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Vision outcomes in children with fetal alcohol spectrum disorders

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Abstract

Background: Previous studies demonstrated that children with Fetal Alcohol Spectrum Disorders (FASD) are more likely to have vision impairments. However, existing human clinical and epidemiological investigations are few and include limited sample sizes. This study aimed to explore the association between ophthalmologic abnormalities and FASD in a sample of 5–7 year old children in the general population.

Methods: This was a cross-sectional study nested in a larger study intended to estimate the prevalence of FASD in San Diego, California, conducted between 2012 and 2014. Prenatal exposure to alcohol, dysmorphology examinations, and a neurobehavioral testing battery were collected for each child and an FASD diagnosis was assigned. Parents of participating children were asked to release their child's vision screening or diagnostic records.

Results: Vision records were obtained for 424 participants in the larger prevalence study. Of these, 53 children were classified as having FASD. A statistically significant association was found between FASD and a diagnosis of strabismus; 5/42 (11.9%) of children who were classified as having FASD had strabismus compared to 6/290 (2.1%) of children who were not classified as having FASD ($p = .01$). All five cases of strabismus in the FASD group occurred in 19 children classified as having partial fetal alcohol syndrome (pFAS). No association was found between FASD and vision impairment ($p = .23$), refractive errors ($p = .66$), glasses/contact lens prescription ($p = .30$), or having one or more ophthalmological abnormalities ($p = .97$).

Conclusions: An association between strabismus and FASD, specifically partial FAS, suggests that the effect of alcohol exposure on risk of strabismus must be severe enough to result in facial

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

features consistent with FASD. This emphasizes the importance of vision screening in children with FASD.

Keywords

alcohol; fetal alcohol spectrum disorders; pregnancy; vision

1 | INTRODUCTION

Alcohol is the most common human teratogenic exposure resulting in developmental disabilities in children in the Western World (Genetic Alliance, 2010). The US Centers for Disease Control and Prevention estimates that the prevalence of fetal alcohol syndrome (FAS) in the US is 0.2–3.0 per 1000 live births (MMWR, 2002; MMWR, 2015). Scientists believe that the true prevalence may be three times higher due to difficulties in recognition and diagnosis of the disorder. In 1973, FAS was first described as a clinical diagnosis of birth defects in children due to alcohol exposure during gestation (Jones & Smith, 1973). Birth defects associated with prenatal alcohol include facial dysmorphic features, growth retardation and central nervous system (CNS) abnormalities (Williams & Smith, 2015). Fetal alcohol spectrum disorders (FASD) encompasses a group of disorders that demonstrate a range of teratogenic outcomes of alcohol (Manning & Hoyme, 2007). It includes FAS, partial FAS (pFAS), and Alcohol-Related Neurodevelopmental Disorder (ARND) (Bertrand et al., 2004).

Since the fetus lacks an efficient alcohol elimination system, alcohol may cause multiple abnormalities in various organ systems (Heller & Burd, 2014). While most of the previous research on prenatal alcohol has focused on the teratogenic effects of alcohol on the brain, a few human studies have demonstrated that alcohol might have detrimental effects on the visual system. These effects include, but are not limited to, reduced visual acuity, refractive errors, strabismus, anomalies of the anterior segment and media, and malformations of the retina and optic nerve (Autti-Rämö et al., 2006; Gronlund et al., 2010; Ribeiro et al., 2007; Strömmland, 1985; Strömmland, 2004; Strömmland & Pinazo-Duran, 2002; Tsang et al., 2023). However, existing human clinical and epidemiological investigations are few and include limited sample sizes (Strömmland & Pinazo-Duran, 2002). To our knowledge, the only study that reported vision outcomes in a relatively large number of children with FAS was the Australian national surveillance study (Elliott et al., 2008). They reported that of the 92 cases of FAS, 4 (4.3%) children had visual impairment. This rate was much higher than the rate of pediatric vision impairment rate in the general population of about 1 in 2500 reported by Australian Royal Institute for Deaf and Blind Children (Royal Institute for Deaf and Blind Children, n.d.). However, the aforementioned study did not use ophthalmological evaluations. Cases were classified as vision impaired based on questionnaires filled out by general pediatricians and criteria for vision impairment were not defined. This made the comparison of reported vision impairment rates in children with FAS to such rates in the general population difficult.

