Approaching the Prevalence of the Full Spectrum of Fetal Alcohol Spectrum Disorders in a South African Population-Based Study

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Background: The prevalence and characteristics of fetal alcohol spectrum disorders (FASD) were determined in this fourth study of first-grade children in a South African community.

Methods: Active case ascertainment methods were employed among 747 first-grade pupils. The detailed characteristics of children within the continuum of FASD are contrasted with randomly selected, normal controls on (i) physical growth and dysmorphology; (ii) cognitive/behavioral characteristics; and (iii) maternal risk factors.

Results: The rates of specific diagnoses within the FASD spectrum continue to be among the highest reported in any community in the world. The prevalence (per 1,000) is as follows: fetal alcohol syndrome (FAS)—59.3 to 91.0; partial fetal alcohol syndrome (PFAS)—45.3 to 69.6; and alcohol-related neurodevelopmental disorder (ARND)—30.5 to 46.8. The overall rate of FASD is therefore 135.1 to 207.5 per 1,000 (or 13.6 to 20.9%). Clinical profiles of the physical and cognitive/behavioral traits of children with a specific FASD diagnosis and controls are provided for understanding the full spectrum of FASD in a community. The spectral effect is evident in the characteristics of the diagnostic groups and summarized by the total (mean) dysmorphology scores of the children: FAS = 18.9; PFAS = 14.3; ARND = 12.2; and normal controls, alcohol exposed = 8.2 and unexposed = 7.1. Documented drinking during pregnancy is significantly correlated with verbal ($r = -0.253$) and non-verbal ability ($r = -0.265$), negative behaviors ($r = 0.203$), and total dysmorphology score ($r = 0.431$). Other measures of drinking during pregnancy are significantly associated with FASD, including binge drinking as low as 3 drinks per episode on 2 days of the week.

Conclusions: High rates of specific diagnoses within FASD were well documented in this new cohort of children. FASD persists in this community. The data reflect an increased ability to provide accurate and discriminating diagnoses throughout the continuum of FASD.

Key Words: Fetal Alcohol Spectrum Disorders, Epidemiology, Prevalence, Diagnosis, South Africa, Alcohol Abuse, Cognition, Maternal Drinking.

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ALCOHOL IS A teratogen affecting birth outcomes for centuries (Armstrong, 2003; Sullivan, 1899). But the fetal alcohol syndrome (FAS) diagnosis was not formalized until 1973 (Jones and Smith, 1973). Further delineation of the diagnosis of FAS continues (Bertrand et al., 2005), especially of the specific characteristics of diagnoses within the continuum of fetal alcohol spectrum disorders (FASD; Aase, 1994; Astley and Clarren, 2000; Chudley et al., 2005; Hoyme et al., 2005; Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders [ICCFASD], 2011; Sokol and Clarren, 1989; Stratton et al., 1996). This article describes a population-based study of all Institute of Medicine (IOM)-based FASD diagnoses including alcohol-related neurodevelopmental disorder (ARND).

In 3 previous, active case ascertainment studies carried out in this South African (ZA) community, only FAS and partial fetal alcohol syndrome (PFAS) were the foci in this community where rates of FAS and FASD have been extremely high (May et al., 2000, 2007; Viljoen et al., 2005). First-grade children have been studied as endorsed by the IOM, and all 3

domains of diagnostic criteria have been fully addressed: child physical, behavioral, and maternal (Stratton et al., 1996). This is the fourth in-school study of this particular community (May et al., 2000, 2007; Viljoen et al., 2005) and the fifth reported from ZA overall (Urban et al., 2008). Similar studies have been reported from Italy (May et al., 2006, 2011a), Croatia (Petković and Barišić, 2010), and a study and 2 pilots from the United States (Clarren et al., 2001; May et al., 2009). In-school studies have produced much higher rates of FASD than studies using other methodologies (May and Gossage, 2001; May et al., 2009), and they hold potential for clarifying the entire continuum of specific FASD diagnoses. The population of the Western Cape Province (WCP) of ZA is 5.3 million people (Statistics South Africa, 2007); 50% are Cape Colored (mixed race): 30% Black African, 18% White, and 2% other. Cape Town is the principal urban area of the WCP, and 40% of the population lives in small towns and rural areas. The study community is similar to others in socioeconomic character in the WCP; the 2011 population was 58,300 (28.1% rural).

Drinking among subsegments of the Colored population of the WCP has historically been documented to have a high rate of abusive drinking among men and women (Crome and Glass, 2000; London, 2000; Mager, 2004; Parry and Bennetts, 1998). Recreational binge drinking occurs regularly on weekends and holidays for many people (May et al., 2005, 2008a; Viljoen et al., 2002). Partially because of the research initiated in 1997, high rates of FASD and alcohol abuse among females have become major concerns (Croxford and Viljoen, 1999; Khaole et al., 2004; Morojele et al., 2010). Baseline and ongoing assessment of FASD prevalence is needed for evaluating changes and prevention efficacy.

This paper describes a population-based sampling and diagnostic process, and the characteristics of FAS, PFAS, and ARND in a single population.

MATERIALS AND METHODS

The IOM diagnostic system (Stratton et al., 1996) has been used among first-grade students in all ZA studies. Classification of children is based on a full consideration of (i) physical growth and dysmorphology, (ii) cognitive/behavioral assessments, and (iii) maternal alcohol consumption, while ruling out other known genetic and teratogenic anomalies. Final diagnoses are made for each child in a formal, data-driven case conference as per the clarified guidelines and operational criteria suggested by the IOM (Hoyme et al., 2005).

The IOM continuum of FASD contains 4 diagnoses: FAS, PFAS, ARND, and alcohol-related birth defects (ARBD; Stratton et al., 1996). Each of the IOM diagnoses as presented in Fig. 1 was utilized in this study. We have found ARBD to be rare in any population; and no cases were diagnosed in this study. While the diagnosis of FAS or PFAS without a confirmed history of alcohol exposure is viewed as tentative, original IOM criteria allow for an FAS diagnosis without direct (maternal) reports of use (Stratton et al., 1996): Similarly, revised criteria (Hoyme et al., 2005) permit a diagnosis of PFAS if other evidence of drinking exists (e.g., collateral reports). Many women underreport drinking during pregnancy (Alvik et al., 2006; Wurst et al., 2008), but in this study ZA population, the diagnosis is rarely made without direct maternal reporting of alcohol use.

