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Estimating the community prevalence, child traits, and maternal risk factors of fetal alcohol spectrum disorders (FASD) from a random sample of school children

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ABSTRACT

Objective: Utilize a random sample to estimate the prevalence, child traits, and maternal risk for fetal alcohol spectrum disorders (FASD) in a Southeastern United States county.
Methods: From all first-grade students ($n = 1073$) a simple random sample was drawn, and 32 % ($n = 231$) were consented. All 231 children were examined for dysmorphology and growth, 84 were tested and rated on neurobehavior, and 72 mothers were interviewed for maternal risk.
Results: Significant differences ($\alpha = .05$) between the physical traits of children diagnosed with FASD and the entire sample were height, weight, head circumference, body mass index, and total dysmorphology scores, and all three cardinal features of fetal alcohol syndrome: palpebral fissure length, smooth philtrum, and narrow vermilion. Intellectual function and inhibition were not significantly different between FASD and typically-functioning children, but two executive function measures and one visual/spatial measure approached significance ($\alpha = .10$). Six behavioral measures were significantly worse for the FASD group: teacher-rated aggressive behavior, oppositional defiant problems, and conduct problems, and parent-rated problems of communication, daily living, and socialization. Significant maternal risk factors reported were postpartum depression, frequency of drinking, and recovery from problem drinking. The prevalence of FASD was 71.4 per 1,000 or 7.1 %. This rate falls clearly within the prevalence range identified in eight larger samples of other communities in the Collaboration on FASD Prevalence (CoFASP) study in four regions of the United States.
Conclusion: Careful and detailed clinical evaluation of children from small random samples can be useful for estimating the prevalence and traits of FASD in a community.

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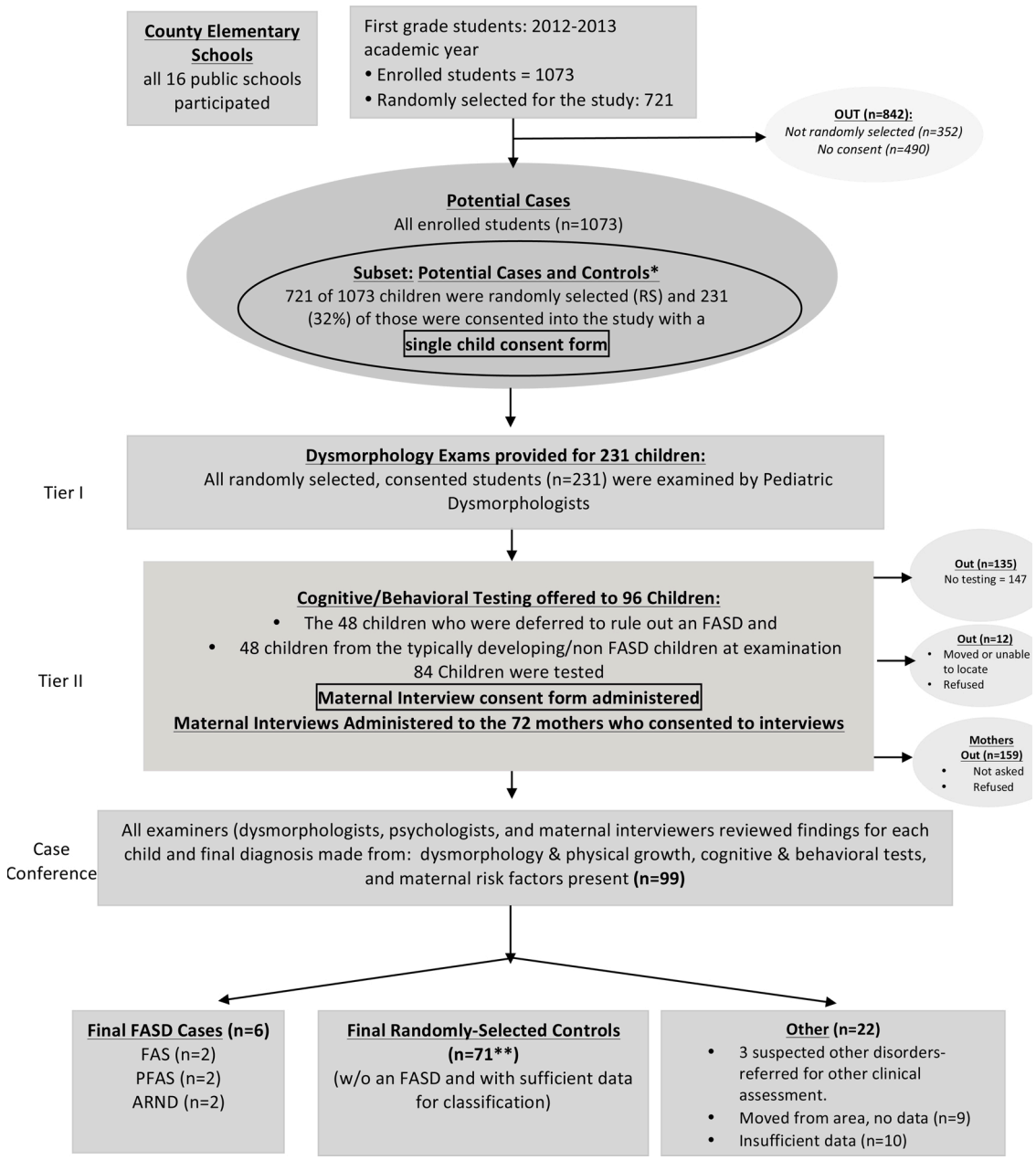
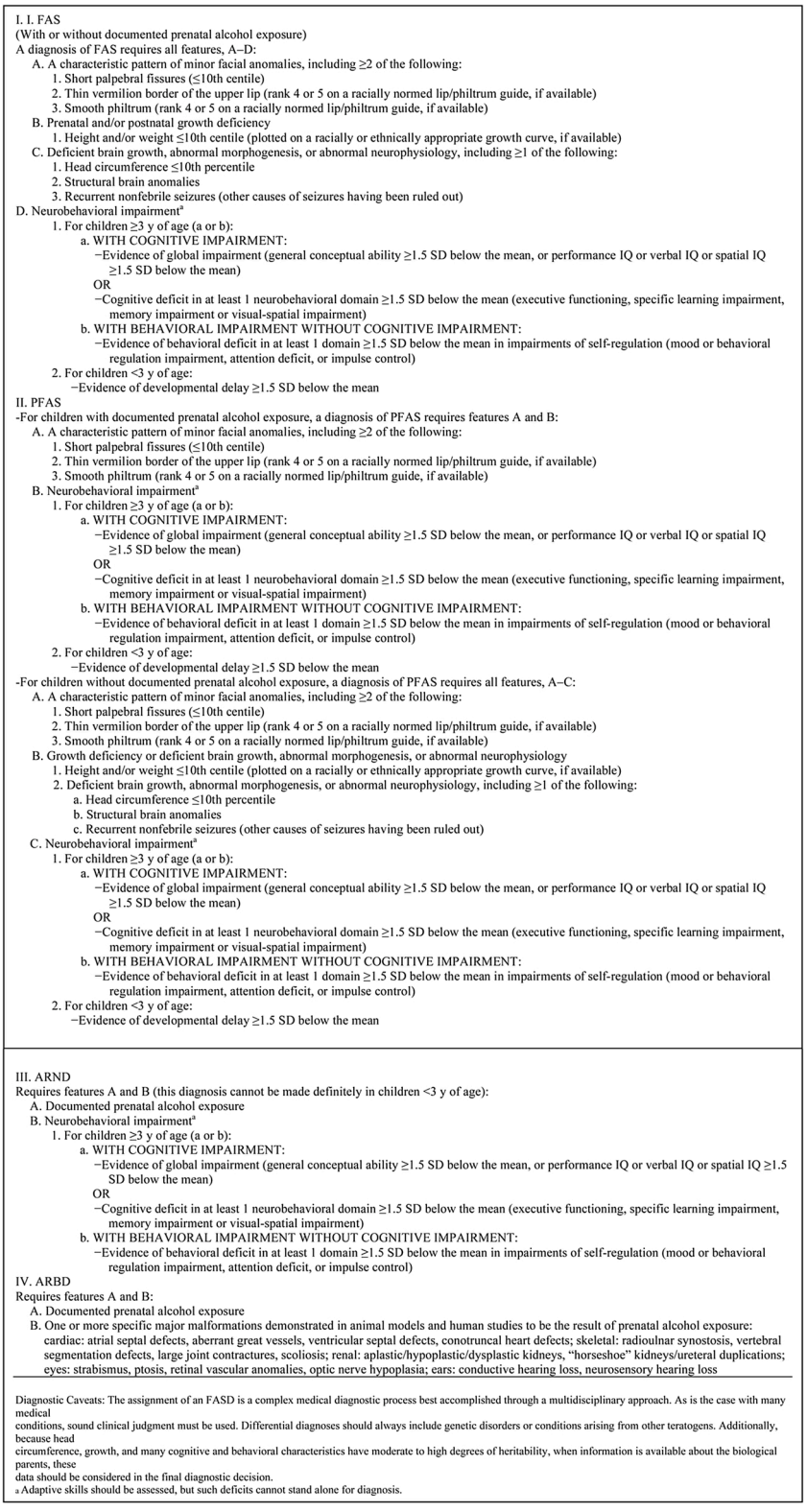