If children with FASD are at higher risk for vision abnormalities, it is crucial that we have solid scientific evidence that allows for clinical recommendations of early and detailed

ophthalmological examination of children with the disorder. Recognition of significant predictors of visual impairment is important for identification of children at risk and early intervention. Therefore, we sought to evaluate vision outcomes in children with FASD in a sample of school age children selected from the general population.

2 | METHODS

2.1 | Study design

This study utilized a cross-sectional, observational design to investigate the association between ophthalmological abnormalities and prenatal alcohol exposure/FASD in 5–7 year old children living in San Diego, California. The project was nested in a larger cross-sectional study, the Collaboration for Fetal Alcohol Spectrum Prevalence or CoFASP, which was funded by the National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism (NIAAA) to establish a prevalence estimate for FASD in four regions of the US. The overall study has been previously described elsewhere (May et al., 2018).

2.2 | Study participants

The larger study sample involved 5–7 year old children who attended the first grade in approximately 30 participating schools in the San Diego Unified School District over two academic years between 2012 and 2014. Children in the same age range receiving developmental services from the San Diego Regional Center were also eligible to participate. The study was approved by the Institutional Review Board at the University of California, San Diego and all participants' parents or guardians provided written informed consent.

2.3 | Evaluation for FASD

Parents/guardians of participating children underwent initial screening that included telephone administration for developmental concerns using the Parents' Evaluation of Development Status (PEDS) instrument (Woolfenden et al., 2014), and measurement of height, weight, and head circumference of the child. One or more developmental concerns noted on the PEDS and/or a height, weight or head circumference measurement less than the 25th centile for age and sex led to a referral for a full evaluation. In addition, a subset of children who screened negative on both the PEDS and growth measurements were selected for full evaluation.

This comprehensive assessment included the following:

1. Neurobehavioral testing using a comprehensive battery to assess cognitive, behavioral and adaptive function.
2. Maternal interviews (or interviews with relatives or other collateral reporters if the mother was not available) to assess mother's alcohol consumption during pregnancy and her child's behavior.
3. A dysmorphology examination conducted by one of a team of four dysmorphologists/geneticists to evaluate the child for physical features of FASD.

4. Teacher Report Forms completed by the child's teacher to assess behavioral functioning at school.

Based on alcohol history, physical features, growth, and neurobehavioral performance, children with completed assessments were classified as having FAS, partial Fetal Alcohol Syndrome (pFAS), ARND, or no disorder on the FASD spectrum according to a standard diagnostic algorithm (Hoyme et al., 2016). In the Hoyme diagnostic classification system, children with FAS or pFAS who have sufficient numbers of the characteristic physical features, growth deficiency, and neurobehavioral impairment can qualify for the diagnosis of pFAS or FAS in the absence of documented prenatal alcohol exposure. Thus, children with FAS or pFAS were further subclassified as having prenatal exposure to frequent or heavy episodic alcohol consumption or maternal social history of alcohol problems surrounding pregnancy, versus those children whose mothers reported less alcohol or where alcohol information was unavailable.

Parents or guardians of all children eligible for the comprehensive evaluation were asked to release existing vision screening or diagnostic records for their children.

2.4 | Collection and evaluation of ophthalmological data

All participating parents/guardians were asked to provide medical records or release authorization for vision records for their child should they exist. In the San Diego community, the University of California San Diego MobileEye program provides no cost vision screening for preschool children in many venues, and these screening records were obtainable with parent consent. In addition, some children had ophthalmologic screenings or evaluations performed by their own provider.