Sampling of First-Grade Children with FASD and Controls

Three-tier screening methods were used to identify FASD cases (Fig. 2). Oversampling for growth deficiency and small head circumference and random selection of controls was undertaken among all students in the first grade of the primary schools of the community. There were 1,147 first-grade children enrolled in 13 primary schools, and 747 (65.1%) children had active consent to participate. The control children provide a representative, community-specific comparison group; 225 enrolled student's numbers were randomly selected (with replacement). The final control sample represents 119 children, 7 of whom had their number chosen twice and 1 whose number was drawn 3 times. Therefore, the final number of control cases in the Tables is 128 (Fig. 2). Sampling with replacement selects values that are truly independent of each other, have zero covariance with each other, and is particularly useful when the theoretical distribution of a condition is unknown (Adèr et al., 2008). Identical examinations and testing were performed on subjects and controls.

Screening and Testing in 3 Tiers I Through III

In Tier I, all consented children were measured on height, weight, and head circumference (occipital frontal circumference [OFC]). Any consented child $\leq$25th centile on head circumference (OFC) and/or both height and weight, and all children whose numbers had been randomly selected from class rolls as candidates for controls were referred to Tier II (physical examination); 538 children met these criteria (Fig. 2). Surveillance of local institutions for developmental disabilities yielded no additional age-appropriate cases of suspected FASD.

In Tier II, 4 dysmorphology examination teams provided examinations covering facial and body dysmorphology, growth, and heart function. Each team had a pediatric dysmorphologist; a scribe to record data; program staff to oversee clinic flow and 2 dimensional photographs. All examiners were blinded from prior knowledge of children and mothers. Interrater reliability for quantitative measurements was found to be good in previous ZA samples (May et al., 2000; Viljoen et al., 2005) and more recently in American schools where Cronbach's alpha coefficients were 0.993 for OFC, 0.957 for inner canthal distance (ICD), 0.951 for palpebral fissure length (PFL), and 0.928 for philtrum length. For the more subjective elements of the diagnosis of an FASD, reliability measures for this sample were lipometer ratings (Astley and Clarren, 2000) which produced a Cronbach's alpha of 0.761 for the philtrum and 0.648 for the vermillion.

After the Tier II dysmorphology examinations, a preliminary diagnosis was assigned: (i) not-FAS, (ii) diagnosis deferred—possible FASD, or (iii) probable FAS. Therefore, children with the appearance, growth, or some minor anomalies characteristic of an FASD (ii and iii above), and also the randomly selected, potential controls, were advanced to Tier III.

Development and behavior were assessed in Tier III with the following cognitive and behavioral testing and maternal risk factor questionnaires: Tests of the Reception of Grammar (TROG), a measure of verbal IQ (Bishop, 1989); Colored Progressive Matrices (Raven, 1981) for nonverbal IQ; the WISC-IV Digit-Span Scaled Score (Wechsler, 2003) for executive functioning; and the Teacher Report Form for problem behaviors (Achenbach and Rescorla, 2001).

The mothers of randomly selected controls were the maternal controls. All maternal risk interviews were administered in the field by experienced, Afrikaans-speaking staff. Multiple items were

Fetal Alcohol Syndrome (FAS)

For ***FAS*** a child must have: 1.) a characteristic pattern of minor facial anomalies including at least 2 or more of the key facial features of FAS (palpebral fissures $\leq 10^{th}$ centile, thin vermilion border, or smooth philtrum), 2.) evidence of prenatal and/or postnatal growth retardation (height or weight $\leq 10^{th}$ centile), 3.) evidence of deficient brain growth (structural brain anomalies or occiptofrontal head circumference (OFC) $\leq 10^{th}$ centile), and if possible, 4.) confirmation of maternal alcohol consumption from the mother or a knowledgeable collateral source.

Partial Fetal Alcohol Syndrome (PFAS)

For ***PFAS*** a child must have: 1.) evidence of a characteristic pattern of facial anomalies including 2 or more of the 3 key features of FAS (above), 2.) one or more other characteristics such as prenatal or postnatal growth retardation ($\leq 10^{th}$ centile in height or weight), hypoplastic midface, ocular defects, abnormalities of the fingers, or other physical defects linked to prenatal alcohol exposure in humans, 3.) small OFC ($\leq 10^{th}$ centile), and/or evidence of a complex pattern of behavioral or cognitive abnormalities inconsistent with developmental level and unexplainable by genetic composition, family background, or environment alone; and if possible, 4.) direct or collateral confirmation of maternal alcohol consumption.

Alcohol-Related Neurodevelopmental Disorders (ARND)

For ***ARND*** documentation of significant prenatal alcohol exposure is required, the child displays neurological or structural brain abnormalities (e.g. microcephaly), or manifests evidence of a complex and characteristic pattern of behavioral or cognitive abnormalities inconsistent with developmental level as measured by test batteries (as in Table 2) and that are not explained by genetic predisposition, family background, or environment alone.

Alcohol-Related Birth Defects (ARBD)

For ***ARBD*** **criteria include;** prenatal alcohol exposure, evidence of two or more of the characteristic pattern of facial anomalies, as well as either congenital structural defects of varying degree and number, but generally normal neurobehavioral performance.

