via mediation of the immune system (27). A relatively high prevalence of both respiratory symptoms and asthma-related symptoms across all exposure groups implies that something other than alcohol, such as stress and/or other risk factors, is contributing to the poor lung function seen in these subjects.

There were 27 subjects classified as preterm or full term births based on their birth weight; however the use of this criterion might have introduced residual confounding. Those classified as preterm birth using their birth weight were more likely to have a full FAS diagnosis compared to those being classified as full term. Thus, the observed univariate association between preterm birth and FAS diagnosis may be stronger than the true association; however, there is a strong and well-established relationship between FAS and preterm birth and we would thus expect and in fact did see a significant association ($P = 0.02$). Using the birth weight criterion might also have introduced misclassification of a confounder (maturity at birth) which could have contributed to the lack of statistical confounding seen in the logistic model.

Insurance provider was examined as a proxy measure for socioeconomic status, but a large majority of the study population was covered by Medicaid. The lack of variance in this variable suggests that the study population was from a similar social class and therefore negates the potential for significant confounding by socioeconomic status. However, insurance provider may not fully be representative of socioeconomic status; children in foster care may be covered by Medicaid, yet this does not necessarily mean that their biological mother was of low socioeconomic status during her pregnancy. Furthermore, but less common, the child may have been covered by Medicaid at birth, implying the biological parents were of low socioeconomic status (as seen by low income), yet had another insurance provider at the time of their visit due to adoption. Thus, the potential for confounding by socioeconomic status cannot be dismissed.

Univariate analyses showed that having allergies was strongly associated with having reported respiratory problems or asthma-related symptoms. This might suggest

non-differential misclassification of the outcome and presents a strong likelihood that many subjects with reported respiratory conditions were truly experiencing temporary allergic reactions or frequent nasal allergies. This misclassification would bias the association between respiratory symptoms and FAS diagnosis towards the null; the odds ratios observed in these analyses may thus be weaker than the true associations.

The final logistic model was defined based on the literature because none of the assessed variables (gender, insurance provider, maturity at birth, and race/ethnicity) were found to statistically confound the data; this lack of observed confounding may be the result of a small sample size and not enough power to detect confounding. Furthermore, the likely misclassification of the outcome due to self-reporting errors and mistaken allergic reactions would have made the identification of statistical confounding more difficult.

Noting that having allergies was significantly associated with both FAS diagnostic groups and the presence respiratory symptoms, the variable for allergies was also assessed for confounding and found to be a statistically significant confounder in the logistic model (results not shown). This variable was left out of the final model due to the imprecision and selection bias that resulted from its inclusion; however, this implies that the reported association from the gold standard model (without allergies) is weaker than the true association between respiratory symptoms and FAS diagnosis.

When stratifying on children at age 5, no significant association was seen for either ever-reported respiratory symptoms or asthma-related symptoms. The group of children less than 5 may have been equally likely to experience wheezing or respiratory symptoms, regardless of their FAS diagnosis, due to small airways that are prone to

constriction and their frequent encounter with bacteria and viruses in early childcare settings. Older children are also likely to have experienced the outcome (ever-reported respiratory symptoms or asthma) regardless of their FAS diagnosis simply because they have lived longer. Thus, these reasons may explain the lack of significant findings seen in either stratum and may be responsible for biasing the results in each stratum towards the null.

When partial FAS alone was compared as an exposure group, the association with both respiratory symptoms and asthma-related symptoms reversed directions between children less than 5 and children 5 years old or older. For children less than 5, partial FAS was protective compared to full FAS and no diagnosis, however in children older than 5, the opposite effect was seen whereby partial FAS had a higher reported prevalence of symptoms compared to full FAS and no diagnosis. In very young children, a full FAS diagnosis may be presented by more prominent facial dysmorphia and CNS damage compared to older children. Older, school-aged children are more likely to have been diagnosed only after discovering learning or behavioral problems in a school or social setting (otherwise, they would have been diagnosed at a younger age). Thus, there may be harsher medical problems and other alcohol-related effects in those patients diagnosed with full FAS at an earlier age, logically implying that a partial FAS diagnosis would have a lower prevalence of respiratory or other medical problems compared to a full FAS diagnosis. Because it took at least 5 years to recognize symptoms of FAS in the older children, their full FAS may not be as medically or physiologically damaging as the same diagnosis in younger children. Thus, the distinction between full and partial FAS may be blurred for older children presenting with learning and behavioral problems rather

than facial or growth deformities, and misclassification in these older children would explain the reversed association seen. While this may also imply weak interaction between FAS and age, no significant statistical interaction was found.

