Fetal Alcohol Syndrome Epidemiology in a South African Community: A Second Study of a Very High Prevalence Area*

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ABSTRACT. Objective: The aim of the study was to determine the prevalence and characteristics of fetal alcohol syndrome (FAS) in a second primary school cohort in a community in South Africa. **Method:** Active case ascertainment, two-tier screening, and Institute of Medicine assessment methodology were employed among 857 first grade pupils, most born in 1993. Characteristics of children with FAS were contrasted with characteristics of a randomly selected control group from the same classrooms. Physical growth and development, dysmorphology and psychological characteristics of the children and measures of maternal alcohol use and smoking were analyzed. **Results:** The rate of FAS found in this study is the highest yet reported in any overall community in the world, 65.2-74.2 per 1,000 children in the first grade population. These rates are 33-148 times greater than U.S. estimates and higher than in a previous cohort study in this same community (40.5-46.4 per 1,000). Detailed documentation of physical features indicates that FAS children in South Africa have characteristics similar to those elsewhere: poor growth and development, facial and limb dysmorphology, and lower intellectual functioning. Frequent, severe episodic drinking of beer and wine is common among mothers and fathers of FAS children. Their lives are characterized by serious familial, social and economic challenges, compared with controls. Heavy episodic maternal drinking is significantly associated with negative outcomes of children in the area of nonverbal intelligence but even more so in verbal intelligence, behavior and overall dysmorphology (physical anomalies). Significantly more FAS exists among children of women who were rural residents (odds ratio: 7.36, 95% confidence interval: 3.31-16.52), usually among workers on local farms. **Conclusion:** A high rate of FAS was documented in this community. Given social and economic similarities and racial admixture, we suspect that other communities in the Western Cape have rates that also are quite high. (*J. Stud. Alcohol* **66:** 593-604, 2005)

IN A PREVIOUS STUDY in the community in South Africa that was studied here, the fetal alcohol syndrome (FAS) rate among first graders was 40.5-46.4 per 1,000 (May et al., 2000). This rate contrasts with estimated FAS rates of 0.33-2.2 in the United States (Abel and Sokol, 1991; May and Gossage, 2001) and with an average for the developed world of 0.97 per 1,000 (Abel, 1998; Abel and Sokol, 1987). In a few high-risk American Indian reservation communities in the United States, the rate of FAS derived from active case ascertainment methods seldom exceeds 10 per 1,000 (Abel, 1995; May, 1991; May et al., 1983), with an average rate of 8 per 1,000 from 1970 to 1982 (May et al., 2002). The clinic-based rate of FAS for African Americans of low socioeconomic status (SES) from a few inner-city areas is 2.29 per 1000 (Abel, 1995, 1998).

Estimations of FAS prevalence in the United States come from birth records, child disability registries, clinic-based studies and a few population-based initiatives (Stratton et al., 1996; May, 1996). Because of the wide variation in methodologies, comparison of FAS prevalence and characteristics among populations is difficult and almost impossible. For example, all but three active case ascertainment studies, where outreach in major geographical areas focuses on aggressive case finding, were carried out among American

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Indians (Clarren et al., 2001; May et al., 2002). Passive, record-based systems and clinic-based methods that investigate FAS among clients presenting for medical services (e.g., in prenatal clinics) are most commonly used in other U.S. and European populations (Abel, 1995; Abel and Sokol, 1987, 1991; Chavez et al., 1988; Egeland et al., 1995, 1998; May, 1996). Active case ascertainment for FAS studies was endorsed by a study committee of the Institute of Medicine (IOM) as the most accurate method for epidemiological studies of FAS, but such studies are logistically challenging, expensive and time consuming (Stratton et al., 1996).

This article summarizes a second active case ascertainment initiative in a first grade cohort to assess the prevalence of FAS in the Western Cape Province (WCP) of the Republic of South Africa. Although FAS had been diagnosed in South Africa before (Palmer, 1985), a first study in this community was prompted by a binational (United States and South African) commission initiated by the vice presidents of the two countries (National Institute on Alcohol Abuse and Alcoholism, 1996, 1998). An initial, comprehensive inquiry in 1997 produced the highest rate of FAS ever reported, more than 40 per 1,000, and raised many issues regarding the exact conditions producing FAS in South Africa and generally in human populations (Adnams, 2001; May et al., 2000; Viljoen et al., 2002).

Fruit, grape and wine production dominate the region. Wine production over the past 300 years has influenced the modal drinking patterns. Wine was historically distributed daily to workers as partial payment for labor, under what was called the "Dop" system. Dop was outlawed by multiple statutes, and there is general public sentiment against its practice, but residual patterns of regular, heavy episodic alcohol consumption by some are a legacy. Furthermore, increased contemporary availability of inexpensive commercial beer, wine and distilled spirits, primarily in "take-away"(carry-out) sources and shebeens (illegal bars), has maintained or exacerbated severe drinking (London et al., 1995; Mager, 2004; Parry, 1998). Episodic drinking is a major form of recreation among subsegments of the WCP population, causing many problems (King et al., 2004).

The population of the WCP is 3,721,200: 57% "Cape Coloured" (mixed race), 18% black, 25% white and 1% of other races. Cape Town is the major city, but 40% of the population lives outside of the metropolitan area in small towns and rural areas. The study community is similar in social and economic character to others in the Winelands of WCP, with a 1996 population of 45,255 (35,364 urban and 9,861 rural; Bureau of Census, 1997). The vast majority are classified as Coloured. *Coloured* denotes people in South Africa originating from intermarriage of African tribal populations (particularly the Khoi and San), European whites and Asians (primarily Malaysians).