Fig. 1. Summary of the diagnoses within the fetal alcohol spectrum disorders as defined by the Institute of Medicine and Revised Criteria by Hoyme et al. (2005).

carefully sequenced to enhance sensitivity and maximize accurate reporting. They covered general health, reproduction, nutrition, alcohol use, socioeconomic status (SES), and physical measurements. Drinking questions followed a timeline, follow-back sequence (Sobell et al., 1988, 2001) and used vessels methodology pictures tailored to the common, local community alcohol products and drinking practices (Kaskutas and Graves, 2000, 2001; Kaskutas and Kerr, 2008). A 7-day, retrospective drinking log of alcohol consumption during the week preceding the interview was embedded into the nutrition questions. Current drinking data establish a baseline understanding of alcohol use and aid accurate calibration of drinking quantity, frequency, and timing (QFT; during pregnancy) for subsequent questions regarding alcohol use: 3 months prior to the index pregnancy, during the pregnancy (for each trimester by weekend, by weekdays, and by month; May et al., 2000, 2005, 2007, 2008a,b; Viljoen et al., 2002). This sequencing minimizes underreporting (Alvik et al., 2006). Retrospective reports of alcohol use during pregnancy are considered more accurate for determining prenatal drinking levels than those reported during the prenatal period (Czarnecki et al., 1990; Hannigan et al., 2010). These methods, sequencing, and contextual frameworks work well, especially when embedded within a dietary inventory (King, 1994).

Information on maternal risk factors for the index pregnancies was gathered for 377 women. All but 13 mothers of cases and controls were interviewed: 5 (1.3%) had moved and 8 (2.1%) refused. Some data regarding alcohol consumption during the index pregnancy (17.2% of cases) were obtained via collaterals (usually relatives). Maternal data presented here focus primarily on confirmation of maternal drinking for case diagnosis in the

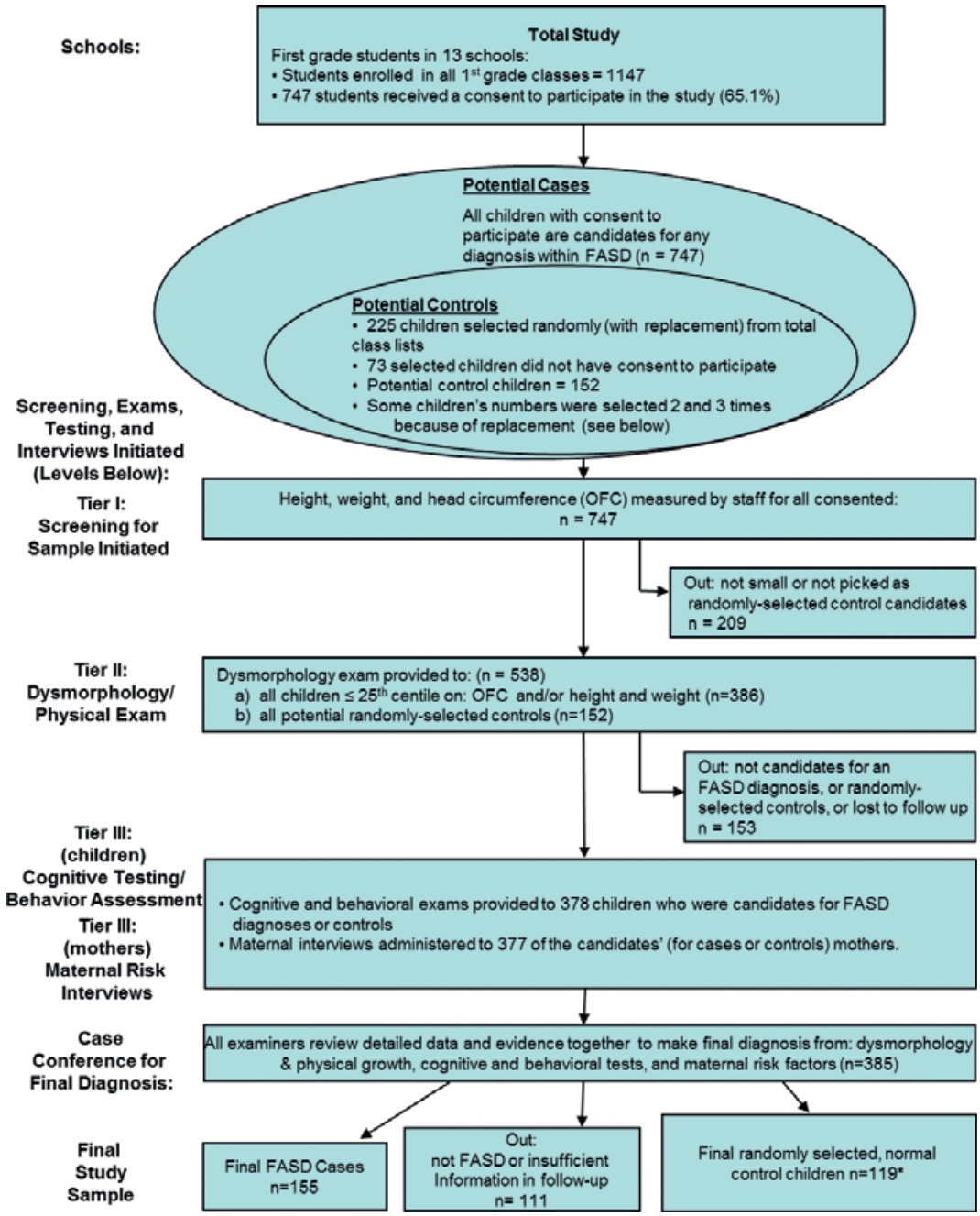

Fig. 2. Methodology of the South African IV fetal alcohol spectrum disorders (FASD) study with sampling procedures and numbers.

epidemiological study, while other maternal risk factors for this community have been reported elsewhere (May et al., 2005, 2008a,b). Alcohol use during the index pregnancy was confirmed directly or through collateral sources in 100% of the ARND cases. Nine of the 68 (13.2%) FAS cases and 6 of the 52 PFAS (11.5%) cases were diagnosed without confirmation of prenatal drinking.

Tobacco use data both current and during the prenatal period were also obtained in the interviews. In earlier community trials, we determined that each cigarette averaged 1 g of tobacco (May et al., 2000; Viljoen et al., 2002), similar to machine-rolled cigarettes in the U.S.A. (http://www.cancer.gov/cancertopics/factsheet/Tobacco/cigars).