The overall results of our study indicate that there is no significant relationship between the prevalence of FAS and the prevalence of respiratory symptoms. It is likely that our entire study population, regardless of exposure group, had some form of harmful prenatal exposures and/or experienced other harmful stressors as infants and young children (e.g., unstable living conditions). Literature confirms that chronic stress mediates the immune system and influences its reactivity, thereby increasing the risk for asthma and asthma-related illnesses (27). Thus, it is possible that overall, we are seeing the effects of stress on the entire study population as it relates to increasing their risk for respiratory problems. Compared to animal trials that had a true control population, our study lacked a proper comparison group (one that was truly unexposed to harmful toxins or stressors), and we were therefore unable to replicate the results seen in animal trials.

Conclusions

In conclusion, there may in fact be a significant association between FAS diagnosis and respiratory and asthma-related symptoms, but due to misclassification, low power, the lack of a proper control group, and residual confounding, our results were biased towards the null and we were unable to detect an association.

While allergies were more prevalent in children with an FAS diagnosis compared to those without, there was not a significant difference in the prevalence of reported asthma and respiratory symptoms between the different levels of FAS diagnosis. A thorough understanding of the range and severity of potential medical effects due to

alcohol consumption during fetal development is essential for physicians to accurately consult patients on the comprehensive treatment options that may be needed. Future studies should be undertaken in order to thoroughly investigate respiratory effects resulting from fetal alcohol exposure. A prospective cohort study with a well-defined control population would be the ideal study design; it should include detailed information on the amount and duration of maternal alcohol consumption, gather information on maternal smoking (both currently and during pregnancy) and family history of asthma, and have objective and consistent diagnostic information (from an appropriate professional) on the presence of respiratory illnesses in the subjects. Furthermore, a larger study across multiple states would be needed to ensure the appropriate degree of power is available and that the results could be applied to the general population at large.

STRENGTHS AND WEAKNESSES

A primary strength of this study was the fact that all diagnoses of FAS were made by the same professionals at Marcus using the same criteria; we can be reasonably sure that there are minor, if any, inconsistencies in the way FAS was diagnosed, and thus misclassification of the exposure can be assumed to be insignificant.

There were several weaknesses associated with this study. The study was a retrospective cross-sectional study with all information abstracted from medical charts; no new information could be gathered. We could not control for maternal smoking, both currently or during pregnancy, or possible genetic causes of asthma, because such information was not reliably gathered from every patient. These could be major factors influencing the development of asthma or other respiratory symptoms and have the potential to confound a study's results away from the null. However, these variables were probably not a major source of confounding in our study considering all of our results were not significantly different from the null. Furthermore, the sensitivity analysis proved that even with a very high prevalence of maternal smoking among those with a full FAS diagnosis, the fully-adjusted odds ratio was not significant in describing the association between respiratory symptoms and FAS diagnosis.

Marcus was not screening for respiratory problems, and thus all medical problems involving the respiratory system were diagnoses made from other providers or based on notes from the parental report. Because data on respiratory symptoms were not explicitly asked for on the questionnaire or in patient medical charts, respiratory symptoms could have been under-reported among the entire study population decreasing the likelihood of identifying a significant association. Furthermore, because respiratory ailments can be

commonly mis-diagnosed or not reported, there was a strong potential for misclassification of the outcome, as mentioned earlier. We were also unable to tell at what age the child was diagnosed with the respiratory condition or for how long symptoms were present. Knowing the age that the child experienced respiratory symptoms may help in the understanding and identification of a more precise estimate of the relationship between FAS and respiratory problems.

