

# Epidemiology of Fetal Alcohol Syndrome in a South African Community in the Western Cape Province

## ABSTRACT

**Objectives.** This study determined the characteristics of fetal alcohol syndrome in a South African community, and methodology was designed for the multidisciplinary study of fetal alcohol syndrome in developing societies.

**Methods.** An active case ascertainment, 2-tier methodology was used among 992 first-grade pupils. A case-control design, using measures of growth, development, dysmorphology, and maternal risk, delineated characteristics of children with fetal alcohol syndrome.

**Results.** A high rate of fetal alcohol syndrome was found in the schools—40.5 to 46.4 per 1000 children aged 5 to 9 years—and age-specific community rates (ages 6–7) were 39.2 to 42.9. These rates are 18 to 141 times greater than in the United States. Rural residents had significantly more fetal alcohol syndrome. After control for ethnic variation, children with fetal alcohol syndrome had traits similar to those elsewhere: poor growth and development, congruent dysmorphology, and lower intellectual functioning.

**Conclusions.** This study documented the highest fetal alcohol syndrome rate to date in an overall community population. Fetal alcohol syndrome initiatives that incorporate innovative sampling and active case ascertainment methods can be used to obtain timely and accurate data among developing populations. (*Am J Public Health*. 2000;90:1905-1912)

Philip A. May, PhD, Lesley Brooke, BS, J. Phillip Gossage, PhD, Julie Croxford, RN, BS, Colleen Adnams, MD, FCP, Kenneth L. Jones, MD, Luther Robinson, MD, and Denis Viljoen, MD

In the United States, the rate of fetal alcohol syndrome has been estimated to range from 0.33 per 1000<sup>1</sup> to 2.2 per 1000.<sup>2</sup> A more recent average has placed the rate for the developed world at 0.97 per 1000.<sup>3</sup> In certain American Indian reservation communities in the United States that are considered by some to be at very high risk, the rate of fetal alcohol syndrome seldom exceeds 10 per 1000.<sup>4,5</sup> The average rate of fetal alcohol syndrome found among American Indians, based on active case ascertainment methods, was 8 per 1000 in the birth cohorts 1970 through 1980.<sup>6</sup> Studies of African Americans of low socioeconomic status (SES) in selected inner-city areas have yielded a rate of 2.29.<sup>3</sup>

Various methods, including both active and passive case ascertainment, have been used to determine the prevalence of fetal alcohol syndrome. Information for estimating fetal alcohol syndrome prevalence comes from birth records, registries, clinic-based studies, and population-based initiatives.<sup>7</sup> Because of wide variation in methodologies, comparison of fetal alcohol syndrome prevalence and the epidemiologic characteristics of fetal alcohol syndrome between populations is often difficult to impossible. For example, virtually all active case ascertainment studies, in which outreach in major geographic areas focuses on aggressive case finding, have been carried out among American Indians. Passive, record-based systems and clinic-based methods have been used to study fetal alcohol syndrome among patients presenting for routine medical services (e.g., prenatal and birthing services). Passive case ascertainment has been used predominantly in mainstream populations in North America and Europe.<sup>6,8</sup> Data from these different methods vary greatly in their completeness and in the types obtained in each setting.<sup>7,9,10</sup>

Recently, a study committee of the Institute of Medicine endorsed active case ascertainment as the most accurate method for epidemiologic

studies, but active methods are logistically challenging, expensive, and time-consuming.<sup>7</sup>

In this article, we summarize an active case ascertainment initiative funded by US and South African sources to establish the prevalence of fetal alcohol syndrome in a community in the Western Cape Province of the Republic of South Africa. As part of a binational commission initiated by the vice presidents of the 2 countries, scientists from the United States visited parts of South Africa to lecture, share information, and survey potential research opportunities.<sup>11</sup> These visits, sponsored by the National Institute on Alcohol Abuse and Alcoholism,<sup>12</sup> raised concern about the frequent occurrence of fetal alcohol syndrome in various South African subpopulations. Epidemiologic studies of fetal alcohol syndrome seemed necessary in the Western Cape Province in the southwest of the country. The total population of the province is 3 721 200, of which 57% is Cape Coloured (mixed race), 18% is Black, 24% is White, and 1% is other. Cape Town is

Philip A. May and J. Phillip Gossage are with the University of New Mexico, Center on Alcoholism, Substance Abuse, and Addictions, Albuquerque, NM. Lesley Brooke, Julie Croxford, and Denis Viljoen are with the Foundation for Alcohol Related Research, The University of Cape Town, Cape Town, South Africa. Colleen Adnams is with the Department of Paediatrics, The University of Cape Town. Kenneth L. Jones is with the Division of Dysmorphology/Teratology, Medical Center, University of California-San Diego. Luther Robinson is with Dysmorphology and Clinical Genetics, State University of New York at Buffalo. Denis Viljoen is also with the Department of Medical Genetics, University of Witswatersrand, Johannesburg, South Africa, and South African Institute for Medical Research, Johannesburg, South Africa.

Requests for reprints should be sent to Philip A. May, PhD, University of New Mexico, Center on Alcoholism, Substance Abuse, and Addictions, 2350 Alamo SE, Albuquerque, NM 87106 (e-mail: pmay@unm.edu).

This article was accepted April 20, 2000.

the most densely populated area of the region, but 40% of the population live outside the Cape Town metropolitan area in small towns and rural settlements like the one studied here.<sup>11</sup>

Many people of the Western Cape are involved in growing grapes and producing wine, and this has influenced the modal regional drinking patterns. For several centuries, wine was distributed among and consumed daily by workers as partial payment for labor. This custom is referred to as the "Dop" system. Dop has been outlawed by at least 2 legislative acts, but residual patterns of regular and heavy alcohol consumption by workers remain today as its legacy in Western Cape society. Furthermore, increased availability of inexpensive commercial wine, beer, and liquor today in shebeens (illegal bars) and carry-out sources has exacerbated problems of heavy drinking.<sup>13,14</sup> Weekend binge drinking is a major form of recreation among subsegments of the population.

The anonymous study community has been a willing research host. Similar in social and economic character to many others in the Western Cape, the community had a population of 45 225 (35 364 urban and 9861 rural) in 1996,<sup>15</sup> the vast majority of whom were classified as Coloured.

## Methods

The diagnosis of fetal alcohol syndrome, first formulated in 1973 by Kenneth L. Jones and David Smith,<sup>16</sup> describes a pattern, which few had recognized earlier,<sup>17,18</sup> of anomalies and deficits in children prenatally exposed to large amounts of alcohol. Children with fetal alcohol syndrome have characteristic facial and body dysmorphology, a pattern of delayed physical growth and development, and mental and behavioral deficits.<sup>18,19</sup> Many investigators, including study groups of The Research Society on Alcoholism and the Institute of Medicine,<sup>7,19-21</sup> have refined, catalogued, and quantified these 3 hallmarks of fetal alcohol syndrome over the years. Even though fetal alcohol syndrome can be diagnosed without confirmation of heavy maternal drinking,<sup>7</sup> a detailed maternal history is very desirable to confirm the nature of gestational drinking and to document social circumstances, particularly in cases in which dysmorphology is less consistent.<sup>19</sup>

In this study, we did not attempt to aggregate the individual traits of prenatal alcohol exposure into lesser, nonsyndrome diagnoses commonly referred to as fetal alcohol effects, alcohol-related birth defects, or alcohol-related neurodevelopmental deficits.<sup>7,22,23</sup> Only fetal alcohol syndrome (or not fetal alcohol syndrome), the most accurate and rigorous diagnosis, was used. Fetal alcohol syndrome had been diagnosed previously in South Africa<sup>24</sup> but not in an explicit epidemiologic study.

Specific fetal alcohol syndrome diagnostic components of the US Institute of Medicine<sup>7</sup> were used: (1) facial and other dysmorphology, (2) diminished structural growth for age, (3) developmental (intelligence and social skills) delay, and, when possible, (4) confirmation of maternal alcohol consumption. Once data for each of these components were independently collected, quantified, and analyzed, a structured case conference of examining specialists in each domain was held (Figure 1).

### *Establishing 2-Tier Screening Through Preliminary Physical/Dysmorphology Assessment*

Dysmorphology, growth, and developmental data for the children were collected with a 2-tier screening method *after* normative data were assessed for this particular population. Four 2-person teams (1 expert dysmorphologist and 1 South African physician training in fetal alcohol syndrome diagnosis) worked independently but simultaneously and used standardized assessment criteria to examine all children in sub-A (first-grade) classrooms. Twelve of the 13 elementary schools in the community (N=992 sub-A children) were accessed. The one school that refused to participate was an all-White school with 80 children. Ethnographic knowledge of the community indicates that this school sample was representative of the community. The low mobility of the local population ensures that the vast majority of the study children underwent gestation and were born locally.

Furthermore, the research team searched for out-of-school children and found only 2 children without a major developmental delay in the targeted age range (5-7 years). Children from the community who were in special schools for the developmentally delayed also were examined. Two cases of fetal alcohol syndrome from the community were confirmed via diagnostic methods similar to those described below.

The screening of schoolchildren proceeded as follows. First, a complete dysmorphology examination was given to each of the initial 406 schoolchildren from classrooms in 6 of the rural and urban schools to gauge both local normative growth parameters and possible fetal alcohol syndrome dysmorphology relative to US National Center for Health Statistics charts. Second, data for these 406 children were analyzed. All the children with suspected classic fetal alcohol syndrome had height, weight, and occipitofrontal circumference measurements below the 10th centile on 1 of the 3 measures. Third, with local parameters

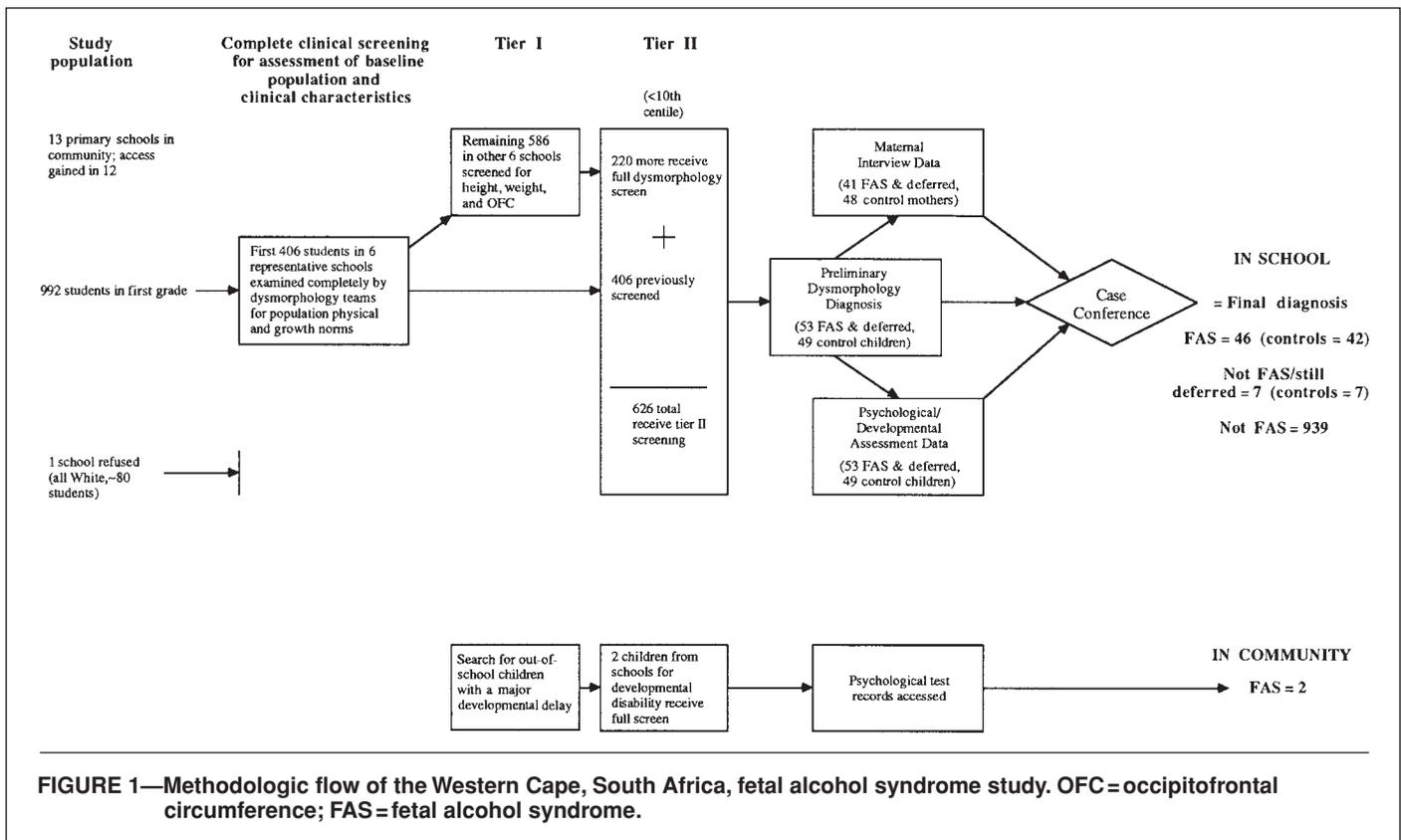
assessed, cutoff points were set for implementing the 2-tier screening system. Fourth, all of the 586 children in sub-A classrooms in the remaining 6 schools received tier I screening (height, weight, and occipitofrontal circumference). Children whose measurements were below the 10th centile on occipitofrontal circumference or on both height and weight were referred for the complete examination (tier II) by the dysmorphology teams. Finally, 220 of the remaining children met these criteria and were referred for complete examinations. Therefore, 626 children (63%) received full dysmorphology examinations (see Figure 1).

Full examinations for so many children also provided intensive training for South African physician trainees. Every child receiving the complete screen (tier II) was examined by 2 of the physician teams. Each 2-member team examined and measured the child's occipitofrontal circumference, palpebral fissure length, philtrum length, inner and outer canthal distance, and other indicators such as abnormalities in joints, heart function, and palmar creases. Findings were recorded on child data forms, and physicians in each team verified each other's findings. All physicians were "blinded" from any prior knowledge of the child or mother. Once seen by 1 team, the child was directed to another "blinded" team who repeated the examination and measurements as a reliability check.

Mean differences between dysmorphologists' measurements for the first 25 children were checked and were insignificant for key measures: inner canthal distance (0.22 cm), interpupillary distance (0.29 cm), and palpebral fissure length (0.04 cm). Interrater reliability was later checked for 194 matched pairs with the square root of the Pearson product moment correlation (*r*). Results were 0.91 for inner canthal distance, 0.85 for interpupillary distance, and 0.84 for philtrum measurements.

### *Complete Diagnostic Sequence*

After the dysmorphology examination had been completed by 2 teams, a child was assigned a preliminary diagnosis of not fetal alcohol syndrome, deferred, or fetal alcohol syndrome based on the quantified fetal alcohol syndrome checklist and all clinical findings. Children with a deferred diagnosis had the appearance and some anomalies of fetal alcohol syndrome with growth delay, but developmental test and maternal interview data were definitely required for a final diagnosis. Only those with the classic fetal alcohol syndrome phenotype and measurements well below the fifth centile on all measures received a *preliminary* fetal alcohol syndrome diagnosis. All children with a preliminary or deferred diagnosis of fetal alcohol syndrome then under-



**FIGURE 1—Methodologic flow of the Western Cape, South Africa, fetal alcohol syndrome study. OFC= occipitofrontal circumference; FAS= fetal alcohol syndrome.**

went developmental testing and prenatal risk assessment.

### Controls

Once subjects were identified, a control subject was selected for each, matched for sex, age, and classroom. Identical developmental and life skills testing was performed on subjects and control subjects with the Griffiths Intelligence and Development Test, a standard test translated to Afrikaans and used throughout South Africa.

### Maternal Data

The mothers of the control children became the maternal controls. Structured maternal interviews contained 114 items: childbearing pattern; drinking patterns before, during, and after the index pregnancy; SES indicators; demographic variables; and other risk factors in the social context. Questions from prenatal risk factor questionnaires from the United States were rewritten for South Africa, locally relevant questions were added, questions were pilot tested with 6 local subjects, and adaptations were made.

The protocols used drinking questions that were designed to elicit accurate reporting of both “free” alcohol supplied as part of their work compensation, as was the custom in this province, and alcoholic beverages purchased. Photographs of standard beer and wine con-

tainers sold locally were shown to the respondents so that proper quantification of quantity, frequency, and variability of drinking was assessed in standard ethanol units. All interviews were administered in Afrikaans in the field by a public health nurse (J.C.).

Because mothers of children with fetal alcohol syndrome often lead chaotic lives, several were deceased or could not be located, as was common in other studies.<sup>5,25</sup> Specifically, 35 of the 48 mothers of the children with fetal alcohol syndrome were contacted and interviewed. For the remaining 13, some data were obtained for 11 via collaterals (usually relatives of the mother); no knowledgeable collaterals were located for 2 mothers. Six (12.5%) of the 48 mothers of children with fetal alcohol syndrome were deceased (1 in a house fire, 1 from pulmonary tuberculosis, and 4 from murder or other violent death), and 6 were nomadic or had moved from the area. Therefore, 2 children were given the diagnosis of fetal alcohol syndrome without alcohol exposure data per Institute of Medicine guidelines.<sup>7</sup>

### Results

Table 1 summarizes the key variables for all children studied. A total of 992 children were examined: 52.8% male and 47.2% female. The mean age was 6.6 years. Basic anthropometric parameters established for the

local children are also found in Table 1. The children averaged 116.2 cm in height, weighed an average of 21.1 kg, and had a mean occipitofrontal circumference of 50.8 cm. None of these measures or deviations are remarkable.

Subjects were primarily of the Coloured, or mixed ancestry, group; fewer than 5% were exclusively Black African, and fewer than 6% were White. This unique racial admixture necessitated the previously described assessment of local physical traits. For example, preliminary information suggested that the interpupillary and inner canthal distances in local subpopulations (e.g., Khoisan tribal background) were greater than United States norms, and in many children, the proximal portion of the philtral columns was smoother than found in the United States. Furthermore, mid-face hypoplasia was so commonly recorded that it was considered a normal variation in this population.

However, in none of the study population of fetal alcohol syndrome or deferred children did microcephaly (occipitofrontal circumference <25%) and micropthalmos (palpebral fissure length <25%) fall within the normal range. The phenotypes of the deferred cases on these and other measures were sufficiently abnormal to justify further inquiry for fetal alcohol syndrome because deferred cases had many fetal alcohol syndrome traits (see dysmorphology scores in Table 1). Conversely, a child with isolated microcephaly (or another

**TABLE 1—Demographic and Growth Parameters for All Sub-A Children, Children With Fetal Alcohol Syndrome, Control Subjects, and Children With Deferred Diagnosis: Western Cape Community, South Africa**

	All Sub-A Children (N=992)	Children With Fetal Alcohol Syndrome (n=46)	Control Children <sup>a</sup> (n=42)	Children With Still-Deferred/Unconfirmed Diagnosis (n=7)	P
Sex, %					
n	988	46	42	7	
Male	52.8	54.3	54.8	28.6	
Female	47.2	45.7	45.2	71.4	NS <sup>b</sup>
Age, y					
n	977	45	42	7	
Mean	6.6	7.0	6.7	6.6	
SD	0.73	0.84	0.67	0.54	NS <sup>c</sup>
Height, cm					
n	985	46	40	7	
Mean	116.2	109.5	115.7	109.5	
SD	6.15	6.06	6.68	3.43	<.000 <sup>c</sup>
Weight, kg					
n	987	46	40	7	
Mean	21.1	17.8	20.8	17.9	
SD	3.46	2.34	2.41	1.10	<.000 <sup>c</sup>
Occipitofrontal circumference, cm					
n	987	46	40	7	
Mean	50.8	48.5	50.9	49.7	
SD	1.60	1.46	1.42	1.39	<.000 <sup>c</sup>
Dysmorphology score <sup>d</sup>					
n	582	46	40	7	
Mean	3.0	10.7	2.3	9.3	
SD	3.68	4.47	2.56	4.54	<.000 <sup>c</sup>
Residence, %					
Urban	74	39 (n=18)			
Rural	26	61 (n=28)			<.001 <sup>b</sup>

Note. Columns one and two provide all the necessary data for analysis of urban/rural patterns by indirect standardization of rates. NS = not significant.

<sup>a</sup>Data are for control subjects matched only to the children who received a *final* diagnosis of fetal alcohol syndrome. Control subjects matched to the children with a final deferred/unconfirmed diagnosis were eliminated from the analyses. Four children with fetal alcohol syndrome from the first grade could not be matched for age with first-grade control subjects because of advanced age.

<sup>b</sup> $\chi^2$  test.

<sup>c</sup>Analysis of variance (F test).

<sup>d</sup>The dysmorphology score was assigned only to those children seen in the initial growth parameter assessment phase or in tier II screening and control subjects.

single trait) and no additional features of fetal alcohol syndrome was diagnosed as having microcephaly (or the isolated trait) and not given a preliminary or deferred diagnosis of fetal alcohol syndrome.

After the dysmorphology examination, 17 children had a preliminary diagnosis of fetal alcohol syndrome, and 36 had a deferred diagnosis. These 53, along with their matched control subjects, were the subjects of further research (Figure 1).

Final diagnoses were made only after all data were gathered in the 3 domains and case conferences were held. Developmental testing and maternal interview data were completed by other professionals and combined with dysmorphology examination results for a final diagnosis of fetal alcohol syndrome for 46 schoolchildren. Seven of the deferred children received a final diagnosis of "not fetal alcohol syndrome/still deferred" because they had either insufficient symptoms of fetal alcohol syndrome or a normal diagnosis. The 49 control children also were tested by the same diag-

nostic criteria; none had fetal alcohol syndrome or indicators sufficient for deferred status. However, because 7 of the control subjects were matched with children who were ultimately classified as not fetal alcohol syndrome/still deferred, they are not included in the data in Tables 1 and 2.

Table 1 also presents the demographic and growth parameters of all children who received a final diagnosis of fetal alcohol syndrome and their matched control subjects. A slightly higher percentage of the control subjects were males (54.8%) than of the children with fetal alcohol syndrome (54.3%), because 4 of the older subjects could not be matched with control subjects from the same grade in their school. The difference was not statistically significant. The average age was 7.0 years for children with fetal alcohol syndrome and 6.7 years for control subjects, indicating that children with fetal alcohol syndrome were, on average, already showing delay in school by the first grade. The mean age of the control subjects and subjects with fetal alcohol syndrome straddles that of all

first graders (6.6 years). Height, weight, occipitofrontal circumference measurements, and dysmorphology scores for fetal alcohol syndrome and control subjects differed significantly, with deferred children similar to children with fetal alcohol syndrome. Mean dysmorphology scores were 10.7 (possible 0–35) for the children with fetal alcohol syndrome, 2.3 for control subjects, and 9.3 for the children with a still-deferred/unconfirmed diagnosis.

Scores on the neurodevelopmental tests (Table 2) were lower for children with fetal alcohol syndrome on each of the 3 composite measures. For mental age, performance IQ, and verbal IQ, the children with fetal alcohol syndrome scored 16 to 20 points lower on each. The overall mental age of children with fetal alcohol syndrome was 77.5 and that of control subjects was 95.3. In all measures, control subjects were close to average but below the South African average of 100, underscoring the importance of comparison with local norms.

Analysis of maternal drinking variables (Table 3) indicates that mothers of children with

**TABLE 2—Neurodevelopmental Assessment of the Children Included in Case Conferences**

	Children With Fetal Alcohol Syndrome (n=46)	Control Children <sup>a</sup> (n=42)	Children With Still-Deferred/Unconfirmed Diagnosis (n=7)	P
Mental age				
Mean	77.5	95.3	88.4	
SD	13.36	8.50	9.54	<.000 <sup>b</sup>
Performance IQ				
Mean	74.1	94.2	84.4	
SD	11.13	13.56	11.97	<.000 <sup>b</sup>
Verbal IQ				
Mean	71.7	88.3	79.5	
SD	12.45	9.66	15.87	<.000 <sup>b</sup>

<sup>a</sup>Data are for control subjects matched only to the children with fetal alcohol syndrome. Control subjects matched to the children with a final deferred/unconfirmed diagnosis were eliminated from the analyses. Four children with fetal alcohol syndrome from the first grade could not be matched for age with first-grade control subjects because of advanced age.

<sup>b</sup>Analysis of variance (F test).

fetal alcohol syndrome reported much greater current use of alcohol and more drinking before the index pregnancy and during each trimester than mothers of control children. A majority of the women (controls and subjects) were current drinkers. The mothers of children with fetal alcohol syndrome reported current consumption of 12.6 drinks per week, compared with 2.4 for the control subjects, and more than 50% said that they drank more during the pregnancy that resulted in fetal alcohol syndrome. From the maternal questionnaire and interview, the context of life and drinking was explored. Mothers of children with fetal alcohol syndrome especially characterized the index pregnancy as a time in their lives when they had many life problems and drank more heavily.

Alcohol was the drug of choice; the use of other drugs, covered extensively in the interview, was low to nonexistent, except for tobacco. A high percentage of the mothers of both control children and children with fetal alcohol syndrome smoked tobacco during pregnancy (46.3% vs 87.9%;  $\chi^2=8.96$ ,  $P=.000$ ; odds ratio [OR]=14.8).

### Prevalence Rates

The urban vs rural distribution of fetal alcohol syndrome cases (Table 1) was tested against the overall residence pattern of the schoolchildren through indirect standardization. Rather than 26% of the fetal alcohol syndrome cases coming from rural areas as predicted by residence, the data indicate that 61% (28) of the fetal alcohol syndrome cases were from rural schools, a significant departure from random distribution (OR=4.41). The rates of fetal alcohol syndrome are much higher in the rural areas.

The rate of fetal alcohol syndrome in the first graders screened was 46.4 per 1000. Furthermore, if the all-White school that did not allow screening had no fetal alcohol syndrome cases, the overall in-school rate of fetal alcohol syndrome was 42.9 per 1000. All children with fetal alcohol syndrome were Coloured or Black. The fetal alcohol syndrome rate for the children in the White school was zero; the Coloured/Black in-school rate was therefore 49.3 per 1000.

Because of poor school performance among children with fetal alcohol syndrome, 9 of the 46 first-grade children with fetal alcohol syndrome were older than most first-grade students (children in the targeted age range). Appropriate age ranges for calculating an age-based rate can be maintained through the elimination of older ( $\geq 8$  years) first graders from the numerator and denominator. Subtracting the older children from the calculations yields an age-specific, in-school prevalence of 40.5 per 1000.

When the 2 additional fetal alcohol syndrome cases identified in the community (in schools for the developmentally delayed) in this age group ( $> 5$  years and  $< 8$  years) were considered, a total of 48 children with fetal alcohol syndrome were identified. The communitywide, age-specific rate was 39.2 per 1000 children aged 6 and 7 years. Therefore, the range of minimal prevalence rates for this community was 39.2 to 42.9 per 1000.

### Discussion

Active case ascertainment of fetal alcohol syndrome through population-based screening has not been reported except among American Indian and Alaskan native popula-

tions.<sup>5,6,8</sup> To our knowledge, active case ascertainment methods have not been used previously in developing nations. Furthermore, screening all children in a particular school or grade has not been done before. Active case ascertainment can effectively and efficiently identify children with fetal alcohol syndrome ranging in age from 3 years to the early teens, particularly in relatively small populations. The interdisciplinary, multiple-domain, case-control design described here produces what we believe is complete, accurate, and reliable knowledge of the prevalence and characteristics of fetal alcohol syndrome. It does not provide the actual birth prevalence (incidence) of fetal alcohol syndrome of a population such as this because the effect of infant and child mortality rates (10 to 30 per 1000 in the Western Cape) on children with fetal alcohol syndrome cannot be assessed with these methods (J. Miles, Offices of the Provincial Administration of the Western Cape, Republic of South Africa; oral communication; January 2000).