Final Diagnoses Made in Multidisciplinary Case Conferences

After completing collection of all data, final diagnoses for each child were made in structured, case conferences at the program offices at Stellenbosch University. The researchers who had performed the examinations, testing, and the maternal interviews all participated and provided their data and assessments for each child. During the case conference, 2-dimensional pictures of each child were projected on a screen for viewing. After a detailed review of data for each child on the 3 domains of information and discussion of how the totality of the findings met the criteria for an FASD diagnosis, another anomaly, or not FASD, final diagnoses were made by the dysmorphologists.

Data Analysis

Data were entered via EPI Info (Dean et al., 1994), and the analyses were performed using SPSS version 19 (SPSS, 2010). Categorical variables comparing cases to controls were analyzed by chi-square, continuous variables by 1-way analysis of variance, and bivariate, post hoc comparisons with Dunnett's C, which is a post hoc analysis that controls for the alpha error (Type 1; false positive) produced when performing multiple comparisons of group means (Tabachnick and Fidell, 2007). In Table 4, Pearson's correlation coefficients compare selected variables, 2 of which were utilized as dummy variables (3 or more drinks per occasion or 5 or more drinks per occasion), with alpha levels set at 0.05 (2-tailed). In Table 5, the estimated prevalence rates for the diagnoses within the FASD continuum are calculated as a range of low to high based on 2 denominators: (i) all students in the first grade (enrollment rate) and (ii) all consented children (sample rate). Because of oversampling of smaller children in Tier II (physical examination) of the study ($\leq$25th centile on height and weight and/or OFC), the high rate may be too high, and the lower rate is likely more realistic, with the actual prevalence within the range (May et al., 2011a,b).

RESULTS

In Table 1, column 1, data are presented for all consented children who were measured only for height, weight, and head circumference. The mean age was 6.8 years (81.4 months), children averaged 115.8 cm in height, weighed 20.7 kg, and had OFC of 50.9 cm. Comparing the combined control groups with the total consented column, there are minimal differences. In the other columns, 68 of the children were diagnosed with FAS, 52 with PFAS, and 35 with ARND. Thirty-one of the children who were initially chosen randomly for the control group (20.4%) were eventually diagnosed within the FASD spectrum (7 with FAS, 12 with PFAS, and 12 with ARND). These children were removed from the potential control group and assigned to their respective FASD group (Table 1).

Average age varies significantly across diagnostic groups, as the FAS and ARND children are older due to repeating first grade. Overall, the difference of means of 20 variables in Table 1 are statistically significant between the 5 groups: age, height, weight, body mass index (BMI), BMI percentile, head circumference, PFL, percentage the PFL is of the ICD, maxillary arc, mandibular arc, short inner pupillary distance, hypoplastic midface, smooth philtrum, narrow vermilion border, ptosis, epicanthal folds, flat nasal bridge, camptodactyly, altered palmar creases, and total dysmorphology score. Also, ICD and hirsutism approached significance. Many of the traits exhibit a spectrum across the 5 study categories, with PFAS means having the most frequent divergence from of the spectral pattern. The high standard deviations for the PFAS group on many traits indicate a higher degree of variability for many of the features than the variability within other diagnostic groups. Most of the nonsignificant variables are clinical observational variables and are proximal to the FASD diagnosis. Total dysmorphology scores, which represent a summary value and where higher values indicate more features of FASD, form a perfect spectrum for the diagnostic groups (18.9 for FAS, 14.3 for PFAS, 12.2 for ARND) and for the controls based on alcohol exposure, 8.2 for the exposed and 7.1 for unexposed controls ($F = 123.43$, $p < 0.001$).

Also in Table 1, Dunnett's C post hoc bivariate between-group analyses indicate that weight, OFC, PFL, and total dysmorphology score are the most significant differentiators between each and every one of the specific FASD diagnostic groups including exposed and unexposed controls. ARND was differentiated from the alcohol-exposed control group by 3 of the above 4 variables and also by mandibular arc measures.

Developmental Indicators

Table 2 presents cognitive/behavioral test results. Children with PFAS are inconsistent with a linear spectral pattern within the 3 FASD categories, but their performance is inferior to either of the control groups. The exposed controls performed worse on all measures than unexposed controls. PFAS children are again demonstrating less homogeneity as indicated by larger standard deviations for most measures. Verbal and nonverbal ability and Digit-Span performance were significantly lower for FAS and ARND groups than for PFAS; but all FASD groups performed poorly when compared to controls. ARND children had the most reported behavioral problems (the Achenbach scores) followed by FAS, PFAS, and alcohol-exposed controls. The post hoc analyses in Table 2 indicate that nonverbal IQ and the Digit-Span are discriminating cognitive/behavioral measures between FASD groups and controls, particularly the unexposed controls. Only nonverbal ability discriminates between the FAS and PFAS group and PFAS and ARND groups. None of the cognitive/behavioral tests are effective at discriminating between exposed and unexposed controls. Dysmorphology discriminates more consistently than these tests alone.

Maternal Drinking and Smoking

In Table 3, 91, 89.1, and 96.8% of the mothers of FAS, PFAS, and ARND children reported drinking during pregnancy, compared to 29.7% (38/128) of the mothers of normal controls. The remaining data in Table 3 further support, with only a few exceptions, the causal role that alcohol consumption plays in FASD. Mean number of drinks per week and drinking 3 and 5 or more drinks per occasion during pregnancy both illustrate the significant difference between mothers of FASD children and those of normal children. Mothers of FAS, PFAS, and ARND children report drinking an average of 13 drinks per week, with large standard deviations indicating many drinkers are well above the average. Control mothers who drink consumed 5.6 drinks each week and are less likely to binge with 5 or more drinks. In the post hoc analyses for Table 3, average number of drinks per week differentiates the various groups the best.