Fig. 1. Sampling Methodology for Prevalence of FASD in a County (II) in the Southeastern Region.
*if a child was randomly selected and found to have an FASD or another known genetic or teratogenic disorder, he/she was classified appropriately and not eligible as a control. **3 children were not FASD and found to have another genetic disorder at dysmorphology examination. They did not advance to Tier II, but were referred to clinics for other assessment.

1. Introduction

Determining or estimating the prevalence of fetal alcohol syndrome (FAS), or any of the specific disorders of the fetal alcohol spectrum disorders (FASD), has challenged researchers since the diagnosis of FAS was first described (Jones and Smith, 1973). The four most common approaches to determining the prevalence of FASD are: 1.) surveillance record systems (Bower et al., 2000; Centers for Disease Control and Prevention, 1995, 1993; Chávez et al., 1988); 2.) individual studies in existing prenatal clinics (Sokol et al., 2003, 1981); 3.) meta-analyses of multiple individual studies utilizing multiple methods (Abel and Sokol, 1987; Lange et al., 2017; Roozen et al., 2016); or 4.) active case ascertainment in a circumscribed population. Of these four, the most effective has been active case ascertainment (ACA) employed in certain well delineated and receptive populations (May et al., 2009; May and Gossage, 2001; Roozen et al., 2018; Stratton et al., 1996). Once a population has been identified for an ACA study, the two most common methods have been active recruitment to a centralized clinical venue (May et al., 1983) or ACA employed via field studies among school children (Burd et al., 1999; Chambers et al., 2019; May et al., 2006, 2000, 2021, 2020b, 2020a, 2020c, 2018, 2014, 2011, 2007; Okulicz-Kozaryn et al., 2017; Petkovic and Barisic, 2013, 2010; Poitra et al., 2003; Popova et al., 2019; Viljoen et al., 2005). Within these school-based field studies, there have been three common methods of sampling employed (May, Chambers et al., 2018): 1) utilizing a behavioral/developmental screening tool for stand alone observations of individual children to directly estimate the prevalence of FASD (Poitra et al., 2003), or for screening prior to full examinations and testing (Burd et al., 1999; Chambers et al., 2019); 2) preliminary screening of all (a census) small children (generally ≤10th or ≤25th on height, weight, or



I. I. FAS
(With or without documented prenatal alcohol exposure)
A diagnosis of FAS requires all features, A–D:
- A. A characteristic pattern of minor facial anomalies, including ≥2 of the following:
  1. Short palpebral fissures (≤10th centile)
  2. Thin vermilion border of the upper lip (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
  3. Smooth philtrum (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
- B. Prenatal and/or postnatal growth deficiency
  1. Height and/or weight ≤10th centile (plotted on a racially or ethnically appropriate growth curve, if available)
- C. Deficient brain growth, abnormal morphogenesis, or abnormal neurophysiology, including ≥1 of the following:
  1. Head circumference ≤10th percentile
  2. Structural brain anomalies
  3. Recurrent nonfebrile seizures (other causes of seizures having been ruled out)
- D. Neurobehavioral impairment[a]
  1. For children ≥3 y of age (a or b):
     a. WITH COGNITIVE IMPAIRMENT:
        −Evidence of global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verbal IQ or spatial IQ ≥1.5 SD below the mean)
        OR
        −Cognitive deficit in at least 1 neurobehavioral domain ≥1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment or visual-spatial impairment)
     b. WITH BEHAVIORAL IMPAIRMENT WITHOUT COGNITIVE IMPAIRMENT:
        −Evidence of behavioral deficit in at least 1 domain ≥1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control)
  2. For children <3 y of age:
     −Evidence of developmental delay ≥1.5 SD below the mean

II. PFAS
-For children with documented prenatal alcohol exposure, a diagnosis of PFAS requires features A and B:
- A. A characteristic pattern of minor facial anomalies, including ≥2 of the following:
  1. Short palpebral fissures (≤10th centile)
  2. Thin vermilion border of the upper lip (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
  3. Smooth philtrum (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
- B. Neurobehavioral impairment[a]
  1. For children ≥3 y of age (a or b):
     a. WITH COGNITIVE IMPAIRMENT:
        −Evidence of global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verbal IQ or spatial IQ ≥1.5 SD below the mean)
        OR
        −Cognitive deficit in at least 1 neurobehavioral domain ≥1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment or visual-spatial impairment)
     b. WITH BEHAVIORAL IMPAIRMENT WITHOUT COGNITIVE IMPAIRMENT:
        −Evidence of behavioral deficit in at least 1 domain ≥1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control)
  2. For children <3 y of age:
     −Evidence of developmental delay ≥1.5 SD below the mean

-For children without documented prenatal alcohol exposure, a diagnosis of PFAS requires all features, A–C:
- A. A characteristic pattern of minor facial anomalies, including ≥2 of the following:
  1. Short palpebral fissures (≤10th centile)
  2. Thin vermilion border of the upper lip (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
  3. Smooth philtrum (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
- B. Growth deficiency or deficient brain growth, abnormal morphogenesis, or abnormal neurophysiology
  1. Height and/or weight ≤10th centile (plotted on a racially or ethnically appropriate growth curve, if available)
  2. Deficient brain growth, abnormal morphogenesis, or abnormal neurophysiology, including ≥1 of the following:
     a. Head circumference ≤10th percentile
     b. Structural brain anomalies
     c. Recurrent nonfebrile seizures (other causes of seizures having been ruled out)
- C. Neurobehavioral impairment[a]
  1. For children ≥3 y of age (a or b):
     a. WITH COGNITIVE IMPAIRMENT:
        −Evidence of global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verbal IQ or spatial IQ ≥1.5 SD below the mean)
        OR
        −Cognitive deficit in at least 1 neurobehavioral domain ≥1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment or visual-spatial impairment)
     b. WITH BEHAVIORAL IMPAIRMENT WITHOUT COGNITIVE IMPAIRMENT:
        −Evidence of behavioral deficit in at least 1 domain ≥1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control)
  2. For children <3 y of age:
     −Evidence of developmental delay ≥1.5 SD below the mean