Previous studies have left unanswered many questions about the epidemiology of fetal alcohol syndrome. Epidemiologic, clinic, and laboratory studies all indicate that major risk factors for fetal alcohol syndrome are associated with the mother's individual characteristics and her social milieu. Specific traits such as advancing maternal age; high gravidity and parity; early age at onset of regular drinking; length of drinking career; and quantity, frequency, and timing of maternal drinking during the child's gestation partially explain the prevalence of fetal alcohol syndrome.<sup>26,27</sup> Furthermore, SES is a major risk factor in the United States.<sup>3,27-29</sup> However, these variables have rarely been studied simultaneously in nonclinic populations. Rather, passive case ascertainment methods are commonly used with existing data sources that are often incomplete and selective.<sup>30,31</sup> This proactive methodology yielded rich epidemiologic data useful for prevention, and it identified "gold standard" cases for further research and clinical services.

The only other paper to report a higher rate of fetal alcohol syndrome was completed in Canada in a highly "disrupted" American Indian reserve with high unemployment, substantial outmigration of nondrinkers, and therefore a concentration of drinkers. Robinson et al.<sup>32</sup> used active case ascertainment methods and reported a rate of 120 children younger than 19 years per 1000 with fetal alcohol syndrome. In our study, more sophisticated and strict assessment measures were used in all domains (dysmorphology, intellectual development, and maternal interviews) for children at ages more suitable to the accurate diagnosis of fetal alcohol syndrome. Furthermore, this South African community is stable, not char-

**TABLE 3—Substance Use by Mothers and Fathers of the Children Included in Case Conferences**

	Mothers of Children With Fetal Alcohol Syndrome <sup>a</sup> (n = 35)	Mothers of Control Children <sup>b</sup> (n = 41)	Mothers of Children With Deferred/Unconfirmed Diagnosis (n = 6)	P
Current use of alcohol, drinks per week				
Mean	12.6	2.4	3.7	
SD	12.21	4.68	6.20	<.000 <sup>c</sup>
Drinks consumed on Saturday				
Mean	7.3	1.9	1.8	
SD	6.17	2.84	3.25	<.000 <sup>c</sup>
Drinking in months before pregnancy with index child, %				
Drank about the same (as current use)	25.7	45.0	50.0	
Drank less (than current use)	20.0	40.0	50.0	
Drank more (than current use)	54.3	15.0	0.0	<.005 <sup>d</sup>
Drinking during first trimester of pregnancy with index child, %				
Drank about the same (as current use)	25.7	45.0	50.0	
Drank less (than current use)	17.1	40.0	50.0	
Drank more (than current use)	57.1	15.0	0.0	<.003 <sup>d</sup>
Drinking during second trimester of pregnancy with index child, %				
Drank about the same (as current use)	22.9	50.0	50.0	
Drank less (than current use)	20.0	40.0	50.0	
Drank more (than current use)	57.1	10.0	0.0	<.000 <sup>d</sup>
Drinking during third trimester of pregnancy with index child, %				
Drank about the same (as current use)	22.9	52.5	50.0	
Drank less (than current use)	25.7	42.5	50.0	
Drank more (than current use)	51.4	5.0	0.0	<.000 <sup>d</sup>
Smoked during index pregnancy, %				
Yes	87.9	46.3	50.0	<.000 <sup>d</sup>
Drinking habits of father of index child during the index pregnancy, %				
Nondrinker or light drinker	8.6	38.5	33.3	<.003 <sup>d</sup>
Occasional or moderate drinker	5.7	23.1	0.0	
Frequent or heavy drinker	74.3	28.2	33.3	
Has had problems with alcohol	11.4	10.3	33.3	

<sup>a</sup>Mortality and mobility reduced the number of available mothers of children with fetal alcohol syndrome by 11. See “Methods” section of the text for details.

<sup>b</sup>Mothers of control children matched only to the mothers of children with fetal alcohol syndrome. Mothers of control subjects matched to the children with a final deferred/unconfirmed diagnosis were eliminated from the analyses.

<sup>c</sup>Analysis of variance (F test).

<sup>d</sup> $\chi^2$  test.

acterized by social disruption, displacement, or selection by social pathology. It is an established community with a viable (yet low-wage) economy that is undergoing only moderate rates of modernization. Therefore, such a high rate of fetal alcohol syndrome is very worrisome. Many mothers in this community give birth to children with fetal alcohol syndrome compared with the relatively small number of US women (0.3 to 3.3 per 1000 women of childbearing age) who bear 1 or more children with fetal alcohol syndrome.<sup>3,4,32,33</sup>

This study and the race/ethnicity of the children with fetal alcohol syndrome provided insight into gross social influences on fetal alcohol syndrome. The research team was able to access all children in 11 predominantly Coloured and Black schools and 1 predominantly White school. Because of past apartheid policy (enforced segregation by race/

ethnicity), darker-skinned peoples are over-represented in the lower SES categories. This obviously has affected fetal alcohol syndrome rates, given that all of the children with fetal alcohol syndrome were Coloured, and within the Coloured group, those with the lowest SES indicators were overrepresented in the fetal alcohol syndrome cases.

Because virtually all of the women in this community had low SES, the community is at high risk for fetal alcohol syndrome, as suggested by studies from the United States.<sup>3,33</sup> Unknown is whether similar rates exist in other low-SES areas of South Africa. Some visits to informal settlements (squatter camps) on the fringe of the major South African metropolitan areas led us to believe that rates of fetal alcohol syndrome also may be elevated there. But this study clearly illustrates that the historical presence of the wine industry in the Western Cape and the drinking

patterns that have developed have produced a high fetal alcohol syndrome rate.

Fetal alcohol syndrome was more common in the rural schools than in the urban schools. This may reflect increasing socioeconomic resources among urban dwellers, or urban areas may simply provide escape from a heavy-drinking social milieu. Clearly, residence on certain of the grape-growing, wine-producing farms is a grave risk factor.

All women likely underreported the extent of drinking. Owing to the residual Dop system and drinking pattern of many female farm laborers in this community, many did not report alcohol consumed that was not purchased, even though our instrument prompted them in several ways to report *all* consumption. Furthermore, respondents may have found it difficult to answer in standard drink units (even though pictures were used by the interviewer), because

alcoholic beverages are commonly shared from nonstandard containers. It was a challenge to use wording that would elicit exact reports of the quantities of alcohol consumed daily on the farms. Respondents, however, seemed able to recall and willing to report alcohol purchased in standard containers. Most drinking is binge drinking, and most alcohol was purchased on weekends because this is frequently the only time that women on the farms have the means to purchase it.

Thus, even though the current drinking quantities reported by both subjects and controls were not high in *absolute* standards, the most important interpretation of the data is the large *differential* between subjects and controls. There is no doubt, however, that these mothers drank sufficiently to produce verifiable cases of fetal alcohol syndrome as severe as we have seen anywhere in the United States.

The results of this study were presented to the schools, parents, and community leaders. The local school psychologist was provided the results of the testing to benefit individual children. Furthermore, a fetal alcohol syndrome prevention initiative based on the study findings was quickly initiated in the community with assistance from the National Institute on Alcohol Abuse and Alcoholism research team. The prevention coalition is headed by the mayor and regional officials in education, government, and public health. The comprehensive fetal alcohol syndrome prevention model of the Institute of Medicine<sup>7</sup> and other specific prevention techniques are being used.<sup>26</sup>

## Conclusion

In this article we report the highest rate of fetal alcohol syndrome ever documented in a stable community and the specific conditions with which it is associated. Some South African public health professionals stated that this may be only one of several regional towns with similar problems. One might ask whether similar social and economic conditions produce problem drinking and fetal alcohol syndrome elsewhere in the developing world. The early stages of economic development, low education attainment, low SES, increased access to alcohol, and loss of folk and traditional culture may cause extreme alcohol misuse, which elevates the risk of fetal alcohol syndrome. Methods described here are applicable for research and for designing targeted prevention initiatives in populations elsewhere in the developing world. □

## Contributors

P.A. May was the principal investigator of the National Institute on Alcohol Abuse and Alcoholism grant that funded this study. He oversaw all methodology

and implementation of the study and was the major author of the first and all drafts. L. Brooke was the field coordinator of all the child clinic data, made the first entry of all data, consulted on data processing and sample characteristics, and edited all drafts. J.P. Gossage was the data manager of the project who processed and analyzed all data, produced and corrected the tables, and edited and provided suggestions for and rewrites of each draft. J. Croxford was the maternal interviewer and a field coordinator for the child data; she helped write all sections dealing with the maternal facts and data and edited all drafts. C. Adnams was responsible for the professional quality of all of the psychologic and neuropsychologic data; she worked on and edited the sections of the paper pertaining to child development. K.L. Jones was the senior dysmorphologist and clinical team diagnostician; he reviewed, edited, and provided suggestions on all drafts. L. Robinson helped write and edit the sections on clinical (child) screening methodology and edited all sections; he was a member of the clinical team that examined all of the children in the study. D. Viljoen was the South African co-principal investigator who made major suggestions on each of the drafts; he, along with P.A. May, was responsible for all phases of the research project in addition to serving as 1 of the 4 primary child diagnosticians.

## Acknowledgments

This project was funded by National Institute on Alcohol Abuse and Alcoholism Grant RO1 AA09440, the Office of Research on Minority Health (National Institutes of Health), and the Foundation for Alcohol Related Research.

Our deepest thanks go to Mayor Herman Bailey, the (Western Cape Community) town council, Cecil Driver, and the other principals of the 12 primary schools where the research was performed. Jon M. Aase, MD, was the dysmorphologist who designed and wrote the first screening and training protocols for the initial wave of examinations in this study. We are indebted to him in many ways. Furthermore, Chris Shaw, Andrea Riley, and Carolyn Tullett, RN, of the Foundation for Alcohol Related Research and other individuals were indispensable colleagues in the data collection and local research process, as were the 11 South African physicians who participated in the screening process.

The protocols and consent forms used for human subjects were approved by the University of New Mexico Medical School (HRRC 96-209) and the College of Arts and Sciences (01-93-86-9908). They also were reviewed and approved by the Research Ethics Committee of the University of Cape Town, the Office for Protection From Research Risks of the National Institutes of Health, and a single site assurance committee in the Western Cape. All participating children in the study had active consent to participate granted from their parents or guardians.

## References

1. Abel EL, Sokol RJ. A revised conservative estimate of the incidence of fetal alcohol syndrome and its economic impact. *Alcohol Clin Exp Res*. 1991;15:514-524.
2. Abel EL, Sokol RJ. Incidence of fetal alcohol syndrome and economic impact of FAS related anomalies. *Drug Alcohol Depend*. 1987;19:51-70.

3. Abel EL. An update on the incidence of FAS: FAS is not an equal opportunity birth defect. *Neurotoxicol Teratol*. 1995;17:437-443.
4. May PA. Fetal alcohol effects among North American Indians. *Alcohol Health Res World* 1991;15:239-248.
5. May PA, Hymbaugh KJ, Aase JM, Samet JM. Epidemiology of fetal alcohol syndrome among American Indians of the Southwest. *Soc Biol*. 1983;30:374-385.
6. May PA, McCloskey J, Gossage JP. Fetal alcohol syndrome among American Indians: epidemiology, issues, and research. *NIAAA Res Monogr*. In press.
7. Institute of Medicine. *Fetal Alcohol Syndrome Diagnosis, Epidemiology, Prevention, and Treatment*. Stutton K, Howe C, Battaglia F, eds. Washington, DC: National Academy Press; 1996.
8. May PA. Research issues in the prevention of fetal alcohol syndrome and alcohol-related birth defects. In: Howard J, Martin S, Mail P, Hilton M, Taylor E, eds. *Women and Alcohol: Issues for Prevention Research*. Rockville, Md: National Institute on Alcohol Abuse and Alcoholism; 1996: 93-131. *NIAA Res Monogr*, No. 32. DHHS publication 96-3817.
9. Egeland GM, Perham-Hester KA, Hook EB. Use of capture-recapture analyses in fetal alcohol syndrome surveillance in Alaska. *Am J Epidemiol*. 1995;141:335-341.
10. Egeland GM, Perham-Hester KA, Gesaner BO, Ingle D, Berner JE, Middaugh JP. Fetal alcohol syndrome in Alaska, 1977-1992: an administrative prevalence service from multiple sources. *Am J Public Health*. 1998;88:781-786.
11. National Institute on Alcohol Abuse and Alcoholism. *Fetal Alcohol Syndrome: Report on the Site Visit to South Africa*. Rockville, Md: National Institute on Alcohol Abuse and Alcoholism; 1996.
12. National Institute on Alcohol Abuse and Alcoholism. *Fetal Alcohol Syndrome: South Africa, A Progress Report on the 1997 Pilot Study, Information Exchange, and Prevention Workshop*. Rockville, Md: National Institute on Alcohol Abuse and Alcoholism; 1998.
13. London L, Meyers J, Nell V, Taylor T, Thompson ML, Milbuli SS. *An Investigation Into the Neurological and Neurobehavioral Effects of Long Term Agrochemical Exposure Among Deciduous Fruit Farm Workers in the Western Cape, South Africa* [MD thesis]. Cape Town, South Africa: University of Cape Town; 1995.
14. Parry CDH, Bennetts AL. *Alcohol Policy and Public Health in South Africa*. Cape Town, South Africa: Oxford University Press; 1998.
15. Republic of South Africa. *1996 Census of the Population*. Pretoria, South Africa: Bureau of Census; 1997.
16. Jones KL, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. *Lancet*. 1973;2:999-1001.
17. Sullivan WC. A note on the influence of maternal inebriety on the offspring. *J Ment Sci*. 1899; 45:489-503.
18. Lemoine P, Harouseau H, Borteryn JT, Menuet JC. Les enfants de parents alcooliques: anomalies observées à propos de 127 cas. *Quest Med*. 1968;21:476-482.
19. Aase JM. Clinical recognition of FAS: difficulties of detection and diagnosis. *Alcohol Health Res World*. 1994;18:5-9.

20. Rosett HL. A clinical perspective of the fetal alcohol syndrome. *Alcohol Clin Exp Res*. 1980;4:119–122.
21. Sokol RF, Clarren SK. Guidelines for use of terminology describing the impact of prenatal alcohol on the offspring. *Alcohol Clin Exp Res*. 1989;13:597–598.
22. Aase JM, Jones KL, Clarren SK. Do we need the term “FAE”? *Pediatrics*. 1995;95:428–430.
23. Sampson PD, Streissguth AP, Bookstein FL, et al. Incidence of fetal alcohol syndrome and prevalence of alcohol-related neuro-developmental disorder. *Teratology*. 1997;56:317–326.
24. Palmer C. Fetal alcohol effects—incidence and understanding in the Cape. *S Afr Med J*. 1985;68:779–780.
25. Streissguth AP, Clarren SK, Jones KL. Natural history of the fetal alcohol syndrome, a ten-year follow-up of eleven patients. *Lancet*. 1985;2:85–92.
26. May PA. A multiple-level, comprehensive approach to the prevention of FAS and other alcohol-related birth defects. *Int J Addict*. 1995;30:1549–1602.
27. Abel EL, Hannigan JH. Maternal risk factors in fetal alcohol syndrome: provocative and permissive influences. *Neurotoxicol Teratol*. 1995;17:445–465.
28. Bingol N, Schuster C, Fuchs J, et al. The influence of socioeconomic factors on the occurrence of FAS. *Adv Alcohol Subst Abuse*. 1987;6:105–118.
29. Pierog S, Chandavasu O, Waxler I. The fetal alcohol syndrome: some maternal characteristics. *Int J Gynaecol Obstet*. 1979;16:412–415.
30. Chavez GF, Cordero JF, Becera JE. Leading major congenital malformations among minority groups in the United States, 1981–1986. *MMWR Morb Mortal Wkly Rep*. 1988;37:17–24.
31. Little BB, Snell LM, Gilstrap LCI, Gant NF. Failure to recognize fetal alcohol syndrome in newborn infants. *Am J Dis Child*. 1990;144:1142–1146.
32. Robinson GC, Conry JL, Conry RF. Clinical profile and prevalence of fetal alcohol syndrome in an isolated community in British Columbia. *Can Med Assoc J*. 1987;137:203–207.
33. Abel EL. *Fetal Alcohol Abuse Syndrome*. New York, NY: Plenum Press; 1998.

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

DENIS L. VILJOEN, M.D., J. PHILLIP GOSSAGE, PH.D.,<sup>†</sup> LESLEY BROOKE, B.S. (HONS.),<sup>†</sup> COLLEEN M. ADNAMS, M.D., F.C.P.,<sup>†</sup> KENNETH L. JONES, M.D.,<sup>†</sup> LUTHER K. ROBINSON, M.D.,<sup>†</sup> H. EUGENE HOYME, M.D.,<sup>†</sup> CUDORE SNELL, D.S.W.,<sup>†</sup> NATHANIEL C.O. KHAOLE, M.D.,<sup>†</sup> PIYADASA KODITUWAKKU, PH.D.,<sup>†</sup> KWADWO OHENE ASANTE, M.D.,<sup>†</sup> RICHARD FINDLAY, M.D.,<sup>†</sup> BARBARA QUINTON, M.D.,<sup>†</sup> ANNA-SUSAN MARAIS, R.N.,<sup>†</sup> WENDY O. KALBERG, M.A., CED.,<sup>†</sup> AND PHILIP A. MAY, PH.D.,<sup>†</sup>

*Department of Human Genetics, Faculty of Health Sciences, University of Witwatersrand, National Health Laboratory Services, South Africa, and the Foundation for Alcohol Related Research*

**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 non-verbal 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 1,000 (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

Received: August 2, 2004. Revision: March 23, 2005.

\*This project was funded by the National Institute on Alcohol Abuse and Alcoholism grants RO1 AA09440 and RO1 AA11685, the National Institute on Minority Health and Health Disparities and the Foundation for Alcohol Related Research of South Africa.

<sup>†</sup>Philip A. May is with the University of New Mexico, Center on Alcoholism, Substance Abuse and Addictions (CASAA), 2650 Yale SE, Albuquerque, NM 87106. Correspondence should be sent to him at that address, or via email at: pmay@unm.edu. J. Phillip Gossage, Piyadasa Kodituwakku and Wendy O. Kalberg are with CASAA, the University of New Mexico. Lesley Brooke, Nathaniel C.O. Khaole and Anna-Susan Marais are with the

University of Cape Town and the Foundation for Alcohol Related Research. Colleen M. Adnams is with the Department of Paediatrics, University of Cape Town. Kenneth L. Jones is with the Division of Dysmorphology/Teratology, Medical Center, University of California, San Diego. Luther K. Robinson is with Dysmorphology and Clinical Genetics, State University of New York at Buffalo. H. Eugene Hoyne is with the Division of Medical Genetics, Stanford University School of Medicine. Cudore Snell is with the Department of Social Work, Howard University. Kwadwo Ohene Asante is in Pediatrics, British Columbia. Richard Findlay is with the Department of Pediatrics, King/Drew Medical Center. Barbara Quinton is with the Department of Pediatrics, Howard University.

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 Wine-lands 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 dysmorphism 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 dysmorphism, 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), dysmorphism, 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-

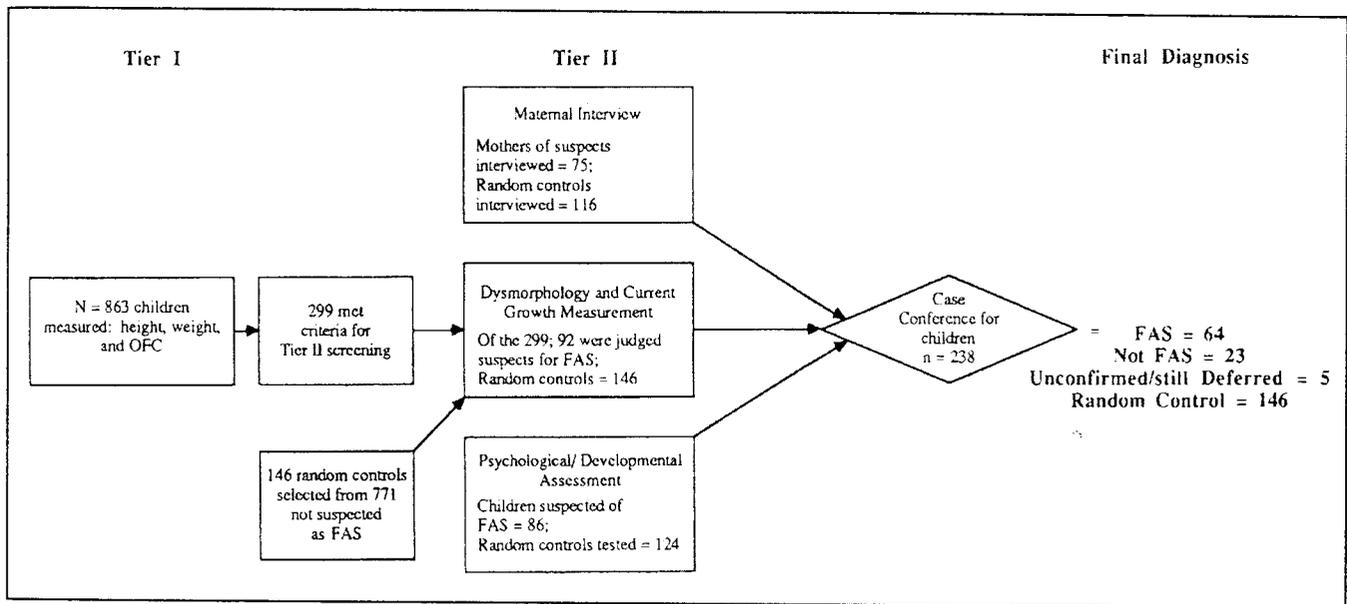


FIGURE 1. The Methodological Flow of the Wave II Western Cape, South Africa FAS Study

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  $2 \times 2$  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 <sup>a</sup>
Age, in months, mean (SD)	77.6 (9.00)	78.5 (7.62)	76.3 (6.61)	.046 <sup>b</sup>
Height, cm, mean (SD)	113.7 (6.47)	108.6 (4.54)	119.2 (7.47) <sup>c</sup>	<.001 <sup>b</sup>
Weight, kg, mean (SD)	19.1 (3.83)	15.7 (1.68)	22.6 (4.82) <sup>c</sup>	<.001 <sup>b</sup>
Occipitofrontal circumference, cm, mean (SD)	50.6 (1.67)	48.2 (1.28)	51.4 (1.63) <sup>c</sup>	<.001 <sup>b</sup>
Palpebral fissure length, cm, mean (SD)	—	2.3 (0.13)	2.6 (0.14) <sup>d</sup>	<.001 <sup>b</sup>
Philtrum length, mm, mean (SD)	—	13.39 (2.33)	12.58 (2.04) <sup>d</sup>	.018 <sup>b</sup>
Short intercanthal distance, %	—	7.8	1.6	.048 <sup>a</sup>
Short interpupillary distance, %	—	12.5	1.6	.003 <sup>a</sup>
Hyperactivity, %	—	3.1	0.0	ns <sup>a</sup>
Fine motor, %	—	0.0	0.0	ns <sup>a</sup>
Hypoplastic midface, %	—	35.9	1.6	<.001 <sup>a</sup>
"Railroad track" ears, %	—	7.8	0.8	.019 <sup>a</sup>
Strabismus, %	—	3.1	0.0	ns <sup>a</sup>
Ptosis, %	—	6.3	0.0	.013 <sup>a</sup>
Epicanthal folds, %	—	53.1	31.1	.003 <sup>a</sup>
Flat nasal bridge, %	—	39.1	9.0	<.001 <sup>a</sup>
Anteverted nostrils, %	—	12.5	0.0	<.001 <sup>a</sup>
Long philtrum, %	—	21.9	15.6	ns <sup>a</sup>
Smooth philtrum, %	—	60.9	22.1	<.001 <sup>a</sup>
Narrow vermillion border, %	—	50.0	2.5	<.001 <sup>a</sup>
Prognathism, %	—	1.6	0.0	ns <sup>a</sup>
Heart murmur, %	—	9.4	0.0	<.001 <sup>a</sup>
Limited elbow supination, %	—	6.3	1.6	ns <sup>a</sup>
Clinodactyly, %	—	31.3	24.6	ns <sup>a</sup>
Camptodactyly, %	—	20.3	1.6	<.001 <sup>a</sup>
Palmar crease alteration, %	—	40.6	17.2	<.001 <sup>a</sup>
Hypertrichosis, %	—	3.1	0.8	ns <sup>a</sup>
Dysmorphology score, mean (SD)	—	14.0 (4.31)	2.2 (2.68)	<.001 <sup>b</sup>
Foster care or adopted, %	—	17.5	10.7	ns <sup>a,c</sup>

Notes: ns = not significant; <sup>a</sup>χ<sup>2</sup> test; <sup>b</sup>t test; <sup>c</sup>measurements at time of Tier I screen; therefore they are directly comparable to all other groups; <sup>d</sup>palpebral fissure length and philtrum length was 7 months after exam of children with FAS; other variables are age-corrected by percentile; <sup>e</sup>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<sup>a</sup> of children with FAS (by preliminary diagnosis after dysmorphology exam) and randomly selected controls

Variable	Final Dx FAS			Significance ANOVA
	Preliminary Dx FAS	Preliminary Dx Deferred	Controls	
Child developmental traits	(n = 28)	(n = 36)	(n = 123)	
Verbal IQ, mean (SD) <sup>b</sup>	68.3 (6.50) <sup>c</sup>	73.9 (8.50) <sup>d</sup>	82.5 (15.20)	F = 15.9, 2/185 df, p < .001
Nonverbal IQ, mean (SD) <sup>c</sup>	79.7 (8.20) <sup>d</sup>	83.2 (9.00)	84.6 (10.00)	F = 2.90, 2/187 df, NS (p = .057)
Behavior, mean (SD) <sup>f</sup>	15.3 (7.60) <sup>d</sup>	12.9 (9.00) <sup>d</sup>	6.7 (6.80)	F = 21.0, 2/185 df, p < .001
Total dysmorphology score, mean (SD) <sup>g</sup>	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) <sup>h</sup>	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) <sup>g</sup>	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. <sup>a</sup>All scores standardized for age of child at time of testing; <sup>b</sup>Tests of the Reception of Grammar (TROG); <sup>c</sup>t test significantly different from both children with preliminary diagnosis of deferred and controls, significance < .002; <sup>d</sup>t test significantly different from controls, significance < .02; <sup>e</sup>Ravens Colored Progressive Matrices; <sup>f</sup>Personal Behavior Checklist (PBCL-36); <sup>g</sup>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 <sup>a</sup> (n = 53)		Mothers of controls (n = 116)		p, OR (95% CI) <sup>b</sup>
	Whole sample (n = 53)	Drinkers only (n = 35)	Whole sample (n = 109)	Drinkers only (n = 19)	
Current drinker, in last year, %	69.8		21.1		<.001 <sup>c</sup> , OR = 8.14 (3.7-18.4)
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 <sup>d</sup> Drinkers only < .001 <sup>d</sup>
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 <sup>d</sup> Drinkers only < .001 <sup>d</sup>
Percentage on weekends	88.1	89.5	90.0	92.6	Whole sample NS <sup>e</sup> Drinkers only NS <sup>e</sup>
Drank before pregnancy with index child, % <sup>f</sup>	92.3		25.7		<.001 <sup>e</sup> , OR = 34.76 (10.6-126.3)
Did not drink or stopped	7.7		74.3		
Drank during index pregnancy, %	92.3 <sup>g</sup>		19.5		<.001 <sup>c</sup> , OR = 39.71 (15.1-188.1)
Drank during 1st trimester, % <sup>f</sup>	92.5		19.5		<.001 <sup>c</sup> , OR = 50.67 (15.1-188.1)
Did not drink or stopped	7.5		80.5		
Drank during 2nd trimester, % <sup>f</sup>	92.5		13.3		<.001 <sup>c</sup> , OR = 80.03 (22.8-311.2)
Did not drink or stopped	7.5		86.7		
Drank during 3rd trimester, % <sup>f</sup>	88.7		13.3		<.001 <sup>c</sup> , OR = 51.18 (16.9-163.6)
Did not drink or stopped	11.3		86.7		
Current user of tobacco, %	67.9		28.6		<.001 <sup>c</sup> , 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 <sup>c</sup> Smokers only NS <sup>e</sup>
Used tobacco during index pregnancy, %	75.5		26.8		<.001 <sup>c</sup> , OR = 8.41 (3.7-19.4)
Tobacco use during index pregnancy, used same or more, than current use, %	65.6		17.2		<.001 <sup>c</sup>
	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 <sup>d</sup> Drinkers only < .002 <sup>d</sup>
Fathers with drinking problems in past, %	36.2		2.0		<.001 <sup>c</sup> , OR = 28.33 (5.6-191.4)
Fathers currently have drinking problem, %	21.4		4.0		.001 <sup>c</sup> , OR = 6.55 (1.6-27.7)
Usual occupation, % farm laborer	34.6		12.4		.003 <sup>c</sup>

Notes: FAS = fetal alcohol syndrome; OR = odds ratio; CI = confidence interval. <sup>a</sup>Mortality and mobility reduced the number of available mothers of FAS children by 10, see Method section text for details; <sup>b</sup>95% CIs calculated via the Cornfield technique; <sup>c</sup> $\chi^2$  test; <sup>d</sup>t test; <sup>e</sup>difference of proportions test; <sup>f</sup>drank "less," the "same amount" or "more" than use at time of interview; <sup>g</sup>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 re-

ported 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<sup>a</sup> and physical dysmorphology versus selected maternal drinking measures (*n* = 164)

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

<sup>a</sup>All scores standardized for age of child at time of testing; <sup>b</sup>Tests of the Reception of Grammar (TROG); <sup>c</sup>Ravens Colored Progressive Matrices; <sup>d</sup>Personal Behavior Checklist (PBCL-36).