An additional weakness of this study was caused by selection bias; the study population was not a random sample and there was no true 'control' population from which to compare those with an FAS diagnosis. All subjects were evaluated by the Fetal Alcohol Clinic at the Marcus Autism Center and thus, all had reason to suspect fetal alcohol exposure or a related diagnosis in the child. Those who had 'no (FAS) related diagnosis' may still have been exposed to alcohol during fetal development, but the effects were minor and did not warrant an FAS diagnosis (possibly due to a lesser degree or frequency of alcohol exposure). Both groups in any of our five comparisons may likely have been exposed to alcohol which would have biased our results towards the null, implying that a stronger association exists than what we observed. Furthermore, it can also be said that the assumed universal prenatal exposure to alcohol or drugs explains why the prevalence of asthma and other respiratory symptoms was so high in the entire study population.

While controlling for alcohol exposure in this study may have been possible, many of the maternal reports do not include such information, and the validity of that which was available was questionable. It can be assumed that a mother who used alcohol during her pregnancy would not readily reveal this information or would under-report the

amount and duration of consumption, if such information from the biological mother was even available. Many of the patients seen at Marcus were receiving their evaluation as part of an adoption process, and thus information about exposures during the birth mother's pregnancy were difficult to obtain.

Another weakness of this study was its substantially low power; with less than 20% power to detect a significant difference in prevalence (alpha = 0.05) on every diagnostic comparison, the likelihood of identifying a significant association, even if one existed, was very limited in this study. The statistical power of the logistic model with asthma-related symptoms as the outcome was also very low; each comparison had a power of less than 20% to detect any significant difference in prevalence of the outcome, and the minimum detectable protective odds ratio was 0.60. Thus, it was very unlikely that we could have identified a significant association between FAS diagnoses and asthma-related symptoms, even if a true relationship existed, and especially if the prevalence difference between FAS groups was not relatively high.

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TABLES

Table 1. Demographics of study population: eligible[1] pre-adolescent (<13 yrs) children seen at Marcus Autism Center's Fetal Alcohol Clinic, 1990-2008, n=625

	Diagnosis				
Characteristic	**Full FAS**	**Partial FAS**	**None**	**Total**	**p-value [2]**
N (%)	169 (27.0)	115 (18.4)	341 (54.6)	625 (100)	-
Female (%)	77 (45.6)	48 (41.7)	128 (37.5)	253 (40.5)	0.21
Average age, yrs (sd)	4.5 (3.4)	5.2 (3.1)	5.1 (3.1)	5.0 (3.2)	0.69
Race/ethnicity: White (%)	63 (37.3)	55 (47.8)	150 (44.0)	268 (42.9)	0.18
Full term or normal BW[a] (%)	108 (63.9)	86 (74.8)	258 (75.7)	452 (72.3)	0.02
Average birth weight[b], kg (sd)	2.3 (0.7)	2.7 (0.7)	2.9 (0.9)	2.7 (0.8)	<0.0001
Known medical problems[b] (%)	93 (57.8)	50 (48.1)	129 (42.4)	272 (47.8)	0.01
Covered by Medicaid (%)	151 (89.4)	100 (87.0)	302 (88.6)	553 (88.5)	0.82
From local GA county* (%)	15 (8.9)	11 (9.6)	24 (7.0)	50 (8.0)	0.61
Allergies[b] (%)	22 (16.3)	21 (23.3)	34 (12.4)	77 (15.4)	0.04
Asthma symptoms (%)	32 (18.9)	21 (18.3)	76 (22.3)	129 (20.6)	0.53
Any respiratory symptom (%)	34 (20.1)	24 (20.9)	81 (23.8)	139 (22.2)	0.60

[1]Subjects that could not be placed into a diagnostic category, were less than 13 years old, were missing information on preterm status, gestation age, and birth weight, or had a genetic, neurological, or vascular disorder were excluded from analysis

[2] p-values are from chi-squared or ANOVA (birth weight and age) tests, underlined values are statistically significant; $P < 0.05$

[a] Full term indicates $\geq$ 37 gestational weeks or birth weight $\geq$ 2.5 kg. BW=birth weight.