III. ARND
Requires features A and B (this diagnosis cannot be made definitely in children <3 y of age):
- A. Documented prenatal alcohol exposure
- B. Neurobehavioral impairment[a]
  1. For children ≥3 y of age (a or b):
     a. WITH COGNITIVE IMPAIRMENT:
        −Evidence of global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verbal IQ or spatial IQ ≥1.5 SD below the mean)
        OR
        −Cognitive deficit in at least 1 neurobehavioral domain ≥1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment or visual-spatial impairment)
     b. WITH BEHAVIORAL IMPAIRMENT WITHOUT COGNITIVE IMPAIRMENT:
        −Evidence of behavioral deficit in at least 1 domain ≥1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control)

IV. ARBD
Requires features A and B:
- A. Documented prenatal alcohol exposure
- B. One or more specific major malformations demonstrated in animal models and human studies to be the result of prenatal alcohol exposure: cardiac: atrial septal defects, aberrant great vessels, ventricular septal defects, conotruncal heart defects; skeletal: radioulnar synostosis, vertebral segmentation defects, large joint contractures, scoliosis; renal: aplastic/hypoplastic/dysplastic kidneys, “horseshoe” kidneys/ureteral duplications; eyes: strabismus, ptosis, retinal vascular anomalies, optic nerve hypoplasia; ears: conductive hearing loss, neurosensory hearing loss

Diagnostic Caveats: The assignment of an FASD is a complex medical diagnostic process best accomplished through a multidisciplinary approach. As is the case with many medical conditions, sound clinical judgment must be used. Differential diagnoses should always include genetic disorders or conditions arising from other teratogens. Additionally, because head circumference, growth, and many cognitive and behavioral characteristics have moderate to high degrees of heritability, when information is available about the biological parents, these data should be considered in the final diagnostic decision.

[a] Adaptive skills should be assessed, but such deficits cannot stand alone for diagnosis.

Fig. 2. Institute of Medicine Diagnostic Guidelines for Specific Fetal Alcohol Spectrum Disorders (FASD) as clarified by Hoyme (2016). Reproduced with permission from Pediatrics, Vol. 138, Pages 3-4, Copyright © 2016 by the AAP.

head circumference) prior to physical/dysmorphology exams and developmental testing (May et al., 2021, 2020a, 2020b, 2020c); and 3) from a simple random sample (May et al., 2020a, 2020b). Recently a combination of ACA methods have been used simultaneously in some populations in independent samples of school cohorts and they have yielded similar results, although the random samples have generally yielded higher overall FASD rates (May et al., 2020a, 2020b). These higher rates were due to a greater capture of children with alcohol-related neurodevelopmental disorder (ARND), who are by definition (Hoyme et al., 2016), not required to have growth deficiency or cardinal FASD dysmorphia. ARND cases, therefore, are more likely to be identified in simple random samples due to no preliminary screen for

size or dysmorphic traits.

1.1. This study

Described here is a study carried out from a simple random sample among first grade children attending public schools in a single county in the southeastern region of the United States (USA). Initially there were no plans for pre-screening of children by size, dysmorphology, or developmental trait assessment for entry into the study. Entry into the full study was to be completely by random numbers. However, due to pressing limitations of time and budget, dysmorphology examinations were ultimately used to determine entry into Tier II of the study. Therefore, the sample, although small, should represent a relatively accurate cross-section of the first-grade population in this county, or at least of the consented population.

2. Methods

2.1. Sampling

Following university IRB approvals, a presentation to the County Board of Education, and the Board's approval, enrollment data lists were obtained from the County Superintendent of Public Education for all enrolled students in first grade schools in the county. The 16 public elementary schools had 1,073 first grade students enrolled (Fig. 1). Using the computer program Research Randomizer, a first random sample was drawn for 400 children (without replacement). Each of those children chosen was sent home with a study program description and consent form for their parents to read and sign if their child was given permission to participate. After a second set of information materials and forms were again sent to the same 400 families, and the response yielded only a little over 100 children, a second set of random numbers of unduplicated children was drawn (again without replacement), and materials and consent forms were sent home with these newly chosen children. After a second set of requests from this second group was pursued, the selection process was ended and physical/dysmorphology exams were scheduled and carried out in each of the schools. From the total of 721 selected participants, 231 children were provided consent from their parents to participate. This consented sample represented 21.5 % of the enrolled students, and 32 % of the randomly-selected students (Fig. 1).

2.2. Diagnostic criteria

The Revised Institute of Medicine (IOM) diagnostic guidelines for FASD (Hoyme et al., 2005) were used along with revised cut-off values established by the NIAAA-funded, Collaboration on FASD Prevalence (CoFASP) advisory group (Hoyme et al., 2016). The domains assessed for all study participants who completed the entire study were: (1) physical growth, (2) dysmorphology; (3) cognitive tests and behavioral assessments, and (4) maternal risk factors impacting the index pregnancy (see Fig. 2). The continuum of FASD has four specific diagnoses: fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (PFAS), alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defects (ARBD) (Hoyme et al., 2016). Criteria for each diagnostic category were utilized in this study (see Fig. 2), yet ARBD has been found to be rare in any population (May et al., 2016a, 2016b, 2015, 2014, 2011). The diagnosis of FAS without a confirmed history of alcohol exposure can be made according to the original IOM criteria (Stratton et al., 1996), and revised criteria (Hoyme et al., 2016, 2005). Revised criteria also permit diagnosis of PFAS without evidence of prenatal drinking reported directly by the mother. However, the diagnosis of FASD in epidemiology studies is rarely made without direct maternal reports of alcohol use prior to pregnancy recognition, during pregnancy, or collateral reports. An ARND diagnosis always requires direct confirmation of alcohol use in the index pregnancy. Final diagnoses were assigned by a multidisciplinary team headed by the dysmorphologists in formal, structured, data-driven case conferences after the examiners of the individual domains presented detailed findings and assessments for each child.

2.3. Tier I - assessment of physical traits and growth

All randomly-selected, consented children were then engaged into Tier I of the two-tiers of the diagnostic process. In Tier I, 231 children were provided a physical examination by one member of our team of pediatric dysmorphologists at their school. All medical examiners were fellowship-trained pediatricians in medical genetics/dysmorphology, all were unfamiliar with the children in the study, and were blinded from any medical/school records or other previous information on the children and their mothers. Multiple measurements of growth and development traits were taken, two-dimensional photographs were taken, and a complete, standard dysmorphology assessment for the full complement of known birth defects/anomalies was completed on each child. A research team member assisted each physician by recording the exam information on a project-specific standardized form. At the end of each examination day, the dysmorphologists and scribes completed each child's form with age and sex-specific growth centiles from pediatric growth charts of the Centers for Disease Control and Prevention (CDC) and from clinical trait distribution charts (Nellhaus, 1968; Thomas et al., 1987). Once completed, the forms yielded the specific number of dysmorphology traits and a total dysmorphology score specific to the FASD-linked traits identified for each child (Hoyme et al., 2005). Once the forms had been tabulated for all children seen that day, the findings for each child were reviewed by the entire clinical team. Over the course of all the clinic exam days, 48 children were assessed by the dysmorphologists to be preliminary candidates for one of the diagnoses on the FASD continuum; but final diagnose were deferred until neurobehavioral tests and maternal risk interviews were completed. Because of the random selection process and the research plan to test all consented children and interview all mothers, all 231 selected and consented children were referred on to Tier II for neurobehavioral assessment and their mothers to be interviewed about the index pregnancy.