\**p* < .05; <sup>†</sup>*p* < .01; <sup>‡</sup>*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 <sup>a</sup> ( <i>n</i> = 53)	Mothers of control children ( <i>n</i> = 116)	<i>p</i> , OR (95% CI) <sup>b</sup>
Residence during index pregnancy, from interview (%)			
Rural	66.0 ( <i>n</i> = 35)	20.9 ( <i>n</i> = 28)	<.001 <sup>c</sup> , OR = 7.36 (3.31-16.52)
Urban	34.0 ( <i>n</i> = 18)	79.1 ( <i>n</i> = 87)	
Residence of FAS mothers (indirect standardization by frequency)			
Actual	35	18	<.001 <sup>c</sup> , OR = 5.42 (2.18-13.69)
Predicted	14	39	
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. <sup>a</sup>Mortality and mobility reduced the number of available mothers of FAS children by 10, see Method section text for details; <sup>b</sup>95% CIs calculated via the Cornfield technique; <sup>c</sup> $\chi^2$  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 payday. 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.

### Acknowledgments

We extend our deepest thanks to Mayor Herman Bailey, the (Western Cape Community) Town Council, Cecil Driver and the other principals of the twelve primary schools where research was performed. Jon M. Aase, M.D., helped design the first clinical screening and training protocols used, and Phyllis Trujillo supported this project with manuscript preparation, administrative help and logistical energy. Carolyn Tullet, Loretta Hendricks, Julie Croxford, Andrea Hay, Ansie Kitching, Chris Shaw, Chan Makan, Ph.D., Sandra Hawk, and other colleagues participated with dedication and energy in the data collection and local research process.

Protocols and consent forms were approved by the University of New Mexico (UNM) Medical School (HRRC 96-209), the UNM College of Arts and Sciences (01-93-86-9908), the Research Ethics Committee of the University of Cape Town, the Office for Human Research Protection of the National Institutes of Health and a single-site assurance committee in the local town. Active consent for children to participate in this study was obtained from parents or other legal guardians. Mothers interviewed also consented to participate.

### References

- AASE, J.M. Clinical recognition of FAS: Difficulties of detection and diagnosis. *Alcohol Hlth Res. World* **18**: 5-9, 1994.
- AASE, J.M., JONES, K.L. AND CLARREN, S.K. Do we need the term "FAE"? *Pediatrics* **95**: 428-430, 1995.
- ABEL, E.L. An update on the incidence of FAS: FAS is not an equal opportunity birth defect. *Neurotoxicol. Teratol.* **17**: 437-443, 1995.
- ABEL, E.L. *Fetal Alcohol Abuse Syndrome*, New York: Plenum Press, 1998.
- ABEL, E.L. AND HANNIGAN, J.H. Maternal risk factors in fetal alcohol syndrome: Provocative and permissive influences. *Neurotoxicol. Teratol.* **17**: 445-462, 1995.
- ABEL, E.L. AND SOKOL, R.J. Incidence of fetal alcohol syndrome and economic impact of FAS-related anomalies. *Drug Alcohol Depend.* **19**: 51-70, 1987.
- ABEL, E.L. AND SOKOL, R.J. A revised conservative estimate of the incidence of FAS and its economic impact. *Alcsm Clin. Exp. Res.* **15**: 514-524, 1991.
- ADNAMS, C.M., KODITUWAKKU, P.W., HAY, A., MOLTENO, C.D., VILJOEN, D. AND MAY, P.A. Patterns of cognitive-motor development in children with fetal alcohol syndrome from a community in South Africa. *Alcsm Clin. Exp. Res.* **25**: 557-562, 2001.
- BARCLAY, G.W. *Techniques of Population Analysis*, New York: John Wiley & Sons, 1958.
- BINGOL, N.; SCHUSTER, C., FUCHS, M., ISOSUB, S., TURNER, G., STONE, R.K. AND GROMISCH, D.S. The influence of socioeconomic factors on the occurrence of fetal alcohol syndrome. *Adv. Alcsm Subst. Abuse* **6**: 105-118, 1987.
- BLALOCK, H.M., JR. *Social Statistics*, 2nd Edition, New York: McGraw-Hill, 1972.
- BUREAU OF CENSUS. 1996 Census of the Population, Pretoria, South Africa: Republic of South Africa, 1997.
- CHAVEZ, G.F., CORDERO, J.F. AND BECERRA, J.E. Leading major congenital malformations among minority groups in the United States, 1981-1986. *MMWR* **37** (SS-3): 17-24, 1988.
- CLARREN, S.K., RANDELS, S.P., SANDERSON, M. AND FINEMAN, R.M. Screening for fetal alcohol syndrome in primary schools: A feasibility study. *Teratology* **63**: 3-10, 2001.
- CZARNECKI, D.M., RUSSELL, M., COOPER, M.L. AND SALTER, D. Five-year reliability of self-reported alcohol consumption. *J. Stud. Alcohol* **51**: 68-76, 1990.
- DEAN, A.G., DEAN, J.A., COULOMBIER, D., BRENDEN, K.A., SMITH, D.C., BURTON, A.H., DICKERS, R.C., SULLIVAN, K., FAGAN, R.F. AND ARNER, T.G. *Epi Info, Version 6: A word processing, data base, and statistics program for epidemiology on microcomputers*. Centers for Disease Control and Prevention: Atlanta, Georgia, 1994.
- EGELAND, G.M., PERHAM-HESTER, K.A., GESASER, B.D., INGLE, D., BERNER, J.E. AND MIDDAGH, J.P. Fetal alcohol syndrome in Alaska, 1977-1992: An administrative prevalence derived from multiple data sources. *Amer. J. Publ. Hlth* **88**: 781-786, 1998.
- EGELAND, G.M., PERHAM-HESTER, K.A. AND HOOK, E.B. Use of capture-recapture analyses in fetal alcohol syndrome surveillance in Alaska. *Amer. J. Epidemiol.* **141**: 335-341, 1995.
- HOYME, H.E., MAY, P.A., KALBERG, W.O., KODITUWAKKU, P., GOSSAGE, J.P., TRUJILLO, P.M., BUCKLEY, D.G., MILLER, J.H., ARAGON, A.S., KHAOLE, N., VILJOEN, D.L., JONES, K.L. AND ROBINSON, L.K. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: Clarification of the 1996 Institute of Medicine criteria. *Pediatrics* **115**: 39-47, 2005.
- JACOBSON, J.L. AND JACOBSON, S.W. Prenatal alcohol exposure and neurobehavioral development: Where is the threshold? *Alcohol Hlth Res. World* **18**: 30-36, 1994.
- JACOBSON, S.W., CHIODO, L.M., SOKOL, R.J. AND JACOBSON, J.L. Validity of maternal report of prenatal alcohol, cocaine, and smoking in relation to neurobehavioral outcome. *Pediatrics* **109**: 815-825, 2002.
- JACOBSON, S.W., JACOBSON, J.L., SOKOL, R.J., MARTIER, S.S., AGER, J.W. AND KAPLAN, M.G. Maternal recall of alcohol, cocaine, and marijuana use during pregnancy. *Neurotoxicol. Teratol.* **13**: 535-540, 1991.
- JONES, K.L. AND SMITH, D.W. Recognition of the fetal alcohol syndrome in early infancy. *Lancet* **2**: 999-1001, 1973.
- KASKUTAS, L.A. AND GRAVES, K. An alternative to standard drinks as a measure of alcohol consumption. *J. Subst. Abuse* **12**: 67-78, 2000.
- KASKUTAS, L.A. AND GRAVES, K. Pre-pregnancy drinking: How drink size affects risk assessment. *Addiction* **96**: 1199-1209, 2001.
- KHAOLE, N.C.O., RAMCHANDANI, V.A., VILJOEN, D.L. AND LI, T.-K. A pilot study of alcohol exposure and pharmacokinetics in women with or without children with fetal alcohol syndrome. *Alcohol Alcsm* **39**: 503-508, 2004.
- KING, A.C. Enhancing the self-report of alcohol consumption in the community: Two questionnaire formats. *Amer. J. Publ. Hlth* **84**: 294-296, 1994.
- KING, G., FLISHER, A.J., NOUBARY, F., REECE, R., MARAIS, A. AND LOMBARD, C. Substance abuse and behavioral correlates of sexual assault among South African adolescents. *Child Abuse Negl.* **28**: 683-696, 2004.
- LEMOINE, P., HAROUSSEAU, H., BORTEYRU, J.-P. AND MENUET, J.C. Les enfants de parents alcooliques: Anomalies observées à propos de 127 cas (Children of alcoholic parents: Anomalies observed in 127 cases). *Quest Med.* **21**: 476-482, 1968.
- LITTLE, B.B., SNELL, L.M., ROSENFELD, G.R., GILSTRAP, L.C., 3RD AND GANT, N.F. Failure to recognize fetal alcohol syndrome in newborn infants. *Amer. J. Dis. Child.* **144**: 1142-1146, 1990.
- LONDON, L., MEYERS, J., NELL, V., TAYLOR, T., THOMPSON, M.L. AND MILBULL, S.S. An Investigation into the Neurological and Neurobehavioral Effects

- of Long Term Agrochemical Exposure among Deciduous Fruit Farm Workers in the Western Cape, South Africa, M.D. thesis, Cape Town, South Africa: University of Cape Town, 1995.
- LONDON, L. Alcohol consumption amongst South African farm workers: A challenge for the post-apartheid health sector transformation. *Drug Alcohol Depend.* **59**: 199-206, 2000.
- MAGER, A. "White liquor hits black lives": Meaning of excessive liquor consumption in South Africa in the second half of the twentieth century. *Social Sci. Med.* **59**: 735-751, 2004.
- MAY, P.A. Fetal alcohol effects among North American Indians: Evidence and implications for society. *Alcohol Hlth Res World* **15**: 239-248, 1991.
- MAY, P.A. A multiple-level, comprehensive approach to the prevention of fetal alcohol syndrome (FAS) and other alcohol-related birth defects (ARBD). *Int. J. Addict.* **30**: 1549-1602, 1995.
- MAY, P.A. Research issues in the prevention of fetal alcohol syndrome and alcohol-related birth defects. In: HOWARD, J.M., MARTIN, S.E., MAIL, P.D., HILTON, M.E. AND TAYLOR, E.D. (Eds.) *Women and Alcohol: Issues for Prevention Research*. NIAAA Research Monograph No. 32, NIH Publication No. 96-3817, Washington: Government Printing Office, 1996, pp. 93-131.
- MAY, P.A., BROOKE, L.E., GOSSAGE, J.P., CROXFORD, J., ADNAMS, C., JONES, K.L., ROBINSON, L. AND VILJOEN, D. Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. *Amer. J. Publ. Hlth* **90**: 1905-1912, 2000.
- MAY, P.A., GOSSAGE, J.P., BROOKE, L.E., SNELL, C.L., MARAIS, A.S., HENDRICKS, L.S., CROXFORD, J.A. AND VILJOEN, D.L. Maternal risk factors for fetal alcohol syndrome in the Western cape province of South Africa: A population-based study. *Amer. J. Publ. Hlth*, **95**: 1190-1199.
- MAY, P.A. AND GOSSAGE, J.P. Estimating the prevalence of fetal alcohol syndrome: A summary. *Alcohol Res. Hlth* **25**: 159-167, 2001.
- MAY, P.A., GOSSAGE, J.P., WHITE-COUNTRY, M., GOODHART, K., DECOTEAU, S., TRUJILLO, P.M., KALBERG, W.O., VILJOEN, D.L. AND HOYME, H.E. Alcohol consumption and other maternal risk factors for fetal alcohol syndrome among three distinct samples of women before, during, and after pregnancy: The risk is relative. *Amer. J. Med. Genet. Seminars Med. Genet.* **127** (Pt C): 10-20, 2004.
- MAY, P.A., HYMBAUGH, K.J., AASE, J.M. AND SAMET, J.M. Epidemiology of fetal alcohol syndrome among American Indians of the Southwest. *Social Biol.* **30**: 374-387, 1983.
- MAY, P.A., MCCLOSKEY, J. AND GOSSAGE, J.P. Fetal alcohol syndrome among American Indians: Epidemiology, issues, and research. In: MAIL, P.D., HEURTIN-ROBERTS, S., MARTIN, S.E. AND HOWARD, J. (Eds.) *Alcohol Use Among American Indians and Alaska Natives: Multiple Perspectives on a Complex Problem*. NIAAA Research Monograph No. 37, NIH Publication No. 02-4231, Bethesda, MD: Department of Health and Human Services, 2002, pp. 321-369.
- NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM. Fetal Alcohol Syndrome: Report on the Site Visit to South Africa. Bethesda, MD: Department of Health and Human Services, 1996.
- NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM. Fetal Alcohol Syndrome. South Africa: A Progress Report on the 1997 Pilot Study, Information Exchange, and Prevention Workshop, Bethesda, MD: Department of Health and Human Services, 1998.
- PALMER, C. Fetal alcohol effects: Incidence and understanding in the Cape. *S. Afr. Med. J.* **68**: 779-780, 1985.
- PARRY, C.D.H. AND BENNETTS, A.L. *Alcohol Policy and Public Health in South Africa*, Cape Town, South Africa: Oxford Univ. Press, 1998.
- PIEROG, S., CHANDAVASU, O. AND WEXLER, I. The fetal alcohol syndrome: Some maternal characteristics. *Int. J. Gynecol. Obstet.* **16**: 412-415, 1979.
- ROBINSON, G.C., CONRY, J.L. AND CONRY, R.F. Clinical profile and prevalence of fetal alcohol syndrome in an isolated community in British Columbia. *Can. Med. Assoc. J.* **137**: 203-207, 1987.
- ROSSETT, H.L. A clinical perspective of the fetal alcohol syndrome. *Alcsm Clin. Exp. Res.* **4**: 119-122, 1980.
- SOBELL, L.C., AGRAWAL, S., ANNIS, H., AYALA-VELAZQUEZ, H., ECHEVERRIA, L., LEO, G.I., RYBAKOWSKI, J.K., SANDAHL, C., SAUNDERS, B., THOMAS, S. AND ZIOLKOWSKI, M. Cross-cultural evaluation of two drinking assessment instruments: Alcohol timeline followback and inventory of drinking situations. *Subst. Use Misuse* **36**: 313-331, 2001.
- SOBELL, L.C., SOBELL, M.B., LEO, G.I. AND CANCELLA, A. Reliability of a timeline method: Assessing normal drinker's reports of recent drinking and a comparative evaluation across several populations. *Brit. J. Addict.* **83**: 393-402, 1988.
- SOKOL, R.F. AND CLARREN, S.K. Guidelines for use of terminology describing the impact of prenatal alcohol on the offspring. *Alcsm Clin. Exp. Res.* **13**: 597-598, 1989.
- STRATTON, K., HOWE, C. AND BATTAGLIA, F. (Eds.) *Fetal Alcohol Syndrome Diagnosis, Epidemiology, Prevention, and Treatment*, Washington, DC: National Academy Press, 1996.
- STREISSGUTH, A.P., CLARREN, S.K. AND JONES, K.L. Natural history of the fetal alcohol syndrome: A 10-year follow-up of eleven patients. *Lancet* **2**: 85-91, 1985.
- SULLIVAN, W.C. A note on the influence of maternal inebriety on the offspring. *J. Ment. Sci.* **45**: 489-503, 1899.
- TSAI, J. AND FLOYD, R.L. Alcohol consumption among women who are pregnant or who might become pregnant - United States, 2002. *MMWR* **53** (50): 1178-1181, 2004.
- VILJOEN, D.L., CRAIG, P., HYMBAUGH, K., BOYLE, C. AND BLOUNT, S. Fetal alcohol syndrome—South Africa, 2001. *MMWR* **52** (28): 660-662, 2003.
- VILJOEN, D., CROXFORD, J., GOSSAGE, J.P., KODITUWAKKU, P.W. AND MAY, P.A. Characteristics of mothers of children with fetal alcohol syndrome in the Western Cape Province of South Africa: A case control study. *J. Stud. Alcohol* **63**: 6-17, 2002.

# Alcohol Consumption and Other Maternal Risk Factors for Fetal Alcohol Syndrome among Three Distinct Samples of Women before, during, and after Pregnancy: The Risk Is Relative

PHILIP A. MAY,\* J. PHILLIP GOSSAGE, MARY WHITE-COUNTRY, KAREN GOODHART, SARA DECOTEAU, PHYLLIS M. TRUJILLO, WENDY O. KALBERG, DENIS L. VILJOEN, AND H. EUGENE HOYME

Data were obtained from three samples of women of childbearing age. One sample of women is from prenatal clinics serving Plains Indian women. The second sample is of women from the Plains whose children were referred to special diagnostic developmental clinics, as their children were believed to have developmental issues consistent with prenatal alcohol consumption. The third sample is of women from South Africa, each of whom has given birth to a child diagnosed with full fetal alcohol syndrome (FAS). Data across samples conform to expected trends on many variables. For example, the maternal age at time of pregnancy, a major risk factor for FAS, ranged from a mean of 23.5 years for the prenatal clinic sample, to 23.8 years for the developmental clinic sample, to 27.6 for the sample of women who have delivered children with FAS. Other variables of maternal risk for FAS expected from the extant literature, such as high gravidity and parity, binge drinking, heavy intergenerational drinking in the mother's extended family and immediate social network, and length of drinking career, were compared across the three samples with variable results. However, normative measures of drinking problems are unreliable when reported across cultures. An unexpected finding from this three-sample comparison was the differential risk found when comparing U.S. women to South African women. Women in the U.S. Plains Indian samples report a high consumption of alcohol in a binge pattern of drinking, yet there is less detectable damage to the fetus than among the South African women. Body mass index (BMI) and lifelong and current nutrition may have a substantial impact, along with the above factors, in relative risk for an FAS birth. The level of risk for producing a child with FAS is influenced by environmental and behavioral conditions that vary between populations and among individual women. Also, because many syndromes are genetically based, there is a need for full behavioral and genetic histories of the mother, family, and child being studied. Collecting extensive behavioral information as well as genetic histories will provide the requisite information for making an accurate diagnosis of FAS. © 2004 Wiley-Liss, Inc.

**KEY WORDS:** fetal alcohol syndrome; alcohol; prenatal binge drinking; American Indians; South Africa

Philip A. May is a Professor of Sociology and Associate Director of the University of New Mexico (UNM) Center on Alcoholism, Substance Abuse, and Addictions (CASAA). A major focus of Dr. May's over the past 24 years has been FAS epidemiology and prevention.

J. Phillip Gossage is a Senior Research Scientist at UNM/CASAA. FAS has been a major focus of his work over the past 12 years.

Mary White-Country is a FAS Prevention and Research Site Director for UNM/CASAA at one research location in South Dakota.

Karen Goodhart is a Case Manager and Research Aide at the same research site in South Dakota.

Sara DeCoteau is the Health Coordinator for the Sisseton-Wahpeton Oyate of the Lake Traverse Reservation. She has been the Health Coordinator for the tribe for 29 years and has long had an interest in preventing FAS and long-term care.

Phyllis Trujillo is an Administrative Coordinator at UNM/CASAA. She is the maternal interviewer for the Plains FAS study described in this paper.

Wendy Kalberg is an Educational Diagnostician and Senior Program Manager at UNM/CASAA. Her primary professional focus for the past seven years has been FAS diagnosis and educational planning.

Denis Viljoen is the Chair of the Department of Human Genetics, University of Witwatersrand; he is also with the South African Institute for Medical Research and the Foundation for Alcohol Related Research. Dr. Viljoen is the primary person responsible for identifying the high prevalence of FAS in South Africa.

H. Eugene Hoyme is the Chair of the Division of Medical Genetics, Department of Pediatrics, Stanford University School of Medicine. He has experience with a broad range of issues in genetics and teratology and has worked with the diagnosis of FAS for over 20 years.

Grant sponsor: NIAAA; Grant numbers: RO1 AA09440, RO1 AA11685; Grant sponsor: National Center on Minority Health and Health Disparities (NCMHD).

\*Correspondence to: Philip A. May, University of New Mexico Center on Alcoholism, Substance Abuse, and Addictions, 2650 Yale Blvd. SE, Suite 100, Albuquerque, NM 87106-3202. E-mail: pmay@unm.edu

DOI 10.1002/ajmg.c.30011

Published online 8 April 2004 in Wiley InterScience (www.interscience.wiley.com)

## INTRODUCTION

Fetal alcohol syndrome (FAS) has been found to occur in all human racial and ethnic groups [Abel, 1995]. Estimates of the prevalence of FAS range from 0.5–2.0 per 1,000 births in the United States [May and Gossage, 2001]. A review of studies in American Indian groups, often cited as high risk, has determined that the rate of FAS among American Indians ranges between 1.0 and 8.97 per 1,000 births [Duimstra et al., 1993; May et al., 2002]. A world record rate of FAS (39.2–46.4 per 1,000 births) has been

---

***A world record rate of FAS  
(39.2–46.4 per 1,000 births)  
has been reported for children  
in South Africa.***

---

reported for children in South Africa [May et al., 2000].

The term *fetal alcohol syndrome* was first used when Jones and Smith [1973] and Jones et al. [1973] described all of the major malformations and disabilities in offspring of alcoholic mothers, making FAS a topic of medical and social concern. Prior to this, indications that alcohol was teratogenic were not frequently recognized or were generally ignored [Abel, 1998]. But Sullivan [1899], a physician working in the prisons of London, described some features of FAS (including mental retardation and convulsions) among children of female alcoholics and described the mechanism of damage as prenatal alcohol exposure. Much later, Lemoine et al. [1968] described abnormal features in 127 offspring of alcoholics in France. These abnormal features were later independently catalogued by Jones and Smith [1973], and the diagnosis of FAS was created. It is likely that FAS has been commonly misdiagnosed throughout the world [Little et al., 1989; Abel, 1995; Karp et al., 1995; Institute of Medicine, 1996].

FAS symptoms fall into three major categories: 1) a characteristic pattern of facial anomalies such as short palpebral

fissures and abnormalities in the premaxillary zone; 2) evidence of growth retardation—low birth weight for gestational age, decelerating weight over time not due to nutrition, and disproportional low weight to height; and 3) evidence of central nervous system abnormalities (e.g., microcephaly) and neurological hard or soft signs [Institute of Medicine, 1996]. Full FAS can be diagnosed with or without confirmation of alcohol exposure. Furthermore, the Institute of Medicine (IOM) committee described partial FAS” with confirmed alcohol exposure. Also defined were alcohol-related birth defects (ARBDs, the physical defects) and alcohol-related neurodevelopmental disorders (ARNDs), which evidence central nervous system damage manifested by either structural brain or neurodevelopmental/behavioral abnormalities. Children with ARBDs and ARNDs do not have the full syndrome, but the specific symptoms of these classifications have been linked to prenatal alcohol exposure by research. These later diagnostic categories must be linked to confirmed alcohol exposure in each particular child [Institute of Medicine, 1996]. The entire array of fetal alcohol diagnoses is currently called fetal alcohol spectrum disorder (FASD).

Prenatal alcohol damage in children varies tremendously with QFT: *quantity* of alcohol consumed, *frequency* with which it is consumed, and *timing* of the consumption to the gestational age of the fetus [May, 1995]. The QFT and individual characteristics of each mother influence both level and type of damage in the fetus. Heavy and frequent doses of alcohol in the first trimester affect the facial and structural features; spontaneous abortion rates are heightened by drinking during the second trimester; and growth is affected in the third trimester

---

***Heavy drinking at any time  
throughout the pregnancy can  
cause neurodevelopmental,  
intellectual, and behavioral  
problems.***

---

[Little and Wendt, 1991; Russel, 1991; Abel, 1995]. Heavy drinking at any time throughout the pregnancy can cause neurodevelopmental, intellectual, and behavioral problems [West and Goodlett, 1990; Pierce and West, 1986; Abel, 1995]. High blood alcohol concentrations (BACs) cause many symptoms of FAS, making heavy, sporadic drinking a prime risk factor [Pierog et al., 1979; Maier and West, 2001; Viljoen et al., 2002; Kvigne et al., 2003].

As alcoholism and FAS cluster in certain families, heritability, and therefore some genetically determined susceptibility factors, are issues to be explored. But to date only one identifiable genetic protective factor has been linked to FAS. Among liver isoenzyme polymorphisms, one pattern of alleles, alcohol dehydrogenase (ADH) 2\*2, has been suggested as protective. This pattern is relatively rare, yet is found in a higher proportion of control mothers and their children in South Africa than among mothers of children with FAS. Mothers of children with FAS are more likely to have the ADH 2\*1 pattern [Viljoen et al., 2001].

The primary cause or risk factor for FAS is consumption of large quantities of alcohol, usually in a heavy, episodic (binge) pattern, during a woman's pregnancy. Past and recent studies have identified additional risk factors among women who give birth to children with FAS: advanced maternal age, high gravidity and parity, unmarried status, use of tobacco and other drugs, low socioeconomic status (SES) indicators (such as low education, unskilled job classifications), low levels of religiosity, and cohabitation with a heavy-drinking male [Sokol et al., 1980, 1986; May et al., 1983; Abel and Sokol, 1986; Darrow et al., 1992; Abel, 1995; Abel and Hannigan, 1995; Bagheri et al., 1998; Astley et al., 2000a,b; Viljoen et al., 2002].

Given our ongoing research efforts on FAS among American Indians and in South Africa, we thought it would be instructive to examine these variables across three samples of women whom we thought would be easily categorized as lowest to highest risk for producing a child with FAS. In other words, from

women attending prenatal clinics to those who had given birth to a child with FAS would theoretically form a continuum from low to high risk.

## METHODOLOGY

A large FAS epidemiology and prevention study is under way in collaboration with Indian tribes of the Northern Plains of the United States. The first two sets of data come from this study. The *prenatal clinic sample* originates from Indian Health Service (IHS) clinics. In the 1990s the Aberdeen Area IHS began assessing the use of tobacco, alcohol, and other drugs via a brief self-administered questionnaire (SAQ) [Bad Hart Bull et al., 1999] and a variation called the prenatal questionnaire. These two questionnaires are about 80% similar. Women typically fill out these questionnaires during their first visit to IHS prenatal clinics. The majority of the women visited the clinic in their first trimester. The questionnaires are reviewed by IHS staff and used as tools for a healthy pregnancy. SAQ data were collected from those women who presented at prenatal clinics in three tribal communities. Data from 840 anonymous SAQs were analyzed. Data were missing from a variety of variables on some questionnaires; hence, there is variance in sample size across analyses. These omissions may mean that these women were hiding their use of these substances, particularly alcohol, or simply indicate a busy clinic schedule. The data were merged into a single set resulting in a usable sample of 755.