Method

Although indications that alcohol was teratogenic had been raised earlier in Europe (Sullivan, 1899; Lemoine et al., 1968), the diagnosis of FAS was formulated by Jones and Smith in 1973 (Jones and Smith, 1973), with further delineation in recent years (Aase, 1994; Aase et al., 1995; Hoyme et al., 2005; Stratton et al., 1996; Rossett, 1980; Sokol and Clarren, 1989, 1995). FAS is a pattern of anomalies and developmental deficits in children who were exposed prenatally to large amounts of alcohol. Children with FAS have a characteristic pattern of facial and body dysmorphology and delayed physical growth and development, as well as specific mental and behavioral deficits (Stratton et al., 1996). For a diagnosis of FAS, all three categories of problems must be present (Stratton et al., 1996), and the diagnosis should be made only after excluding other genetic and teratogenic anomalies (Hoyme et al., 2005). Even though an FAS diagnosis can be made without confirmation of maternal drinking (Stratton et al., 1996), a detailed maternal history is best to confirm gestational drinking.

In this study, no attempt was made to diagnose lower-severity fetal alcohol outcomes, previously called "fetal alcohol effects." Currently these other diagnoses are referred to as "alcohol-related birth defects" or "alcohol-related neurodevelopmental deficits" (Stratton et al., 1996). The continuum of effects, from mild to severe, is called "fetal alcohol spectrum disorder." Only the most definite diagnosis was used in this study—full-blown FAS/not FAS. Diagnostic components of the IOM were strictly used: (1) facial and other dysmorphology, recorded using a quantified checklist (see Hoyme et al., 2005), where high scores indicate more features consistent with FAS; (2) diminished growth for age (occipitofrontal head circumference [OFC], weight and height; (3) developmental delay (in intelligence, behavioral functioning and social skills); and, if possible, (4) confirmation of maternal alcohol consumption from maternal or collateral sources.

Once data were collected and analyzed by independent examiners for each component, a structured case conference was held (Figure 1) for final diagnoses (see Hoyme et al., 2005). Every child with an FAS diagnosis met each of the IOM criteria 1-3 above, and criteria for number 4 were met in 90.6% of cases.

Two-tier screening system

In the previous study in this community (May et al., 2000), dysmorphology, growth and developmental data for more than 406 unselected first grade children were collected initially to provide norms for this particular population relative to National Center for Health Statistics growth charts and clinical presentation. The unique racial mixture of the WCP necessitated this first step. For example, pre-

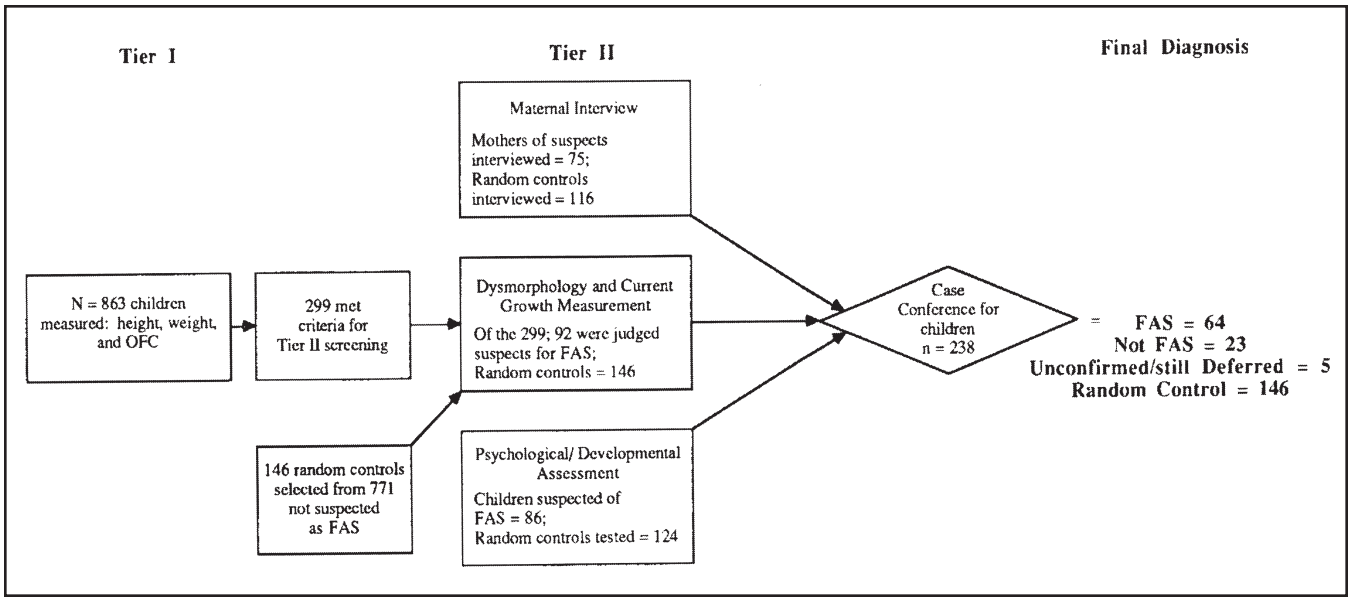

FIGURE 1. The Methodological Flow of the Wave II Western Cape, South Africa FAS Study

liminary information suggested that the interpupillary distance (IPD) and the inner canthal distance (ICD) in local subpopulations were greater than U.S. norms; and in many children the proximal portion of the philtral columns were smoother than found in America. Small head size is more common in this population, but a child with isolated microcephaly (or another single trait) and no additional features of FAS was diagnosed with microcephaly (or the isolated trait). The growth and clinical data from the first study were utilized primarily to calibrate the expectations of the clinicians and to set the cutoff criteria for Tier II screening in all phases of the study (see below).