There were three general types of vision records available for children in the study:

1. Vision screening completed by a nurse—records varied from “pass/fail” documentation to documentation of best corrected vision acuity (BCVA), refractive error, strabismus, and color vision. Screening typically utilized inspection, eye charts, cover testing, photo-screener or autorefractors. For those participants who had previously been screened as part of the Save Our Children's Sight model program at the UCSD Shiley Eye Center, the screening was performed with the use of an autorefractor. If a vision problem was identified, a child was referred for a detailed ophthalmological examination.
2. Examination completed by an ophthalmologist—full medical note convention records that entailed BCVA, intraocular pressure, refraction, extraocular motions, confrontational visual fields, external exam, eye dilation for cup to disc ratio, retina and fundus examination. Records varied among the providers.
3. Routine physical examination completed by general pediatricians that included comments about external eye exams or extraocular motions. This examination was usually performed by inspecting the eye with a flashlight for normal pupil dilation and external structure.

Data from each type of record was abstracted using a standard checklist including the following items:

- Type of vision evaluation
- Best Corrected Visual Acuity (BCVA)—used to classify visual impairment according to ICD-10 criteria. Visual impairment was defined as BCVA worse than 0.3
- refractive error;
- glasses/contact lenses prescription;
- strabismus;
- 1 ophthalmological abnormality;
- retinal abnormality;
- optic nerve abnormality;
- glaucoma.

2.5 | Statistical analysis

Children with a diagnosis of osteogenesis imperfecta or whose visual acuity was not measurable, for example, those with a diagnosis of Down Syndrome, were excluded from the analysis. Univariate categorical analyses were conducted comparing the vision outcomes in children with an FASD diagnosis and participants without an FASD diagnosis using Chi-square or Fisher's exact test.

Secondary analyses were conducted comparing vision outcomes in the four FASD diagnostic subgroups (FAS, pFAS, and ARND) with the no FASD group and FAS, pFAS with and without documented substantial alcohol use, using univariate categorical analysis and the likelihood Ratio test.

The statistical software package SPSS Version 23 was used for all analyses (IBM, Armonk, NY).

3 | RESULTS

The original pool of eligible participants consisted of 4625 children from participating elementary schools and clients of San Diego Regional Center (Figure 1). In this study, 1688 children, whose parent or guardian agreed to participate, were screened on growth or parental developmental concerns and a subset of 1187 children was selected for the full evaluation. Among those who were eligible for and agreed to the full evaluation, 749 parents provided the signed medical records release form, and records were received for 588 children. A total of 92 children were excluded from analysis (90 children had records that were missing any ophthalmological information, one participant had osteogenesis imperfecta, and one participant had Down Syndrome). A total of 496 participants had records with ophthalmological information. Of these, 53 children were classified as having FASD (1 FAS, 27 pFAS and 25 ARND). Among these, 35 had confirmed history of an

alcohol-exposed pregnancy with documentation of frequent or heavier episodic drinking or social history surrounding the pregnancy of problems with alcohol.

Among the records obtained, 273 were vision screening records, 140 were ophthalmological evaluations, and 11 were general pediatric examinations that contained information on an external eye examination.

Table 1 illustrates characteristics of participants in the FASD and no FASD groups. Groups were similar with regard to most characteristics. However, there were more males in the FASD group.

One child with pFAS had retinopathy of prematurity and optic neuropathy. Another child with protein C deficiency and no FASD had macular retinal puckering in the right eye, which suggested old hemorrhage or atrophic hole. One child without FASD was suspected to have glaucoma. Since there was an insufficient number of cases for analysis, we did not include retinal, optic nerve abnormalities, or glaucoma in statistical analysis as separate variables. However, these findings were included in the category of having 1 ophthalmologic abnormality.

A statistically significant association was found between FASD and the diagnosis of strabismus. Specifically, 5/42 children with FASD (11.2%) had strabismus compared to 6/290 (2.1%) of children without FASD ($p = .0$) (Table 2). All other vision outcomes were similar between the group without FASD and the group with FASD ($p = .23$ for vision impairment, $p = .66$ for refractive error, $p = .30$ for glasses/contact prescription, $p = .97$ for having 1 ophthalmologic abnormality).

When vision outcomes were compared across the FASD subcategories, the strabismus association with FASD was driven by the incidence among children with pFAS where all 5 cases of strabismus among 19 children with pFAS (26.3%) occurred (Table 3). There were no cases of strabismus among either the 1 child with FAS or the 22 children with ARND (Table 3). Four out of five strabismus cases were identified in children with partial FAS without documented alcohol exposure, but with cognitive impairment ($n = 18$), and one strabismus case was identified in children with partial FAS with confirmed alcohol exposure ($n = 9$). All other vision outcomes did not show significant association in this comparison ($p = .54$ for vision impairment, $p = .55$ for refractive error, $p = .52$ for glasses/contact prescription, $p = .48$ for having 1 ophthalmologic abnormality).