The *developmental clinic sample* originates from a broad National Institute on Alcohol Abuse and Alcoholism (NIAAA)-funded epidemiologic study, which uses active case ascertainment for identifying cases of FAS [Institute of Medicine, 1996; May and Gossage, 2001] through outreach in entire Plains Indian communities. Educators, community health representatives, and others are trained to recognize symptoms of FASD and to refer children and mothers to special developmental clinics. Children with a previous diagnosis of FAS or other FASDs, those in the care of social service agencies, and

children having difficulties in school or who have behavioral problems are the bulk of the referrals. An interdisciplinary team examines each child for the full range of dysmorphology and known birth defects, IQ, life skills, and neuropsychology. Mothers of these children are interviewed about prenatal experience with the index pregnancy, other pregnancies, diet, medical history, social and demographic conditions, and consumption of alcohol during pregnancy. Data are evaluated for a diagnosis of FAS, partial FAS, ARBDs, ARNDs, and/or another problem, or normal [Institute of Medicine, 1996]. Randomly selected normal children and their mothers are also examined and interviewed as matched case-controls,<sup>1</sup> but controls are not consistently included in this paper, as the emphasis is on comparison across populations. When this paper was prepared, 133 women had been interviewed by one author (P.M.T.) in our developmental clinics. The developmental clinic sample is therefore the group we envisioned as having intermediate maternal risk, as 11% of their children were found to have FAS or partial FAS. Some had diagnosable ARBDs or ARNDs, and others were found to be relatively to completely normal.

The *South African sample* of mothers consists only of those women who have given birth to a child with FAS. In the South Africa study, a two-tiered process in elementary schools identified children with FAS. All children in first-grade classrooms of community elementary schools were screened for height, weight, and head circumference (OFC), and those at or below the 10th centile on both of the first two variables and/or on the third received a full dysmorphology/birth defects screening, including physical, IQ, behavioral, and neuropsychological measures [May et al., 2000; Adnams et al., 2001]. Biological mothers or guardians of those children and matched case-controls<sup>2</sup> were interviewed on a

large range of maternal risk variables, including the mother's use of alcohol during gestation of the index child [Viljoen et al., 2002]. There have been three waves of research in South Africa, beginning in 1997, 1999, and 2002. Data from waves 1 and 2 were merged into a single data set for the third sample of women (n = 88) in this paper. Since all South African women in this third group had given birth to a child with FAS, we envisioned it to be the highest-risk group. All but one of the South African mothers were Colored (mixed ancestry from Black, European, and Asian origins).

In both our Plains and South Africa studies, we gathered drinking data with an extensive questionnaire utilizing a modified timeline follow-back technique [Sobell et al., 1988, 2001] and photographs of the most popular sizes and brands of each type of alcoholic beverage. In this way we were able to establish standard ethanol units more precisely for calculating the number of drinks consumed [Kaskutas and Graves, 2001].

In addition to Institutional Review Board (IRB) committee approvals in the United States (from our university and the IHS) and ethics committee approvals in South Africa, a formal tribal council resolution of approval preceded all activity in the Northern Plains, as did a single site assurance committee approval from the South African community.

The *Epi-Info* software package was used to analyze the data. Chi-square tests were calculated on frequencies for those research questions (variables) that involved data with nominal or ordinal level measurement. In these comparisons percentages are reported in the tables for the reader's convenience. Analyses of variance (ANOVAs) and *t*-tests were utilized for testing differences of means with interval-level data. All analyses

<sup>2</sup>For the first wave of data from South Africa, once the children with a diagnosis of FAS were identified, they were matched by sex, age, and classroom to control children. For the second wave of data from South Africa, control children were randomly selected. Mothers of those four samples of children became the matched cases and controls.

<sup>1</sup>Control children for the developmental clinic part of the study were matched by sex and age ( $\pm 6$  months) to children with a diagnosis of FAS. Mothers of those two samples of children became the matched cases and controls.

were two-tailed. In those analyses where cases were compared to controls, matched statistics were used.

## RESULTS

Selected sociodemographic and maternity variables are presented in Table I.

The mean maternal age at time of pregnancy ranged from 23.5 years for the prenatal clinic sample, to 23.8 for the developmental clinic sample, to 27.6 for the South African sample of women. Older women are at higher risk for producing FAS births. Concerning educational attainment, 47.1% of the women

### *Older women are at higher risk for producing FAS births.*

in the developmental clinic sample had not graduated from high school or

**TABLE I. Demographic, Socioeconomic, and Maternity Variables for Women in Three Studies**

Variable	Plains prenatal clinic	Plains developmental clinic	South African mothers of children with FAS	Statistical tests
Age when pregnant with index child, yrs				
n =	755	133	88	
Mean (SD)	23.5 (5.80)	23.8 (5.96)	27.6 (6.81)	$F = 18.79, P < .01$
Educational attainment, %				
n =	—	119	89	
<HS diploma or GED	—	47.1	98.9	
HS diploma or GED	—	31.9	1.1	
Vocational school +	—	21.0	0.0	$X^2 = 68.64, 2 \text{ df}, P < .01$
Religiosity, %				
n =	—	117	76	
Not at all religious	—	11.1	10.5	
Somewhat religious	—	78.6	71.1	
Very religious	—	10.3	18.4	$X^2 = 2.64, 2 \text{ df}, P = \text{NS}^a$
Marital Status, % <sup>b</sup>				
n =	—	118	89	
Married	—	25.4	23.6	
Widowed/separated/divorced	—	5.1	1.1	
Single	—	29.7	28.1	
Not married but living with partner	—	39.8	47.2	$X^2 = 3.11, 3 \text{ df}, P = \text{NS}$
Maternity				
n =	—	119	93	
Gravidity (mean) (SD)	—	4.7 (2.20)	3.7 (1.51)	$t = 3.75, P < .01$
Parity (pre-term) (mean) (SD)	—	0.2 (0.74)	0.4 (0.65)	$t = 1.72, P = \text{NS}$
Parity (full-term) (mean) (SD)	—	3.5 (1.88)	3.0 (1.47)	$t = 2.77, P < .01$
Miscarriages (mean) (SD)	—	0.5 (0.89)	0.3 (0.64)	$t = 0.52, P = \text{NS}$
Induced abortions (mean) (SD)	—	0.2 (0.43)	—	
Stillbirths (mean) (SD)	—	0.0 (0.19)	—	
Number of living children (mean) (SD)	—	3.9 (1.87)	3.1 (1.24)	$t = 3.07, P < .01$
Birth order of index child				
n =	—	294	89	
Mean (SD)	—	3.0 (1.73)	2.9 (1.57)	$t = 0.56, P = \text{NS}$

<sup>a</sup>NS, not statistically significant.

<sup>b</sup>During pregnancy, or at birth of the index child.

earned a GED; among the South African women that percentage was 98.9%. Data on religiosity were mixed and not significant across populations, probably due to normative and definitional differences and because of time lag (6.5 years) between the FAS birth and interview in both samples. Marital status comparisons conformed to expectations; both the developmental clinic mothers and South African mothers were frequently not married, and a high percentage were living in common-law relationships.

There were some significant and contradictory differences between the higher-risk developmental clinic mothers and South African mothers on the various maternity variables (gravidity, full-term parity, and number of living children) and also some nonsignificant differences (miscarriages and birth order of the child). Although case-control studies in many populations have demonstrated that women who have children with FAS are more likely to be higher gravidity and parity and to suffer more miscarriages than the general

maternity population [Abel, 1998; Bagheri et al., 1999; Astley et al., 2000a,b; May and Gossage, 2001], the developmental clinic mothers of children referred for screening had significantly higher values on most of these measures than did the South African mothers of children with FAS in spite of being a younger sample.

Alcohol consumption among family and friends can have a profound impact on female drinking. Data on problem drinking by the woman's father, mother, brother, sister, or biological father of the index child, and the woman's closest female and male friends are presented in Table II. All of these trends are significantly opposite what we would expect.

*Alcohol consumption among family and friends can have a profound impact on female drinking.*

Prenatal clinic and developmental clinic women report that 47.7–83.3% of the individuals in their social network have had problems with alcohol. South African women, on the other hand, reported substantially lower rates of problem drinking in their extended family, 0.0–39.1% (odds ratios (ORs) were 2.27 for the woman's mother, 6.35 for the father, and 52.50 for the first brother). Even the father of the index child was reported to have more problems in the developmental clinic sample (OR = 7.41). London [1999, 2000], Parry [2000], and Parry et al. [2002] report, and our own research has revealed, very high risk drinking among farm workers in the Western Cape, particularly on weekends. The low rates of perceived/reported drinking problems among South African women seem to be simply a matter of norms, expectations, and defining and interpreting "problem drinking" in this subculture. These assumptions are essentially confirmed when we transition to the data in Table III.

**TABLE II. Prevalence of Drinking Problems Within Woman's Social Network**

Variable	Plains prenatal clinic	Plains developmental clinic	South African mothers of children with FAS	Statistical tests
Has individual had problems with alcohol				
Woman's father, %				
Yes	—	66.3	23.6	$X^2 = 24.05, P < .01, OR 6.35$
Woman's mother, %				
Yes	—	59.4	39.1	$X^2 = 2.79, P = NS^a, OR 2.27$
Woman's brother, % <sup>b</sup>				
Yes	—	83.3	8.7	$X^2 = 39.00, P < .01, OR 52.50$
Woman's sister, % <sup>b</sup>				
Yes	—	50.0	14.0	$X^2 = 11.50, P < .01, OR 6.17$
Father of index child during the index pregnancy, %				
Yes	—	82.1	38.3	$X^2 = 20.88, P < .01, OR 7.41$
Woman's best/closest female friend, %				
Yes	—	47.7	10.5	$X^2 = 8.51, P < .01, OR 7.75$
Woman's best/closest male friend, %				
Yes	—	38.5	0.0	$X^2 = 1.23, P = NS$

<sup>a</sup>NS, not statistically significant.

<sup>b</sup>Data pertain to the first brother or sister for South African women.

**TABLE III. Initiation and Current Use of Alcohol Among Women**

Variable	Plains prenatal clinic	Plains developmental clinic	South African mothers of children with FAS	Statistical tests
Age first tried alcohol, yrs				
n =	—	119	83	
Mean (SD)	—	14.0 (3.39)	19.5 (3.95)	$t = 20.12, P < .01$
Age began drinking regularly, yrs				
n =	—	115	82	
Mean (SD)	—	17.4 (3.84)	20.8 (4.29)	$t = 11.66, P < .01$
Age at interview, yrs				
n =	755	119	87	
Mean (SD)	23.5 (5.82)	31.2 (7.06)	35.4 (6.79)	$F = 211.67, P < .01$
Drinking career, yrs				
n =	—	108	73	
Mean (SD)	—	13.6 (6.75)	15.8 (6.72)	$t = 74.78, P < .01$
Has women ever had a problem with alcohol, %				
n =	—	117	50	
Yes	—	91.5	6.0	$X^2 = 113.78, P < .01,$ OR 167.63

As shown in Table III, developmental clinic women first tried alcohol 5.5 years earlier than South African women (mean = 14.0 vs. 19.5) and also began drinking regularly 3.5 years earlier (17.4 vs. 20.8). But South African women, because the sample was older at interview, had a significantly longer "drinking career" with a mean of 15.8 vs. 13.6 years. Almost all of the developmental clinic women who were suspected of drinking during pregnancy (91.5%) reported that they had had problems with alcohol at some time in their life. Conversely, while *every one* of the South African women in the 1999 study had given birth to a child with FAS, only 6% admitted to having had problems with alcohol at some time in their life (OR = 167.63). Normative definitions are again important, as the developmental clinic women define problem drinking to be significantly greater. While not shown in the table, these South African mothers of a child with FAS worked on farms and consumed twice as many drinks as did the prenatal clinic sample (mean = 14.0 vs. 6.6 drinks) in the seven days preceding their interview. Virtually all (94.9%) South African drinking occurred on

***Virtually all (94.9%) South African drinking occurred on weekends (Friday—Sunday), thereby indicating binge drinking as the major pattern.***

weekends (Friday–Sunday), thereby indicating binge drinking as the major pattern. This conforms with the FAS literature from both animal [Maier and West, 2001] and human [Viljoen et al., 2002] studies.

A woman's consumption of alcohol in the months just before pregnancy is key to reconstructing the risk for FASDs. In Table IV, 74.5–88.9% of the women of the three samples consumed alcohol before pregnancy, conforming to expectations of high risk for FASDs. For the rest of the variables in that table, the developmental clinic women of higher risk who reported drinking before learning they were pregnant consumed the most drinks per occasion (11.3,  $P < 0.01$ ). The developmental clinic women also drank alcohol on more days

of the month (7.6) than the prenatal clinic women, but not more often than the South African FAS women (10.2). Developmental clinic women also had the highest percentage, binging at the three- and five-drink thresholds (89.7 and 81.8%, respectively). Developmental clinic women who drank consumed an average of over 100 drinks over a 30-day period, while the South African women consumed an average of 55 drinks over that same time frame. These data place both the developmental clinic women and the South African women at high risk for FASDs.

Table V addresses alcohol use during the index pregnancy. Conforming to expectations, the South African women who have borne children with FAS significantly exceed the other two groups on the percentage who report consuming alcohol during that pregnancy (94.3 vs. 47.0 vs. 16.2%). Five South African women claimed no alcohol consumption during pregnancy even though they gave birth to a child with FAS. The developmental clinic women who continued to drink consumed more average drinks per occasion (7.7), with the South African women consuming only slightly less (7.0). The data conform to expecta-

TABLE IV. Use of Alcohol Among Women Before Pregnancy

Variable	Plains prenatal clinic	Plains developmental clinic	South African mothers of children with FAS	Statistical tests
Percent who consumed alcohol				
n =	741	112	81	
Yes	74.5	80.4	88.9	$X^2 = 9.48, 2 \text{ df}, P < .01$
Among those who were drinking, on days she drank, how many drinks did woman usually drink				
n =	542	83	72	
Mean (SD)	6.6 (5.05)	11.3 (10.86)	6.7 (5.08)**	$F = 21.92, P < .01$
Among those who were drinking, how often over 30 days did woman drink her usual amount				
n =	455	81	72	
Mean (SD)	2.4 (2.33)	7.6 (8.73)	10.4 (1.51)**	$F = 178.57, P < .01$
Among those who were drinking, did woman binge (consume three or more drinks), %				
n =	544	88	72	
Yes	87.3	89.7	76.4**	$X^2 = 25.96, 2 \text{ df}, P < .01$
Among those who were drinking, did woman binge (consume five or more drinks), %				
n =	544	88	72	
Yes	63.6	81.8	63.9**	$X^2 = 11.33, 2 \text{ df}, P < .01$
Among those who were drinking, total number of drinks woman consumed over 30 days				
n =	551	80	72	
Mean (SD)	16.5 (27.65)	102.2 (201.50)	55.0 (55.93)**	$F = 51.06, P < .01$

\*\*Estimated from drinking logs at time of interview, daily, seven and 30 days.

tions on the number of days each woman consumed her usual amount of alcohol. Here the South African women drank 2.3 more days per month than the developmental clinic women and 8.1 more days than the prenatal clinic women. A substantial percentage of women binged at the three-drink threshold at least once during pregnancy (68.8–89.1%), with the developmental clinic women the highest ( $P < 0.05$ ). The percentages are relatively high at the five-drink threshold as well, with 40.6–73.6% of the women drinking five or more drinks per occasion during pregnancy. The developmental clinic women (suspected risk) and the South African women (highest risk) on average consumed significantly more drinks over a typical 30 days during pregnancy than did the prenatal clinic women (prenatal clinic women = 8.6, developmental clinic women = 69.8, South African women = 55.4). The developmental clinic women who continued to drink consumed 15 to 16 more drinks during pregnancy than did the South African women.

From Tables IV and V, therefore, it seems quite apparent that the devel-

opmental clinic women are more likely to quit drinking (over 50%) once pregnancy is suspected or confirmed, but those who continue to drink consume more alcohol per occasion, but slightly less often than the South African mothers of children with FAS.

Just as we have compared the three groups of women, we digress to compare women within the developmental clinic sample. We separated those women into two subgroups: those who have given birth to children with FAS or partial FAS (FAS = 22, partial FAS = 16) and the other 95 women whose children did not have FAS or partial FAS. Examining four current drinking measures, the data reveal that the mothers of FAS or partial FAS children consumed 8.3 drinks in the seven days preceding their interview, compared to 6.2 for the women whose children did not have FAS or partial FAS. During that same time frame, 33.3% of the mothers of FAS or partial FAS children binged (3+), while 40.3% of the mothers whose children did not have FAS or partial FAS binged. Both groups of women consumed similar amounts of

alcohol in the 30 days preceding their interview; mothers of FAS or partial FAS children consumed 32.7 drinks vs. 33.7 for the mothers whose children did not have FAS or partial FAS. The women whose children did not have FAS or partial FAS report being "high" or drunk a few more times in the 12 months preceding their interview than the women whose children were diagnosed as FAS or partial FAS (17.1 vs. 15.8). None of these comparisons reached a level of statistical significance. These data suggest that even those women whose children do not have FAS could be considered at risk for producing a future child with FAS, but threshold and outcomes are different individual by individual. One protective factor in this comparison is age. The Plains women whose children did not have FAS were significantly younger than the women giving birth to children with FAS or partial FAS at the time of the interview (30.7 vs. 38.1,  $t = 3.65, P < 0.01$ ) and at the birth of the index child (23.4 vs. 27.8,  $t = 2.49, P = 0.014$ ). We will explore some of these differential risk factors below.

TABLE V. Use of Alcohol Among Women During Pregnancy

Variable	Plains prenatal clinic	Plains developmental clinic <sup>a</sup>	South African mothers of children with FAS <sup>b</sup>	Statistical tests
Percent who consumed alcohol				
n =	661	116	88	
Yes	16.2	47.0	94.3	$\chi^2 = 257.57, 2 \text{ df}, P < .01$
Among those who were drinking, on days she drank, how many drinks did woman usually drink				
n =	106	50	83	
Mean (SD)	4.3 (2.83)	7.7 (5.04)	7.0 (5.64) <sup>c</sup>	$F = 13.23, P < .01$
Among those who were drinking, how often over 30 days did woman drink her usual amount				
n =	97	49	82	
Mean (SD)	1.7 (1.32)	7.7 (8.36)	10.0 (1.96)	$F = 95.48, P < .01$
Among those who were drinking, did woman binge (consume three or more drinks), %				
n =	106	55	83	
Yes	68.9	89.1	75.9 <sup>c</sup>	$\chi^2 = 8.08, 2 \text{ df}, P < .05$
Among those who were drinking, did woman binge (consume five or more drinks), %				
n =	106	53	83	
Yes	40.6	73.6	68.7 <sup>c</sup>	$\chi^2 = 22.28, 2 \text{ df}, P < .01$
Among those who were drinking, total number of drinks woman consumed over 30 days				
n =	105	47	83	
Mean (SD)	8.6 (12.51)	71.2 (107.66)	55.4 (54.76) <sup>c</sup>	$F = 24.44, P < .01$

<sup>a</sup>Control children for the developmental clinic part of the study were matched by sex and age ( $\pm 6$  months) to children with a diagnosis of FAS. Mothers of those two samples of children became the matched cases and controls.

<sup>b</sup>For the first wave of data from South Africa, once the children with a diagnosis of FAS were identified, they were matched by sex, age, and classroom to control children. For the second wave of data from South Africa, control children were randomly selected. Mothers of those four samples of children became the matched cases and controls.

<sup>c</sup>Estimated from drinking logs at time of interview: daily, seven and 30 days.

## DISCUSSION

Substantial alcohol consumption just before and during pregnancy is confirmed in all three of these samples, and many of the risk factor levels conform to expectations from the literature. Included in the prenatal clinic sample are some questions about each woman's knowledge, attitudes, and beliefs about the use of alcohol during pregnancy. Ninety-eight percent of the prenatal clinic women knew that they should not drink any alcohol during their pregnancy; however, 6–10% were continuing to binge drink occasionally. One or more of the children born to women from the developmental clinic sample were suspected of prenatal alcohol exposure or were having problems that were believed to be related to alcohol exposure. More than half of the children in the developmental clinic sample were exposed to alcohol. At the time of inter-

view, all but a few of these women were still in the childbearing years (15–44). Among those developmental clinic women who confirmed drinking just before and during pregnancy, an average of 70 drinks was reported over a 30-day period, a higher mean number of drinks than the South African women who have borne at least one child with FAS (52 drinks). In addition to confirming the value of cutting down or quitting drinking during pregnancy, this raises the question of different thresholds of consumption in different populations.

While binge drinking is described in the literature as the consumption of five or more drinks per occasion, we also include a threshold in our studies of three drinks per occasion for women because of physiologic differences between women and men and because there is a major risk for FASDs even at this level of sporadic drinking. Indeed,

research by Day et al. [2002], Baer et al. [2003], and others [Jacobson and Jacobson, 1994; Streissguth et al., 1990, 1994, 1996] suggests that alcohol, even in relatively light doses, may change the fetus in ways that persist long after birth, particularly behavior and intellectual functioning.

Certainly, higher age at pregnancy has been confirmed in this paper as a major risk factor for FAS. Length of drinking career is also a factor. But additionally, from our studies over the years, we have begun to suspect that smaller women are more likely to have lower thresholds of drinking for producing FAS symptoms than larger women. Furthermore, heavy alcohol consumption can interfere with regular eating habits and result in less body mass, as can poor nutrition. Body mass index (BMI) data conform to these observations; the women in the developmental clinic sample who bore children with FAS or

partial FAS ( $n = 8$ ) had an average BMI of 29.7 vs. 31.5 for the women whose children did not have FAS or partial FAS ( $n = 35$ ) ( $t = 0.55$ ,  $P = 0.583$ ).

Consumption data for the South African women seem puzzling at first. The South African women had little prior knowledge of the risk of drinking during pregnancy. Most of the South African women who had children with FAS came from families with several generations of individuals who drank heavily, and the mothers themselves continued to drink heavily during the index pregnancy. Equally important is the issue of nutrition. In South Africa, we have been impressed by the relative smallness of many Colored women and their children. The mothers of children with FAS were not only much smaller than women in the United States, specifically Plains Indian women, but they were smaller than many other South African Colored women in the same population. It follows then that even though the South African women report consuming less alcohol per occasion, they have less body mass to assist in dispensing and metabolizing the alcohol they consume. There may be, therefore, substantial differential risk based on body size and also nutrition. The South African mothers of children with FAS had a mean BMI of 24.9 vs. 27.2 for South African controls ( $t = 2.184$ ,  $P = 0.03$ ). Therefore, even at lower levels of gravidity, age, and other risk variables, these small, less adequately nourished South African women may be at higher risk than the Plains Indian women because of body size.

### Differential Diagnosis

Because high-risk environmental and behavioral conditions vary between populations and risk factors also vary among individual women (e.g., size and differential genetic traits yet to be determined), we conclude with some comments on the importance of collecting a full behavioral and genetic history of the child and his/her family. The "face" of FAS is not unique [Jones, 1997]. By means of a variety of mechanisms,

ethanol leads to a highly characteristic pattern of abnormalities related to cell migration and cell death in the premigratory and migratory neural crest cells that normally populate midfacial structures. This hypoplasia of the midface can be considered to be in the spectrum of holoprosencephaly, a severe problem with early morphogenesis of the forebrain [Cohen and Shiota, 2002]. In fact, recent data suggest that ethanol causes a marked downregulation of *sonic hedgehog* (*Shh*) and other components of the hedgehog gene-signaling network, a network necessary for early forebrain and midfacial development [Ahlgren et al., 2002]. *Shh* may represent a pivotal checkpoint in craniofacial development on which many environmental and growth factors act. Thus, the facial characteristics of FAS are the nonspecific visible end results of the effects of alcohol on the developing forebrain.

Therefore, in the evaluation of children with disabilities who have been prenatally exposed to alcohol, it is important to rule out both genetic and other teratogenic disorders with similar abnormalities in midfacial development that may have morphological similarities to children with FASDs. Children with prenatal toluene exposure (following maternal inhalant abuse) have been shown to manifest facial characteristics similar to those observed in FAS [Pearson et al., 1994]. Similarly, children with a variety of genetic disorders, including chromosomal anomalies, Cornelia deLange syndrome, Williams syndrome, blepharophimosis syndrome, and velocardiofacial syndrome, among others, can be associated with short palpebral fissures and midfacial hypoplasia [Jones, 1997]. Thus, a careful family history, maternal and pregnancy history (including exposure to other potential teratogens), and dysmorphology examination are essential in evaluating children with prenatal alcohol exposure.

### CONCLUSIONS

Comparisons of these three samples from two very distinct racial/ethnic popula-

tions underscore the fact that maternal risk may vary substantially by population. Also, as shown in case-control studies within these populations, risk is not equal from one individual to the next [Viljoen et al., 2002]. The threshold of alcohol consumption for FAS, normative patterns of consumption before, during, and after pregnancy, and social, cultural, and demographic patterns/variables differ widely by human group and individual. Abel [1998] has written of the American paradox. It holds that even though Americans have a lower per capita consumption of alcohol than most every European country, higher rates of FAS have been reported in the United States [see also Institute of Medicine, 1996]. Binge drinking has been suggested as one major factor for the higher FAS rate in the United States, and this pattern is also very influential in South Africa. Nutrition, body size, normative perceptions (expectations), education, low SES, and cultural practices, including patterns of food consumption, also play a role in alcohol metabolism, BACs, and the teratogenic effects on the fetus. The prenatal clinic and developmental clinic samples, although practicing binge drinking in the prepregnancy period similar to or even more severe than the South African women who have children with FAS, are more likely to quit drinking or cut down during pregnancy. Furthermore, the developmental clinic women are much larger women (BMI = 31.0 vs. 24.9 for South African women) who are better nourished in both the short and long term. These factors may produce a relative protection for the developmental clinic women and an increased relative risk for the South African women.

Finally, it should be noted that some women in the prenatal clinic sample and many women in the developmental clinic sample are candidates for selective prevention (e.g., information and referral for alcohol abuse screening). Those women who have given birth to children with FAS must receive indicated prevention, such as case management and alcohol abuse therapy as outlined in the IOM report [Institute of Medicine, 1996, Chapter 7].

## ACKNOWLEDGMENTS

We thank Joan Alvord, Lorinda Beck, Lesley Brooke, Julie Croxford, Mabel Granados, Loretta Hendricks, and Cudore Snell, who also collected some of the data. We thank David Buckley, Matthew Hernandez, and Gwyneth Moya, who assisted with data processing. The opinions expressed in this paper are those of the authors and do not necessarily reflect the view of the IHS.