Four two-person teams (one expert pediatric dysmorphologist and a physician being trained in FAS diagnosis) worked independently but simultaneously, using standardized assessment criteria. Twelve of the 13 elementary schools of the community were accessed in both studies. The school that declined participation was a private, all-white school with 60 first graders. More than 90% of the children in the study were Coloured; the remainder were black or white. Relatively low mobility of the local population ensured that most of the study children underwent gestation locally.

In the previous South Africa study, cutoff points were set to ensure capture of all FAS children, and they were used again in this study. In this study, 863 (93.6%) of 922 children on the rolls in first grade classrooms had parental consent to participate and received Tier I screening, where height, weight and OFC were measured. If a child was at or below the 10th centile on OFC and/or on *both* height and weight, he or she was referred for a complete physical examination (Tier II). Two hundred and ninety-nine (34.9%) children met these criteria (see Figure 1). In our first study, one child with FAS from the community was not in a standard school (<2% error), and in this study no FAS cases were found out of standard schools.

Every child receiving a complete (Tier II) dysmorphology screen was examined completely by *two* of the physician teams. Each two-member team measured OFC, palpebral fissure length (PFL) and philtral length (PL) as well as ICD and outer canthal distance, and examined other indicators such as joint abnormalities, heart function and palmar creases. Findings were recorded, and physicians within each team verified one another's findings (the expert checked those of the trainee). All physicians were blinded from prior knowledge of the child and the mother. After one team examined them, a second team repeated the examination. Interrater reliability was checked for the expert dysmorphologists' (not trainees) independent measurements, rounded to the nearest 0.1 cm, using the square root of the Pearson correlation (r). Results were 0.86 for ICD, 0.92 for IPD, 0.91 for PFL and 0.82 for PL, indicating substantial reliability among experienced examiners.

Complete diagnostic sequence—case and control identification

After the dysmorphology examinations, a child was assigned a *preliminary* diagnosis of not-FAS, deferred or FAS. Only those with the classic FAS phenotype and measurements were assigned a *preliminary* diagnosis of FAS. Children with a deferred diagnosis had the appearance, growth deficits and some anomalies of FAS, but developmental tests and maternal interviews were especially necessary for final diagnosis of these children. Children with a preliminary

FAS or a deferred diagnosis (n = 92) were advanced to developmental and prenatal risk assessment.

A child with a final diagnosis of FAS had sufficient dysmorphology, was approximately two standard deviations below the mean on either verbal or nonverbal intelligence quotient (IQ) tests, had substantial behavioral problems as measured by the Personal Behavior Checklist (PBCL) and had confirmation of prenatal alcohol consumption. In less than 10% of cases were IOM criteria permitting an FAS diagnosis without confirmation of alcohol exposure invoked (see below).

Control children (n = 146) were randomly selected from first grade students without a preliminary diagnosis of FAS or a deferred diagnosis. Identical examinations and testing were performed on subjects and controls. Developmental tests included Tests of the Reception of Grammar (TROG), Ravens Colored Progressive Matrices and the PBCL-36, providing measures of nonverbal and verbal IQ, cognitive skills and behavioral problems. One hundred twenty-four (84.9%) of the randomly selected controls were located and agreed to participate.

Maternal data

The mothers of control children became maternal controls. Structured interviews contained items covering reproduction, alcohol use before and during the index pregnancy, SES, demographic variables, nutrition, physical status of the mother and social context.

Protocols utilized drinking questions in a Timeline Followback methodology (Sobell et al., 1988, 2001) designed to elicit accurate reporting of alcohol consumed from both Dop and commercial sources (London, 2000; London et al., 1998; Parry and Bennetts, 1998). Photographs of standard beer, wine and spirit containers and tobacco products sold locally were shown to respondents for accurate assessment of quantity, frequency, and variability (Kaskutas and Graves, 2000, 2001). A 7-day current drinking log was used as a benchmark to calibrate extant quantity and frequency of drinking and for accurate recall of drinking during the pregnancy with the index child (see May et al., 2000, 2005; Viljoen et al., 2002). This method is used because prenatal drinking is underreported with direct reporting (Czarnecki et al., 1990; Jacobson et al., 1991, 2002; Jacobson and Jacobson, 1994) unless information is gathered through unique questions, methods and contextual frameworks, such as a part of general nutrition screen (King, 1994). Drinking questions followed nutrition questions. All maternal interviews were administered by Afrikaans-speaking interviewers in the field.

Because mothers of FAS children often lead chaotic lives, death or mobility obviated some interviews (May et al., 1983; Streissguth et al., 1985). Specifically, 54 of the 64 mothers of the FAS children were contacted; 53 agreed to be interviewed. For the remaining 10, data were obtained via collaterals (usually relatives). Only one (1.6%) of the 64 case mothers was deceased, likely from tuberculosis. Eight (12.5%) were nomadic or had moved from the area. Drinking data were obtained from collateral sources on 9 of the 10 women not located. All 10 of the children of mothers not interviewed were in foster or adoptive placement (2 in an orphanage and 4 with relatives). Maternal data presented here are focused primarily on confirmation of maternal drinking for case assessment/diagnosis. A detailed profile and discussion of a variety of maternal risk factors for FAS in this setting are given elsewhere (Viljoen, et al., 2002; May et al., 2005). Four (7.5%) of the 53 mothers of children with FAS denied drinking during the index pregnancy. To ensure accuracy, two dysmorphologists revisited these four children to rule out other anomalies and to confirm the diagnosis. After further review of all results, five (9.4%) children were diagnosed without confirmed alcohol exposure.

The maternal control group consisted of the 116 mothers of the randomly selected control children located alive and agreeing to interviews. Of the 30 mothers not interviewed, 15 (10.3%) were not located, 3 (2.1%) refused and 12 (8.2%) had their children in foster placement.