*local Georgia counties include: Cobb, DeKalb, Fulton, and Gwinnett

[b] birth weight, medical problems, and allergies had n < 625 (584, 569, 499)

Table 2. Univariate analyses and unadjusted associations between covariates and each outcome measure

	All Respiratory Symptoms			
Characteristic	**Respiratory Symptoms**	**No Respiratory Symptoms**	**Odds Ratio**	**CI†**
N	139	486	-	-
Female (%)	46 (33.1)	207 (42.6)	0.67	(0.45, 0.99)
Age ≥ 5 yrs old (%)	51 (36.7)	225 (46.3)	0.67	(0.46, 0.99)
Race/ethnicity: White (%)	53 (38.1)	215 (44.2)	0.78	(0.53, 1.14)
Full term or normal BW[a] (%)	97 (69.8)	335 (68.9)	0.85	(0.56, 1.29)
Allergies[b]	27 (23.7)	50 (13.0)	2.08	(1.23, 3.51)
Covered by Medicaid (%)	129 (92.8)	424 (87.2)	1.89	(0.94, 3.79)
	Asthma-like Symptoms*			
Characteristic	**Asthma**	**No Respiratory Symptoms**	**Odds Ratio**	**CI†**
N	129	486	-	-
Female (%)	38 (29.5)	207 (42.6)	0.56	(0.37, 0.86)
Age ≥ 5 yrs old (%)	50 (38.8)	225 (46.3)	0.73	(0.49, 1.09)
Race/ethnicity: White (%)	47 (36.4)	215 (44.2)	0.72	(0.48, 1.08)
Full term or normal BW[a] (%)	90 (69.8)	335 (68.9)	0.85	(0.56, 1.30)
Allergies[b]	25 (23.2)	50 (13.0)	2.02	(1.18, 3.45)
Covered by Medicaid (%)	119 (92.25)	424 (87.2)	1.74	(0.87, 3.50)

† CI=95% confidence interval

*Asthma-like symptoms include: asthma, required breathing treatments, reactive airway disease, wheezing

[a] Full term indicates ≥ 37 gestational weeks or birth weight ≥ 2.5 kg. BW=birth weight.

[b] n=57; 548 observations are missing

underlined odds ratios are significant, $P < 0.05$

Table 3. Model-based evaluation of potential confounders for the main effect of FAS diagnosis on the presence of respiratory symptoms, n=625

Diagnostic Comparison	Crude Odds Ratio	CI†	Gold Standard Odds Ratio°	CI†
FAS vs. no dx	0.81	(0.52, 1.27)	0.80	(0.51, 1.27)
pFAS vs. no dx	0.85	(0.51, 1.42)	0.87	(0.52, 1.46)
FAS vs. pFAS	0.95	(0.53, 1.72)	0.92	(0.51, 1.67)
FAS and pFAS vs. no dx	0.82	(0.56, 1.21)	0.83	(0.56, 1.22)
FAS vs. pFAS and no dx	0.84	(0.55, 1.30)	0.83	(0.53, 1.29)

Remove Gender	Odds Ratio	CI†	Gold Standard Odds Ratio°	Change in Odds Ratio by ≥ 10%
FAS vs. no dx	0.78	(0.49, 1.23)	0.80	N
pFAS vs. no dx	0.86	(0.51, 1.44)	0.87	N
FAS vs. pFAS	0.90	(0.50, 1.63)	0.92	N
FAS and pFAS vs. no dx	0.81	(0.55, 1.19)	0.83	N
FAS vs. pFAS and no dx	0.81	(0.52, 1.25)	0.83	N

Remove Insurance Provider	Odds Ratio	CI†	Gold Standard Odds Ratio°	Change in Odds Ratio by ≥ 10%
FAS vs. no dx	0.80	(0.51, 1.27)	0.80	N
pFAS vs. no dx	0.87	(0.52, 1.45)	0.87	N
FAS vs. pFAS	0.93	(0.51, 1.68)	0.92	N
FAS and pFAS vs. no dx	0.83	(0.56, 1.22)	0.83	N
FAS vs. pFAS and no dx	0.83	(0.54, 1.29)	0.83	N