## REFERENCES

- Abel EL. 1995. An update on the incidence of FAS: FAS is not an equal opportunity birth defect. *Neurotoxicol Teratol* 17:437-443.
- Abel EL. 1998. Fetal alcohol abuse syndrome. New York: Plenum Press. p 139-157.
- Abel EL, Hannigan JH. 1995. Maternal risk factors in fetal alcohol syndrome: provocative and permissive influences. *Neurotoxicol Teratol* 17:445-462.
- Abel EL, Sokol RJ. 1986. Maternal and fetal characteristics affecting alcohol's teratogenicity. *Neurobehav Toxicol Teratol* 8:329-334.
- Adnams CM, Kodituwakku PW, Hay A, Molteno CD, Viljoen D, May PA. 2001. Patterns of cognitive-motor development in children with fetal alcohol syndrome from a community in South Africa. *Alcohol Clin Exp Res* 25:557-562.
- Ahlgren SC, Thakur V, Bronner-Fraser M. 2002. Sonic hedgehog rescues cranial neural crest from cell death induced by ethanol exposure. *Proc Natl Acad Sci USA* 99:10476-10481.
- Astley SJ, Bailey D, Talbot C, Clarren SK. 2000a. Fetal alcohol syndrome (FAS) primary prevention through FAS diagnosis. I. Identification of high-risk birth mothers through the diagnosis of their children. *Alcohol Alcohol* 35:499-508.
- Astley SJ, Bailey D, Talbot C, Clarren SK. 2000b. Fetal alcohol syndrome (FAS) primary prevention through FAS diagnosis. II. A comprehensive profile of 80 birth mothers of children with FAS. *Alcohol Alcohol* 35:509-519.
- Bad Hart Bull L, Kvigne V, Leonardson GR, Lacina L, Welty TK. 1999. Validation of a self-administered questionnaire to screen for prenatal alcohol use in Northern Plains Indian women. *Am J Prev Med* 16:240-243.
- Baer JS, Sampson PD, Barr HM, Connor PD, Streissguth AP. 2003. A 21-year longitudinal analysis of the effects of prenatal alcohol exposure on young adult drinking. *Arch Gen Psychiatry* 60:377-385.
- Bagheri MM, Burd L, Martsolf JT, Klug MG. 1998. Fetal alcohol syndrome: maternal and neonatal characteristics. *J Perinat Med* 26:263-269.
- Cohen MM Jr, Shiota K. 2002. Teratogenesis of holoprosencephaly. *Am J Med Genet* 109:1-15.
- Darrow SL, Russel M, Cooper ML, Mudar P, Frone MR. 1992. Sociodemographic correlates of alcohol consumption among African-American and white women. *Women Health* 18:35-51.
- Day NL, Leech SL, Richardson GA, Cornelius MD, Robles N, Larkby C. 2002. Prenatal alcohol exposure predicts continued deficits in offspring size at 14 years of age. *Alcohol Clin Exp Res* 26:1584-1591.
- Duimstra C, Johnson D, Kutsch C, Wang B, Zentner M, Kellerman S, Welty T. 1993. A fetal alcohol syndrome surveillance pilot project in American Indian communities in the Northern Plains. *Public Health Rep* 108:225-229.
- Institute of Medicine. 1996. Fetal alcohol syndrome: diagnosis, epidemiology, prevention, intervention, research. Washington, DC: National Academy Press. p 63-81, 82-99; 123-153.
- Jacobson JL, Jacobson SW. 1994. Prenatal alcohol exposure and neurobehavioral development: where is the threshold? *Alcohol Health Res World* 18:30-36.
- Jones KL. 1997. Smith's recognizable patterns of human malformation, 5th ed. Philadelphia: W.B. Saunders Co. p 555-558.
- Jones KL, Smith DW. 1973. Recognition of the fetal alcohol syndrome in early infancy. *Lancet* 2:999-1001.
- Jones KL, Smith DW, Ulleland CN, Steissguth AP. 1973. Pattern of malformation in offspring of chronic alcoholic mothers. *Lancet* 1:1267-1271.
- Karp RJ, Qazi QH, Moller KA, Angelo WA, Davis JM. 1995. Fetal alcohol syndrome at the turn of the 20th century: an unexpected explanation of the Kalikak family. *Arch Pediatr Adolesc Med* 149:45.
- Kaskutas LA, Graves K. 2001. Pre-pregnancy drinking: how drink size affects risk assessment. *Addiction* 96:1199-1209.
- Kvigne VL, Leonardson GR, Borzelleca J, Brock E, Neff-Smith J, Welty TK. 2003. Characteristics of mothers who have children with fetal alcohol syndrome or some characteristics of fetal alcohol syndrome. *J Am Board Fam Pract* 16:296-303.
- Lemoine P, Harosusseau H, Borteyru JP, Menuet JC. 1968. Les enfants des parents alcooli-ques: anomalies observees a propos de 127 cas. *Quest Med* 21:476-482.
- Little RE, Wendt JK. 1991. The effects of maternal drinking in the reproductive period: an epidemiologic review. *J Subst Abuse* 3:187-204.
- Little BB, Snell LM, Gilstrap LC III, Gant NF, Rosenfeld CR. 1989. Alcohol abuse during pregnancy: changes in frequency in a large urban hospital. *Obstet Gynecol* 74:547-550.
- London L. 1999. Addressing the legacy of the Dop system: tackling alcohol abuse among South African farm workers. *Urban Health Dev Bull* 2:33-35.
- London L. 2000. Alcohol consumption amongst South African farm workers: a challenge for post-apartheid health sector transformation. *Drug Alcohol Depend* 59:199-206.
- Maier SE, West JR. 2001. Drinking patterns and alcohol-related birth defects. *Alcohol Res Health* 25:168-174.
- May PA. 1995. A multiple-level, comprehensive approach to the prevention of fetal alcohol syndrome (FAS) and other alcohol-related birth defects (ARBD). *Int J Addict* 30:1549-1602.
- May PA, Gossage JP. 2001. Estimating the prevalence of fetal alcohol syndrome: a summary. *Alcohol Res Health* 25:159-167.
- May PA, Hymnbaugh KJ, Aase JM, Samet JM. 1983. Epidemiology of fetal alcohol syndrome among American Indians of the Southwest. *Soc Biol* 30:374-387.
- May PA, Brooke L, Gossage JP, Croxford J, Adnams C, Jones KL, Robinson L, Viljoen D. 2000. Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. *Am J Public Health* 90:1905-1912.
- May PA, McCloskey J, Gossage JP. 2002. Fetal alcohol syndrome among American Indians: epidemiology, issues, and research review. NIAAA monograph 37. Bethesda, MD: U.S. Department of Health and Human Services.
- Parry CDH. 2000. Alcohol problems in developing countries: challenges for the new millennium. *Suchtmed* 2:216-220.
- Parry CDH, Bhana A, Myers B, Pluddemann A, Fisher AJ, Peden MM, Morojole NK. 2002. Alcohol use in South Africa: findings from the South African Community Epidemiology Network on Drug Use (SACENDU) Project. *J Stud Alcohol* 63:430-435.
- Pearson MA, Hoyme HE, Seaver LH, Rimsza ME. 1994. Toluene embryopathy: delineation of the phenotype and comparison with fetal alcohol syndrome. *Pediatrics* 93:211-215.
- Pierce DR, West JR. 1986. Alcohol-induced microencephaly during the third trimester equivalent: relationship to dose and blood alcohol concentration. *Alcohol* 3:185-191.
- Pierog S, Chandavasu O, Wexler I. 1979. The fetal alcohol syndrome: some maternal characteristics. *Int J Gynaecol Obstet* 16:412-415.
- Russel M. 1991. Clinical implications of recent research on the fetal alcohol syndrome. *Bull NY Acad Med* 67:207-222.
- Sobell LC, Sobell MB, Leo GI, Cancilla A. 1988. Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. *Br J Addict* 83:393-402.
- Sobell LC, Agrawal S, Annis H, Ayala-Velazquez H, Echeverria L, Leo GI, Rybakowski JK, Sandahl C, Saunders B, Thomas S, Ziolkowski M. 2001. Cross-cultural evaluation of two drinking assessment instruments: alcohol timeline followback and inventory of drinking situations. *Subst Use Misuse* 36:313-331.
- Sokol RJ, Miller SI, Reed G. 1980. Alcohol abuse during pregnancy: An epidemiologic study. *Alcoholism: Clinical and Experimental Research* 4:135-145.
- Sokol RJ, Ager J, Martier S, Debanne S, Ernhart C, Kuzma J, Miller SI. 1986. Significant determinants of susceptibility to alcohol teratogenicity. *Ann NY Acad Sci* 447:87-102.
- Streissguth AP, Barr HM, Sampson PD. 1990. Moderate prenatal alcohol exposure: effects on child IQ and learning problems at age 7 1/2 years. *Alcohol Clin Exp Res* 15:662-669.

- Streissguth AP, Barr HM, Sampson PD, Bookstein FL. 1994. Prenatal alcohol and offspring development: the first fourteen years. *Drug Alcohol Depend* 36:89–99.
- Streissguth AP, Barr HM, Kogan J, Bookstein FL. 1996. Understanding the occurrence of secondary disabilities in clients with fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE). Final report to the US Centers for Disease Control and Prevention, Grant No. R04/CCR008515. Seattle, Washington: Fetal Alcohol and Drug Unit, Department of Psychiatry. 71p.
- Sullivan WC. 1899. A note on the influence of maternal inebriety on the offspring. *J Ment Sci* 45:489–503.
- Viljoen DL, Carr LG, Foroud TM, Brooke L, Ramsay M, Li TK. 2001. Alcohol dehydrogenase-2\*2 allele is associated with decreased prevalence of fetal alcohol syndrome in the mixed-ancestry population of the Western Cape Province, South Africa. *Alcohol Clin Exp Res* 25:1719–1722.
- Viljoen D, Croxford J, Gossage JP, Koditwakku PW, May PA. 2002. Characteristics of mothers of children with fetal alcohol syndrome in the Western Cape Province of South Africa: a case control study. *J Stud Alcohol* 63:6–17.
- West JR, Goodlett CR. 1990. Teratogenic effects of alcohol on brain development. *Ann Med* 22:319–325.

# Characteristics of Mothers of Children with Fetal Alcohol Syndrome in the Western Cape Province of South Africa: A Case Control Study\*

DENIS VILJOEN, M.D., JULIE CROXFORD, R.N., B.S.,<sup>†</sup> J. PHILLIP GOSSAGE, PH.D.,<sup>†</sup>  
PIYADASA W. KODITUWAKKU, PH.D.,<sup>†</sup> AND PHILIP A. MAY, PH.D.<sup>†</sup>

*Department of Medical Genetics, University of Witswatersrand, South African Institute for Medical Research & Foundation for Alcohol Related Research, University of Cape Town, Cape Town, South Africa*

**ABSTRACT.** *Objective:* Factors associated with alcohol consumption during pregnancy and with fetal alcohol syndrome (FAS) births were examined as part of a larger epidemiologic study of FAS in a community in the Western Cape Province of South Africa. *Method:* Using retrospective case-control methodology, 31 mothers who had given birth to FAS children 6 to 9 years previously were compared with 31 matched controls on a variety of demographic, socioeconomic, drinking, family and maternity variables. Descriptive analyses were utilized to determine major differential characteristics between the two groups. *Results:* In this community with a very high rate of FAS and rather uniform low socioeconomic status, the two groups were found to be comparable with respect to age, annual income, ethnic background, age of initiation of regular drinking, age at birth of the index child, gravidity and parity.

However, mothers of FAS children reported initiating drinking at an earlier age, as well as reporting higher rates of heavy alcohol consumption in their extended family, current use of alcohol, drinking before and during pregnancy, and smoking of tobacco (percentage who smoke) during each trimester of the pregnancy. Mothers of FAS children had lower educational attainment and reported lower religiosity than control mothers. *Conclusions:* This study in South Africa draws upon the experience of mothers of 31 children with FAS to confirm many of the same high-risk variables identified in maternal risk studies in the United States and Europe. Some factors associated with less maternal alcohol abuse in this high-risk population were also identified, which may be helpful for implementing prevention in this region as well as in other developing countries. (*J. Stud. Alcohol* 63: 6-17, 2002)

SINCE THE FIRST recognition and documentation of fetal alcohol syndrome (FAS) as a distinct birth defect (Jones and Smith, 1973), the search for unique maternal characteristics, risk factors and protective factors has been a goal of researchers, both for determining the specific etiology of FAS and for prevention. Epidemiologic studies of mothers who drink during pregnancy have identified traits, in addition to drinking alcohol heavily during pregnancy, that are strongly associated with FAS births. Women who were older, multigravidas, not currently married, and who smoked cigarettes and used other drugs were more likely to have children with FAS (Sokol et al., 1980). Later studies identified a greater risk for FAS among women characterized by advanced maternal age, high parity, low socioeco-

nomical status (SES), African-American race and with severe drinking patterns, most particularly heavy episodic use (Abel, 1995; Abel and Hannigan, 1995; Abel and Sokol, 1986; Darrow et al., 1992; Sokol et al., 1986). Studies of mothers who had produced children with what was then diagnosed and referred to as "fetal alcohol effects" (FAE; a lesser degree and consistency of symptoms than the full syndrome) provided further understanding of maternal risk factors.

Alcohol, in a dose response effect, is likely to produce not only FAS, but such individual features as growth and developmental delay, neurobehavioral defects, microcephaly and craniofacial anomalies in children born to women who are older and of low socioeconomic status (Day et al., 1991, 1999; Ernhart et al., 1987; Jacobson et al., 1996). FAE is now referred to as alcohol-related birth defects (ARBD) and alcohol-related neurodevelopmental disorder (ARND) (Stratton et al., 1996). These lesser effects, when combined with the prevalence of FAS, are believed to affect approximately 1% of all births in the United States (Sampson, et al., 1997).

The influence of socioeconomic status on the characteristics and rates of FAS, ARBD and ARND has been a particularly common finding in various studies, and the association appears to hold even in one retrospective control study. Bingol et al. (1987b) compared two groups of alco-

Received: February 19, 2001. Revision: August 7, 2001.

\*This project was funded by National Institute on Alcohol Abuse and Alcoholism grant R01 AA09440, by the National Institutes of Health Office of Research on Minority Health, and by the Foundation for Alcohol Related Research of South Africa.

<sup>†</sup>Julie Croxford was with the Foundation for Alcohol Related Research, University of Cape Town, Cape Town, South Africa. J. Phillip Gossage, Piyadasa W. Kodituwakku and Philip A. May are with the Center on Alcoholism, Substance Abuse, and Addictions, University of New Mexico (UNM-CASAA), Albuquerque, NM. Correspondence should be addressed to Philip A. May, UNM-CASAA, 2650 Yale SE, Albuquerque, NM 87106, or via email to pmay@unm.edu.

holic women of different social strata who drank an average of 6 ounces of absolute alcohol a day (12 drinks) and who had begun drinking during their teens. The rate of FAS and alcohol-related effects in this study was 16 times greater among women of low SES than among the upper middle-class sample (4.6% vs 70.9%). There was variance between the two groups in family histories of alcoholism, percentage of college graduates, percent married and other variables; however, the women's current SES was highly influential (Bingol et al., 1987b). Abel's (1995) summary of the worldwide epidemiology literature also demonstrates a consistently elevated rate of FAS births among African-American women of low SES, when coupled with drinking heavily.

In the United States and other developed countries, between 16% and 32% of women who are pregnant drink during gestation (Centers for Disease Control and Prevention, 1997; Day et al., 1993; Serdula et al., 1991). In some other western countries, maternal drinking is substantially higher, reaching over 50% (Godel et al., 1992; Waterson and Murray-Lyon, 1989). Obvious variations in this percentage of at-risk drinkers exist throughout the world, with subpopulations of high-risk drinkers contained within the overall category of female drinkers.

Studies of alcohol dependence and alcohol misuse have reported that these behaviors do run in families, therefore implying heritability or a genetic influence in susceptibility. Twin studies have estimated that the heritability for susceptibility to alcoholism in women is in the range of 50% to 60% (Kendler et al., 1992). Among men, those who came from families with a large number of alcoholics have been shown to have more alcohol misuse than are those from families with a low density of alcoholics (McCaul et al., 1991; Schuckit, 1998; Schuckit and Smith, 1996). Siblings with a history of alcohol-related illness and frequent drinking with family members were associated in one study with women who continued to drink throughout pregnancy (Smith et al., 1987). Epidemiologic studies of the occurrence of FAS have also shown familial clustering (Abel, 1988; May et al., 1983; Pierog et al., 1979). Families with FAS children, particularly those with multiple FAS cases, present a tremendous challenge both to clinicians and prevention programs (Davis and Lipson, 1984). Influences on maternal drinking are complex and originate from a combination of factors: biological, familial, social and psychological (Gomberg, 1993). Prevention of FAS is thus a multifaceted enterprise (May, 1996).

The general literature regarding alcohol misuse among women (i.e., that which does not specifically address prenatal drinking) contributes additional information for understanding maternal drinking and risk factors for FAS (Stratton et al., 1996). Women at high risk for alcohol-related problems and for continued drinking have some of the following traits: cohabitation with men when not mar-

ried, part-time employment, frequent sexual dysfunction and living with others (usually male) who drink heavily (Wilsnack, 1989). Alcohol misuse is frequently found among young women (ages 21 to 34) who are the daughters of alcoholics (either mother or father), and who report regular drinking early in life (Wilsnack, 1991; Wilsnack and Beckman, 1984; Wilsnack et al., 1991). Furthermore, these women commonly use and misuse other drugs, including tobacco (Serdula et al., 1991; Sokol et al., 1986). Their social context is characterized by many alcohol-use or drug-use situations that are socially condoned, sanctioned and/or at least not disapproved of by significant others (Shore and Batt, 1991; Shore and Pieri, 1992). In addition, women who misuse alcohol report multiple social and psychological risk factors, particularly low self-efficacy, low purpose in life, depression and feelings of powerlessness (Baily, 1990; Schlesinger et al., 1990).

Whereas the above variables may imply relative helplessness in certain contexts, some authors have identified protective factors (e.g., cultural support and unique personality traits) that assist particular individuals in avoiding alcohol misuse (Blume, 1990). Further explication and clarification of protective factors are needed for evidence-based prevention and intervention initiatives (Hanna et al., 1993; Stratton et al., 1996; Jacobson et al., 1991; Schmidt et al., 1990), especially in unstudied and unique populations.

### *The study setting*

This study attempted to identify specific risk factors for drinking heavily during pregnancy and for FAS, in a community in the Western Cape Province of South Africa. The population of the community was enumerated in 1996 as 45,225 (35,364 urban and 9,861 rural) (Republic of South Africa, 1997). The majority of the population is "Cape coloured" (mixed race), with less than 25% white and a few black Africans. The "coloured" population is polyethnic and polygenetic, with influences from several indigenous South African tribes and European and Asian admixture. This community is similar to others in grape-growing and wine-producing regions, in which problem-drinking practices and patterns have existed among the agriculture laborers for multiple generations. For many years, alcohol was supplied to workers on a daily basis as partial payment for labor, a system of payment referred to as the "Dop system." Although outlawed today, vestiges of the system still exist in patterns of frequent and severe episodic drinking (Crome and Glass, 2000). It is still apparent today that alcohol is a favored, valued and expected commodity among many of the local population of workers, who receive low pay and who live in very humble circumstances.

A high rate of problematic drinking behavior has been documented in the region. As measured by standard screening instruments (e.g., CAGE and MAST) and serum GGT

levels, alcohol misuse was found to affect 83% of the male fruit-farm workers (London et al., 1995). This was, by far, the highest rate in any South African population studied by that time (Parry and Bennetts, 1998). A more recent study classified 87% of the farm workers in the region as problem drinkers; half consume more alcohol per week than is considered safe (>210 g) and 9.3% consume amounts considered dangerous (>490 g per week) (London, 2000).

In this study community and others like it, a number of commercial sources of alcohol exist. Although alcohol may be consumed on a daily basis (through "Dop") on some farms, it is quite common for a substantial segment of the population to participate in regular and extended drinking parties on the weekends and, occasionally, on weekday evenings. Wine and beer are the beverages of choice and are relatively inexpensive. Drinking at "shebeens" (informal bars), in the home and in other venues is a major form of recreation for a substantial subculture of the population.

Drinking during pregnancy has been reported to be frequent in parts of the Western Cape, even among prenatal clinic patients. Croxford and Viljoen (1999) reported that 34.4% of prenatal patients in the large metropolitan areas of the Cape drank during pregnancy, as did 46.1% to 50.8% in the rural Cape regions (Croxford, 1998). Concern about FAS has grown in recent years in parts of South Africa (National Institute on Alcohol Abuse and Alcoholism, 1996, 1998).

The study of the characteristics of Western Cape mothers who have FAS children is useful for understanding their lifestyle, and maternal drinking in this region, among women in general and, more particularly, in other parts of the developing world. Since the current study was the first ever undertaken on the epidemiology of FAS in a South African community, no specific hypotheses were formulated.

## Method

### *Participants*

The data in this article are an integral part of a larger epidemiologic study of the prevalence and characteristics of FAS in the Western Cape (May et al., 2000). Subjects in this study of maternal characteristics were chosen based on the characteristics of their children. Children in Sub-A (first grade) classrooms ( $N = 992$ ) received an initial brief (Tier I) screening for height, weight and head circumference. After local growth and development norms were established, those who were below the 10th percentile for head circumference and/or both height and weight were also given full dysmorphology evaluations by a team of international experts on FAS. Dysmorphologists working in blinded teams utilized established active-case ascertainment methodologies, including a quantified checklist for a preliminary diagnosis of FAS or not FAS. Fifty-three children were

identified with a preliminary diagnosis of FAS or possible FAS. Each of these 53 children received developmental and life-skills testing (Griffiths Intelligence and Developmental Test; Griffiths, 1984), and their mothers were interviewed extensively on various risk factors (Adnams et al., 2001). After all screening, testing and information gathering were completed by the blinded, independent examiners from each domain (dysmorphology, developmental and maternal), a case conference of the examiners determined the final diagnosis. Institute of Medicine (IOM; Stratton et al., 1996) criteria for FAS were followed: evidence of pre- and postnatal growth retardation, dysmorphology consistent with prenatal alcohol exposure and evidence of developmental delay. Maternal drinking data were used as confirmatory as per IOM criteria, and only one child was diagnosed with FAS in its absence.

The protocols and consent forms used for human subjects were approved by the University of New Mexico Medical School (HHRC 96-209) and the College of Arts and Sciences (01-93-86-9908). The methodology was also reviewed and approved by the University of Cape Town Ethics Committee, the Office of Protection from Research Risks (OPRR) of the National Institutes of Health, and by a single site assurance committee in the Western Cape community. All participating mothers provided active consent for inclusion in the study, and the parents and guardians also consented to FAS screening for their child.

FAS, as diagnosed by strict IOM criteria, was the focus of the study, and not ARBD or ARND. In the first-grade population, 46 children received a final diagnosis of FAS, yielding a very high (world record) in-school FAS rate of 46 per 1,000 (May et al., 2000). Because of the high-risk lifestyle of the mothers of FAS children, only 35 were accessible for follow-up study. Reasons for the others' inaccessibility, and the effect of the reduced sample, are presented in the Results section and in Table 1.

The control group consisted of the mothers of the control children in the epidemiology study. One control child was selected from the same grade and school as each FAS child, matched for age (within 1 year), gender and rural/urban residence. Of the 35 FAS children whose mothers were both alive and interviewed, we were able to match 31 to controls, exactly by gender, rural/urban school attendance and age (mean [SD] difference = 3.8 [3.5] months). Because of age differences (some FAS children were older than other first graders), perfect matches were not possible for four FAS children. Four mothers of FAS children and 20 controls were excluded as a result of the strict case-control matching process used in this study.

Most studies of maternal risk factors have studied women who drink alcohol during pregnancy; very few of these have had or will have children with FAS. This article focuses on the characteristics of mothers who have had FAS children (i.e., the highest risk mothers). Some researchers have re-

ported that a previous child with FAS is the single best indicator of maternal risk (Abel, 1988; May, 1995).

### Measures

The interview questions utilized in this study were drawn from questionnaires first developed among populations in the southwestern United States. They were adapted specifically for the South-African population and pilot tested in the target community. There are 114 items covering such basic demographics as residence; religion, and ethnicity; social and economic variables; family health; diet; and quantity, frequency, variability and social context of drinking. Questions focused on reconstructing the general characteristics of the women's lives, including history of drinking during the pregnancy of the index child. To establish rapport, nonthreatening questions were asked first, regarding where they were born, grew up, worked, their parents' lives and deaths, education, diet, child bearing and general health. Alcohol consumption responses have been found to be more accurate when included in such a format, especially in the context of dietary questions (King, 1994).

In the alcohol section of the questionnaire, respondents were first asked about the drinking habits of their parents, siblings and friends. The context and details of the mother's current drinking then were explored orally via a 1-week, day-by-day log methodology. Drinks were measured in standard ethanol units, in which one unit was a 340 ml can of beer (10.2 oz of 5% ethanol), 120 ml of wine (4 oz of 11.5% ethanol) or 44 ml of distilled spirits (1.5 oz of 86 proof). Respondents were shown pictures of standardized containers utilizing local brands and vessels familiar to them. Questions on current drinking were then used as benchmarks, for reconstructing drinking patterns during the period of gestation of the index child. This order refreshed the respondents' recall of drinking and life context before moving to sensitive and distant questions about life and pregnancy some years earlier.

Smoking was measured more directly. Local informants indicated that smoking purchases and practices were less stigmatized, more regular, more stable and memorable due to cost, lack of sharing of individual cigarettes and the need to pause from the daily routine to "roll" cigarettes. Respondents were asked how much tobacco (for hand-rolled) or packaged cigarettes they usually bought in a week (most were paid and went to town once a week) and smoked each day, currently and during the index pregnancy. Questions on other drugs utilized both open-ended and fixed-response items to assess the quantity, frequency and type of drugs used.

Interviews were performed in Afrikaans, the primary language of the area. All of the respondents, both mothers of FAS children and controls, were South African "coloured."

The analyses utilize comparisons of the two groups. Statistical tests (two-tailed) are used to assess significance (at <0.05) and, where appropriate, odds ratios (OR) are provided.

### Results

Of the 46 mothers of FAS children in the larger epidemiology study, 35 were interviewed (May et al., 2000). Six (13%) of the mothers were dead at the time of the study: four from violent death, one from a house fire and one from pulmonary tuberculosis. Five (10.9%) were so nomadic that either repeated attempts to contact them were unsuccessful, or they had permanently moved from the area. Thus, 11 mothers could not be reached for participation in the maternal characteristics study. In Table 1, the effect of missing mothers from the FAS sample is described via data from the FAS children in the study. There are only two significant differences, overall, between the FAS children of the interviewed mothers and the FAS offspring of mothers not available. The children of the missing mothers had significantly lower performance IQ scores and higher mean dysmorphology scores (more physical anomalies consistent with prenatal drinking). However, all of the nonsignificant

TABLE 1. Physical and mental development of FAS children by mother's availability for interview

Growth and development, mean (SD)	FAS children		Test, significance
	Mothers interviewed (n = 35)	Mothers not available for interview (n = 11)	
Height percentile	5.2 (4.15)	3.0 (1.41)	$t = 1.695, p = .097^a$
Weight percentile	11.4 (14.03)	3.8 (2.32)	$t = 1.760, p = .085^a$
Occipitofrontal circumference (%)	9.2 (17.45)	7.1 (8.11)	$t = 0.391, p = .697^a$
Mental age score	78.8 (13.39)	73.7 (13.11)	$t = 1.101, p = .277^a$
Performance IQ score	76.0 (10.79)	68.3 (10.53)	$t = 2.084, p = .043$
Verbal IQ score	72.4 (12.42)	69.3 (12.82)	$t = 7.300, p = .469^a$
Dysmorphology score <sup>b</sup>	9.9 (4.25)	13.0 (4.52)	$t = 2.060, p = .044$

<sup>a</sup>Not significant. <sup>b</sup>The higher the dysmorphology score the higher the frequency and severity of structural anomalies.

TABLE 2. Demographic, socioeconomic and maternity variables for mothers of children with FAS ( $n = 31$ ) and control mothers ( $n = 31$ )

	Mothers of children with FAS (SD)	Control mothers (SD)	Test,significance
<b>Demographic and socioeconomic</b>			
Age on day of interview (mean)	34.3 (7.7)	33.8 (7.2)	$t = 0.259, p = .797^a$
Residence (% rural)	64.5	64.5	$\chi^2 = 0.00, 1 \text{ df}, p = 1.000^a$
Educational attainment (years)	4.4 (3.2)	6.1 (2.6)	$t = 2.269, p = .027$
Religion (% practicing)	80.6	87.1	$\chi^2 = 0.48, 1 \text{ df}, p = .489, \text{OR} = 1.62^a$
Religiosity (church attendance or prayer)(%)			
Never or not very often	54.8	41.9	
Often	38.7	16.1	$\chi^2 = 4.239, 1 \text{ df}, p = .040^b$
Very often	6.5	41.9	$t = 2.402, p = .019$
Usual occupation (%)			
Factory worker	16.7	13.8	
Farm worker	50.0	34.5	
Office worker or other (i.e., cook, etc.)	33.3	51.7	$\chi^2 = 2.09, 2 \text{ df}, p = .351^a$
Employment status (%)			
Full-time	38.7	41.9	
Part-time	6.5	12.9	
Seasonal	29.0	16.1	
Unemployed	16.1	19.4	
Not employed/not looking for work	9.7	9.7	$\chi^2 = 1.94, 4 \text{ df}, p = .747^{a,b}$
Income (weekly in Rand)(mean)	99.8 (91.5)	135.5 (158.3)	$t = 1.083, p = .283^a$
<b>Maternity</b>			
Gravidity (mean)	3.9 (1.7)	3.1 (1.4)	$t = 1.953, p = .055^a$
Parity (pre- and full-term)(mean)	3.5 (1.5)	2.9 (1.2)	$t = 1.788, p = .078^a$
Miscarriages (mean)	0.5 (0.9)	0.3 (0.4)	$t = 1.085, p = .282^a$
Living children (mean)	3.3 (1.3)	2.8 (1.2)	$t = 1.527, p = .132^a$
Age at birth of the index child (mean)	26.7 (7.6)	26.3 (7.2)	$t = 0.233, p = .816^a$
Birth order of index child (mean)	2.9 (1.7)	2.3 (1.4)	$t = 1.479, p = .145^a$
Marital status during pregnancy with index child (%)			
Married	12.9	25.8	
Single	29.0	35.5	
Unmarried, living with partner	58.1	38.7	$\chi^2 = 2.73, 2 \text{ df}, p = .255^{a,b}$

<sup>a</sup>Not significant. <sup>b</sup>Cell(s) <5 detract(s) from significance.

differences also document greater severity of FAS traits in the children of the missing mothers. Therefore, although the entire sample of 35 FAS mothers contacted and interviewed (none refused) was very high risk, they may not represent all of the very highest risk mothers of the FAS children. The results that follow present a comparison only of the two groups of the 31 matched cases and controls.