Case conferences for final diagnoses

Final diagnoses were made only after case conferences were held for each child. Results from dysmorphology examinations, developmental testing and maternal interviews (each domain completed by independent investigators) were presented at the structured case conference.

Data analysis

Data were entered and analyzed using the Epi Info software of the U.S. Centers for Disease Control and Prevention (Dean et al., 1994). Categorical variables comparing cases with controls were analyzed by chi-square and Fisher's exact tests. Odds ratios (ORs) were calculated in 2 × 2 comparisons. Confidence intervals for ORs were computed for 95% confidence levels by the Cornfield technique. For continuous variables, t tests, one-way analysis of variance and difference of proportions tests (Blalock, 1972) were used. In Table 4, Pearson correlation coefficients are used to compare selected variables, two of which were utilized as dummy variables (3 and 5 or more drinks per occasion). With certain variables, comparisons are made between subsets of cases and controls, based on current drinking and smoking.

Results

As shown in Table 1 (data column 1), of 863 children examined, 50.8% were male. The overall mean (SD) age

TABLE 1. Demographic and growth parameters for all sub-A (first grade) children, children with FAS and randomly selected controls: Western Cape Community, South Africa

Variable	All sub-A children (n = 863)	Children with FAS (n = 64)	Control children (n = 146)	p value
Gender, % male	50.8	46.9	47.9	NS[a]
Age, in months, mean (SD)	77.6 (9.00)	78.5 (7.62)	76.3 (6.61)	.046[b]
Height, cm, mean (SD)	113.7 (6.47)	108.6 (4.54)	119.2 (7.47)[c]	<.001[b]
Weight, kg, mean (SD)	19.1 (3.83)	15.7 (1.68)	22.6 (4.82)[c]	<.001[b]
Occipitofrontal circumference, cm, mean (SD)	50.6 (1.67)	48.2 (1.28)	51.4 (1.63)[c]	<.001[b]
Palpebral fissure length, cm, mean (SD)	–	2.3 (0.13)	2.6 (0.14)[d]	<.001[b]
Philtrum length, mm, mean (SD)	–	13.39 (2.33)	12.58 (2.04)[d]	.018[b]
Short intercanthal distance, %	–	7.8	1.6	.048[a]
Short interpupilary distance, %	–	12.5	1.6	.003[a]
Hyperactivity, %	–	3.1	0.0	NS[a]
Fine motor, %	–	0.0	0.0	NS[a]
Hypoplastic midface, %	–	35.9	1.6	<.001[a]
"Railroad track" ears, %	–	7.8	0.8	.019[a]
Strabismus, %	–	3.1	0.0	NS[a]
Ptosis, %	–	6.3	0.0	.013[a]
Epicanthal folds, %	–	53.1	31.1	.003[a]
Flat nasal bridge, %	–	39.1	9.0	<.001[a]
Anteverted nostrils, %	–	12.5	0.0	<.001[a]
Long philtrum, %	–	21.9	15.6	NS[a]
Smooth philtrum, %	–	60.9	22.1	<.001[a]
Narrow vermillion border, %	–	50.0	2.5	<.001[a]
Prognathism, %	–	1.6	0.0	NS[a]
Heart murmur, %	–	9.4	0.0	<.001[a]
Limited elbow supination, %	–	6.3	1.6	NS[a]
Clinodactyly, %	–	31.3	24.6	NS[a]
Camptodactyly, %	–	20.3	1.6	<.001[a]
Palmar crease alteration, %	–	40.6	17.2	<.001[a]
Hypertrichosis, %	–	3.1	0.8	NS[a]
Dysmorphology score, mean (SD)	–	14.0 (4.31)	2.2 (2.68)	<.001[b]
Foster care or adopted, %	–	17.5	10.7	NS[a,e]

Notes: NS = not significant; [a]χ^2 test; [b]t test; [c]measurements at time of Tier I screen; therefore they are directly comparable to all other groups; [d]palpebral fissure length and philtrum length was 7 months after exam of children with FAS; other variables are age-corrected by percentile; [e]OR = 1.76 (95% confidence interval [CI]: 0.68-4.54); 95% CI calculated via Cornfield technique.

was 6.5 years, or 77.6 months. The children averaged 113.7 cm (3 feet, 8 inches) in height, weighed 19.1 kg (42 lbs, 3 oz) on average and had an OFC of 50.6 cm. After the dysmorphology examination, 28 children had a *preliminary* diagnosis of FAS, and 64 were classified as deferred. These 92, along with the 146 control children, were the subjects of further research (see Figure 1).

Sixty-four of the school children received a final diagnosis of FAS. Also at final diagnosis, five initially deferred children were considered "still deferred" because of an inability to locate them for testing. None of the control children had FAS or indicators sufficient for deferral. In Table 1 (data columns 2 and 3), more FAS children and controls were females (53.1% and 52.1%, respectively) than in the entire school population (49.2%), but the difference was not statistically significant. The average age was 6.5 years for FAS children and 6.4 years for the controls. Height, weight, OFC, PFL and almost every variable used in the clinical examination were significantly different between subjects and controls, including total dysmorphology scores (14.0 vs 2.2, $p < .001$). Higher scores indicate more features of FAS. The only variables not significantly different in Table 1 are peripheral to the dysmorphology examination for FAS diagnosis: observations of gross hyperactivity, fine motor coordination, strabismus, long philtrum (by observation, although actual measurements did differ), prognathism, limited elbow supination, clinodactyly (usually of the fifth finger) and hypertrichosis. More of the children with FAS were in foster or adoptive placement (17.5% vs 10.7%), a nonsignificant difference.