2.4. Tier II - neurobehavioral assessment and maternal interviews

The initial plan was for all 231 children to be assessed for neurobehavior, and all mothers interviewed for complete coverage of the consented sample. Therefore, the study would accommodate discovery of all cases of FASD and provide a large number of verified, typically-developing controls. However, time and budgetary limitations intervened, and complete coverage for all 231 children was not possible. A team decision was made, and cleared with school officials, to limit full testing and assessment beyond the dysmorphology exam to the 48 FASD suspects and the first 48 children who were all contacted and found to be present in the county and available for testing. And the teachers and parents of these 48 children were believed to be available for behavioral assessments. Ultimately, not all mothers consented to a maternal risk interview, and some failed to make an appointment or failed to show up for an interview. Full or sufficient data (e.g., Teacher Report Forms and/or Parent Reports) for neurobehavioral assessments were completed on 84 children; 12 of the final 96 were either not located, could not be scheduled for an interview, or had moved before the end of the study.

Of the 84 mothers of the Tier II child participants who were tested, 72 mothers were either interviewed (n = 69) or maternal data were obtained from a co-lateral source familiar with the mother during the gestational period of the index child (n = 3). Other mothers (n=12) either refused consent to the interview or were impossible to schedule for the in-person interview.

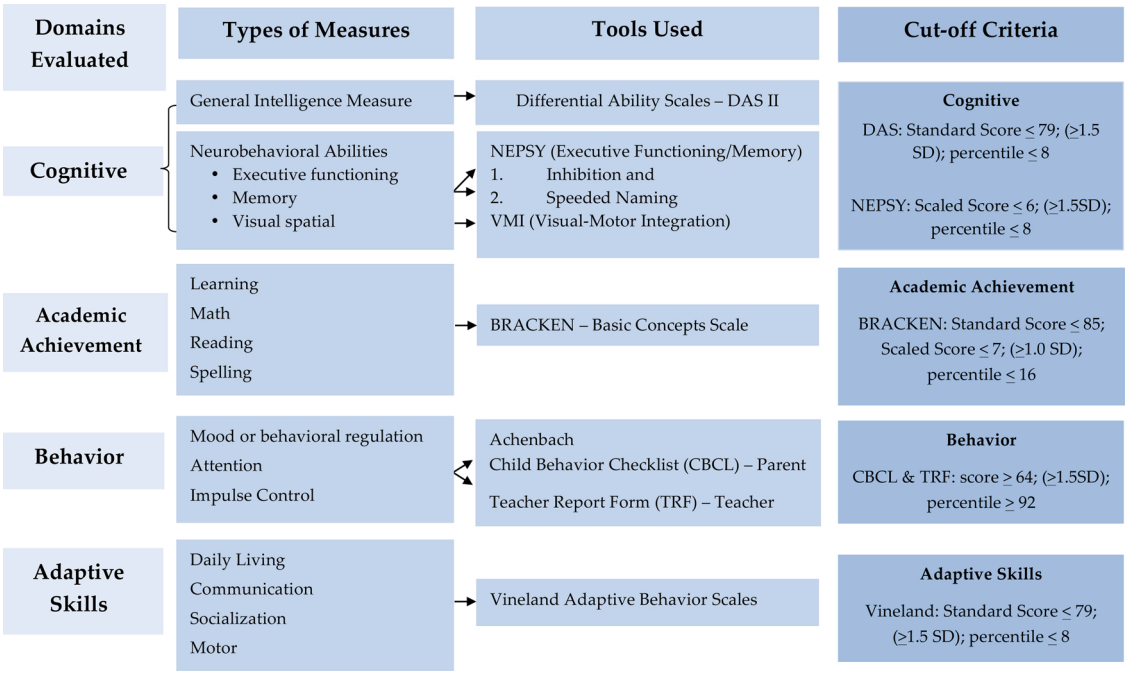


Fig. 3. CoFASP Cut-Off Criteria: Neurobehavioral Testing Battery.

2.5. Tier II - neurobehavioral testing and maternal risk questionnaires

Development and behavior were assessed by professional staff and/or graduate students from the Carolina Institute for Developmental Disabilities with the CoFASP-endorsed battery (Fig. 3). The battery was designed to evaluate the following domains: cognitive development, executive functioning, academic achievement, behavior, and adaptive skills. Instruments included were: Differential Abilities Scale (DAS-II) (Elliott, 2007) to assess general intelligence; NEPSY-II (Korkman et al., 2007) to assess executive functioning, memory, and visual/spatial integration; Developmental Test of Visual-Motor Integration (VMI) (Beery and Beery, 2004) to assess eye-hand coordination; Bracken Basic Concepts Scale (Bracken, 1998) to assess basic concept development in math, reading, and spelling; the Achenbach (Achenbach and Rescorla, 2001) Child Behavior Checklist (CBCL) and Teachers Report Form (TRF) to assess behavior; and Vineland Adaptive Behavior Scales (Sparrow et al., 2005) to examine activities of daily living and adaptive skills.

All consenting mothers of children in Tier II (potential cases and controls) who could be scheduled successfully, were provided face-to-face interviews by grant-funded project staff. Sequencing of questions was designed to maximize accurate self-reporting of: general health, reproduction, nutrition, alcohol and drug use, and socioeconomic status (SES). Maternal height, weight, and OFC were directly measured. Drinking questions employed a timeline, follow-back sequence (Sobell et al., 2001, 1988) and Vessels alcohol quantity methodology for accurate calibration of standard alcohol units (Kaskutas and Graves, 2001, 2000; Kaskutas and Kerr, 2008). The American "Standard Drink" was used, where one drink was equal to consuming 14 g of absolute alcohol: 12 oz. (350 mL at 5 % alcohol by volume) of beer; 5 oz. (150 mL) of wine (12 % by volume); and 1.5 oz. (44 mL of 40 % alcohol by volume) of liquor (NIAAA, 2021). Current alcohol consumption for the week preceding the interview was embedded into dietary intake questions (King, 1994) to aid accurate calibration of quantity, frequency, and timing of alcohol use before and during the index pregnancies (Alvik et al., 2006; May et al., 2013, 2008, 2005). Retrospective reports of alcohol use have been found to be highly accurate in some populations when designed and administered properly (Czarnecki et al., 1990; Fortin et al., 2017; Hannigan et al., 2010; May et al., 2018).

Maternal risk data gathered from the mothers directly, or from knowledgeable collateral sources (relative or close associates), indicated that drinking prior to pregnancy recognition or during the index pregnancy was confirmed with the CoFASP criteria (Hoyme et al., 2016) if at least one of these measures were reported: a) six or more standard drinks per week for two or more weeks during pregnancy; b) a binge of 3 or more drinks per occasion on two or more occasions during pregnancy; or c) documentation of social or legal problems in proximity to the index pregnancy (e.g. treatment of alcohol abuse or infractions of driving under the influence). These criteria were not intended to reflect a threshold for damage associated with FASD. Rather, cut-off levels were established based on previous experience with responses in prior self-reported drinking surveys that were associated with dysmorphology and neurobehavioral impairment characteristic of an FASD.

2.6. Multidisciplinary case conferences for final diagnoses

Following data collection and aggregation, final diagnoses were made in confidential, multidisciplinary case conferences. The findings for each child in each domain were discussed in a structured manner where summary results were presented by the research team members who produced them. While findings were being presented and discussed, two-dimensional, digital photos of the child's face (frontal and profile views) were projected to contextualize the discussion. Findings from each domain and examiner were weighed throughout the presentation, and the final diagnosis was made by the examining dysmorphologists with the consensus of the group. In rare cases, where there was lack of agreement among participants, the final diagnosis was delayed until clarification or additional details were brought to the table from the child's file for the group to weigh. In classifying children, consistency and quality assurance were enhanced by strict application of the CoFASP criteria when preparing for and during case conferences. After the conference was completed, final diagnoses and data were double-checked for consistency and accuracy by the data management team and examiners.