Table 1. South Africa Wave IV Children's Demographic and Growth Parameters and Post Hoc Analyses

Variable	All children (n = 747)[a]	Children with FAS (n = 68)	Children with PFAS (n = 52)	Children with ARND (n = 35)	Exposed randomly-selected (R-S) controls (n = 38)	Unexposed R–S controls (n = 90)	Statistical test	p
Sex (%)								
Males	49	50	48.1	51.4	50	54.4	χ^2 = 0.64	0.958
Females	51	50	51.9	48.6	50	45.6		
Age (months)								
mean (SD)	81.4 (7.1)	85.4 (8.7)	81.4 (9.5)	84.0 (7.9)	80.7 (6.7)	80.0(6.2)	F = 5.57	0.000
Height (cm)								
mean (SD)	115.8 (5.9)	111.9 (5.5)	114.8 (7.5)	113.5 (4.9)	115.6 (5.5)	116.3 (6.3)	F = 5.50	0.000
Weight (kg)								
mean (SD)	20.7 (3.6)	17.7 (2.1)	20.0 (3.1)	18.9 (1.9)	20.5 (2.7)	21.1 (3.5)	F = 15.83	0.000
Average BMI for age								
mean (SD)	16.0 (9.0)	15.5 (0.2)	15.4 (0.2)	15.5 (0.2)	15.4 (0.2)	16.9 (14.8)	F = 0.49	0.743
Child's BMI								
mean (SD)	15.3 (1.6)	14.2 (1.1)	15.0 (1.0)	14.6 (1.2)	15.3 (1.1)	15.4 (1.8)	F = 9.24	0.000
BMI percentile								
mean (SD)	42.9 (27.5)	16.5 (16.9)	37.0 (21.2)	27.8 (25.3)	43.6 (25.0)	47.4 (24.9)	F = 20.49	0.000
Occipital circumference (OFC; in cm) mean (SD)	50.9 (2.4)	48.6 (1.3)	50.0 (1.3)	49.4 (0.8)	51.1 (1.2)	51.1 (1.5)	F = 42.69	0.000
Palpebral fissure length (cm) mean (SD)	–	2.31 (0.2)	2.35 (0.1)	2.39 (0.1)	2.43 (0.1)	2.45 (0.1)	F = 17.80	0.000
Inner canthal distance (cm)	–	2.80 (0.2)	2.88 (0.4)	2.73 (0.2)	2.81 (0.3)	2.91 (0.5)	F = 2.04	0.090
Percent palpebral fissure length (%) is of inner canthal distance	–	83.1 (9.7)	82.7 (10.2)	87.8 (7.9)	87.4 (9.6)	85.7 (9.7)	F = 2.87	0.024
Inner pupillary distance (cm)	–	5.0 (0.2)	5.0 (0.4)	5.0 (0.2)	5.1 (0.7)	5.1 (0.5)	F = 1.30	0.270
Philtrum length (cm) mean (SD)	–	1.3 (0.2)	1.4 (0.2)	1.5 (0.7)	1.3 (0.2)	1.3 (0.2)	F = 1.81	0.126
Maxillary arc (cm)	–	23.2 (0.8)	23.8 (1.0)	23.5 (1.1)	24.1 (0.9)	23.8 (2.6)	F = 2.59	0.037
Mandibular arc (cm)	–	23.9 (0.9)	24.7 (1.2)	24.4 (1.1)	25.1 (1.1)	25.1 (0.9)	F = 15.28	0.000
Short inner canthal distance (%)	–	32.8	21.2	38.2	23.7	20	χ^2 = 6.70	0.153
Short inner pupillary distance (%)	–	60.6	36.5	51.4	28.9	12.2	χ^2 = 44.22	0.000
Hypoplastic midface (%)	–	82.4	71.72	62.9	50	42.2	χ^2 = 30.54	0.000
Philtrum[b] (%)	–	80.9	80.8	22.9	31.6	22.5	χ^2 = 87.93	0.000
Vermillion border[c] (%)	–	89.7	94.2	25.7	42.1	28.1	χ^2 = 106.69	0.000
"Railroad track" ears (%)	–	10.3	5.8	5.7	10.5	5.6	χ^2 = 2.16	0.706
Strabismus (%)	–	5.9	1.9	0	7.9	4.4	χ^2 = 3.95	0.413
Ptosis (%)	–	14.7	7.7	0	0	5.6	χ^2 = 12.40	0.015
Epicanthal folds (%)	–	63.2	63.5	80	52.6	39.3	χ^2 = 21.04	0.000
Flat nasal bridge (%)	–	60.3	55.8	57.1	42.1	37.1	χ^2 = 11.13	0.025
Anteverted nostrils (%)	–	50	38.5	31.4	34.2	36	χ^2 = 5.02	0.285
Prognathism (%)	–	7.4	5.8	2.9	0	2.2	χ^2 = 4.94	0.294
Heart murmur (%)	–	17.6	13.5	8.6	10.5	6.7	χ^2 = 5.18	0.296
Heart malformations (%)	–	0	0	0	0	3.3	χ^2 = 6.50	0.165
Hypoplastic nails (%)	–	5.9	5.8	5.7	2.6	2.2	χ^2 = 2.04	0.728
Limited elbow supination (%)	–	1.5	1.9	0	5.3	1.1	χ^2 = 3.56	0.471
Clinodactyly (%)	–	60.3	63.5	48.6	57.9	65.2	χ^2 = 3.20	0.525
Camptodactyly (%)	–	27.9	23.1	11.4	10.5	6.7	χ^2 = 16.25	0.003

Continued.

Table 1. (Continued)

Variable	All children (n = 747)[a]	Children with FAS (n = 68)	Children with PFAS (n = 52)	Children with ARND (n = 35)	Exposed randomly-selected (R-S) controls (n = 38)	Unexposed R–S controls (n = 90)	Statistical test	p
Palmar crease alteration (%)	–	48.5	28.8	37.1	39.5	21.3	χ^2 = 14.07	0.007
Hirsute (%)	–	0	3.8	0	0	0	χ^2 = 8.95	0.062
Total dysmorphology score mean (SD)	–	18.9 (3.9)	14.3 (3.1)	12.2 (3.3)	8.2 (3.6)	7.1(3.6)	F = 123.43	0.000

Dunnett's C post hoc analyses[d]