The mothers of FAS children and controls in this sample (Table 2) did not differ significantly by age, current rural/urban residence, profession of a religion, usual occupation, current employment status or weekly income, although the indicators were generally poorer for the FAS mothers. This provides validity to matching via the case control design. By South African standards, they were of relatively similar background and SES. By U.S. standards, respondents had a 1997 weekly income of \$22 to \$30; all, therefore, had very humble economic resources. Two variables in this category were significant: educational attainment and religiosity. Mothers of FAS children had significantly less formal education (1.7 years [28%] less), and were less likely to prac-

tice regular religious behaviors (measured by church attendance and prayer). Therefore, in spite of the two groups being relatively equal in SES, two specific social risk factors were identified in this category of SES and demographic variables.

Table 2 also highlights the maternity variables for the two groups. FAS mothers did not differ from controls on any of the standard measures commonly used in studies of this type: gravidity, parity, miscarriage, number of living children, age at birth of index child, birth order of index child or marital status during pregnancy of index child. All of the differences between the two groups, however, are in the direction predicted by the extant literature (e.g., higher gravidity, parity, miscarriage, etc. for FAS mothers). If one-tailed test criteria were used for gravidity and parity, they would be significantly different between groups. The lack of significant difference in maternal age is addressed in the Discussion section.

Details of the drinking habits of the family and friends reported by the maternal informants are presented in Table

TABLE 3. Reported drinking habits of family and friends of mothers of children with FAS ( $n = 31$ ) and control mothers ( $n = 31$ )

Measures of alcohol consumption	Mothers of children with FAS	Control mothers	Test, significance
Drinking habits of woman's father (%)			
Nondrinker or light drinker	27.6	22.2	
Occasional or moderate drinker	6.9	25.9	
Frequent or heavy drinker	48.3	33.3	$\chi^2 = 4.08, 3 \text{ df}, p = .253^{a,b}$
Has had problems with alcohol	17.2	18.5	$\chi^2 = 1.08, 1 \text{ df}, p = .298, \text{OR} = 1.76^{a,c}$
Drinking habits of woman's mother (%)			
Nondrinker or light drinker	51.6	77.4	
Occasional or moderate drinker	12.9	6.5	
Frequent or heavy drinker	25.8	9.7	$\chi^2 = 4.74, 3 \text{ df}, p = .192^{a,b}$
Has had problems with alcohol	9.7	6.5	$\chi^2 = 3.03, 1 \text{ df}, p = .082, \text{OR} = 2.86^{a,c}$
Drinking habits of woman's brothers (%)			
<i>N</i>	57	83	
Nondrinker or light drinker	35.1	43.4	
Occasional or moderate drinker	10.5	21.7	
Frequent or heavy drinker	43.9	24.1	$\chi^2 = 7.14, 3 \text{ df}, p = .067^a$
Has had problems with alcohol	10.5	10.8	$\chi^2 = 5.22, 1 \text{ df}, p = .022, \text{OR} = 2.22^c$
Drinking habits of woman's sisters (%)			
<i>N</i>	70	86	
Nondrinker or light drinker	57.1	72.1	
Occasional or moderate drinker	5.7	19.8	
Frequent or heavy drinker	30.0	4.6	$\chi^2 = 23.46, 3 \text{ df}, p = .000^b$
Has had problems with alcohol	7.1	3.5	$\chi^2 = 19.46, 1 \text{ df}, p = .000, \text{OR} = 6.67^c$
Drinking habits of father of index child during index pregnancy (%)			
Nondrinker or light drinker	6.5	37.9	
Occasional or moderate drinker	3.2	20.7	
Frequent or heavy drinker	77.4	34.5	$\chi^2 = 16.08, 3 \text{ df}, p = .001^b$
Has had problems with alcohol	12.9	6.9	$\chi^2 = 16.15, 1 \text{ df}, p = .000, \text{OR} = 13.22^c$
Drinking habits of woman's best friend (%)			
Does not have a best friend	38.7	19.4	
Nondrinker or light drinker	29.0	71.0	
Occasional or moderate drinker	12.9	6.5	
Frequent or heavy drinker	19.4	3.2	$\chi^2 = 11.69, 3 \text{ df}, p = .009^b$

<sup>a</sup>Not significant. <sup>b</sup>Cell(s) <5 detract(s) from significance. <sup>c</sup> $\chi^2$  calculated from data collapsed to  $2 \times 2$  table to maximize possibility of significance. The two categories of nondrinker or light drinker and occasional or moderate drinker were collapsed together and compared to the other two categories that were also collapsed together.

3. Many controls and mothers of FAS children reported fathers and mothers who drank heavily, but more of the maternal grandmothers of FAS children were heavy drinkers, as indicated in Table 3. This comparison approached significance when items were aggregated into a  $2 \times 2$  configuration by collapsing and comparing the two lowest-drinking categories (nondrinkers through moderate drinkers) with the two problem-drinking categories ( $p = .08$ ; odds ratio [OR] = 2.86). All the other variables are significantly different. Three were significant when tested in either the  $4 \times 2$  or  $2 \times 2$  configuration described above. The heavy-drinking pattern of the fathers of FAS children ( $p = .000$ ; OR = 13.22) is worth noting. Mothers of FAS children more frequently had brothers, sisters, male partners and friends who drank heavily. The mothers of FAS children live in an environment full of heavy drinkers. Yet social isolation is also an issue, for the last variable in Table 3 indicates that FAS women reported not having a "best friend" more frequently than did controls; and when they do have friends, those friends are more likely to be heavy drinkers ( $p = .009$ ).

The only two substances used by women in this Western Cape region were tobacco and alcohol; virtually none of the respondents reported use of any other drugs currently or during pregnancy. The two groups did differ significantly (Table 4) in the mean age at which they first drank alcohol ( $p < .05$ ), but not in the age at which they commenced regular drinking. All other variables were significant. Current use of alcohol, use prior to the pregnancy of the index child and use during all trimesters of the pregnancy were reported to be higher for the mothers of FAS children. Virtually all of the mothers of FAS children (81%) are current drinkers, compared with 45% of controls. Beer and wine constitute the vast majority of all alcoholic beverages consumed (not shown). When all respondents are considered, the average FAS mother currently drinks a mean (SD) of 13.0 (12.6) standard drinks per week compared to 2.8 (5.3) for the control sample. When current abstainers are eliminated from the analysis (six of the mothers of FAS children have quit), the mean drinks per week is 16.1 (12.1) for FAS mothers and 6.3 (6.4) for controls. Heavy drinking (5+ standard drinks per day) is by far the most prevalent

TABLE 4. Drinking and smoking behaviors of mothers of children with FAS ( $n = 31$ ) and control mothers ( $n = 31$ )

	Mothers of children with FAS (SD)		Control mothers (SD)		Test, significance
	Whole sample ( $n = 31$ )	Drinkers only ( $n = 25$ )	Whole sample ( $n = 31$ )	Drinkers only ( $n = 14$ )	
<b>Drinking variables</b>					
Age first drank alcohol (mean)	18.3 (3.3)		20.9 (6.2)		$t = 2.025, p = .047$
Age began drinking regularly (mean)	20.5 (4.7)		22.9 (6.9)		$t = 1.425, p = .161^a$
Current drinker (%)	80.6		45.2		$\chi^2 = 8.36, 1 \text{ df}, p = .004$
Current use of alcohol (mean drinks per week)	13.0 (12.6)	16.1 (12.1)	2.8 (5.3)	6.3 (6.4)	Whole sample, $t = 4.125, p = .000$ Drinkers only, $t = 2.804, p = .008$
Current consumption on weekends					
Friday (mean)	3.4	4.2	0.6	1.3	
Saturday (mean)	7.2	8.9	1.9	4.3	
Sunday (mean)	2.0	2.5	0.2	0.4	
Total for weekends (mean)	12.6	15.6	2.7	6.0	Whole sample, $t = 3.92, p = .000$ Drinkers only, $t = 2.86, p = .007$
Percentage on weekends	(97.7%)	(96.9%)	(51.3%)	(93.8%)	
<b>Drinking in months before pregnancy with index child (%)</b>					
Drank about the same (as current use)	19.4		48.4		
Drank less (than current use)	22.6		38.7		
Drank more (than current use)	58.1		12.9		$\chi^2 = 14.08, 2 \text{ df}, p = .000^b$
<b>Drinking during 1st trimester of pregnancy with index child (%)</b>					
Drank about the same (as current use)	19.4		48.4		
Drank less (than current use)	19.4		38.7		
Drank more (than current use)	61.3		12.9		$\chi^2 = 15.64, 2 \text{ df}, p = .000^b$
<b>Drinking during 2nd trimester of pregnancy with index child (%)</b>					
Drank about the same (as current use)	16.1		51.6		
Drank less (than current use)	22.6		38.7		
Drank more (than current use)	61.3		9.7		$\chi^2 = 18.71, 2 \text{ df}, p = .000^b$
<b>Drinking during 3rd trimester of pregnancy with index child (%)</b>					
Drank about the same (as current use)	16.1		51.6		
Drank less (than current use)	29.0		41.9		
Drank more (than current use)	54.8		6.5		$\chi^2 = 18.33, 2 \text{ df}, p = .000^b$
<b>Smoking variables</b>					
Current smoker (%)	83.9		48.4		$\chi^2 = 8.71, 1 \text{ df}, p = .003$
Smoked during index pregnancy (%)	83.9		45.2		$\chi^2 = 10.15, 1 \text{ df}, p = .001, OR = 6.31$
	Whole sample ( $n = 31$ )	Smokers only ( $n = 26$ )	Whole sample ( $n = 31$ )	Smokers only ( $n = 15$ )	
Current use of tobacco (grams per week)(mean)	50.4 (44.6)	60.0 (42.2)	29.5 (43.9)	61.1 (45.6)	Whole sample, $t = 1.851, p = .069^a$ Smokers only, $t = 0.073, p = 0.942^a$
Grams of tobacco used per week					
1st trimester (mean)	43.7 (37.9)	52.1 (35.6)	25.7 (39.0)	53.1 (41.2)	Whole sample, $t = 1.843, p = .070^a$ Smokers only, $t = 0.083, p = .934^a$
2nd trimester (mean)	44.7 (38.3)	53.3 (35.9)	22.2 (33.9)	49.1 (35.2)	Whole sample, $t = 2.451, p = .017^a$ Smokers only, $t = 0.358, p = .722^a$
3rd trimester (mean)	42.1 (38.1)	50.2 (36.3)	19.7 (32.6)	43.6 (36.5)	Whole sample, $t = 2.482, p = .016^a$ Smokers only, $t = 0.540, p = .592^a$

<sup>a</sup>Not significant. <sup>b</sup>Cell(s) <5 detract(s) from significance.

pattern of consumption. These bouts are characteristic of heavy episodic drinking, as the mothers of FAS children and the drinking controls consume 97% and 94%, respectively, of all of their alcohol on the weekends. In open-ended comments, mothers of FAS children commonly characterized the index pregnancies as extremely stressful and particularly trying times in their lives, which they linked to heavier drinking. A source of stress cited frequently was a poor relationship with a heavy-drinking man. During the

trimesters of the pregnancy, control mothers generally (87% to 94%) continued to drink the same amount of alcohol or less, compared with their current level. The majority (55% to 64%) of the mothers of FAS children, however, reported drinking the same amount or substantially more, during the index pregnancy. The average daily alcohol consumption of the mothers of FAS children was 2.3 standard drinks per day (i.e., 1.2 oz of absolute alcohol per day). It is of particular importance that the mothers of FAS children who

are currently drinking are consuming eight standard drinks (4 oz of absolute alcohol) on the typical drinking day. This is the most meaningful measure of drinking risk, in this population that drinks episodically.

Maternal smoking data (Table 4) reveal that mothers of FAS children were more likely than controls to be current smokers (84% vs 48%) and to have smoked during the index pregnancy (84% vs 45%). There is little change in percent smoking, over time, in either group. Also, the number of cigarettes smoked per week or daily did not differ significantly between the individuals in the two groups either currently or during any trimester of the index pregnancy. The current smoking levels are calculated for both the entire sample and for smokers only (Table 4). Among current smokers, mothers of FAS children consume 60 grams (1 gram = 1 hand-rolled cigarette in South Africa) of tobacco per week, and controls 61.1 grams. This translates to 8.6 cigarettes per day for FAS mothers and 8.7 per day for controls. Therefore, control mothers who smoke report smoking quantities similar to those of FAS mothers for both current and index pregnancy. Both groups report slightly lower levels of smoking during the index pregnancy, particularly in the last two trimesters of the control pregnancies. However, since the differences between the smoking quantity of smokers in the two groups is not significant, either currently or in any of the trimesters, smoking seems less important than alcohol as a teratogenic risk. Women of both groups smoke only a moderate amount per day (by U.S. standards). This is likely due to a lack of disposable income for purchase and because "rolling one's own" takes more time, concerted action and thought than using prerolled cigarettes. Whereas the *quantity* of cigarettes smoked seems to present neither a major differential nor overall influence on the smoking pregnancies across groups, smoking is twice as common among the mothers who have had FAS children.

### Discussion

This study has examined South-African data on known maternal risk factors that have been described in other studies in the United States. The samples were drawn from an active case ascertainment study of FAS in a predominantly lower-SES population, from a developing region dominated by over 200 years of grape and wine production. The characteristics of maternal alcohol use described here, quite specific to the Western Cape population, may also have implications for other mixed-ancestry, low-SES groups in South Africa and elsewhere. This study, most importantly, has raised questions relevant to low SES and to developing areas, throughout the world, in which unique lifestyles and episodic drinking patterns combine to produce high blood alcohol concentrations in a substantial number of pregnant women.

The mothers of FAS children and controls were matched to represent similar cultural, racial and specific community backgrounds. The mothers of FAS children had lower educational attainment and less regular practice of religion, but were not significantly lower on other SES variables. An additional demographic risk factor that had been identified in our overall epidemiological study of this region was rural residence. This variable was controlled here, however, by case-control matching techniques. We reported previously (May et al., 2000) that FAS cases in this community were found more frequently in rural areas than in the overall population. Instead of 26% of the FAS cases originating in the rural areas as predicted by the population distribution, 61% were from rural environs ( $\chi^2 = 8.96$ ,  $p = .003$ ; OR = 14.8). Because of the residence matching in this study, the rural/urban variable is controlled, leaving educational attainment and religiosity as the major social differences.

The mothers of FAS children were not found to be of significantly higher gravidity or parity, or less likely to be married at the conception and birth of the index child; this is unlike the results of U.S. studies. Small sample size may be partly responsible for these results; however, it should also be noted that marriage rates were low in the control groups as well. As in other studies (Wilsnack et al., 1991), there is some tendency for the FAS mothers to be cohabitating while single.

The mothers of FAS children were from families with more extensive histories of heavy drinking and alcohol abuse than families of controls (Pascoe et al., 1995; Smith et al., 1987). This difference was more prominent among maternal grandmothers than maternal grandfathers, and more significant among sisters than brothers. Furthermore, as in the U.S. literature, the partners of women who had FAS children were more likely to drink heavily. The current and past drinking patterns of the mothers of FAS children were confirmed to be significantly heavier than those of the controls for all data points; this was notably true for continuing to drink heavily and/or increasing drinking throughout the gestation of the index child. The control mothers reported significantly lower current drinking levels, which generally declined during pregnancy. Episodic drinking on weekends was the modal pattern for both groups, with "bingeing" (5+ drinks) normative on 2 consecutive days during the weekend for the FAS mother group. More mothers of FAS children smoked than did controls and smoking quantities were identified for smokers of both groups. Members of neither group smoked high numbers of cigarettes (by U.S. standards) or reported cutting tobacco use substantially during pregnancy.

Because it was retrospective, this study had to confirm alcohol intake during the index pregnancy while dealing with problems related to recall of alcohol consumption many years earlier. Measurement of drinking during pregnancy has presented problems in studies of maternal behavior in

both prospective and retrospective studies. In prenatal settings, recall and self report of drinking 3 and 5 months after first report was considered "moderately reliable," with correlations for average daily volume between 0.61 and 0.53 (Robles and Day, 1990). A summary of reliability studies indicated that "research has failed to establish the parameters of reliable recall of alcohol consumption, including the type of information reliably obtained (e.g., quantity, frequency, specific beverages), the relationship between current drinking practices, retrospective reliability, and the reliability of reporting over longer time intervals" (Czarnecki et al., 1990, p. 69). However, a test of the reliability of long-term (5-year), self-report of maternal alcohol consumption concluded that original and retrospective data were highly correlated (Czarnecki et al., 1990). Studies also indicate that *frequency* of drinking is recalled better than *quantity*, that the heaviest drinkers tend to report disproportionately greater consumption when questioned 5 years after the pregnancy, and that "considerable confidence can be placed in retrospective reports of total alcohol consumption by nonalcoholic women over a relatively long-term interval" (Czarnecki et al., 1990, p. 68). Heavy drinking may be reported more accurately retrospectively than when current measurements are taken during pregnancy (Czarnecki et al., 1990; Jacobson et al., 1991). Some mothers may tend to understate their actual levels of drinking during pregnancy due to stigma, low self-esteem and depression (Jacobson et al., 1991).

Recall of exact quantities of alcohol consumed 6 to 9 years earlier in a low SES population in which the modal drinking pattern is a heavy episodic pattern could be problematic and inaccurate. Individuals in such populations experience a greater frequency of blackouts and memory loss, most likely related to quantity of consumption. In this exploratory, community-based study in a unique social and cultural setting, the research team chose to concentrate on current recall of drinking and on ordinal measures of retrospective maternal drinking (e.g., more than or less than) rather than assume that long-term recall or reporting of exact quantities of fetal alcohol exposure was going to be accurate. Stigma could have had an influence on validity in this community; furthermore, we could not assume that methods established in prenatal clinic settings in lower-risk, western populations were directly applicable. As these maternal interviews were tied to the larger study, they were designed to accomplish three tasks: to rule out confounding factors (e.g., smoking and other drugs) that might be of significance for the diagnosis of FAS, to define the general social and biological risk factors extant among these subjects and to provide confirmation of alcohol consumption during pregnancy (as per Stratton et al., 1996, criteria). The prenatal drinking questions were, therefore, asked in a unique, less threatening manner, and we based our quantitative measures on current drinking recall before moving to

simple but meaningful questions regarding the pregnancies 6 to 9 years earlier. The interdisciplinary research team developed this conservative approach as the questionnaires were drafted, piloted and finalized.

We have described a population in which the identified current and past high levels of episodic drinking and other maternal risk factors stand out among the mothers of FAS children, although a number of high-risk factors are found in both controls and mothers of FAS children. The percentages of smoking and drinking, for example, are higher for both groups than are reported rates for women in prenatal studies in the United States. Prenatal surveys in three nearby locales in the Western Cape indicated that 42.8% drank alcohol and 45.6% smoked during pregnancy (Croxford, 1998; Croxford and Viljoen, 1999). These percentages are virtually identical to the levels reported by our control group. In this study, however, the case control comparisons have identified some other variables, lifestyle patterns and levels of alcohol misuse that appear to be associated with births of FAS children.

#### *Important questions remain*

The amount of alcohol currently consumed by the mothers of FAS children is not dramatically high by most standards (16.1 drinks per week). But the data clearly indicate that episodic drinking is the norm among all drinkers in this community, and "binge" drinking may be the norm for mothers of FAS children. Therefore, high blood alcohol concentrations during episodes and "binges" elevate the likelihood of fetal damage for at least 2- to 3-day periods per week. Furthermore, women may not be reporting (or be able to report) all of the alcohol that they consume. In piloting the study questionnaire, women were found to emphasize alcohol that they had purchased and to possibly overlook or "skip" reporting alcohol distributed to them by others (e.g., fellow workers, spouses or employers). Attempts were made by the research team to remedy this by piloting several revisions of the questionnaire, using pictures of standard alcohol containers of various sizes, and vigilance and persistence by the interviewer. We still believe, however, that alcohol distributed and consumed under group-sharing practices or the vestiges of the Dop system remains underreported, at least among those who live on farms where it is still available in spite of illegality. Furthermore, there are likely to be biologic and genetic variables that exacerbate fetal damage, which were not included in this study. We have reported a very substantial difference in alcohol consumption between subjects and controls and documented the propensity for heavy episodic drinking among mothers of FAS children. A further question raised is: Are these mothers likely to produce FAS children when consuming relatively lower quantities of alcohol than has been shown in studies elsewhere? The physiological char-

acteristics of the female population in this study (e.g., small body size, relatively poor nutrition and diet, and possibly unique genetic traits) suggest that researching other variables (e.g., metabolism and body composition) may eventually elucidate whether there is a particularly high propensity in this population to produce high blood alcohol concentrations per unit of alcohol consumed and, therefore, elevate the overall risk for FAS births.

Advancing age among mothers is a generally established risk factor for FAS elsewhere (see Abel, 1998, pp. 162-166 for a review). The average (SD) age of this study's mothers (26.7 [7.2]) at the birth of an FAS child is several years younger than previously reported in the United States and Western Europe (Abel and Hannigan, 1995; Abel and Sokol, 1986; Bingol et al., 1987a; Jacobson et al., 1996; May et al., 1983; Sokol et al., 1986). Neither initiation of drinking at an early age, nor early onset of regular drinking, explain this difference (Chou and Pickering, 1992). The exclusive episodic drinking pattern among the mothers of FAS children in this study (possibly combined with lifelong and current nutritional deficiency), may lead to higher blood alcohol concentrations in mother and fetus and/or a more rapid degradation of the body (e.g., the liver, leaching of trace minerals, concentration of free radicals, etc.), making FAS more likely to appear in the offspring at an earlier age (see Abel and Hannigan, 1995). More research within this population is needed to answer the question: Why do mothers of the Western Cape seem to be bearing children with FAS at a younger average age than those elsewhere?

#### *Limitations of the study*

As noted above, possible biological and genetic risk factors were not included in this study, and other variables that can adversely influence the mother's drinking behavior and alcohol processing could not be addressed. Given that maternal grandmothers tended to drink heavily, a significant number of mothers of FAS children probably were exposed themselves to alcohol prenatally. Since the results of the current study indicate that mothers of FAS children had lower educational attainment than did control mothers, a question raised is whether mothers of FAS children had more neuropsychological deficits than control mothers, leading to diminished self-regulation and alcohol abuse. There exists, also, the possibility that mothers of FAS children had more social and emotional problems than controls. The data suggest that mothers of FAS children felt socially more isolated and "more stressed" during pregnancy. The association between maternal depression, self-esteem, emotions and drinking was not assessed. Finally, small sample size limits the generalizability of the results. Despite the above limitations, this is the first systematic study to report risk factors for prenatal alcohol effects in a large group of mothers who have borne children in a developing country.

#### *Prevention issues*

The results show that maternal characteristics and risk factors found among South African mothers were similar to those reported in the West. Also, it is encouraging that many of the factors that have been identified as possible protective mechanisms from the heaviest maternal drinking in this community are malleable or subject to change. Higher educational attainment is a primary or broad-based universal level prevention option that may well be available to the next generation of mothers in this community, given the rapid changes in South Africa today. Furthermore, the acquisition and daily practice of spiritual beliefs can be facilitated, for religiosity may be a stabilizing force in the lives of the control mothers. The question remains, however, whether these are truly protective factors. Are the lower levels of education and religiosity among the mothers of FAS children merely a result of the stifling effect of growing up and living in an alcohol-saturated family environment (see Hill et al., 1999; Rhodes and Jasinski, 1990)?

Individual and family improvement is amenable to change through both therapy and general social and economic development. Viable alternatives of selective and indicated prevention are new prenatal policies and practices, screening for early detection of alcohol problems, case management of high-risk women and treatment for alcohol misuse (Stratton et al., 1996; May, 1995).

After the initial screening for FAS was undertaken, a number of the members of the South-African and U.S. research teams, combined with local and U.S. prevention specialists, held a 2-day community workshop to plan and establish an ongoing prevention initiative. The session was attended by knowledgeable and concerned people from all over the Western Cape. The power structure of the study community (including the mayor) was well represented. The Institute of Medicine (Stratton et al., 1996) comprehensive prevention model was employed as a framework and as a menu of possible techniques. A coalition was formed that developed a strategy and a multifaceted plan. Prevention efforts are currently underway, and awareness of the FAS and alcohol abuse problems is increasing among many in the Western Cape.

#### *Conclusion*

This study, of the characteristics of 31 mothers of children with classic FAS in a unique population, has proven to be both confirming and enlightening. Socioeconomic status, race and some of the local conditions affecting pregnancy were relatively controlled by the homogeneity of the community and the matching of the case-control sample. That the sample is small, unfortunately limits statistical power. Nevertheless, compared with any single previous study of maternal risk, data have here been presented from

more mothers of "full-blown" FAS children. Confirmation of a high rate of FAS within a predominantly lower-SES population has been documented in a unique setting; even in this predominantly low-SES, high-FAS-rate community, the highest rate of FAS was found among the most socially and economically impoverished women from very chaotic extended families. Therefore, findings regarding general social class and family pathology were quite consistent with the U.S. literature; yet, the study has highlighted some potential risk and protective factors among the two groups. Control mothers have spouses who are less likely to be problem drinkers, report more regular practice of their religion, have higher educational attainment and familial networks characterized by much less drinking. The mothers of FAS children report problem drinking throughout their extended family and during all trimesters of the pregnancy, a sexual partner who drinks heavily, lack of religiosity and lower education levels. Studies such as this, which are based on samples of mothers who have had FAS children and appropriate controls, assist in accurate descriptions and general understanding. In addition, they provide contextual information to guide further research for hypothesis testing and for designing appropriate prevention initiatives useful in both the home community and elsewhere.

### Acknowledgments

The authors gratefully acknowledge and extend their deep and sincere thanks to Mayor Herman Baily, the (Western Cape community) Town Council, Cecil Driver, and the other principals of the 12 elementary schools in which the study was undertaken. In addition, Lesley Brooke, Chris Shaw, Andrea Riley and Carolyn Tullet of the Foundation for Alcohol Related Research were indispensable and steadfast colleagues in the research process, as were many members of the community, including particular farm owners and operators, and many other members of the local citizenry.

The study team initiating this project, along with the authors, was composed of a number of international experts. These included Jon M. Aase, M.D., Kenneth L. Jones, M.D., Luther Robinson, M.D., T.-K. Li, M.D., Faye Calhoun, Ph.D., Kenneth Warren, Ph.D., Karen J. Hymbaugh, M.P.H., Daveen White, R.N., and others. Each of them shares in any credit coming from these findings. The mistakes, errors or omissions contained herein are those of the authors.