Developmental indicators

Scores on neurodevelopmental tests (Table 2) are reported for two FAS groups and the controls. One group with FAS consists of children with consistent and severe

TABLE 2. Developmental and behavioral indicators[a] of children with FAS (by preliminary diagnosis after dysmorphology exam) and randomly selected controls

Variable	Final Dx FAS: Preliminary Dx FAS	Final Dx FAS: Preliminary Dx Deferred	Controls	Significance ANOVA
Child developmental traits	(n = 28)	(n = 36)	(n = 123)	
Verbal IQ, mean (SD)[b]	68.3 (6.50)[c]	73.9 (8.50)[d]	82.5 (15.20)	F = 15.9, 2/185 df, $p < .001$
Nonverbal IQ, mean (SD)[e]	79.7 (8.20)[d]	83.2 (9.00)	84.6 (10.00)	F = 2.90, 2/187 df, NS ($p = .057$)
Behavior, mean (SD)[f]	15.3 (7.60)[d]	12.9 (9.00)[d]	6.7 (6.80)	F = 21.0, 2/185 df, $p < .001$
Total dysmorphology score, mean (SD)[g]	17.8 (3.36)	12.3 (3.11)	3.6 (2.70)	F = 119.3, 2/67 df, $p < .001$
Maternal drinking	(n = 18)	(n = 22)	(n = 28)	
During pregnancy, %	91.7	72.7	19.5	$\chi^2 = 61.3$, $p < .001$
Current drinks/week, mean (SD)[g]	21.4 (13.96)	10.2 (9.06)	3.8 (4.66)	F = 19.9, 2/67 df, $p < .001$
No. drinks per drinking day, mean (SD)[g]	7.6 (5.82)	4.8 (3.80)	3.0 (3.63)	F = 6.05, 2/67 df, $p < .004$

Notes: Dx = diagnosis; FAS = fetal alcohol syndrome; ANOVA = analysis of variance; IQ = intelligence quotient. [a]All scores standardized for age of child at time of testing; [b]Tests of the Reception of Grammar (TROG); [c]t test significantly different from both children with preliminary diagnosis of deferred and controls, significance < .002; [d]t test significantly different from controls, significance < .02; [e]Ravens Colored Progressive Matrices; [f]Personal Behavior Checklist (PBCL-36); [g]of those who report drinking during pregnancy in a full interview.

enough dysmorphology for a preliminary diagnosis of FAS (prior to psychological screening or maternal interview). The second FAS group consists of children who have qualifying dysmorphology but whose diagnosis of FAS was more formally deferred until the case conference. Average IQ scores were worse for children with FAS. Verbal ability was significantly lower for both groups of children with FAS as measured (in Afrikaans) by the TROG ($p < .001$). The differences in nonverbal performance were not as great and not statistically significant between the three groups, although approaching significance ($p = .057$). The scores of the controls and the deferred/then FAS group were quite similar, yet the preliminary FAS group and controls differed significantly on nonverbal performance. Problem behaviors were highly divergent between both FAS groups and controls. The importance of local population controls is underscored by the data, as all children from this population are performing below the norm of 100.

The overall dysmorphology scores, indicating severity of physical deformity and lack of physical development, form a spectrum in Table 2. Children with preliminary FAS had the highest average score of 17.8; the children first deferred had an average score of 12.3; and the controls had an average score of 3.6. Therefore, behavioral indicators and dysmorphology were concordant in pattern, especially regarding verbal IQ, behavioral problems and total dysmorphology. Finally in Table 2, reported maternal drinking also supports the spectrum of damage associated with both physical development and behavioral problems. The mothers of children with preliminary FAS reported the most drinking; the mothers of preliminarily deferred children were intermediate; and the control mothers were lowest on all three maternal drinking measures.

Maternal drinking and smoking

Maternal drinking variables (Table 3) indicate that the mothers of all children with FAS were likely to be drinking more at the time of the interview. Furthermore, almost 90% of all alcohol consumed at the time of the interview by both groups was on weekend days. From the reference drinking level (current 7-day drinking log), 92.3% of the case mothers reported drinking during pregnancy, and 88.7%-92.5% reported drinking about the same amount throughout the trimesters. Among controls, 25.7% drank prior to pregnancy, and 13%-20% drank in the first through third trimesters. The beverage of choice reported by the mothers of FAS children (not in Table 3) was beer (58.5%), followed by wine (45.3%), and a few preferred distilled spirits (5.7%). These percentages exceed 100 because several mothers reported more than one favorite beverage.

More mothers of FAS children used tobacco at the time of the interview (67.9% vs 28.6%; OR = 5.29) and during the index pregnancy (75.5% vs 26.8%; OR = 8.41). By American and European standards, however, smokers consumed low weekly quantities: 27.9-38.2 hand-rolled cigarettes (1 g of tobacco each).

Fathers of children with FAS drank heavily. Ninety-six percent of the case fathers currently drink, compared with 73% of the controls. Drinking fathers of the FAS children consumed 84.6 drinks per month, compared with 47.5 for drinking controls. Fathers of children with FAS were more likely to be reported as having a drinking problem than controls (OR = 28.33) and to be farm laborers (OR = 6.55).