Measure	Groups that differ at the p = 0.05 level
Age (months)	• FAS & Exposed Controls • FAS & Unexposed Controls
Height (cm)	• FAS & Unexposed Controls • FAS & Exposed Controls
Weight (kg)	• FAS & PFAS • FAS & ARND • FAS & Exposed Controls • FAS & Unexposed Controls • ARND & Unexposed Controls • ARND & Exposed Controls
Child's BMI	• FAS & PFAS • FAS & Exposed Controls • FAS & Unexposed Controls
BMI percentile	• FAS & PFAS • FAS & Exposed Controls • FAS & Unexposed Controls • ARND & Unexposed Controls
Occipital circumference (OFC; in cm)	• FAS & PFAS • FAS & ARND • FAS & Unexposed Controls • FAS & Exposed Controls • PFAS & Unexposed Controls • PFAS & Exposed Controls • ARND & Unexposed Controls • ARND & Exposed Controls
Palpebral fissure length (is of inner canthal distance; cm)	• FAS & ARND • FAS & Exposed Controls • FAS & Unexposed Controls • PFAS & Exposed Controls • PFAS & Unexposed Controls • ARND & Unexposed Controls
Maxillary arc (cm)	• FAS & PFAS • FAS & Exposed Controls
Mandibular arc (cm)	• FAS & PFAS • FAS & Exposed Controls • FAS & Unexposed Controls • ARND & Unexposed Controls • ARND & Exposed Controls
Total dysmorphology score	• FAS & PFAS • FAS & ARND • FAS & Exposed Controls • FAS & Unexposed Controls • PFAS & ARND • PFAS & Exposed Controls • PFAS & Unexposed Controls • ARND & Exposed Controls • ARND & Unexposed Controls

[a]The "All Children" group is not included in any of the Table 1 statistical test analyses.
[b]Scores of 4 or 5 on Astley Lip Philtrum Guide.
[c]Scores of 4 or 5 on Astley Lip Philtrum Guide.
[d]Dunnett's C post hoc analyses show the following groups differ at the p = 0.05 level: FAS & Exposed Controls, FAS & Unexposed Controls, PFAS & Unexposed Controls, ARND & Unexposed Controls, Exposed & Unexposed Controls.
FAS, fetal alcohol syndrome; ARND, alcohol-related neurodevelopmental disorder; BMI, body mass index; PFAS, partial fetal alcohol syndrome.

Table 2. South Africa Wave IV Mean Scores on Developmental and Behavioral Indicators[a] of Children with FAS, PFAS, and ARND Compared to Controls & Post Hoc Analyses

Child variables	FAS (SD) (n = 66)	PFAS (SD) (n = 51)	Children with ARND (SD) (n = 35)	Exposed randomly-selected (R-S) controls (SD) (n = 38)	Unexposed R–S controls (SD) (n = 87)	Test score (F)	df	p
Developmental traits								
Verbal IQ[b]	5.1 (7.6)	5.7 (10.2)	5.2 (7.5)	8.2 (7.9)	13.4 (18.2)	5.85	4/272	0.000
Nonverbal IQ[c]	8.9 (7.2)	14.4 (12.1)	7.7 (4.5)	17.8 (10.9)	22.2 (18.1)	14.23	4/272	0.000
WISC-IV Digit-Span Scaled Score	4.4 (2.6)	5.1 (2.8)	4.7 (2.7)	6.8 (3.5)	6.7 (3.3)	8.07	4/271	0.000
Achenbach Teacher Report Form	50.2 (42.6)	45.1 (42.2)	58.3 (33.7)	35.8 (35.5)	29.1 (29.1)	5.63	4/272	0.000

Dunnett's C post hoc analyses

Measure	Groups that differ at the p = 0.05 level
Verbal IQ	• FAS & Unexposed Controls • PFAS & Unexposed Controls • ARND & Unexposed Controls • FAS & PFAS
Nonverbal IQ	• FAS & Exposed Controls • FAS & Unexposed Controls • PFAS & ARND • PFAS & Unexposed Controls • ARND & Exposed Controls • ARND & Unexposed Controls
WISC-IV Digit-Span Scaled Score	• FAS & Exposed Controls • FAS & Unexposed Controls • PFAS & Unexposed Controls • ARND & Unexposed Controls
Achenbach Teacher Report Form	• FAS & Unexposed Controls • ARND & Unexposed Controls
Total dysmorphology score	• FAS & PFAS • FAS & ARND • FAS & Exposed Controls • FAS & Unexposed Controls • PFAS & ARND • PFAS & Exposed Controls • PFAS & Unexposed Controls • ARND & Exposed Controls • ARND & Unexposed Controls

[a]All scores standardized for age of child at time of testing.
[b]Tests of the Reception of Grammar (TROG). A measure of verbal intelligence.
[c]Raven Colored Progressive Matrices. A measure of nonverbal intelligence.
FAS, fetal alcohol syndrome; ARND, alcohol-related neurodevelopmental disorder; PFAS, partial fetal alcohol syndrome.

Also in Table 3, mothers of the 3 FASD groups drank throughout all trimesters with less than half quitting in the second and third trimesters; the drinking mothers of the controls reported an even greater reduction in percent drinking. More mothers of FASD children used tobacco at interview and during the index pregnancy, although the percent smoking was high across groups. Smokers in this ZA population reported smoking 33 to 62 hand-rolled cigarettes per week, which is modest compared to female smokers in the U.S.A. who report an average of 105 per week (Centers for Disease Control and Prevention [CDC], 2005). Fathers are reported by the interviewees to have drinking problems. While 61.9% of FAS case fathers have had drinking problems, 38.7% of the unexposed control fathers have also had problems.

In Table 4, correlations indicate that verbal ability and nonverbal ability are significantly, negatively correlated with mother's reported drinking during pregnancy ($r = -0.253$ and -0.265), and reported episodes of 3 ($r = -0.190$ and -0.218) or 5 alcoholic drinks per day ($r = -0.158$ and -0.210). Behavioral problems are also significantly correlated with the same drinking measures, the more the drinking, the greater the problem behaviors. Also, the more the maternal drinking reported per month and per day, the lower the child's IQ and more behavior problems. The highest correlations in Table 4 are between dysmorphology scores and drinking measures, especially binge episodes of 3 drinks or more ($r = 0.467$).