Remove Full Term Birth	Odds Ratio	CI†	Gold Standard Odds Ratio°	Change in Odds Ratio by ≥ 10%
FAS vs. no dx	0.82	(0.52, 1.29)	0.80	N
pFAS vs. no dx	0.87	(0.52, 1.47)	0.87	N
FAS vs. pFAS	0.94	(0.52, 1.70)	0.92	N
FAS and pFAS vs. no dx	0.84	(0.57, 1.23)	0.83	N
FAS vs. pFAS and no dx	0.85	(0.55, 1.31)	0.83	N

Remove Race/Ethnicity	Odds Ratio	CI†	Gold Standard Odds Ratio°	Change in Odds Ratio by ≥ 10%
FAS vs. no dx	0.81	(0.51, 1.28)	0.80	N
pFAS vs. no dx	0.87	(0.52, 1.45)	0.87	N
FAS vs. pFAS	0.94	(0.52, 1.69)	0.92	N
FAS and pFAS vs. no dx	0.83	(0.57, 1.22)	0.83	N
FAS vs. pFAS and no dx	0.84	(0.54, 1.31)	0.83	N

†CI= 95% confidence interval

°Gold standard odds ratio is calculated from the fully-adjusted logistic model which included gender, insurance provider, full term birth, and race/ethnicity

Table 4. Fully-adjusted effect of FAS diagnosis on the presence of respiratory symptoms stratified by age

	Children < 5 yrs, n=349		Children ≥ 5 yrs, n=276	
Diagnostic Comparison	**Odds Ratio**	**CI[†]**	**Odds Ratio**	**CI[†]**
FAS vs. no dx	0.78	(0.45, 1.35)	0.67	(0.28, 1.58)
pFAS vs. no dx	0.68	(0.33, 1.39)	1.23	(0.57, 2.65)
FAS vs. pFAS	1.15	(0.52, 2.52)	0.54	(0.20, 1.48)
FAS and pFAS vs. no dx	0.74	(0.45, 1.21)	0.93	(0.49, 1.75)
FAS vs. pFAS and no dx	0.84	(0.49, 1.45)	0.63	(0.27, 1.46)

[†]CI=95% confidence interval

Table 5. Sub-analysis of the effect of FAS diagnosis on the presence of asthma-like symptoms* stratified by age

	All Children, n=625	
Diagnostic Comparison	**Odds Ratio**	**CI†**
FAS vs. no dx	0.81	(0.51, 1.30)
pFAS vs. no dx	0.81	(0.47, 1.40)
FAS vs. pFAS	1.00	(0.54, 1.86)
FAS and pFAS vs. no dx	0.81	(0.54, 1.21)
FAS vs. pFAS and no dx	0.85	(0.54, 1.34)
	Children < 5 yrs, n=340	
Diagnostic Comparison	**Odds Ratio**	**CI†**
FAS vs. no dx	0.80	(0.45, 1.42)
pFAS vs. no dx	0.63	(0.29, 1.36)
FAS vs. pFAS	1.28	(0.55, 2.95)
FAS and pFAS vs. no dx	0.74	(0.44, 1.23)
FAS vs. pFAS and no dx	0.88	(0.50, 1.54)
	Children ≥ 5 yrs, n=275	
Diagnostic Comparison	**Odds Ratio**	**CI†**
FAS vs. no dx	0.66	(0.28, 1.58)
pFAS vs. no dx	1.12	(0.51, 2.47)
FAS vs. pFAS	0.52	(0.17, 1.58)
FAS and pFAS vs. no dx	0.87	(0.46, 1.67)
FAS vs. pFAS and no dx	0.64	(0.28, 1.49)

*Asthma-like symptoms include: asthma, required breathing treatments, reactive airway disease, and wheezing

†CI=95% confidence interval