In Table 4, zero-order correlations are presented on the association between four drinking measures and specific

TABLE 3. Substance use by mothers and fathers of the children with FAS and randomly selected controls

Variable	Mothers of children w/FAS[a] (n = 53)		Mothers of controls (n = 116)		p, OR (95% CI)[b]
Current drinker, in last year, %	69.8		21.1		<.001[c], OR = 8.14 (3.7-18.4)
	Whole sample (n = 53)	Drinkers only (n = 35)	Whole sample (n = 109)	Drinkers only (n = 19)	
Current use of alcohol, drinks last week, mean (SD)	12.6 (13.1)	15.2 (11.2)	1.0 (2.9)	5.4 (4.7)	Whole sample < .001[d] Drinkers only < .001[d]
Current consumption on weekends, Fri., Sat., Sun., mean (SD)	11.1 (11.1)	13.6 (8.9)	0.9 (2.7)	5.0 (4.2)	Whole sample < .001[d] Drinkers only < .001[d]
Percentage on weekends	88.1	89.5	90.0	92.6	Whole sample NS[e] Drinkers only NS[e]
Drank before pregnancy with index child, %[f]	92.3		25.7		<.001[c], OR = 34.76 (10.6-126.3)
Did not drink or stopped	7.7		74.3		
Drank during index pregnancy, %	92.3[g]		19.5		<.001[c], OR = 39.71 (15.1-188.1)
Drank during 1st trimester, %[f]	92.5		19.5		<.001[c], OR = 50.67
Did not drink or stopped	7.5		80.5		(15.1-188.1)
Drank during 2nd trimester, %[f]	92.5		13.3		<.001[c], OR = 80.03
Did not drink or stopped	7.5		86.7		(22.8-311.2)
Drank during 3rd trimester, %[f]	88.7		13.3		<.001[c], OR = 51.18
Did not drink or stopped	11.3		86.7		(16.9-163.6)
Current user of tobacco, %	67.9		28.6		<.001[c], OR = 5.29 (2.5-11.6)
	Whole sample (n = 52)	Smokers only (n = 34)	Whole sample (n = 99)	Smokers only (n = 33)	
Current users, quantity tobacco used each week, g, mean (SD)	27.5 (32.0)	38.2 (32.4)	9.3 (17.1)	27.9 (19.1)	Whole sample < .000[c] Smokers only NS[e]
Used tobacco during index pregnancy, %	75.5		26.8		<.001[c], OR = 8.41 (3.7-19.4)
Tobacco use during index pregnancy, used same or more, than current use, %	65.6		17.2		<.001[c]
	Whole sample (n = 49)	Drinkers only (n = 47)	Whole sample (n = 96)	Drinkers only (n = 70)	
Drinks consumed by father during index pregnancy 30 day, mean (SD)	81.1 (81.7)	84.6 (81.7)	34.6 (45.9)	47.5 (47.8)	Whole sample < .001[d] Drinkers only < .002[d]
Fathers with drinking problems in past, %	36.2		2.0		<.001[c], OR = 28.33 (5.6-191.4)
Fathers currently have drinking problem, %	21.4		4.0		.001[c], OR = 6.55 (1.6-27.7)
Usual occupation, % farm laborer	34.6		12.4		.003[c]

Notes: FAS = fetal alcohol syndrome; OR = odds ratio; CI = confidence interval. [a]Mortality and mobility reduced the number of available mothers of FAS children by 10, see Method section text for details; [b]95% CIs calculated via the Cornfield technique; [c]χ^2 test; [d]t test; [e]difference of proportions test; [f]drank "less," the "same amount" or "more" than use at time of interview; [g]four women did not admit to drinking during the index pregnancy, but reexamination confirmed a diagnosis of FAS.

outcomes. Verbal and nonverbal ability are, as expected, negatively correlated with the mother's drinks per month, drinks per day and reported episodes of three or five alcoholic drinks per day. Verbal behavior is most highly correlated with drinks per day on weekends (r = -.31) and heavy episodic drinking (r = -.35 for three drinks per occasion and -.29 for five drinks per occasion). The more the reported maternal drinking per day was during pregnancy, the lower the child's IQ was, especially the verbal IQ. Problem behaviors were significantly correlated with heavy drinking mothers (r = .38-.40). The highest correlations were found between dysmorphology scores and drinks per day on weekends and two other measures of episodic drinking (r = .60-.61).

TABLE 4. Pearson correlation coefficients for developmental[a] and physical dysmorphology versus selected maternal drinking measures (n = 164)

Trait	Drinks per month r	Drinks per day on weekends r	3 drinks per occasion r	5 drinks per occasion r
Verbal ability[b]	-0.27‡	-0.31‡	-0.35‡	-0.29‡
Nonverbal ability[c]	-0.21†	-0.19*	-0.18*	-0.20*
Behavior[d]	0.40‡	0.40‡	0.39‡	0.38‡
Dysmorphology score	0.52‡	0.60‡	0.61‡	0.60‡

[a]All scores standardized for age of child at time of testing; [b]Tests of the Reception of Grammar (TROG); [c]Ravens Colored Progressive Matrices; [d]Personal Behavior Checklist (PBCL-36).
*$p < .05$; †$p < .01$; ‡$p < .001$.

Urban/rural distribution and prevalence of FAS

The mothers of FAS children were much more likely than the controls to have resided in rural areas during gestation of the index child (66.0% vs 20.9%; OR = 7.36; Table 5). They also were more likely to be farm workers than the controls. The urban/rural distribution of FAS cases (Table 5) also was tested against the overall residence pattern through indirect standardization (Barclay, 1958). Because 66.0% (n = 35) of the FAS cases underwent gestation in the rural areas, this is a significant departure from random distribution ($p < .001$, OR = 5.42), as only 26% of the population lived in rural areas.

The prevalence of FAS among children screened was 74.2 per 1,000, or 69.4 if all 922 first graders in public schools are used as the denominator (Table 5). One child with FAS was white, as were three controls, making this rate the predominantly Coloured/black rate. There were few older children in first grade in this study cohort; therefore, there was no need to correct for age. If the approximately 60 children in first grade from the all-white school that did not participate are added to the denominator, and if it is assumed that none have FAS, the most conservative, in-school prevalence is 65.2 per 1,000. Because no out-of-school children were identified with FAS, the range of FAS prevalence for the community was 65.2-74.2 per 1,000.