Urban/Rural Distribution and Prevalence of FAS

In Table 5, mothers of FASD children were disproportionately more likely than controls to have resided in rural areas during gestation. While only 28% of the population

Table 3. Substance Use by Mothers and Fathers of the Children with Fetal Alcohol Spectrum Disorders and Controls: South Africa Wave IV

Maternal variables	Mothers of children with FAS (n = 68)	Mothers of children with PFAS (n = 52)	Mothers of children with ARND (n = 35)	Mothers of randomly-selected (R-S) exposed control children (n = 38)	Mothers of R–S unexposed control children (n = 90)	Statistical test	df	p
Drinking indicators overall reported drinking during pregnancy (%)	91.4	89.1	96.8	100	–	χ^2 = 201.97	4	0.000
Average no. drinks per week (during pregnancy)	13.4 (14.0)	13.1 (16.1)	13.0 (15.0)	5.6 (5.3)	0.0 (0.0)	F = 16.43	4/207	0.000
Consumed 3 drinks or more per occasion during pregnancy (%)	78.8	74.4	80.8	70.6	0	χ^2 = 117.22	4	0.000
Consumed 5 drinks or more per occasion during pregnancy (%)	59.6	53.8	61.5	41.2	0	χ^2 = 69.92	4	0.000
Current drinker in last year (%)	100	96.9	100	92.3	46	χ^2 = 57.70	4	0.000
Drinking before index pregnancy (%)	81.6	94.6	100	93.3	10	χ^2 = 101.28	4	0.000
Drank during trimesters (%)								
First	84.6	82.5	100	88.2	-	χ^2 = 155.09		0.000
Second	73.1	70	84.6	47.1	-	χ^2 = 106.97		0.000
Third	62.7	52	52	41.2	-	χ^2 = 69.65		0.000
Tobacco use								
Smoked during index pregnancy (%)	86	94.3	86.4	52.9	35.2	χ^2 = 51.33		0.000
Current smoker, whole sample (%)	97.7	78.1	100	90.9	92.9	χ^2 = 11.91		0.018
Quantity of tobacco used per week (mean g) (SD)								
Whole sample: quantity of cigarettes smoked per week (each cigarette = 1 g)[a]	33.0 (18.6)	61.9 (54.9)	48.2 (35.2)	40.2 (21.1)	54.5 (32.6)	F = 3.16		0.017
Father's data								
Fathers of index children with drinking problems in the past (%)	61.9	39.1	50	54.5	38.7	χ^2 = 5.13		0.274

[a]Dunnett's C post hoc analyses show that FAS and Unexposed Controls differ at the p = 0.05 level.
FAS, fetal alcohol syndrome; PFAS, partial fetal alcohol syndrome; ARND, alcohol-related neurodevelopmental disorder.

lives in rural areas, between 46 and 49% of the FASD cases come from the rural areas.

The prevalence of FAS among the sample of children examined was 59.3 per 1,000 children enrolled in first-grade classes, or 91.0 if the sample of consented children is used as the denominator (Table 5). The total FASD rate is between 135.1 and 207.5 per 1,000, an unprecedented high prevalence of FASD reported for any population.

Another estimated prevalence rate can be obtained from the proportion of children from the random selection list of

Table 4. Pearson's Correlation Coefficient for Developmental[a] and Physical Dysmorphology vs. Selected Maternal Drinking Measures During Pregnancy: South Africa Wave IV

Trait	Reported drinking during pregnancy (n = 339)	Drinks per month (n = 302)	Drinks per day (n = 302)	3 Drinks per occasion (n = 302)	5 Drinks per occasion (n = 302)
Verbal ability[b]	−0.253***	−0.170**	−0.174**	−0.190**	−0.158**
Nonverbal ability[c]	−0.265***	−0.194**	−0.209***	−0.218***	−0.210***
Behavior[d]	0.203***	0.172**	0.232***	0.237***	0.233***
Dysmorphology score	0.431***	0.353***	0.378***	0.467***	0.384***

[a]All scores standardized for age of child at time of testing.
[b]Tests of the Reception of Grammar (TROG).
[c]Raven Colored Progressive Matrices.
[d]Personal Behavior Checklist (PBCL-36).
**p < 0.01; ***p < 0.001.

Table 5. Prevalence Rates (per 1,000) of Individual Diagnoses Within the Fetal Alcohol Spectrum Disorder and Total FASD: South African Community, Wave IV

Diagnosis	*n*	% Rural*	Enrolled rate[a] (*n* = 1,147)	Consented rate[b] (*n* = 747)
FAS	68	49.1	59.3	91
PFAS	52	47.6	45.3	69.6
ARND	35	46.7	30.5	46.8
Total FASD	155	48.1	135.1	207.5
FAS and PFAS only	120	48.5	104.6	160.6

[a]Denominator is all children attending first grade in local schools.
[b]Denominator is the total number of child with consent to participate in this study.
FAS, fetal alcohol syndrome; FASD, fetal alcohol spectrum disorders; ARND, alcohol-related neurodevelopmental disorder; PFAS, partial fetal alcohol syndrome.
* percentage of the cases in each diagnostic category from rural areas. The total population of this area living in rural areas is 28%.

potential controls who converted to an FASD. Thirty-one of 152 children received an FASD diagnosis, a prevalence of 203.9 per 1,000, within the range produced by the oversampling method above.

DISCUSSION

By screening children into the study with an oversampling of children $\leq$25th centile on 3 measures (rather than a $\leq$10th centile as in past studies), far more (of the larger) children received physical examinations and testing. Therefore, more ARND cases were diagnosed. These sampling criteria and the continued use of randomly selected controls have provided an opportunity to define and diagnose more of the spectrum of specific FASD diagnoses. While the prevalence rates from this study may appear to be a substantial increase in rates for this community over previous studies, the rates of FAS and FAS/PFAS combined in this community appear to have remained relatively stable over the years. Because about half of the women in this community drink alcohol, primarily as a weekend recreational activity, and one-quarter continue through the duration of pregnancy, it is a high FASD prevalence population. Much of the knowledge of the characteristics of FASD from this community can be extrapolated to other populations for we have consistently found that <2% of all women report any use of other drugs, making prenatal exposures to teratogens virtually alcohol exclusive.