### References

- ABEL, E.L. Fetal alcohol syndrome in families. *Neurotoxicol. Teratol.* **10**: 1-2, 1988.
- ABEL, E.L. An update on the incidence of FAS: FAS is not an equal opportunity birth defect. *Neurotoxicol. Teratol.* **17**: 437-443, 1995.
- ABEL, E.L. AND HANNIGAN, J.H. Maternal risk factors in fetal alcohol syndrome: Provocative and permissive influences. *Neurotoxicol. Teratol.* **17**: 445-462, 1995.
- ABEL, E.L. AND SOKOL, R.J. Maternal and fetal characteristics affecting alcohol's teratogenicity. *Neurobehav. Toxicol. Teratol.* **8**: 329-334, 1986.
- ADNAMS, C.M., KODITUWAKKU, P.W., HAY, A., MOLTENO, C.D., VILJOEN, D. AND MAY, P.A. Patterns of cognitive-motor development in children with fetal alcohol syndrome from a community in South Africa. *Alcsm Clin. Exp. Res.* **25**: 557-562, 2001.
- BAILY, S. Women with alcohol problems: A psycho-social perspective. *Drug Alcohol Rev.* **9**: 125-131, 1990.
- BINGOL, N., FUCHS, M., IOSUB, S., KUMAR, S., STONE, R.K. AND GROMISCH, D.S. Fetal alcohol syndrome associated with trisomy 21. *Alcsm Clin. Exp. Res.* **11**: 42-44, 1987a.
- BINGOL, N., SCHUSTER, C., FUCHS, M., IOSUB, S., TURNER, G., STONE, R.K. AND GROMISCH, D.S. The influence of socioeconomic factors on the occurrence of fetal alcohol syndrome. *Adv. Alcsm Subst. Abuse* **6** (4): 105-118, 1987b.
- BLUME, S.B. Chemical dependency in women: Important issues. *Amer. J. Drug Alcohol Abuse* **16**: 297-307, 1990.
- CENTERS FOR DISEASE CONTROL AND PREVENTION. Alcohol consumption among pregnant and childbearing-aged-women: United States, 1991 and 1995. *MMWR* **46**: 346-350, 1997.
- CHOU, S.P. AND PICKERING, R.P. Early onset of drinking as a risk factor for lifetime alcohol-related problems. *Brit. J. Addict.* **87**: 1199-1204, 1992.
- CROME, I.B. AND GLASS, Y. The DOP system: A manifestation of social exclusion. A personal commentary on "Alcohol consumption amongst South African farm workers: A post-apartheid challenge, by L. London, 1999." *Drug Alcohol Depend.* **59**: 207-208, 2000.
- CROXFORD, J.A. Prospective Analysis of Alcohol Ingestion in 636 Pregnant Women in Rural and Urban Areas of the Western Cape. B.S. (Medicine) Honors Thesis, Cape Town, South Africa: Department of Human Genetics, University of Cape Town, 1998.
- CROXFORD, J.A. AND VILJOEN, D. Alcohol consumption during pregnancy in women of the Western Cape. *So. African Med. J.* **89**: 962-965, 1999.
- CZARNECKI, D.M., RUSSELL, M., COOPER, M.L. AND SALTER, D. Five-year reliability of self-reported alcohol consumption. *J. Stud. Alcohol* **51**: 68-76, 1990.
- DARROW, S.L., RUSSELL, M., COOPER, M.L., MUDAR, P. AND FRONE, M.R. Sociodemographic correlates of alcohol consumption among African-American and white women. *Women Hlth* **18**(4): 35-51, 1992.
- DAVIS, A. AND LIPSON, A. A challenge in managing a family with fetal alcohol syndrome. *Clin. Pediat.* **23**: 304, 1984.
- DAY, N.L., COTTREAU, C.M. AND RICHARDSON, G.A. The epidemiology of alcohol, marijuana, and cocaine use among women of childbearing age and pregnant women. *Clin. Obstet. Gynecol.* **36**: 232-245, 1993.
- DAY, N.L., ROBLES, N., RICHARDSON, G.D., TAYLOR, P., SCHER, M., STOFFER, D., CORNELIUS, M. AND GOLDSCHMIDT, L. The effects of prenatal alcohol use on the growth of children at three years of age. *Alcsm Clin. Exp. Res.* **15**: 67-71, 1991.
- DAY, N.L., ZUO, Y., RICHARDSON, G.A., GOLDSCHMIDT, L., LARKBY, C.A. AND CORNELIUS, M.D. Prenatal alcohol use and offspring size at 10 years of age. *Alcsm Clin. Exp. Res.* **23**: 863-869, 1999.
- ERNHART, C.B., SOKOL, R.J., MARTIER, S., MORON, P., NADLER, D., AGER, J.W. AND WOLF, A. Alcohol teratogenicity in the human: A detailed assessment of specificity, critical period, and threshold. *Amer. J. Obstet. Gynecol.* **156**: 33-39, 1987.
- GODEL, J.C., PABST, H.F., HODGES, P.E., JOHNSON, K.E., FROESE, G.J. AND JOFFRES, M.R. Smoking and caffeine and alcohol intake during pregnancy in a northern population: Effect on fetal growth. *Can. Med. Assoc. J.* **147**: 181-188, 1992.
- GOMBERG, E.S. Women and alcohol: Use and abuse. *J. Nerv. Ment. Dis.* **181** (4): 211-219, 1993.
- GRIFFITHS, R. Griffiths Mental Development Scales. Buckinghamshire, UK: ARICD, 1984.
- HANNA, E.Z., FADEN, V.B. AND HARFORD, T.C. Marriage: Does it protect young women from alcoholism? *J. Subst. Abuse* **5**: 1-14, 1993.
- HILL, S.Y., LOCKE, J., LOWERS, L. AND CONNOLLY, J. Psychopathology and achievement in children at high risk for developing alcoholism. *J. Amer. Acad. Child Adolesc. Psychiat.* **38**: 883-891, 1999.
- JACOBSON, J.L., JACOBSON, S.W. AND SOKOL, R.J. Increased vulnerability to alcohol-related birth defects in the offspring of mothers over 30. *Alcsm Clin. Exp. Res.* **20**: 359-363, 1996.

- JACOBSON, S.W., JACOBSON, J.L., SOKOL, R.J., MARTIER, S.S., AGER, J.W. AND KAPLAN, M.G. Maternal recall of alcohol, cocaine and marijuana use during pregnancy. *Neurotoxicol. Teratol.* **13**: 535-540, 1991.
- JONES, K.L. AND SMITH, D.W. Recognition of fetal alcohol syndrome in early infancy. *Lancet* **2**: 999-1001, 1973.
- KENDLER, K.S., HEATH, A.C., NEALE, M.C., KESSLER, R.C. AND EAVES, L.J. A population-based twin study of alcoholism in women. *JAMA* **268**: 1877-1882, 1992.
- KING, A.C. Enhancing the self-report of alcohol consumption in the community: Two questionnaire formats. *Amer. J. Publ. Hlth* **84**: 294-296, 1994.
- LONDON, L. Alcohol consumption amongst South African farm workers: A challenge for post-apartheid health sector transformation. *Drug Alcohol Depend.* **59**: 199-206, 2000.
- LONDON, L., MEYER, J., WELL, V., TAYLOR, T., THOMPSON, M.R. AND MIBULI, S. An Investigation into the Neurological and Neurobehavioral Effects of Long-Term Agrochemical Exposure among Deciduous Fruit Farm Workers in the Western Cape, South Africa. M.D. Thesis, Cape Town, South Africa: University of Cape Town, 1995.
- MCCAUL, M.E., TURKKAN, J.S., SVIKIS, D.S. AND BIGELOW, G.E. Familial density of alcoholism: Effects on psychophysiological responses to ethanol. *Alcohol* **8**: 219-222, 1991.
- MAY, P.A. A multiple-level, comprehensive approach to the prevention of fetal alcohol syndrome and other alcohol-related birth defects (ARBD). *Int. J. Addict.* **30**: 1549-1602, 1995.
- MAY, P.A. Research issues in the prevention of fetal alcohol syndrome and alcohol-related birth defects. In: HOWARD, J.M., MARTIN, S.E., MAIL, P.D., HILTON, M.E. AND TAYLOR, E.D. (Eds.) *Women and Alcohol: Issues for Prevention Research*. NIAAA Research Monograph No. 32, NIH Publication No. 96-3817, Washington: Government Printing Office, 1996, pp. 93-131.
- MAY, P.A., HYMBAUGH, K.J., AASE, J.M. AND SAMET, J.M. Epidemiology of fetal alcohol syndrome among American Indians of the southwest. *Social Biol.* **30**: 374-387, 1983.
- MAY, P.A., BROOKE, L., GOSSAGE, J.P., CROXFORD, J., ADNAMS, C., JONES, K.L., ROBINSON, L. AND VILJOEN, D. Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. *Amer. J. Publ. Hlth* **90**: 1905-1912, 2000.
- NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA). Fetal Alcohol Syndrome: Report of the 1996 Site Visit to South Africa, Rockville, MD: NIAAA Report, 1996.
- NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA). Fetal Alcohol Syndrome: South Africa, A Progress Report on the 1997 Pilot Study, Information Exchange, and Prevention Workshop, Rockville, MD: NIAAA Report, 1998.
- PARRY, C.D.H. AND BENNETTS, A.L. *Alcohol Policy and Public Health in South Africa*, New York: Oxford Univ. Press, 1998.
- PASCOE, J.M., KOKOTAILO, P.K. AND BROEKHUIZEN, F.F. Correlates of multi-gravida women's binge drinking during pregnancy: A longitudinal study. *Arch. Pediat. Adolesc. Med.* **149**: 1325-1329, 1995.
- PIEROG, S., CHANDAVASU, O. AND WEXLER, I. The fetal alcohol syndrome: Some maternal characteristics. *Intern. J. Gynecol. Obstet.* **16**: 412-415, 1979.
- REPUBLIC OF SOUTH AFRICA. 1996 Census of the Population, Pretoria, South Africa: Bureau of Census, 1997.
- RHODES, S.S. AND JASINSKI, D.R. Learning disabilities in alcohol-dependent adults: A preliminary study. *J. Learn. Disab.* **23**: 551-556, 1990.
- ROBLES, N. AND DAY, N.L. Recall of alcohol consumption during pregnancy. *J. Stud. Alcohol* **51**: 403-407, 1990.
- SAMPSON, P.D., STREISSGUTH, A.P., BOOKSTEIN, F.L. AND LITTLE, R.E., CLARREN, S.K., DEHANE, P., HANSON, J.W., AND GRAHAM, J.M., JR. Incidence of fetal alcohol syndrome and prevalence of alcohol-related neurodevelopmental disorder. *Teratology* **56**: 317-326, 1997.
- SCHMIDT, C., KLEE, L. AND AMES, G. Review and analysis of literature on indicators of women's drinking problems. *Brit. J. Addict.* **85**: 179-192, 1990.
- SCHLESINGER, S., SUSMAN, M. AND KOENIGSBERG, J. Self-esteem and purpose of life: A comparative study of women alcoholics. *J. Alcohol Drug Educ.* **36** (1): 127-141, 1990.
- SERDULA, M., WILLIAMSON, D.F., KENDRICK, J.S., ANDA, R.F. AND BYERS, T. Trends in alcohol consumption by pregnant women: 1985 through 1988. *JAMA* **265**: 876-879, 1991.
- SHORE, E.R. AND BATT, S. Contextual factors related to the drinking behaviors of American business and professional women. *Brit. J. Addict.* **86**: 171-176, 1991.
- SHORE, E.R. AND PIERI, S.A. Drinking behaviors of women in four occupational groups. *Women Hlth* **19** (4): 55-64, 1992.
- SMITH, I.E., LANCASTER, J.S., MOSS-WELLS, S., COLES, C.D. AND FALEK, A. Identifying high-risk pregnant drinkers: Biological and behavioral correlates of continuous heavy drinking during pregnancy. *J. Stud. Alcohol* **48**: 304-309, 1987.
- SOKOL, R.J., AGER, J., MARTIER, S., DEBANNE, S., ERNHART, C., KUZMA, J. AND MILLER, S.I. Significant determinants of susceptibility to alcohol teratogenicity. *Ann. N.Y. Acad. Sci.* **447**: 87-102, 1986.
- SOKOL, R.K.J., MILLER, S.I. AND REED, G. Alcohol abuse during pregnancy: An epidemiologic study. *Alcsm Clin. Exp. Res.* **4**: 135-145, 1980.
- STRATTON, K., HOWE, C. AND BATTAGLIA, F. (Eds.) *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment*, Washington, DC: National Academy Press, 1996.
- WATERSON, E.J. AND MURRAY-LYON, I.M. Drinking and smoking patterns amongst women attending an antenatal clinic: II. During pregnancy. *Alcohol Alcsm* **24**: 163-173, 1989.
- WILSNACK, S.C. Women at high risk for alcohol abuse. *Counselor* **7** (1): 16-17 & 20, 1989.
- WILSNACK, S.C. Sexuality and women's drinking: Findings from a U.S. national study. *Alcohol Hlth Res. World* **15**: 147-150, 1991.
- WILSNACK, S.C. AND BECKMAN, L.J. *Alcohol Problems in Women: Antecedents, Consequences, and Intervention*, New York: Guilford Press, 1984.
- WILSNACK, S.C., KLASSEN, A.D., SCHUR, B.E. AND WILSNACK, R.W. Predicting onset and chronicity of women's problem drinking: A five-year longitudinal analysis. *Amer. J. Publ. Hlth* **81**: 305-318, 1991.

# Neurobehavioral Characteristics of Children with Fetal Alcohol Spectrum Disorders in Communities from Italy: Preliminary Results

Piyadasa Kodituwakku, Giovanna Coriale, Daniela Fiorentino, Alfredo S. Aragón,  
Wendy O. Kalberg, David Buckley, J. Phillip Gossage, Mauro Ceccanti, and Philip A. May

**Background:** There has been considerable effort expended on defining neurobehavioral characteristics of children with fetal alcohol spectrum disorders (FASD). Children with FASD display a range of cognitive deficits and behavioral problems. In this article, we report on the neurobehavioral characteristics of children with FASD in selected communities in Italy. It was expected that both inattentive and hyperactive/impulsive characteristics would discriminate children with FASD from controls and that the groups would also differ on intellectual functioning, language comprehension, and academic skills.

**Methods:** Eighty-two children, 22 diagnosed with FASD and 60 control children, participated in this study. The children were administered tests of nonverbal reasoning, language comprehension, academic achievement, and behavior.

**Results:** On tests of nonverbal reasoning and language comprehension, the FASD group earned lower scores than did controls. Moreover, on a test of academic achievement the FASD group scored lower. When comparing these 2 groups on disruptive behavioral symptomatology, similar results were obtained, the FASD group showing greater attentional difficulties and hyperactivity/impulsivity behaviors and more overall behavioral problems. Stepwise logistic regression analysis showed that a model containing inattention and error scores on the language comprehension task correctly classified 85% of the participants. Compared with the control group, a significantly greater proportion of children with FASD met the *Diagnostic and Statistical Manual of Mental Disorders*—fourth edition (DSM-IV) criteria of ADD, inattentive type, as reported by teachers. In contrast, hyperactive symptoms among children with FASD were comparable with the control group. Teachers rated children with FASD as having more inattentive behaviors and as performing lower in academic skills than controls. The association between reported hyperactivity symptoms and achievement scores was nonsignificant for both language and math scores, suggesting that it is not the hyperactivity causing problems, but the child's inattention.

**Conclusions:** This research indicates that a nonclinic-referred sample of Italian children with FASD display a profile of neurobehavioral functioning consistent with that reported by other researchers. Furthermore, the neurobehavioral characteristic most identified with children diagnosed with FASD was inattention followed by hyperactivity.

**Key Words:** Fetal Alcohol Syndrome, Fetal Alcohol Spectrum Disorders, Neurobehavioral Characteristics, Inattention, Italy.

OVER THE PAST 30 years, researchers have expended considerable efforts on defining neurobehavioral

*From The University of New Mexico, Albuquerque, New Mexico (PK, ASA, WOK, DB, JPG, PAM); and the University of Rome, "La Sapienza," Rome, Italy (GC, DF, MC).*

*Received for publication November 1, 2005; accepted May 26, 2006.*

*This project was funded in part by the National Institute on Alcohol Abuse and Alcoholism (NIAAA; pilot project subcontract # 53257 A-P1660-7802-211 CSM from San Diego State University) as part of the International Consortium for the study of FASD (CIFASD)—AA014811 and AA014828 and a grant from the health department of the regional government of the Lazio region, Assessorato alla Sanita della Regione Lazio.*

*Reprint requests: Philip A. May, PhD, Center on Alcoholism, Substance Abuse and Addictions, 2650 Yale Blvd. SE, Albuquerque, NM 87106; E-mail: pmay@unm.edu*

*Copyright © 2006 by the Research Society on Alcoholism.*

DOI: 10.1111/j.1530-0277.2006.00187.x

characteristics of children with fetal alcohol syndrome (FAS) or fetal alcohol spectrum disorders (FASD). It is now known that children with FASD display intellectual deficits, with their average IQs falling in the borderline range (Mattson et al., 1997; Streissguth et al., 1990). Researchers have also obtained evidence that children with FASD perform less competently than controls on a wide range of tasks, including those assessing information processing (Jacobson, 1998), number processing (Kopera-Frye et al., 1996), visual-spatial reasoning (Carmichael Olson et al., 1998), visual memory (Uecker and Nadel, 1996), verbal learning and memory (Mattson et al., 1996), language (Abkarian, 1992), and motor function (Roebuck et al., 1998). Behavioral and emotional difficulties in these children have also been documented (Bailey et al., 2004; Steinhausen and Spohr,

1998). On tests of academic achievement, alcohol-affected children tend to earn lower scores on arithmetic tests than on other tests (Streissguth et al., 1994). There is evidence that children with prenatal alcohol exposure have impaired ability on tests measuring attention and executive functions (Coles et al., 1997; Kodituwakku et al., 2001).

Despite significant advances in delineating neurobehavioral outcomes of prenatal alcohol exposure, a "behavioral phenotype" of FAS or FASD has not yet been defined. A behavioral phenotype refers to "a characteristic pattern of motor, cognitive, linguistic, and social observations that is consistently associated with a biological disorder" (O'Brien and Yule, 1995, p. 2). If there is a set of characteristics consistently associated with FASD, it is reasonable to expect that those characteristics discriminate alcohol-affected children from a random sample of age peers in the general population. This requires identifying a group of children with FASD from a population and comparing them with a random sample of children from the same population on a set of neurobehavioral characteristics. Researchers are now able to conduct population-based neurobehavioral studies of FASD thanks to recent international collaborations (Riley et al., 2003).

In this article, we report on a neurobehavioral study of FASD conducted in the context of an epidemiology project completed in Italy. The Italian FASD epidemiology project, partially funded under the Collaborative Initiative on FASD (CIFASD), provided an opportunity to explore the neurobehavioral characteristics of a well-diagnosed cohort of children with FASD in a Western European population. Although some of the adverse effects of prenatal alcohol exposure on children were first described in the contemporary medical literature in France (Lemoine et al., 1968), drinking during pregnancy has not been recognized as a significant health risk factor in Europe (Room, 2005). A relatively limited number of studies of neurobehavioral outcomes of FAS have been conducted in Western European countries. A large European study of 18-month-old children ( $n = 1,240$ ) found no relationship between maternal drinking and psychomotor abilities, although the level of drinking reported by the mothers of this cohort was very low (EUROMAC, 1992). Other studies in France (Lemoine and Lemoine, 1992), Germany (Spohr et al., 1993; Steinhausen, 1995; Steinhausen and Spohr, 1998), and Scandinavia and Finland (Aronson and Hagberg, 1998; Autti-Ramo, 2000; Larroque and Kaminski, 1998) have revealed a general pattern of cognitive, intellectual, and physical deficiencies for children whose mothers drank moderate to heavy amounts of alcohol. A longitudinal study in Finland with a cohort of alcohol-exposed children reported results on intelligence measures that were somewhat variable (Riley et al., 2003). Whereas the children between the ages of 5 and 9 years scored significantly lower on verbal IQ than controls, in the 12- to 14-year age range, performance IQ was significantly lower. There is 1 Italian

study (Roccella and Testa, 2003) that described various characteristics of 6 subjects diagnosed with FAS. However, to our knowledge, no Italian population-based study of neurobehavioral outcomes of prenatal alcohol exposure has been reported before in the literature.

The selection of a test battery that has desirable psychometric properties, and that can be used cross-culturally, is a challenging task. Several considerations influenced test selection: (1) minimization of burden on test administrators and respondents (e.g., parents and teachers); (2) sensitivity to the effects of prenatal alcohol exposure, as demonstrated by previous research; and (3) having items of graded difficulty and high internal consistency, so that the discrimination power of the test is maximized. Neurobehavioral studies of children with FAS from South Africa revealed that tests assessing fluid intelligence and verbal comprehension discriminated alcohol-affected children from controls (Adnams et al., 2001).

Atypical behavior has been the topic of significant investigation with the FASD population (Bailey et al., 2004; Coles et al., 1997; Streissguth et al., 1998). There is a growing body of literature showing that children with FASD tend to show a cluster of behavior problems notable for impulsivity, disorganization, short-term memory problems, and difficulty in understanding subtle social cues (Streissguth et al., 1998). Previous studies conducted by this group of investigators have shown that alcohol-exposed children exhibit significantly more behavioral problems than their typically developing peers (Kodituwakku et al., 2001; Streissguth et al., 1998). Other studies have reported that alcohol-exposed children display marked behavioral problems, particularly in the realm of social deficits (Kelly et al., 2000). These include difficulty in understanding the social consequences of behavior and inappropriate interactions. This cluster of behavior problems overlaps with poor executive function and has been called by some "dysexecutive syndrome" (Baddeley et al., 2002; Wilson et al., 1996). Researchers have also obtained evidence that children with FASD are slow learners, who become "spacey" during tasks, often making omission errors (Kodituwakku et al., 2001). Children with attention deficit disorder (ADD), inattentive type, are also characterized as being spacey and forgetful. Researchers have also documented consistently that alcohol-affected children are deficient in academic skills, particularly math (Streissguth et al., 1994).

The primary purpose of this study was to compare children with FASD with a sample of age peers, all without FASD, on the above key neurobehavioral characteristics. It was expected that both inattentive/hyperactive characteristics and executive functioning would discriminate children with FASD from a community random sample of age peers (May et al., 2000). It was also expected that the 2 groups would significantly differ on language comprehension, intellectual functioning, and academic skills, particularly in number concepts.

## MATERIALS AND METHODS

### Sample

Eighty-two children, 22 diagnosed with FASD and 60 control children, participated in this study. The FASD group was composed of 11 males and 11 females diagnosed with FAS ( $n = 4$ , 18%), partial FAS ( $n = 17$ , 77%), and ARND ( $n = 1$ , 5%). The child diagnosed with alcohol-related neurodevelopmental deficits (ARND) met the IOM diagnostic criteria as he had microcephaly (head circumference  $< 3$  percentile) and had confirmed heavy maternal alcohol exposure. The children ranged in age from 6.2 to 7.7 years of age with a mean age of 6.8 years. The control group was composed of 29 males and 31 females who ranged in age from 6.1 to 7.2 years of age with a mean age of 6.7 years.

The data originate from children participating in an in-school, first-grade study of the prevalence and characteristics of FASD in a school district in the Lazio Region in central Italy. The data in this wave of research were collected over 7 months in the winter and spring of 2003 to 2004. The school district is composed of 68 schools with first-grade classes across a district some 60 km in circumference and lying between 40 and 100 km from Rome. Twenty-five schools were selected via a random number table. Italian research team members obtained permission to proceed and then contacted all of the parents and guardians for consent via take-home notices. Consent forms were signed and returned by over half (51%) of all parents, and after the first screening (for height, weight, and head circumference) was completed, exactly half, 543, were present and participated in this study. The result was an active case recruitment consent rate of 50%. Of those who consented only 6% refused to participate. Most studies of this type do not use active case findings. Because this study used active case recruitment in a school setting, there is probably less bias than a clinic-based study using passive recruitment. One other study outside of South Africa that had a higher participation rate was carried out in a county in Washington State (Clarren et al., 2001), which used a passive consent procedure that is no longer allowed in the United States and rarely elsewhere.

The children in this sample were enrolled in first grade at randomly selected schools for whom consent to participate was provided. The sampling and research procedures were approved by the Ethics Committee of the regional Italian Health Department and by the University of New Mexico Health Sciences Human Research Review Committee (HRRC), whose approval was contingent on the Italian approval.

### Controls

Matched controls (for grade in school) were chosen from the same schools in this region, randomly selected from those children for whom signed consent forms had been provided. All children underwent the exact same screening and controls were tested simultaneously with the index cases. Testers were blinded as to the group membership of the children. Testers were affiliated with the University of Rome and were not familiar with the particular communities or the individual children before the study. All students and their parents, either suspected subjects or controls, were contacted for testing, and the 2-hour battery was administered in the schools. However, 4 of the original 64 randomly selected control mothers were missing maternal drinking data; thus they were excluded from analysis resulting in a total of 60 control children and their mothers. Given that we maintained a greater than 1:2 ratio of FASD and controls, no attempt to replace the excluded controls was made.

### Data Collection

The data collection for the diagnoses occurred via 3 tiers of screening. First the height, weight, and head circumference were measured for each child by the local school physicians. In addition, teachers

completed the Parent/Teacher Disruptive Behavior Disorder Rating Scale (Pelham DBD Rating Scale; Pelham et al., 1992; only attention and hyperactivity scales) and the "Questionario Osservativo per L'identificazione Precoce delle Difficoltà di Aprendizimento" (IDPA; Terreni et al., 2002). If a child was at or below the 10th percentile in height or weight or head circumference on U.S. National Center for Health Statistics (NCHS) charts or if a child had attention and hyperactivity deficit or learning difficulties, then he/she was advanced to the second tier of the study. In this second tier, the dysmorphological examination was done. Only the children who met the criteria for the diagnosis of FAS and controls group were advanced to the third tier of the study. In this third tier, psychological testing was carried out in the schools of each child by bachelors and master-level psychologists who were employed by the grant to the University of Rome. In addition the mothers of the selected children completed the Pelham DBD Rating Scale (only attention and hyperactivity scales) and the Problem Behaviors Checklist (PBCL-36; Streissguth et al., 1998). The maternal risk factors interview was administered to the entire sample.

Under the diagnostic scheme used, a child meeting the following criteria received a diagnosis within the FASD continuum. These criteria represent modifications of the 1996 Institute of Medicine (IOM) criteria (Stratton et al., 1996), allowing their practical application in clinical settings (Hoyme et al., 2005).

The revised IOM diagnostic guidelines were developed over the past 6 years and recently published by members of the research team (Hoyme et al., 2005). Under these criteria a child who has the following features/characteristics meets the criteria for the diagnosis of FAS: 2 or more of the cardinal facial anomalies of FAS (short palpebral fissures, thin vermilion border, and/or smooth philtrum), prenatal and/or postnatal growth retardation ( $\leq 10$  percentile), and small head circumference ( $\leq 10$  percentile) or other evidence of structural brain abnormalities with or without confirmation of maternal drinking. For partial FAS a child must have 2 or more typical facial features and 1 or more of the following characteristics: prenatal and/or postnatal growth retardation ( $\leq 10$  percentile), evidence of abnormal brain growth or structure (e.g., microcephaly  $\leq 10$  percentile), or evidence of characteristic behavioral or cognitive abnormalities, with or without evidence of maternal drinking during pregnancy. For a diagnosis of ARND a child must have documented prenatal alcohol exposure, display neurological or structural brain abnormalities (e.g., microcephaly), or manifest evidence of a characteristic complex pattern of behavioral or cognitive abnormalities inconsistent with developmental level and not explained by genetic predisposition, family background, or environment alone (see Hoyme et al., 2005; Stratton et al., 1996).

### Instruments Used

The psychological and developmental evaluations were completed using a battery of tests that included measures of perceptual nonverbal reasoning ability, language comprehension measure, academic achievement, and behavior. The instruments used were The Raven-Colored Progressive Matrices (CPM; Raven et al., 1947, 1985), the Rustioni Test of Language Comprehension "Prove di Valutazione Della Comprensione Linguistica" (Rustioni, 1994), an Italian test of academic achievement "Questionario Osservativo per L'identificazione Precoce delle Difficoltà di Aprendizimento" (IDPA; Terreni et al., 2002), the Parent/Teacher Disruptive Behavior Disorder (DBD) Rating Scale (Pelham et al., 1992), and the Problem Behaviors Checklist (PBCL-36; Streissguth et al., 1998).

*Raven CPM.* The Raven CPM is a standardized test designed to assess nonverbal reasoning ability. Specifically, this test assesses reasoning in the visual modality and is a measure of inductive reasoning (Alderton and Larson, 1990). The CPM was designed for use with young children and the elderly. Coupled with a standardized test of language ability, it can take the place of a single test of intelligence. It

was chosen because the child's responses do not require verbalization, skilled manipulative ability, or differentiation of visuospatial information (Zaidel et al., 1981).