Discussion

Active case ascertainment of FAS through population-based screening has rarely been reported except for American Indian and Alaska Native populations (May, 1996; May et al., 2002). Furthermore, screening of all children in a particular school or grade has been reported in only two other published studies (Clarren et al., 2001; May et al., 2000), and one of these was the previous study of this particular South African population.

Active case ascertainment in schools with skilled dysmorphologists, psychologists and maternal interviewers can effectively and efficiently identify children with FAS in the particular age range from 3 years to the early teens. The interdisciplinary, multiple-domain, control-group design described here produced what we believe is complete, accurate and reliable knowledge of the prevalence and characteristics of FAS. This study was rather unique because it was population-based; consent to participate was very high; the host community has a very high prevalence of FAS; and there was relatively low mobility among cases of interest.

Limitations exist, however. First, the diagnosis of FAS is best made when children are between 3 and 12 years of age, so maternal interviews carried out in this time frame

TABLE 5. Distribution of FAS cases by rural and urban calculated from interviews and by indirect standardization and overall prevalence of FAS

Variable	Mothers of children with FAS[a] (n = 53)	Mothers of control children (n = 116)	p, OR (95% CI)[b]
Residence during index pregnancy, from interview (%)			
Rural	66.0 (n = 35)	20.9 (n = 28)	<.001[c], OR = 7.36
Urban	34.0 (n = 18)	79.1 (n = 87)	(3.31-16.52)
Residence of FAS mothers (indirect standardization by frequency)	Rural	Urban	
Actual	35	18	<.001[c], OR = 5.42
Predicted	14	39	(2.18-13.69)
Prevalence rates			
1st grade children screened	74.2 per 1,000		
1st grade children per all enrolled in 12 schools	69.4 per 1,000		
1st grade children per all enrolled in all schools	65.2 per 1,000		

Notes: FAS = fetal alcohol syndrome; OR = odds ratio; CI = confidence interval; NS = not significant.
[a]Mortality and mobility reduced the number of available mothers of FAS children by 10, see Method section text for details; [b]95% CIs calculated via the Cornfield technique; [c]χ^2 test.

are challenged by recall. We used Timeline Followback and 7-day drinking logs of current consumption to calibrate reporting, refresh memory and estimate alcohol consumption during index pregnancies.

Second, a study such as this depends on the honesty of mothers—a problem that has presented challenges elsewhere. In South Africa, however, mothers interviewed are highly forthcoming, and we have confidence in information obtained from 90% of those interviewed.

Third, the fact that one private, all-white school did not participate in this study leaves a gap in our knowledge of the whole community, as 11 of the 13 schools in the community are predominantly Coloured. In the one public predominantly white school participating in the study, only one white child was diagnosed with FAS. We suspect that the rate of FAS among whites in South Africa is low, but a larger sample of whites is desirable.

Fourth, generalizing from the conditions in this small South African town may be difficult. How comparable is the situation to that in other countries, populations and races? We suspect that it is highly generalizable to other towns in the WCP and to some other parts of South Africa (Viljoen et al., 2003). Unique historical and sociocultural conditions in South Africa may limit the broader generalizability of some findings, however.

Child characteristics and their implications to a spectrum of effects

Even though the focus of this study was exclusively on full-blown FAS, a spectrum of severity emerged from the process of screening and diagnosis. Forty-four percent were correctly believed to have FAS at the time of the dysmorphology examination, even before psychological testing and maternal interviews. The remaining 56% had physical symptoms that were less severe (e.g., a lower total dysmorphology score), and their preliminary diagnosis was less definite at the dysmorphology examination. This pattern of findings has occurred in our other field trials and has led to an improved operational definition of physical features of fetal alcohol spectrum disorder (Hoyme et al., 2005). In the article, we have aggregated data for the children by preliminary dysmorphology diagnosis when presenting the findings on the developmental tests, which illustrated that physical anomalies are associated significantly with IQ and development. The more severe the dysmorphology is, the poorer are the IQ (especially verbal) and behavior. Furthermore, this spectrum is clearly associated with drinking severity.

Implications of the prevalence findings

Much drinking in this community is heavy episodic drinking, with alcohol consumed primarily on weekends. On weekends, the women and men on the farms frequently have means to purchase alcohol and unencumbered time to consume it heavily. Fridays are paydays. Thus, even though the current drinking quantities reported by subjects are not outrageously high in absolute quantity, when compared with heavy drinking in the United States (May et al., 2004), most attention should be paid to the episodic nature of the drinking and the large *differential* between subjects and controls. Subjects drink more than controls, drink rapidly and drink heavily in an episodic fashion. Given their small body size (see May et al., 2005), high blood alcohol concentrations are produced (Khaole et al., 2004). Furthermore, it is clearly shown here that mothers of children with FAS do not quit or cut down during pregnancy. Drinkers in this study are more prone to episodic drinking during pregnancy than U.S. women (Tsai and Floyd, 2004). Case mothers drank sufficiently to produce cases of FAS as severe as any we have experienced anywhere in the United States. In two recent articles (May et al., 2004, 2005), we have presented evidence of specific cofactors that combine with episodic drinking in this WCP town to produce FAS. Low SES and the despair of poverty and powerlessness are certainly overarching factors. As presented in our other articles, specific and quantifiable measures of poverty and despair are (1) poor current and lifelong nutrition and (2) multiple generations of fetal alcohol exposure. Episodic drinking was documented, along with poor nutrition, small maternal body size (providing less mass to which the alcohol can be distributed) and the social and economic despair endured by some South African Coloured women (see also May et al., 2000; Viljoen et al., 2002). These findings combine to produce very high rates of FAS in this community. Most of the children were born in 1993, one year before the end of apartheid.