4 | DISCUSSION

We found a significant association between strabismus and FASD with 11.9% of children with FASD having a diagnosis of strabismus compared to 2.1% of children with no FASD. Among those with FASD, all five children with strabismus had partial FAS. This is consistent with prior investigations. Investigators from Finland, Portugal and Sweden reported strabismus in 38%, 28%, and 32% of children with FASD, respectively (Autti-Rämö et al., 2006; Ribeiro et al., 2007; Strömland, 1985; Strömland, 2004). Previous studies have also reported that strabismus is the most common ophthalmological finding in children with abnormalities of the central nervous system (Liu & Ranka, 2014; Mohny & Huffaker,

2003). In a recent systematic review and meta-analysis summarizing prior research, in six studies of children with FAS and pFAS, investigators found a pooled elevated odds ratio of 3.78 (95% Confidence Interval 1.32–10.82) for strabismus in FAS/pFAS compared to controls (Tsang et al., 2023). This elevated risk is of importance as delayed diagnosis and treatment of strabismus may lead to amblyopia, defined as unilateral loss of vision despite normal ocular health (Rosenbaum & Santiago, 1999).

The current US Preventive Services Task Force Recommendation is to perform at least one vision screening for all children between ages of 3–5 years (US Preventive Services Task Force, 2011). Current screening includes a vision acuity test and the use of photo screeners or autorefractors. This screening is designed to diagnose risk factors of amblyopia to allow for timely intervention.

In the present study, out of 588 medical records received, 90 school-aged children did not have any type of vision exam on file. Among these children, two were diagnosed with pFAS. Despite numerous publications describing vision abnormalities in children with FASD, not all children undergo basic recommended vision screening. Neurodevelopmental delay and behavioral issues might preclude these children from early diagnosis and intervention for vision abnormalities. For example, a screening is often rescheduled if a child is unable to cooperate or does not know the letters or figures used by a specific eye chart. This delays a diagnosis, which may further contribute to a child's disability.

Additionally, one prior study that examined whether ophthalmologic findings in children with FASD persisted into young adulthood found that eight participants with FAS, two with pFAS, and one with ARND had increased tortuosity of retinal vessels and four participants with FAS had optic nerve hypoplasia at their follow-up visit 13–15 years later (Gyllencreutz et al., 2020). Another study investigating visual perception problems and vision-related quality of life in young adults with FASD found that 53% of participants in the FASD group had visual perception problems in one or more areas (movement perception, recognition, depth perception, orientation, simultaneous perception) compared to 3% in the control group (Gyllencreutz et al., 2021). Given the serious nature of delayed diagnosis and consequences of vision abnormalities in school-age children and its potential to persist into adulthood, our study highlights the importance of pre-school vision screening in children with FASD.

It is of note that all five strabismus cases were identified in the 19 children with pFAS (26.3%). In contrast, none of the 22 children with ARND had strabismus. This suggests that the effect of prenatal alcohol exposure in order to produce strabismus must be severe enough to result in facial abnormalities of FASD that are seen in pFAS.

No association was found between FASD and other vision outcomes. However, only one child in our sample had a full FAS diagnosis. While this is inconsistent with previous publications, most previous studies used alternative criteria for FASD which may have led to different results. In addition, our study depended on findings from routine clinical care. In contrast, Strömland (2004) has reported a high frequency of vision impairment, refractive errors and other ophthalmological abnormalities in children with FASD. As a

pediatric ophthalmologist, the clinical evaluation and referral patterns for evaluation could have differed from our general population sample.

To our knowledge, this is the first study to investigate ophthalmological outcomes in children with FASD in the general population. Some of the strengths of this study were the sample size, the comprehensive evaluation of children in the general population for features of FASD, and the ability to compare children with FASD to children without who had been evaluated using the same rigorous methods. Another strength of this study was the use of medical records to obtain data on examination of the eyes and vision testing by nurses, ophthalmologists, and/or general pediatricians. Limitations of our study include our inability to utilize a standard ophthalmological examination and the limited number of children with FAS.