2.7. Data analysis and final prevalence rates

Data analyses were performed with SPSS (IBM, 2020). Child physical, cognitive/behavioral, and maternal risk findings were compared

Table 1
Demographic, Physical Growth, Cardinal FAS Features, Other Minor Anomalies, and Total Dysmorphology Score for Southeastern County II.

	Children with FASD (n = 6)		Randomly-Selected Control Children (n = 71)		All Other Randomly-Selected Children (n = 154)		Test-score	p-value
Growth and Cardinal Features								
Sex (% Male)	50.0		50.7		46.8		.313	.855
Current Age (in months) – Mean (SD)	83.7	(3.0)	85.7	(4.9)	85.1	(5.2)	.682	.507
Race/Ethnicity (%)								
White	66.7		64.8		64.3			
Hispanic	0.0		9.9		7.8		1.605	.952
Black	33.3		21.1		24.7			
Other	0.0		4.2		3.2			
Height Percentile – Mean (SD)	31.5	(33.6)	44.5	(29.7)	56.6	(29.0)	5.672	.004[C]
Weight Percentile – Mean (SD)	30.0	(34.2)	49.2	(29.6)	64.0	(29.0)	9.099	<.001[C]
Occipitofrontal Circumference (OFC) Centile – Mean (SD)	16.7	(21.6)	50.4	(33.0)	63.1	(26.8)	11.082	<.001[A,B,C]
OFC centile ≤3rd centile	16.7		11.3		1.3		12.574	.002
OFC centile ≤10th centile	66.7		21.1		3.2		37.642	<.001
Child's BMI Percentage – Mean (SD)	38.7	(33.4)	55.7	(28.0)	65.7	(28.3)	5.098	.007[C]
Palpebral Fissure Length (PFL) Centile – Mean (SD)	21.8	(18.7)	37.4	(22.0)	42.4	(18.1)	4.371	.014
Smooth Philtrum (% Yes)	50.0		25.4		14.9		7.247	.027
Narrow Vermilion (% Yes)	66.7		25.4		19.5		7.846	.020
Other Minor Anomalies								
Inter Pupillary Distance (IPD) Centile – Mean (SD)	41.7	(19.2)	60.5	(24.9)	67.0	(24.7)	4.284	.015
Outer Canthal Distance (OCD) Centile – Mean (SD)	32.2	(14.4)	43.2	(20.2)	47.8	(21.6)	2.444	.089
Maxillary Arc (cm) – Mean (SD)	24.1	(.9)	25.0	(1.3)	25.2	(1.2)	2.455	.088
Mandibular Arc (cm) – Mean (SD)	24.9	(1.4)	26.1	(1.5)	26.3	(1.4)	2.974	.053
Total Dysmorphology Score – Mean (SD)	9.2	(2.6)	5.4	(3.9)	3.8	(3.0)	12.339	<.001[A,B,C]

**Bonferroni adjusted significance level for Growth and Cardinal Features = 0.004; for other minor anomalies = .010 Post-hoc Dunnett C Comparisons were significantly different (p < .05) between: [A.] FASD & Randomly-Selected Control Children; [B.] FASD & All Other Randomly-Selected Children; [C.] Randomly-Selected Control Children & All Other Randomly-Selected Children.

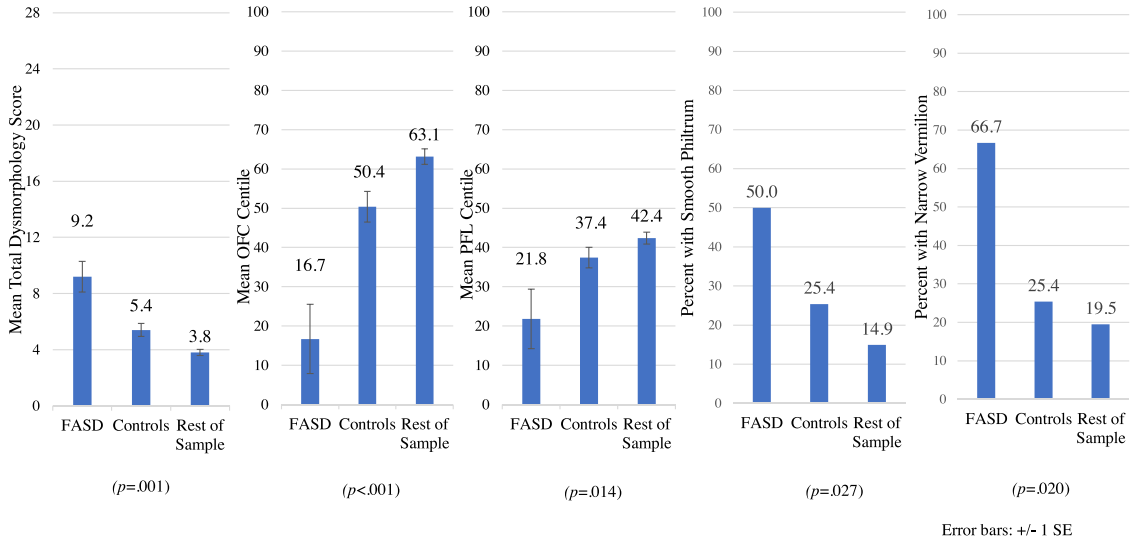


Fig. 4. Total Dysmorphology Score, Occipitofrontal Circumference (OFC), Palpebral Fissure Length (PFL), Smooth Philtrum, and Narrow Vermilion by FASD Diagnosis, Southeastern II County Sample.

across diagnostic groups using one-way analysis of variance, t-tests, and chi square. Statistical significance was determined with alpha of .05 and a significance level between >0.05 and ≤ 0.10 was considered to be approaching significance if the direction of the relationship was consistent with other studies of FASD (one-tailed significance).

3. Results

3.1. The study community

The county that hosted this study is characterized by several small towns in a primarily rural area in the Southeastern Region of the USA. As detailed in Appendix Table A1, the county population was 91,810 and had declined approximately 3% in the last decade. This compares to 6% growth overall in the USA (United States Census Bureau, 2019). The county has approximately the same percentage of Whites, slightly more Blacks, and fewer Hispanics and other minorities than the USA general population. The median household value is approximately 52 % that of the general USA, and education levels are lower than the overall USA, with only half as many college graduates and 7% fewer high school graduates (United States Census Bureau, 2019). The county has lost many of its wage labor jobs (textiles, furniture, and small businesses) over the past 30 years. The county's per capita and household incomes ($24,209 and $43,579) fall well below national averages (71 % and 69 % respectively for US averages), and 18 % of the population lives below the poverty line compared to 10.5 % of the USA. Health behavior is ranked lower in this county than the general population of at least 35 other states (United Health Foundation, 2020). But alcohol use data

Table 2
Neurobehavioral Traits Differentiating Diagnostic Groups in Southeastern County II: Children with FASD vs. Controls.