Because of past apartheid policy (enforced segregation by ethnicity), darker-skinned peoples are overrepresented in lower SES, as is clearly reflected by the concentration of cases in the poorer, rural areas. All but one of the children with FAS was Coloured, and those with the lowest SES indicators were overrepresented. High rates also exist in other low-SES, urban areas of South Africa (Viljoen et al., 2003), but rates published to date for those areas are no higher than 20 per 1,000. The legacy of Dop is influential in the drinking pattern and in a very high rate of FAS. The fact that FAS was more common in the rural areas may reflect higher SES among urban dwellers, or urban areas may simply provide escape from extreme poverty and a heavy drinking social milieu/culture. Other recreational activities are available in town that do not involve alcohol to the same degree. Clearly, residing on *some* of the fruit and wine-producing farms is a grave risk factor, as severe episodic drinking is perpetuated by norms within a context of despair. Prevention is most needed in rural environments.

Why is the rate of FAS increasing?

The rate of FAS in this second study in this community is another record rate for any functional community (65-74 per 1,000) to date. It is 60% higher than reported in our previous South African study (40.5-46.4 per 1,000) of another cohort born 2-3 years earlier (May et al., 2000). Therefore, the increase in an already alarming rate is cause for concern. Much of this increase in rate is likely real, because similar, although slightly refined, methods of diagnosis were used. There was also minimal change in the population composition through migration, social and economic improvement or other forces. It is possible that there was among our physicians some increased sensitivity to and familiarity with the recognition of subtle clinical features of FAS in this population and to the fact that FAS is very prevalent locally. But the psychological/developmental and maternal data provide verification that FAS diagnoses are accurate.

Some of the increase in the FAS rate might be attributed to liberating social changes and an increase in the supply of commercially available alcohol. Both cohorts of children studied thus far underwent gestation during the weakening of the apartheid era, which officially ended in 1994. Therefore, change in individual freedoms has affected the Coloured and Black population, and social liberation seems to have resulted in increased quantity of drinking in individuals or small subsegments of the population. To examine this hypothesis, we reviewed average drinks per drinking day reported by the control groups in the 1997 study and in this later study (1999-2000). The average number of drinks per drinking day was indeed higher among the controls in this study, as it went from 2.2 per day in 1997 to 3.0. On the other hand, some other variables of drinking quantity and frequency among controls in Studies I and II have provided mixed changes. Nevertheless, the daily consumption data and our observations lead us to believe that much of this increase in FAS is real.

Comparison of these findings with those of other studies

The results of previous studies have provided insight into the epidemiology of FAS, paralleling our findings here. Population-based, clinic and laboratory studies all indicate that major risk factors for FAS are associated with the mother's individual characteristics, her environment and her social milieu. Specific traits—such as advancing maternal age; high gravidity and parity; and the quantity, frequency and timing of drinking during gestation—are all important explanations for the prevalence of FAS (May, 1995; Streissguth et al., 1985). All of these risk factors exist in some South African women with a rapid and severe drinking pattern that produces a very high blood alcohol concentration (Khaole et al., 2004), and drinking persists throughout pregnancy in mothers of FAS children. Furthermore, SES is a major risk factor in both the United States and South Africa (Abel, 1998, 1995; Abel and Hannigan, 1995; Bingol et al., 1987; Viljoen et al., 2003). These variables, however, have rarely been studied simultaneously in nonclinic populations. Rather, passive case ascertainment methods are commonly used with existing data sources that are frequently incomplete and selective (Chavez et al., 1988; Little et al., 1990; Pierog et al., 1979). The proactive methodology used in South Africa has yielded rich epidemiological data useful for prevention. Furthermore, as of the completion of this second wave of research in this community, these studies have identified 110 "gold standard" cases for further research and for clinical services.

Unlike one previous study of a very high rate in an Indian community in Canada (Robinson et al., 1987), this South African community is economically and socially stable. As an established community with a viable economy undergoing moderate rates of modernization, such a high rate of FAS is an extreme public health concern. Furthermore, a large number of mothers in this community give birth to children with FAS (approximately 69 per 1,000 of childbearing age), rather than the relatively small number of U.S. women (0.3-3.3) who bear one or more children with FAS (Abel and Sokol, 1987; May and Gossage, 2001; Streissguth et al., 1985). The reasons for such a high rate are found in the socioeconomic milieu, individual drinking patterns, subcultural drinking norms and other cofactors of risk.

In a departure from the U.S. literature, there was no significant difference in cases versus controls in the percentage of children in foster or adoptive placement. In the United States, a much higher percentage of children with FAS are not raised by biological parents (May et al., 1983; Streissguth et al., 1985).

Prevention

Comprehensive, community-wide prevention programs are needed in this area and in other towns and rural areas of WCP. With a small amount of money available in South Africa for public health, however, and with other pressing needs (e.g., tuberculosis and HIV/AIDS), it is unlikely that well-funded, comprehensive prevention initiatives will be undertaken utilizing South African resources alone. Models of comprehensive prevention exist in the literature (Stratton et al., 1996; May, 1995), which can be applied to this problem. Thus, it is imperative that the high rate of FAS gain the attention of international groups and other resource-bearing constituents. The implications of this study and its findings may be important for other parts of the developing world.

Conclusion

This article adds to the knowledge about FAS in a very high-risk population, in many ways confirming facts already

understood in any human population. For example, severe episodic drinking is the pattern of drinking that leads to FAS in low-SES populations, and maybe in any population. This study provided a unique opportunity to employ, test and refine epidemiology research methods applicable to almost any population. Furthermore, psychological testing, interview and diagnostic methodologies are relevant to studies of other populations and cultures. In many ways, the South African studies have opened a new era in the study of FAS. Similar studies are currently under way in other parts of South Africa, in Washington, D.C., and in Italy.

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