Limitations

While this is the most comprehensive population-based study of FASD in a community to date, there are limitations. First, the number providing active consent in this community has degraded slightly over time. Parents providing permission for their children to participate was lower this time: 98.2, 93.6, and 80.7% in Waves I, II, and III and 65.1% in this wave. A shorter turn-around time given to parents for consent and a single distribution of the consent forms in this sample produced this effect. Active consent is still higher than in many other populations and studies. For example, in an in-school study in Washington State with active consent, only "about 25%" consent was obtained (Clarren et al., 2001). In Italy, consent rates averaged 49% in 2 in-school samples (May et al., 2006, 2011a,b); yet, high rates of FASD were found indicating an ability to capture representative cases using oversampling methods for undersized children. And in a recent in-school study in Croatia, 50% of the children were consented, and the rates of FASD were found to be as high as the Italian samples (Petković and Barišić, 2010). By oversampling children who are small for height, weight, and head circumference, we are likely assessing a substantial proportion of the children with an FASD which can then be projected to the entire enrolled population. Furthermore, by calculating rates of the various FASD diagnoses with both consented sample and all enrolled student denominators, a range of estimated (high and low) prevalence is provided. The rate of conversion of randomly selected controls to an FASD diagnosis provides a check. If this rate falls within the upper and lower estimate, then there is some assurance of the accuracy of the range. Some studies of FASD prevalence have ignored the dilemma of nonconsented children and only a single, sample rate is provided. Second, another weakness might be that the FASD rates and traits of FASD found in ZA may have limited comparability to other populations. This particular region in ZA remains unique in culture and character from most others in the world, and it is this unique situation that has led to a "worst-case scenario" for the prevalence and severity of FASD. While FASD rates are far higher than in other populations, study in this community is valuable for advancing basic knowledge about FASD. Examples of this include the opportunity to apply and accurately define specific diagnostic criteria for all forms of FASD; an understanding of the continuum of patterns of fetal damage; and the opportunity to link FASD to specific maternal traits (cofactors of causation) with large numbers of FASD cases that are applicable to all human populations. Because maternal conditions are measurably more challenging in this ZA population, observations are more easily made for enhanced insight, and variable degrees of these same conditions can be examined in other populations. For example, the fact that mothers of FASD children were significantly lower in BMI in the ZA

studies (May et al., 2004, 2005, 2008a,b) provides an important link between adequate maternal nutrition and prenatal alcohol use which can be examined elsewhere. Poor nutrition in this population and others may radically increase the severity of damage to the offspring and limit the growth and development of these children overall. Third, another possible weakness is that we have not diagnosed any cases of ARBD in this large sample. But we have repeatedly found that children with an ARBD are very rare in any population, for prenatal alcohol exposure in the prenatal period rarely damages physical features without also affecting cognitive and behavioral traits. Fourth, this study detected more cases of FAS and PFAS than reported from more developed populations such as Europe or the United States. The preponderance of severe dysmorphology, and therefore FAS and PFAS, is likely due to 2 factors: (i) the surveillance system and first diagnostic examination are based on growth and dysmorphology and (ii) there is severe growth restriction in this population. If a cognitive/behavioral screen were instituted first, then more cases of ARND would likely be diagnosed. And if growth restriction were not so common, then more of the cases classified as FAS might be diagnosed instead of as PFAS or ARND. This may have been the reason that in similar studies in Italy there was a ratio of 4.5 cases of PFAS to every case of FAS (May et al., 2011a,b), very different than in this study. Overall growth in the Italian first-grade population was better than that of this community.

Contributions

This study reports on the full spectrum of FASD diagnoses within a population. Specific traits of the 3 most common diagnoses within the spectrum are provided in detail. The children are well placed into their respective categories of FASD and significantly differentiated by statistical tests of the means of many physical and behavioral variables, especially total dysmorpholgy score. The general, average traits of FAS, PFAS, ARND, and exposed control children are especially recognizable when studying multiple cases at one time in a population. Variance around the mean values is also evident, and progress is being made at differentiating the specific modal traits and characteristics that separate FAS, PFAS, and ARND from controls (both exposed and unexposed) and from one another.

In this cohort, PFAS has proven to be most variable in its defining traits. The FAS and ARND categories seem to be more homogeneous. More analysis of the various alcohol exposure and maternal risk variables is needed, but in this first analysis it seems that the mothers of PFAS children drink episodically at similarly high levels as the mothers of FAS children; but the binge drinking varies more in their frequency causing a less consistent pattern of traits. The post hoc analysis of bivariate group comparisons indicate that the most significant physical differentiators between each FASD diagnostic group and exposed and unexposed controls are child weight, OFC, PFL, and total dysmorphology score. Of the cognitive/behavioral tests employed, nonverbal scores discriminate most between diagnostic groups.

The epidemiological research methods described here continue to improve, and have been used with over 3,500 children in this community alone. With progress made in the in-school studies and case conferences, valid distinctions between levels of dysmorphia and disability have been made. The operational definitions of the IOM categories of FASD are practical and reliable and produce specific diagnoses from applying criteria from all 3 domains of variables: physical, cognitive/developmental, and measures of alcohol QFT. Most of the dysmorphology traits are now consistently quantified and allow comparison and correlation with many variables across the domains. Active outreach in schools ensures that selectivity and/or omission of cases is minimized. Using these methods consistently provides opportunities to compare FASD across populations and examination of relative risk from particular drinking styles, exposures, health, and environmental conditions.

Rates and Prevention

The rate of FAS remains high in this community, and the higher rates in the rural, lower SES areas continue. The total rate of FASD found in this sample is 135.1 to 207.5 per 1,000 (or 13.6 to 20.9%). It is obvious from this fourth study in this community that identifying the substantial FASD problem through research and limited prevention efforts for 3 years prior to the conception of this cohort of children did not reduce problematic maternal drinking among the highest risk individuals. Substantial improvements are needed in specific socioeconomic conditions and drinking subculture patterns that have led to the problem. Also a massive, comprehensive prevention program may be needed to target long-term practices and to leverage change in the highest risk elements of the population.

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