	Children with FASD		Control Children		t-score	p-value
	Mean	(SD)	Mean	(SD)		
Intellectual Domain	**(*n* = 5)**		**(*n* = 68)**			
General Abilities Percentile	37.4	(34.2)	45.7	(27.1)	−.50	.518
Verbal Cluster Percentile	36.2	(34.2)	50.6	(29.1)	−1.059	.293
Nonverbal Reasoning Cluster Percentile	34.4	(26.7)	44.1	(27.3)	−.766	.446
Spatial Cluster Percentile	39.4	(35.8)	45.0	(23.2)	−.507	.614
Executive Function	**(*n* = 5)**		**(*n* = 68)**			
INN vs. INI Contrast Scaled Score	7.0	(1.9)	9.5	(3.2)	−1.679	.098
INI (Inhibition) combined scaled score	6.4	(1.8)	9.1	(3.2)	−1.854	.068
Visual Spatial	**(*n* = 5)**		**(*n* = 68)**			
VMI Standard Score	86.4	(9.9)	92.2	(6.2)	−1.925	.058
Impulse Control – Child Behavior Checklist (CBCL)	**(*n* = 4)**		**(*n* = 50)**			
TRF Aggressive behavior t-score	50.3	(.5)	53.6	(5.7)	−3.973	<.001
TRF Oppositional defiant problems t-score	50.0	(.0)	53.5	(6.6)	−3.723	.001
TRF Conduct problems t-score	50.5	(1.0)	53.3	(5.1)	−3.155	.004
Adaptive Function – Vineland (VABS)	**(*n* = 4)**		**(*n* = 50)**			
Parent Communication Standard Score	85.5	(7.7)	103.7	(16.1)	−2.228	.030
Parent Daily Living Skills Standard Score	83.5	(15.5)	106.3	(14.8)	−2.957	.005
Parent Socialization Standard Score	78.3	(13.4)	101.1	(15.9)	−2.792	.007

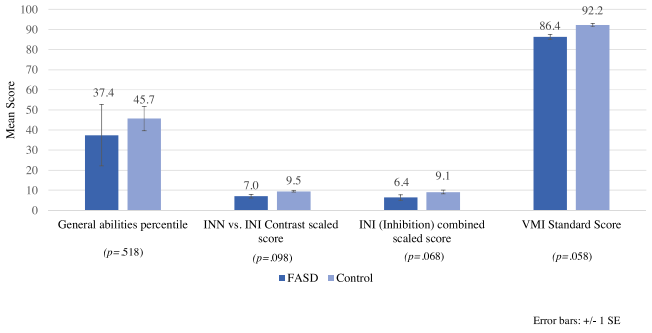


Fig. 5. Selected Cognitive and Executive Function Measures by FASD Diagnoses, Southeastern II County Sample.

from both the CDC (Centers for Disease Control and Prevention, 2020) and NIAAA (Lavallee and Yi, 2011) indicate fewer drinking problems overall in this county and region from binge drinking, excessive drinking, and per capita ethanol consumption than in the USA. Only one drinking measure used by the CDC, heavy drinking (females having one or more drinks per day and males 2 or more) is high at 7.3 % in this region compared to 5.0–5.6 % elsewhere in the USA.

3.2. Child physical traits

Table 1 presents data on the key physical features of all children. In columns 1 and 2 are data on all children who received the full evaluation of physical traits, sufficient evaluation and testing of neurobehavior, and

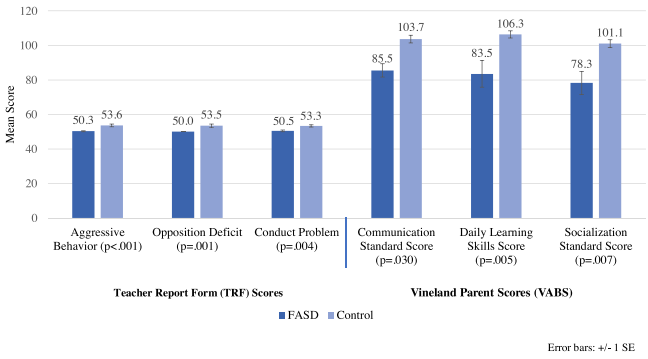


Fig. 6. Significant Behavioral Traits for Children with FASD vs. Controls, Southeastern II County Sample.

sufficient maternal risk information to be diagnosed either as cases or as controls (developing within the normal age-appropriate range). The third column provides data for the remainder of the random sample that were not evaluated or their mothers interviewed. Statistically significant differences across the three groups ($\alpha \leq .05$) were found for the following traits, each representing a characteristic typical of a child with FAS or PFAS: depressed height, weight, OFC (head circumference) ≤10th centile, Body Mass Index (BMI), and inter pupillary distance (IPD). Furthermore, the three cardinal features of FAS were significantly different between the three groups: short palpebral fissure length (PFL), smooth philtrum, and narrow vermilion of the upper lip as was the average total dysmorphology score across categories (see Fig. 4). Approaching significance (≤0.10) in the expected direction for children with an FASD were: three other common features found with FAS and PFAS, decreased outer canthal distance (OCD), and maxillary and mandibular arc measurements. The children with FASD had a higher total dysmorphology score (9.2 vs. 5.4) than the control/comparison group.

The dysmorphology exams performed on the entire sample of 231 children provide an additional description of significant FASD traits versus the physical traits of all of the children who were randomly selected for the study. The physical trait findings comparing the six children with FASD to the rest of the entire sample ($n = 225$) are presented in the Appendix (Table A2). In this comparison most of the traits commonly associated with FAS and PFAS were also significantly different between the children with FASD and the rest of the sample. Children with FASD were smaller than others on weight centile, OFC centile, percent with OFC ≤10th centile, BMI centile, PFL centile, smooth philtrum, narrow vermilion, IPD centile, maxillary and mandibular arcs, and total dysmorphology score.

3.3. Child neurobehavioral traits

Results from selected neurobehavioral traits of the children are found in Table 2, and these measures are illustrated in Figs. 5 and 6. Table 2 includes all intellectual domain variables tested, two executive function summary measures, one visual/spatial measure, and all behavioral checklist measures that significantly discriminated the children with FASD from controls. None of the four intellectual domain variable means were statistically different between groups, two executive function measure means approached significance, and the visual/spatial domain variable (VMI Standard Score) also approached significance. The behavioral measures obtained from the CBCL and the Vineland Adaptive Behavior Scale (VABS) demonstrated significantly greater discrimination of the groups. Three measures of impulse control (aggressive behavior, oppositional defiant behavior, and conduct problems) were all rated by the children's teachers as more characteristic of the children with FASD, although these scores did fall within the average range for both groups. Parents of children with FASD rated their children

Table 3
Selected Maternal Risk Variables: Southeastern County II.