For future studies, it would be useful to explore vision outcomes in a large sample of children with FASD using standard ophthalmological examination for all children. For example, one study investigating the relationship between visual perception and anthropometric features related to prenatal exposure to alcohol had participants undergo a complete ophthalmologic examination that included visual acuity, ocular motility, stereoacuity, and funduscopy (Castejon et al., 2019). Also, fundus morphology should be assessed with digital imaging as there are existing reports of ocular fundal abnormalities in children with FAS (Hellstrom et al., 1997). Ophthalmological changes caused by prenatal alcohol might be too subtle to be detected during a standard vision screening.

The findings of our study contribute to our knowledge of the public health burden of maternal alcohol drinking during pregnancy. Since FASD is a potentially preventable condition, it is important to increase public awareness as we deepen our understanding of the consequences of prenatal alcohol exposure. Clinicians examining children with FASD or prenatal alcohol exposure should always screen for eye disease and refer for additional examination when necessary.

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DATA AVAILABILITY STATEMENT

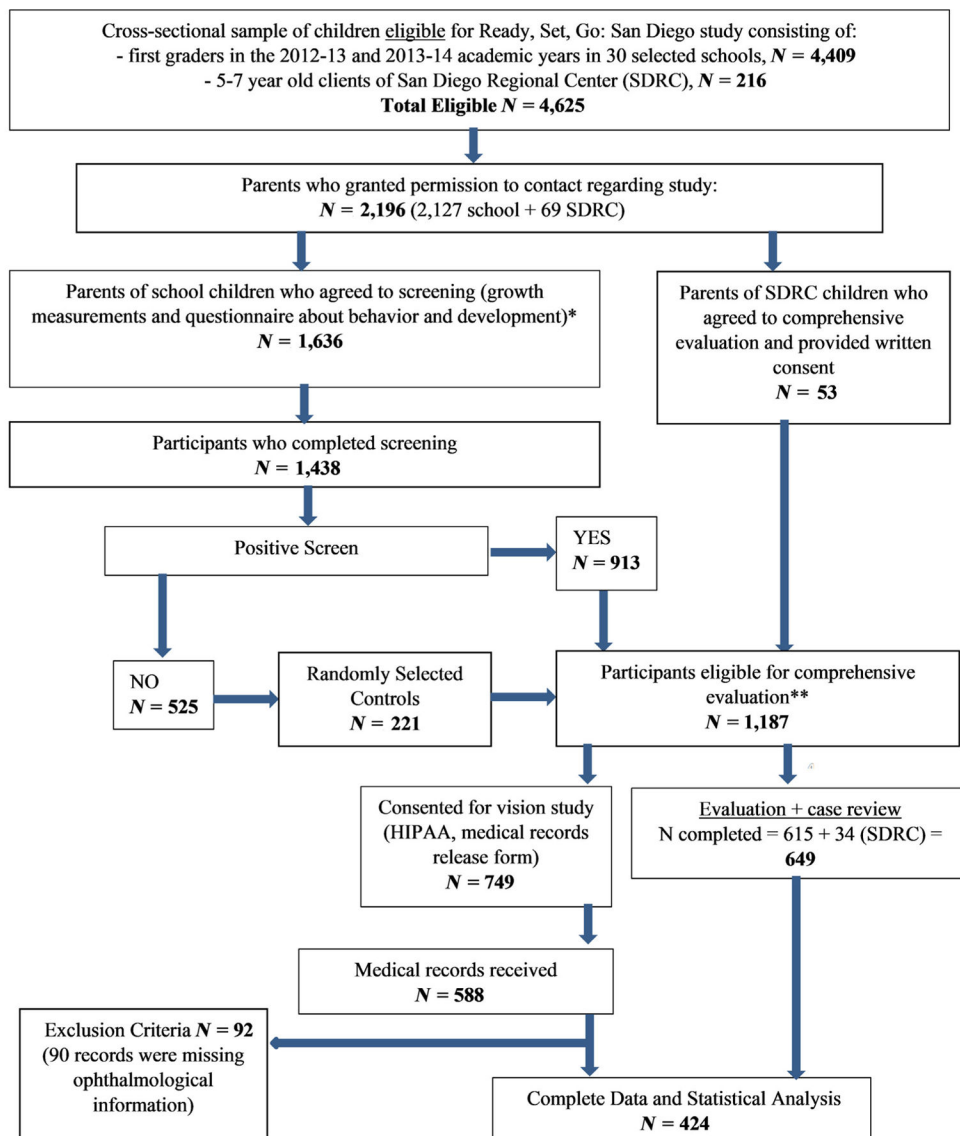
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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*Verbal consent was obtained to perform the screening for the school sample.