	Children with FASD		Control Children		χ^2	p-value
	Mean	(SD)	Mean	(SD)		
Physical	***(n = 5)***		***(n = 61)***			
Age at pregnancy (yrs)	30.4	(7.8)	28.3	(6.4)	.689	.494
Height at interview (cm)	159.4	(8.8)	164.4	(6.8)	−1.517	.136
Weight at interview (kg)	74.3	(25.2)	83.7	(23.1)	-.860	.394
Demographic	***(n = 5)***		***(n=61)***			
Years of Education completed	12.6	(.9)	14.2	(2.5)	−1.414	.163
Household yearly income - during pregnancy	25666	(12423)	45230	(29692)	−1.121	.270
Household yearly income – at interview	22529	(28227)	51168	(38265)	−1.652	.212
Marital Status – current (%)						
Married	40.0		63.3			
Divorced/ Widowed/ Separated/ Single	60.0		32.7			
Living with Partner	0.0		4.1		1.570	.456
Health Status	***(n = 5)***		***(n=59)***			
Postpartum depression (% Yes)	60.0		16.9		5.278	.022
Postnatal Environment	***(n = 5)***		***(n=58)***			
Breastfed (% Yes)	0.0		59.3		4.249	.011
Partner ever had a drinking problem[ˆ] (%)						
Never	50.0		82.8			
In the past, but not currently	0.0		6.9			
Currently	0.0		0.0			
Both past and currently	50.0		10.3		3.839	.129
Alcohol Use – Before and During Pregnancy	***(n = 5)***		***(n = 60)***			
Drank before pregnancy (% Yes)	80.0		48.3		2.115	.146
# of drinks consumed on usual drinking day before pregnancy[1]	2.8	(1.5)	1.9	(1.4)	1.017	.319
Usual frequency – before pregnancy[1]						
Everyday or almost everyday	50.0		0.0			
3-4 times per week	0.0		3.6			
1-2 times per week	25.0		14.3			
2-3 times per month	25.0		17.9			
1 time per month or less	0.0		64.3		17.067	.002
Drank in 1st trimester (% Yes)	20.0		4.0		2.405	.300
Alcohol Use - Current	***(n = 5)***		***(n = 58)***		11.787	.001
	20.0		0.0		9.384	.002
Recovering drinker at interview (% Yes)						
Drug Use	***(n = 5)***		***(n = 60)***			
Used tobacco – in lifetime[ˆ]					.921	.631
Yes, within last 30 days	50.0		21.7			
Yes, in lifetime	50.0		31.7			
Never	0.0		46.7			
Used any drug in lifetime (% Yes)	20.0		47.9		1.424	.233
Used marijuana – in lifetime (% Yes)	20.0		43.8		1.052	.305
Used crack/ cocaine – in lifetime (% Yes)	20.0		8.3		.721	.396
Abused pain killers – in lifetime (% Yes)	20.0		3.4		2.846	.092

1. Among those who reported drinking in the given time period.
[ˆ]Only four respondents answered this question.

Table 4
Final Prevalence Estimates of FASD (with CoFASP criteria) Utilizing Random Selection Only and 95 % Conference Intervals by Specific Diagnoses: Southeastern County II.

Diagnosis	n	Proportion	Rate per 1000	95 % Confidence Intervals
FAS	2	0.02381	23.8	0.0 to 56.4
PFAS	2	0.02381	23.8	0.0 to 56.4
ARND	2	0.02381	23.8	0.0 to 56.4
Total FASD	6	0.07143	71.4	16.4 to 126.5

[ˆ]Total school enrollment n = 1073; children picked from random sampling n = 721 (67.2 % of enrolled students); dysmorphology exams were completed for all consented children, n = 231 (21.5 % of enrolled students; 32.0 % of those selected randomly); 39 of 48 of children suspected as FASD cases completed both dysmorphology exams and neurobehavioral testing + 45 of 48 controls = 84 (7.8 % of enrolled students; 11.7 % of randomly-selected students).

on the VABS as having more problems with communication, daily living skills, and socialization than did the parents of controls.

3.4. Maternal risk findings

Selected maternal risk factors identified from maternal interviews of the mothers of both groups are presented in Table 3, where it can be seen that there were few statistically significant differences registered between groups. The sample size significantly limited statistical power, especially on the large variety of the maternal risk variables considered. Significant maternal risk factors reported by the mothers of children with FASD were post-partum depression, less frequent breastfeeding of the index child, and a higher pre-pregnancy frequency of drinking (drinking every day or 1–4 times per week on average). Additionally, 20 % of the mothers of children with FASD reported that they were "recovering drinkers." Approaching significance was that a higher percentage of mothers of children with FASD reported lifetime misuse of prescription medication/pain killers. There were many other variables addressed in the maternal interviews, but no others were found to be significantly different between maternal groups.

Table A1
Demographic Indicators for Southeastern County II compared to the United States.

Demographic Indicator	SE Study County	United States
Population (7/2019)[1]	91,810	328,239,523
(percentage of US population)	(0.028%)	(100%)
Population change (%) since 2010[1]	−2.8%	6.3%
Race and Hispanic Origin (2010)[1]		
White alone	77.5%	76.3%
Black alone	19.0%	13.4%
American Indian and Alaskan Native alone	0.6%	1.3%
Asian alone	0.7%	5.9%
Two or more races	2.1%	2.8%
Hispanic or Latino	6.3%	18.5%
Foreign born persons[1]	3.8%	13.6%
Age – years (median)	44.5	38.3
Housing[1]		
Median household value	$112,800	$217,500
Education[1]		
High School graduate or higher, % ages ≥25 years	82.7%	88.0%
Bachelor's degree or higher, % ages ≥25 years	15.1%	32.1%
Economy[1]		
Per capita income in past 12 months (2014 dollars)	$24,209	$34,103
Median household income	$43,579	$62,843
Persons in poverty	18.4%	10.5%
Health Behavior State Rank in U.S.[2]	35–40	Median 25
Overall State Health Rank in U.S.[2]	30–34	(Range 1–50)
Alcohol Use		
Excessive drinking[2]	15.4%	18.6%
Binge drinking^, region %	15.6%	16.8%
Heavy drinking#, local region[3]	7.3%	5.0–5.6%
State per capita ethanol consumption (2009), volume per person 14 years and older[4]	2.02 gallons (8th decile)	2.30 gallons
	7.65 liters	8.71 liters

Sources:
1. US Census, Quick Facts for the Southeastern II County, Calendar year 2019.
2. United Health Foundation, America's Health Rankings, 2020; comprised of scores on behaviors, community and environment, policy and clinical care; scores are ranked for each of the 50 states with better scores resulting in a higher rank among the 50 states; ranges indicate that different rankings are provided for each of the four domains named above.
3. BRFSS (Behavioral Risk Factor Surveillance System Survey) data of the CDC. Reported in local regional statistical reports.
4. La Valle and Yi, NIAAA Surveillance Report #92.
^Binge drinking defined as: during the past 30 days, the consumption of 5 or more drinks for men or 4 or more drinks for females on an occasion.
#Heavy drinking is defined as males having more than two drinks per day and females having more than one drink per day.
+Excessive drinking of alcohol is defined as both binge drinking (above) and chronic drinking also referred to as heavy drinking (above).

3.5. Prevalence of FASD

The prevalence of FASD in this population, based on this randomly-selected, active case ascertainment sample, is presented in Table 4. The rates were: two children or 23.8 per 1,000 children qualified for a diagnosis of FAS, 2 children or 23.8 per 1,000 were diagnosed as PFAS, and 2 children or 23.8 per 1,000 were diagnosed with ARND. Based on the six children diagnosed with an FASD, the total FASD rate was 71.4 per 1,000, or stated as a percentage, 7.1 % of first grade children.

4. Discussion

4.1. Feasibility of using random samples to study FASD

As the demographic and economic data indicated, this study took place in a community highly impacted by economic retraction and stagnation, combined with low education and income levels. This created challenges for the data collection process due to transience of families and children and lack of availability of working mothers for interviews, but even in this environment the use of established methods and study protocol resulted in information that can inform prevention and treatment efforts. In other words, given the challenges of conducting studies like these in highly-economically-impacted communities, having the option of doing a smaller scale, but well-developed study that is grounded in established research methods and protocols can lessen barriers to determining community prevalence of FASD, and therefore estimate the need for prevention and intervention.

Table A2
Child Physical Traits for the Total Sample of Randomly-Selected Children: Southeastern County II.