** Written consent was obtained to perform comprehensive evaluation for the participants in the school sample (N = 918)

FIGURE 1.
Graphical schema of the study.

TABLE 1

Selected characteristics of participants in FASD and no FASD groups.*

Characteristic	No FASD (n = 371)	FASD (n = 53)	p**
Child age at consent, mean ± SD, years	6.2 ± 1.3	6.3 ± 1.2	.49
Sex of child, n (%)			.06
Male	187 (50.4)	34 (64.2)	
Female	184 (49.6)	19 (35.8)	
Type of vision records received, n (%)			.19
Vision screening	240 (64.7)	33 (62.3)	
Ophthalmological evaluation	120 (32.3)	20 (37.7)	
Physical examination by pediatrician?	11 (3.0)	0 (0)	
Maternal age at birth of child, mean ± SD years	29.3 ± 6.0	29.5 ± 6.6	.86

* Except where indicated otherwise, values are the number (%). Numbers do not sum up to total in some cases because of missing values.

** Chi-square or likelihood ratio comparisons for categorical variables and analysis of variance comparison for continuous variables.

TABLE 2

Vision outcomes in children with FASD and without FASD.

Vision variables	No FASD n/N (%) [*]	FASD n/N (%) [*]	<i>p</i> ^{***}
Vision impairment	10/354 (2.8)	3/53 (5.7)	.23
Refractive error	107/284 (37.7)	14/41 (34.1)	.66
Strabismus	6/290 (2.1)	5/42 (11.9)	.01
Glasses/contact lenses prescription	98/312 (31.4)	11/46 (23.9)	.30
1 ophthalmologic abnormality	126/367 (34.3)	18/52 (34.6)	.97

* Numbers do not sum up to total in some cases because of missing values.

** Two-group comparisons for categorical variables, by chi-square or Fisher's exact test; bolded *p*-values met statistical significance at cut-off of < .05.

TABLE 3

Vision outcomes in participants by subcategory *

Vision variables	No FASD n/N (%)	ARND n/N (%)	pFAS w/o EtOH n/N (%)	pFAS w/EtOH n/N (%)	FAS n/N (%)	p
Vision impairment	10/354 (2.8)	1/25 (4.0)	2/18 (11.1)	0/9 (0)	0/1 (0)	.54
Refractive error	107/284 (37.7)	6/23 (26.1)	6/12 (50.0)	2/5 (40.0)	0/1 (0)	.55
Strabismus	6/290 (2.1)	0/22 (0)	4/13 (30.8)	1/6 (16.7)	0/1 (0)	<.01
Glasses/contact lenses prescription	98/312 (31.4)	4/23 (17.4)	5/14 (35.7)	2/8 (25.0)	0/1 (0)	.52
1 ophthalmologic abnormality	126/367 (34.3)	7/25 (28.0)	9/18 (50.0)	2/8 (25.0)	0/1 (0)	.48

* pFAS w/o EtOH—sufficient number of alcohol-related features to qualify for partial Fetal Alcohol Syndrome without documented prenatal alcohol exposure. pFAS w/ EtOH—partial Fetal Alcohol Syndrome with documented prenatal alcohol exposure. Values indicate the number (%). Numbers do not sum up to total in some cases because of missing values in varying vision records.

** Two-group comparisons for categorical variables, by likelihood ratio test; bolded *p*-values met statistical significance at cut-off of < .05.