	Children with FASD (n = 6)		All Other Randomly-Selected Children (n = 225)		
	Mean	(SD)	Mean	(SD)	p
Sex (% Male)	50.0		48.0		.923
Current Age (in months)	83.7	(3.0)	85.3	(5.1)	.440
Height Percentile	31.5	(33.6)	52.8	(29.7)	.085
Weight Percentile	30.0	(34.2)	59.3	(29.9)	.019
OFC Percentile	16.7	(21.6)	59.1	(29.5)	.001
OFC centile <3rd centile	16.7		4.4		.165
OFC centile <10th centile	66.7		8.9		<.001
Child's BMI Percentage	38.7	(33.4)	62.5	(28.5)	.045
PFL Percentile	21.8	(18.7)	40.8	(19.5)	.019
Smooth Philtrum (% Yes)	50.0		18.2		.050
Narrow Vermilion (% Yes)	66.7		21.3		.009
ICD Percentile	68.7	(17.3)	61.2	(22.5)	.422
IPD Percentile	41.7	(19.2)	65.0	(24.9)	.024
OCD Percentile	32.2	(14.4)	46.3	(21.2)	.106
Maxillary Arc (in cm)	24.1	(0.9)	25.1	(1.2)	.048
Mandibular Arc (in cm)	24.9	(1.4)	26.2	(1.4)	.028
Total Dysmorphology Score	9.2	(2.6)	4.3	(3.4)	.001

The data presented here provide evidence that even a small random sample of school children can be utilized as a stand-alone method to produce an estimate of the prevalence of FASD in a population even when not all children receive complete, gold standard evaluation. Comparative information on multiple, selected, FASD-linked, physical and behavioral traits in a population of elementary school children can be used to determine average traits for both children developing in the normal range and children with an FASD and as a validation of accurate application of the diagnostic criteria of FASD. But, one can ask, are these prevalence findings creditable? To answer this question, we compared the final prevalence rate of 7.1 % of children with FASD established in this study to findings from eight other regional samples in the CoFASP study. The findings in this community fit squarely in the middle of the range of prevalence estimates from the larger CoFASP samples which used a combination of ACA methods. The range of the weighted estimated prevalence rates in CoFASP was 3.1%–9.9% (May, Chambers et al., 2018). Furthermore, the mean of these weighted CoFASP prevalence estimates from the eight CoFASP regional samples was 6.5 % with a median = 6.7 %, very similar to the 7.1 % prevalence yielded here (May, Chambers et al., 2018). In the two CoFASP samples carried out in a different county of the Southeastern region, the estimated FASD rates were 3.1 % (95 % CI: 1.6–3.8) and 6.7 % (95 % CI: 3.8–10.6) using a larger sample and ACA study entry techniques via two methods: 1) all consented children who screened small (≤25th centile on height, weight, or head circumference) and 2) provided entry via random selection (May et al., 2020c). Therefore, it appears that this study yielded enough complete and creditable data and results that compared favorably with larger samples utilizing other ACA methods. Certainly, the study could have benefitted from more time and resources to collect all data from all domains of the study from all of the 231 randomly-selected children and their mothers. If so, the data would have been far more creditable, more significant in the case control comparisons, and would

have probably yielded a slightly higher prevalence. But we suspect that all of the prevalence rates that we have produced in the US studies represent undercounts or minimal prevalence. Since the CoFASP consent rate average was less than 60 %, many people might suspect that those families with a history of heavy drinking were less likely to provide consent for their children to participate in a FASD study. At this site, because only 32 % of the children who were asked to participate received consent from their parents, one might suspect that this study is also likely to be an underestimate.

4.2. Comparison of trait findings with previous studies

The child physical differences between the children with FASD and without FASD were consistent with all other studies using ACA methods. That is, children with FASD were significantly smaller and less developed physically than the confirmed typically-developing controls in Table 1 and in the comparison of the diagnosed FASD cases with the average traits of all of the rest of the children chosen randomly. In the neurobehavioral domain, the children with FASD had executive function and visual/spatial traits that approached significance, and negative behavioral traits that were quite significantly different. Aggressive behavior, oppositional/defiant, and conduct problems were significantly more common among the children with FASD as were problems of communication, daily learning, and socialization. In the maternal risk data, frequency of pre-pregnancy drinking differentiated the study groups as in other USA studies of FASD (Chambers et al., 2019; May et al., 2020a, 2020b, 2020c). Furthermore, postpartum depression and problem drinking history were confirmed to be greater among the mothers of children with FASD.

4.3. Limitations and strengths

There were obvious limitations to this study. First, the sample size overall was small with only 21.5 % of the first-grade children sampled and complete data collected on all three domains (physical, neurobehavioral, and maternal risk) on 7.8 % of the students. Second, even pursuing complete information on this small sample, the study was labor intensive and expensive due to the logistics of in-person examinations, testing, maternal interviews, and the multidisciplinary nature of the study. The extended period of time and the expenses required for completion caused us to limit the final study numbers; but, the findings still attained similar prevalence results to other ACA studies in the U.S. with larger samples. Third, fewer children were fully tested on neurobehavior and fewer women were interviewed than originally planned, but comparisons of key findings with other studies seemed to indicate reliability of findings on the traits of the children and the prevalence estimates. More time and money could have facilitated validation of the efficacy of this simple random sampling method. Fourth, the final control group was generally representative of children who were developing within the normal range for this community. But since it also contained 36 children who had originally been deferred as suspects for an FASD diagnosis after the initial dysmorphology exam and growth measurements, it may not have been as random as desired, and may not have yielded as many significant differences between children with FASD and controls. The data in Table 1 and Appendix Table A2 confirm that the control group was intermediate between the FASD cases and the other children in the random sample.

One strength of this study was the utilization of the established, revised IOM diagnostic methods with cutoff criteria designed and formulated for the CoFASP studies. This allowed comparison of the results from this study to that of other CoFASP sites in the USA. Secondly, the full dysmorphology exams completed on all of the consented students proved to be an especially valuable contribution to this otherwise small sample study.

5. Conclusion

Utilizing proven clinical methods to diagnose children with FASD drawn from a relatively small random sample in a defined population of first grade school children, proved to be efficacious. Findings compared favorably to other studies on overall prevalence results, family characteristics, physical traits, and neurocognitive abilities, and indicate that previously undiagnosed children can still be identified as early as their entry into formal schooling. Such early identification, in turn, can enable and facilitate early interventions to assist the development of those affected by FASD.

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Contributors

Philip A. May was the Principal Investigator who designed and directed the overall study, received the NIH funding, worked with the local co-investigator Julia Jackson-Newsom to plan and complete operations in the local site and interaction with the school administrators. He wrote the majority of the first and last drafts of the manuscript. Julie Hasken performed the data analyses and, with assistance from Dixie Hedrick, constructed the graphics, tables and figures. Julia Jackson-Newsom was the local PI and oversaw programmatic and logistical matters in the study community. Chalise Mullis and Elizabeth Dobyns were local field coordinators and maternal interviewers who provided liaison and coordination of clinics and data collection with school administrators and individual schools. Wendy Kalberg and David Buckley designed, oversaw and performed various data management tools and files, data entry, and IRB activities at the central data repository. Wendy Kalberg, with input from Claire Coles of Emory University, designed the neurobehavioral battery of tests and checklists for this study and the national CoFASP research. Also, Wendy Kalberg and Stephen Hooper trained local school psychologists, and Dr. Hooper supervised the implementation of neurobehavioral testing and data collection at this site. Drs. Tamison Jewett, Omar Abdul-Rahman, Margaret Adam, Luther Robinson, and Melanie Manning were project dysmorphologists/medical geneticists who performed dysmorphology examinations on all children, generated clinical dysmorphology data in field clinics, and made the final diagnoses of all children in the multidisciplinary case conferences. H. Eugene Hoyme was the chief dysmorphologist who supervised all of the clinical, medical team members, provided clinical exams, and generated some of the pediatric data. Each co-author contributed data and substantive expertise to the study, read drafts of the manuscript, and contributed to the writing and editing.

Declaration of Competing Interest

The authors have no financial relationship relevant to this article to disclose. The authors have no conflict of interest to declare.

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Appendix

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