**Rustioni Test of Language Comprehension and IDPA Questionnaire.** The Rustioni (1994) is an Italian test of linguistic understanding that was developed and normed on the Italian population. Therefore, it provides information that is comparable within the Italian population. It was modeled after the Test for the Reception of Grammar (TROG) (Bishop, 1989). The test is packaged in booklet form with a multiple-choice format. It is designed to assess understanding of grammatical contrasts in Italian. The child is shown a page with 4 picture choices and must select the picture that matches a spoken sentence. The test takes 10 to 20 minutes to administer. It has been standardized on over 2,622 Italian children ages 3.6 to 8 years, and it assesses the comprehension level in respect to the chronological age of the child. Errors are assessed in respect to chronological age, which provides an estimate of the real age-graded comprehension level of the child. Further, children's current levels of academic achievement in the domains of language and math were assessed using the IDPA test (Terreni et al., 2002). This is an Italian normed test designed to identify difficulties in learning by measuring academic achievement.

**Problem Behaviors Checklist.** The Problem Behaviors Checklist (PBCL-36) is a short, easy-to-administer scale that purports to measure the behavioral characteristics of FAS, regardless of age, race, sex, or IQ (Streissguth et al., 1998). The scale consists of 36 items pertaining to several areas of functioning: academic/work performance, social skills and interactions, bodily or physiological functions, communication and speech, personal manner, emotions, and motor skills and activities. The checklist was completed by the child's mother.

**Parent/Teacher Disruptive Behavior Disorder Rating Scale.** The Parent/Teacher Disruptive Behavior Disorder Rating Scale (DBD) Rating Scale provided a measure of attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD) (Pelham et al., 1992). Only the items assessing inattention and hyperactivity/impulsivity were used for this study.

The Raven CPM, DBD, and PBCL-36 have all been used extensively with children from South Africa who were prenatally exposed to alcohol (Adnams et al., 2001; Viljoen et al., 2005). Utilizing the same testing instruments across cultures provides data that can then be compared, thus enhancing our knowledge of the general intellectual and behavioral characteristics of children with FASD (Riley et al., 2003).

### Maternal Questionnaire

The mothers of the FASD and control children became the subjects of a portion of the study concerned with maternal risk. The mothers of randomly selected control children who had no symptoms of FASD are believed to be representative of the average women in this region with regard to drinking patterns, nutrition, demographic variables, fertility and childbearing, and behavioral health issues.

The maternal drinking questions were asked in the context of a set of general health questions and immediately followed questions about daily diet and diet during the index pregnancy (King, 1994; May et al., 2005). The alcohol exposure variable should be as accurate as possible given the sensitive nature of these questions in Italy, where there seems to be a general awareness that alcohol abuse and pregnancy are not compatible. Data were first collected, via time line follow back methods (Sobell and Sobell, 1995; Sobell et al., 2001), on current drinking via a 7-day drinking log that began with the day before the interview and worked backward in time. Questions and sequence were designed to help the interviewee in recall and to realistically calibrate their responses for accurate reporting (Graves and Kaskutas, 2002; Kaskutas and Graves, 2000, 2001). Retrospective reports of drinking levels during pregnancy have reported in some

**Table 1.** Maternal and Child Demographic and Background Information, Means, Standard Deviations, and *p* Values

	FASD	Control	<i>p</i> Value
<b>Maternal demographics</b>			
Maternal age (y) on day of interview (SD)	37.8 (5.27)	36.6 (5.88)	NS (0.413) <sup>a</sup>
Maternal age (y) at birth of index child (SD)	31.8 (4.27)	29.6 (5.73)	NS (0.157) <sup>a</sup>
<b>Maternal education attainment (%)</b>			
Elementary	17.6	1.7	
Junior high	41.2	30.0	0.015 <sup>b</sup>
Senior high	17.6	50.0	
College degree	23.5	18.3	
<b>Among those employed, mother's monthly income (Euros), %</b>			
< 500	66.7	47.5	
501 to 1,000	20.0	22.0	NS (0.457) <sup>b</sup>
1,001 to 1,500	6.7	23.7	
1,501 to 3,000	6.7	6.8	
Estimated number of drinks during pregnancy <sup>c</sup>	0.47 (0.71)	0.30 (0.49)	NS (0.264) <sup>a</sup>
<b>Among current drinkers and smokers</b>			
Estimated number of drinks/d	1.72 (2.17)	0.80 (0.36)	0.008
Estimated number of drinks/wk	8.97 (16.58)	1.59 (2.04)	0.004
Estimated number of drinks/mo	41.90 (73.68)	8.00 (9.03)	0.008
Estimated number of cigarettes/d	9.12 (7.87)	8.75 (4.32)	NS (0.893)
<b>Child demographics and information</b>			
Child age (y)	6.3 (0.456)	6.2 (.376)	NS (0.28) <sup>a</sup>
Child gender (%)			
Males	50.0	48.3	NS (0.893) <sup>b</sup>
Females	50.0	51.7	
Child height (cm)	116.1 (5.22)	121.6 (4.59)	< 0.0001 <sup>a</sup>
Child weight (kg)	21.9 (4.43)	25.4 (4.57)	0.002 <sup>a</sup>
Child head circumference (cm)	50.7 (1.78)	51.8 (1.14)	< 0.0001 <sup>a</sup>
Total child dysmorphology score	12.4 (3.88)	3.3 (3.09)	< 0.0001 <sup>a</sup>

<sup>a</sup>*t*-test.

<sup>b</sup> $\chi^2$  test of data.

<sup>c</sup>Estimated number of drinks consumed on a typical day during pregnancy.

NS, not significant; FASD, fetal alcohol spectrum disorders.

studies as higher and also in some to be as accurate or more accurate than the reporting of drinking during pregnancy (Alvik et al., 2006; Czarnecki et al., 1990). However, Jacobson et al. (1991, 2002) also reported that prospective maternal reporting was likely to be more accurate in detecting behavioral effects than retrospective reports and that retrospective reporting did not consistently detect neurobehavioral outcomes. Nonetheless, accurate maternal drinking reports are key to identifying levels of drinking that are associated with deficits in psychological functioning. Some of the aggregate results of the maternal risk factors are described in another paper of the epidemiological findings of this study. In general, maternal interviews of this sample revealed statistically significant differences in current maternal and drinking before pregnancy (see Table 1).

### Data Analysis

All data were entered, and statistical calculations performed, using SPSS (Version 11.0.0; SPSS for Windows, SPSS Inc., Chicago, IL). Simple comparisons between FASD and control groups were performed using the independent group *t*-test. In cases where Levene's test for equality of variances departed from the normal

distribution, equal variances were not assumed and the appropriate adjusted *t*-value and degrees of freedom are indicated and reported.

A binary logistic regression was performed to determine the association between group membership and neurobehavioral variables, taking the interrelationships among neurobehavioral characteristics into consideration. Logistic regression was preferred to discriminant function analysis because the former makes less restrictive assumptions than the latter (Howell, 2002), in particular with regard to the distributions of independent variables. As there was a colinearity ( $r = -0.81$ ) between the 2 measures of language comprehension, qualitative assessment, and the number of errors, only the error score was used as an index of language ability in the estimation of logistic function. Hyperactivity and inattention subscale scores from the DBD Rating Scale were converted into categorical variables, each consisting of 2 levels: "Met DSM criteria" and "Did not meet DSM criteria." The recommended cutoff score of 6 or more items endorsed was used in creating these categories (Pelham et al., 1992). Thus, the following variables were entered as predictors of group membership (FASD vs controls): Raven's CPM, language errors, inattention (categorical), hyperactivity (categorical), and learning scores. These variables were entered using the stepwise method.

RESULTS

Table 1 presents a summary of both maternal demographic data and child characteristics. The data indicate that, with the exception of education level, there were few differences between the mothers of FASD children and control mothers. Mothers of FASD children were generally lower in education (58.8% had not graduated from high school), although there were slightly more in the FASD group who had a college degree than controls. The mothers of the 2 groups were similar in age at interview, age at birth of index child, income, and estimated number of drinks during pregnancy. However, some of the 21 mothers of children (there was 1 set of twins) diagnosed with FASD appear to have underreported their alcohol use during pregnancy ( $n = 4$ ) as some reported no drinking during pregnancy even though their child had severe characteristics of FASD and were diagnosed as FAS and 5 mothers were not interviewed because of adoption/foster placement or refusal. However, direct and/or collateral evidence of prenatal drinking for the index pregnancy was obtained for 3 of the 4 mothers. When examining current maternal drinking and smoking, estimated number of drinks per day, week, and month were all significantly different between the 2 groups for drinking but not for smoking. The demographic characteristics of children diagnosed with FASD and control children were well matched in terms of sex balance and age. As expected, the 2 groups were significantly different with respect to height, weight, head circumference, and overall dysmorphology score.

Additional analyses (see Table 2) looking at other socio-environmental indicators were conducted, which revealed that maternal education, paternal education, and number of maternal drinks in the past month were not correlated with child behavioral problems as measured by the PBCL, ( $r = 0.17, 0.04, \text{ and } 0.04$ , respectively). These data reflect

**Table 2.** Pearson's Correlation Coefficients for Behavioral Problems, Inattention, and Maternal Education on Select Maternal and Child Variables

Variables	Behavioral problems (PBCL)			
	<i>r</i>	<i>r</i> <sup>2</sup>	<i>F</i> statistic	<i>p</i> Value
Maternal education	0.17	0.03	2.16	NS > 0.05
Paternal education	0.04	0.00	0.09	NS > 0.05
Number of maternal drinks in past month	0.04	0.00	0.13	NS > 0.05
<i>Inattention (DBD)</i>				
Drinks/mo first trimester	0.23	0.05	4.04	< 0.05
Drinks/mo second trimester	0.31	0.09	7.43	< 0.01
Drinks/mo third trimester	0.31	0.09	7.43	< 0.01
Current drinks/d	0.20	0.04	3.04	NS > 0.05
Current drinks/mo	0.24	0.06	4.38	< 0.05
<i>Maternal education</i>				
Raven CPM	-0.03	0.00	0.06	NS > 0.05
Rustioni (total errors)	-0.14	0.02	1.56	NS > 0.05
Teacher DBD rating of attention	0.10	0.01	0.82	NS > 0.05

NS, not significant; PBCL, Problem Behaviors Checklist; CPM, Colored Progressive Matrices; DBD, Disruptive Behavior Disorder.

that maternal and paternal education and current drinks were not related to the PBCL-36. We also explored correlations between prenatal drinking and smoking in 3 trimesters, current drinks per typical drinking day, and current drinks per month with various behavioral outcome measures, such as language comprehension, nonverbal IQ, problem behavior, inattention, and hyperactivity. Of those 25 correlations, several were statistically significant; 4 of the 5 for inattention were significant, drinks in the first, second, and third trimesters and current drinks per month ( $r = 0.23, 0.31, 0.31, \text{ and } 0.24$ , respectively). Also, maternal education was not correlated with the child's nonverbal IQ, language comprehension, or teacher ratings of inattention, ( $r = -0.03, -0.14 \text{ and } 0.10$ , respectively).

The focus of the first set of analyses was to explore the differences between the FASD and control groups on measures of intellectual ability, language, learning, and teacher-rated behavior. A summary of mean ratings on nonverbal IQ, language comprehension, and behavioral symptoms are presented in Table 3. Examining the overall mean ratings for the FASD and controls suggests that the FASD group performed significantly lower than did the control group. More specifically, on a test of nonverbal, abstract reasoning (Raven CPM), the FASD group scored significantly lower (17.86) than the control group (21.78) [ $t(80) = -3.25, p = 0.002$ ]. This finding is also illustrated by the difference in percentile scores (55.00 vs 72.50). It should be noted, however, that the alcohol-exposed group was relatively high functioning on the Raven CPM, with the percentile ranks of this group varying from 25 to 95 and the overall functioning falling in the average range (mean percentile = 55.00).

When comparing the groups on the Rustioni test of language comprehension, the FASD group made significantly more errors (7.95) than did controls (5.27) [ $t(80) = 4.42,$

**Table 3.** Means, Standard Deviations, and *t*-tests on Neuropsychological and Behavioral Tests

	FASD ( <i>n</i> = 22)		Controls ( <i>n</i> = 60)		<i>df</i>	<i>t</i>	<i>p</i> Value
	Mean	SD	Mean	SD			
<i>Nonverbal IQ and language comprehension</i>							
Raven CPM	17.86	3.59	21.78	5.19	80	-3.25	0.002
Raven CPM percentile score	55.00	20.35	72.50	20.78	80	-3.39	0.001
Rustioni (total errors)	7.95	2.32	5.27	2.48	80	4.42	<0.001
Rustioni qualitative	3.36	2.15	4.90	1.74	80	-3.31	0.001
IPDA questionnaire	16.90 <sup>a</sup>	3.41	21.25 <sup>b</sup>	5.60	58.15 <sup>c</sup>	-4.16	<0.001
<i>Behavioral symptoms</i>							
Teacher DBD rating of attention	4.32	3.46	0.65	1.31	23.25 <sup>c</sup>	4.85	<0.001
Teacher DBD rating of hyperactivity/impulsivity	2.14	2.78	0.70	1.76	27.39 <sup>c</sup>	2.26	0.032
Parent DBD rating of attention	2.18	2.97	0.45	0.98	22.70 <sup>c</sup>	2.68	0.013
Parent DBD rating of hyperactivity/impulsivity	1.59	1.74	0.57	1.09	27.36 <sup>c</sup>	2.58	0.015
PBCL-36	9.14 <sup>a</sup>	5.72	3.92 <sup>b</sup>	3.70	54	3.94	<0.001

<sup>a</sup>Not all *n*'s = 22 due to incomplete data.

<sup>b</sup>Not all *n*'s = 60 due to incomplete data.

<sup>c</sup>Levene's Test for Equality of Variance was significant, used equal variances not assumed option in analysis.

PBCL, Problem Behaviors Checklist; CPM, Colored Progressive Matrices; DBD, Disruptive Behavior Disorder.

$p < 0.001$ ]. Impaired performance of the FASD group on linguistic comprehension is further illustrated by a lower mean score earned by this group on the qualitative assessment of test performance [ $t(80) = -3.31, p = 0.001$ ]. On a test of academic achievement (IPDA questionnaire) the FASD group scored significantly lower than did controls [ $t(58.15) = -4.16, p < 0.001$ ]. The FASD group, as rated by teachers, had greater deficits than the control group in basic skills required for learning language [ $t(78) = -3.64, p < 0.001$ ] and math [ $t(79) = -4.08, p < 0.001$ ]. Given that linguistic comprehension errors can be associated with inattention and learning disabilities, Spearman's rank-order correlation coefficients were computed between comprehension error scores, DBD inattention scores, and academic skills ratings for language and math. Results revealed that comprehension errors correlated significantly with inattention and academic skills ratings for language and math. (Spearman's  $\rho = 0.33$  and  $-0.47$  and  $-0.39$ , respectively,  $p < 0.001$ ).

Overall these analyses support the hypothesis that children diagnosed with FASD demonstrated significant difficulty on tests of inductive nonverbal reasoning, language comprehension, and academic achievement when compared with randomly selected Italian control children.

Further, when comparing these 2 groups on disruptive behavioral symptomatology, similar results were obtained (see Table 3). The DBD teacher ratings of behavioral symptoms for the children with FASD suggest significantly more inattention characteristics than controls (4.32 vs 0.65) [ $t(23.25) = 4.85, p < 0.001$ ] and more hyperactivity/impulsivity behaviors (2.14 vs 0.70) [ $t(27.39) = 2.26, p = 0.032$ ]. Further, when parents were asked to make the same ratings, the FASD group was described as having significantly more attentional and hyperactivity/impulsivity-related behaviors [ $t(22.70) = 2.68, p = 0.013$ , and  $t(27.36) = 2.58, p = 0.015$ , respectively]. Finally, on the

PBCL-36 the FASD children were reported to have significantly more behavioral problems than did controls (9.14 vs 3.92) [ $t(54) = 3.94, p < 0.001$ ]. These results suggest that overall, children diagnosed with FASD exhibit significantly more behavioral problems compared with control children.

A binary stepwise logistic regression analysis showed that a model containing inattention (Wald = 10.15,  $df = 1, p = 0.001$ ) and error scores on the language comprehension task (Wald = 5.03,  $df = 1, p = 0.025$ ) correctly classified 85% of the participants. The association between group membership and inattention was further explored by analyzing the frequency of children meeting the DSM criteria in the 2 groups. Compared with the control group, a significantly greater proportion of children with FASD met the DSM-IV criteria of ADD, inattentive type as reported by teachers (2% control vs 55% FASD). In contrast, prevalence rate of hyperactive symptoms among children with FASD was comparable with that observed in the control group. Only 4 (18%) of 22 children with FASD met the DSM-IV criteria of ADD, hyperactive type. It should be underscored that inattentive behaviors in the FASD group were negatively correlated with their teacher-rated language and math skills (Spearman's  $\rho = -0.49$  and  $-0.46; p < 0.001$ , respectively). Thus, teachers rated children with FASD as having more inattentive behaviors and as lower in academic skills than controls. In sharp contrast, the association between reported hyperactivity symptoms and achievement scores was not significant for both language and math scores (Spearman's  $\rho = -0.17$  and  $-0.13$ , respectively). This suggests that it is not the hyperactivity causing problems for the child. Rather, it is the child's inattentiveness.

A second set of analyses was performed to examine possible effects of having some undiagnosed ARND children in our control sample. Controls were selected randomly.

**Table 4.** Means on Neuropsychological and Behavioral Tests Between Control Subjects with no Prenatal Exposure Versus Control Subjects with Prenatal Exposure

	Controls with no prenatal exposure (n = 19), mean (SD)		Controls with prenatal exposure (n = 41), mean (SD)		df	t	p Value
<i>Nonverbal IQ and language comprehension</i>							
Raven CPM	20.63	(5.11)	22.32	(5.21)	58	-1.17	ns .246
Raven CPM %-ile score	65.00	(23.80)	75.98	(18.51)	58	-1.94	ns .056
Rustioni (total errors)	5.63	(2.19)	5.10	(2.61)	58	0.774	ns .442
Rustioni qualitative	4.32	(1.80)	5.17	(1.67)	58	-1.80	ns .077
IPDA questionnaire	21.33 <sup>a</sup>	(6.01)	21.21 <sup>b</sup>	(5.48)	57	0.071	ns .943
<i>Behavioral symptoms</i>							
Teacher DBD rating of attention	0.21	(0.63)	0.85	(1.49)	57.71 <sup>c</sup>	-2.34	.023
Teacher DBD rating of hyperactivity/impulsivity	0.16	(0.76)	0.95	(2.02)	56.51 <sup>c</sup>	-2.19	.032
Parent DBD rating of attention	0.58	(1.26)	0.39	(0.83)	58	0.690	ns .493
Parent DBD rating of hyperactivity/impulsivity	0.37	(0.83)	0.66	(1.20)	58	-0.954	ns .344
PBCL-36	3.50 <sup>a</sup>	(3.86)	4.06 <sup>b</sup>	3.70	40	-0.415	ns .680

<sup>a</sup>Not all n's = 19 due to incomplete data.

<sup>b</sup>Not all n's = 41 due to incomplete data.

<sup>c</sup>Levene's Test for Equality of Variance was significant, used equal variances not assumed option in analysis.

NS, not significant; PBCL, Problem Behaviors Checklist; CPM, Colored Progressive Matrices; DBD, Disruptive Behavior Disorder.

The control children data were further analyzed comparing control children with no prenatal alcohol exposure with control children with prenatal alcohol exposure. A summary of mean ratings on nonverbal IQ, language comprehension, academic achievement, and behavioral symptoms is presented in Table 4. Inspection of overall mean ratings reveals that the data indicate that the 2 groups of control children are comparable on measures of nonverbal IQ, language comprehension, and academic achievement. When comparing the 2 control groups on disruptive behavioral symptomatology, the 2 control groups differed significantly on teacher DBD ratings for inattention and hyperactivity/impulsivity [ $t(57.71) = -2.34, p = 0.023$ , and  $t(56.51) = -2.19, p = 0.032$ , respectively]. The groups, however, were comparable on parent DBD rating of inattention and hyperactivity/impulsivity, as well as on the PBCL-36. These results highlight the possibility that some

children in the control group may have met the criteria for ARND, but were not diagnosed using the population-based methods of random control selection and the revised IOM diagnostic criteria (Hoyme et al., 2005).

For complete clarification of our initial findings, the data were also analyzed comparing the FASD group with those control children with no maternal prenatal alcohol exposure. A summary of mean ratings on nonverbal IQ, language comprehension, academic achievement, and behavioral symptoms is presented in Table 5. Examining the overall mean ratings for the FASD and control groups on measures of nonverbal IQ, language comprehension, and academic achievement, it is suggested that the FASD group performed considerably worse than control children with no prenatal alcohol exposure. They performed significantly lower on the Raven CPM [ $t(39) = -2.02, p = 0.049$ ] and made significantly more errors (7.95) than control

**Table 5.** Means on Neuropsychological and Behavioral Tests Comparing FASD Children and Control Children with No Prenatal Exposure

	FASD (n = 22), mean (SD)		Controls with no prenatal exposure (n = 19), mean (SD)		df	t	p Value
<i>Nonverbal IQ and language comprehension</i>							
Raven CPM	17.86	(3.59)	20.63	(5.11)	39	-2.02	0.049
Raven CPM %-ile Score	55.00	(20.35)	65.00	(23.80)	39	-1.45	NS 0.155
Rustioni (total errors)	7.95	(2.32)	5.63	(2.19)	39	3.28	0.002
Rustioni qualitative	3.36	(2.15)	4.32	(1.80)	39	-1.52	NS 0.136
IPDA questionnaire	16.90 <sup>a</sup>	(3.41)	21.33 <sup>b</sup>	(6.01)	26.01 <sup>c</sup>	-2.76	0.010
<i>Behavioral symptoms</i>							
Teacher DBD rating of attention	4.32	(3.46)	0.21	(0.63)	22.61 <sup>c</sup>	5.47	<0.001
Teacher DBD rating of hyperactivity/impulsivity	2.14	(2.78)	0.16	(0.76)	24.61 <sup>c</sup>	3.19	0.004
Parent DBD rating of attention	2.18	(2.97)	0.58	(1.26)	29.19 <sup>c</sup>	2.32	0.029
Parent DBD rating of hyperactivity/impulsivity	1.59	(1.74)	0.37	(0.83)	31.06 <sup>c</sup>	2.93	0.006
PBCL-36	9.14 <sup>a</sup>	(5.72)	3.50 <sup>b</sup>	(3.86)	22	2.70	0.013

<sup>a</sup>Not all n's = 22 due to incomplete data.

<sup>b</sup>Not all n's = 19 due to incomplete data.

<sup>c</sup>Levene's Test for Equality of Variance was significant, used equal variances not assumed option in analysis.

NS, not significant; PBCL, Problem Behaviors Checklist; CPM, Colored Progressive Matrices; DBD, Disruptive Behavior Disorder.

children who had no prenatal alcohol exposure (5.63) on the Rustioni test of language comprehension [ $t(39) = 3.28, p = 0.002$ ]. Similarly, on a test of academic achievement measured by the IDPA questionnaire, the FASD group scored significantly lower than did controls [ $t(26.01) = -2.76, p = 0.010$ ]. Furthermore, the FASD group as rated by teachers had greater deficits than the control group in basic skills required for learning language [ $t(37) = -2.71, p = 0.010$ ], and math [ $t(38) = -3.82, p = 0.001$ ].

Furthermore, when comparing teacher ratings on disruptive behavioral symptomatology, the FASD group had more attentional problems [ $t(22.61) = 5.47, p < 0.001$ ] and hyperactivity/impulsivity problems [ $t(24.61) = 3.19, p = 0.004$ ]. Similarly, parent ratings of inattention [ $t(29.19) = 2.32, p = 0.029$ ] and hyperactivity/impulsivity [ $t(31.06) = 2.93, p = 0.006$ ] were also significantly different. Lastly, the FASD children were reported to have significantly more behavioral problems as measured by the PBCL-36 [ $t(22) = 2.70, p = 0.013$ ].

## DISCUSSION

The results of these analyses support the overall hypothesis that children diagnosed with FASD would demonstrate significant difficulty on tests of nonverbal reasoning and language comprehension and display significantly more behavioral problems compared with control children. As predicted, the alcohol-exposed children exhibited significantly more difficulty than the control group on the Raven CPM, suggesting impairments of nonverbal intellectual ability and abstract reasoning. Further, these children performed significantly lower on a test of language comprehension (Rustioni) and a test of academic achievement (IPDA). These findings suggest that children with FASD demonstrate impairments on tests of nonverbal IQ and linguistic comprehension, and are consistent with previous research (Kodituwakku et al., 2001; Streissguth et al., 1994). When comparing children with FASD to a group of control children with no prenatal alcohol exposure, the FASD group made significantly more errors on a test of language comprehension and performed significantly lower on a test academic achievement.

On those measures designed to assess problem behaviors associated with FASD, children diagnosed with FASD were rated significantly higher with attentional and hyperactivity problems by both teachers and mothers. The results of the stepwise logistic regression revealed that inattentive characteristics and verbal comprehension difficulty primarily predicted FASD-control group differences. Furthermore, on a problem behavior checklist, the FASD group was reported to have significantly more behavioral problems. Again, these findings are consistent with the literature (Kelly et al., 2000; Kodituwakku et al., 2001; Steinhausen and Spohr, 1998; Streissguth et al., 1998). Further, when the FASD group was compared with a group of control children with *no* prenatal alcohol

exposure, children with FASD were rated by both teachers and parents as having significantly more problem behaviors.

Thus, the results indicate that the FASD group, which was identified through a population-based study, statistically differed from a random sample of peers on all neurobehavioral measures that were utilized. Given that the FASD group did not have prior diagnoses of neurodevelopmental disorders, it is unlikely that confounding factors such as placement in special education classes would account for the observed group differences. Furthermore, Italian children with special needs are primarily mainstreamed. There are no special education classes and children are only pulled out for some limited special education tasks. The 2 groups differed, however, in maternal education, with the number of years of formal education completed by mothers being lower in the FASD group. However, correlation analysis indicated no significant difference by mother's education. Because children in the FASD group had morphological anomalies typically seen in those with prenatal alcohol exposure, it is also highly probable that the teratogenic effects of alcohol contributed to the observed group differences. Given that reported maternal alcohol consumption of the FASD group is low and is not significantly different from that of the control group, one can raise the question of whether an unknown syndrome would account for morphological and behavioral differences in this group. While this possibility cannot totally be ruled out, the most plausible explanation is that mothers of the FASD group underreported their alcohol consumption during pregnancy. Current drinking measures may be better indication of actual drinking levels. Further, the low accuracy of retrospective reporting of prenatal alcohol intake may have influenced maternal data. In support of this explanation is our finding that many of these mothers did not endorse items on the PBCL. Our findings were similar to another study where retrospective reports of behaviors are likely underreported by mothers (Jacobson et al., 2002).

Examination of the clinical literature suggests general that children diagnosed with FASD have ADHD. The finding that inattentive, but not hyperactive, characteristics predicted group membership is consistent with the emerging literature on the cognitive-behavioral phenotype in children with FASD. Inattentiveness is often associated with slow information processing, as failure to comprehend leads to impaired persistence. Numerous researchers have reported that children with FASD display slow information processing (Burden et al., 2005; Jacobson, 1998). Kodituwakku et al. (2001) found that children with FASD made both omission and commission errors, with omission errors being related to parent-reported behavioral problems. Omission errors can be considered related to slow information processing and inattentiveness. In keeping with this finding, the current results show that inattentiveness, but not hyperactivity, is related to lower math and language performance of the FASD group. In

short, impairments of attention are most common in children with FASD.

Deficient language comprehension also predicted group membership. Successful performance on the Rustioni task requires the integrity of a number of processes including verbal working memory and language competence. Adnams et al. (2001) identified language impairments as a primary distinguishing characteristic in a group of children with FAS identified through an epidemiological study in South Africa. Given lower maternal education in the FASD group, it is probable that this group was exposed to lower levels of language skills (language input) than the control group. There exists a large body of literature suggesting that language input is a reliable predictor of syntax and vocabulary development in children (Huttenlocher, 1998). Furthermore, some researchers suggested that children with FASD may have "central hearing impairments" (Church and Kaltenbach, 1997). No functional neuroimaging data exist showing an association between brain dysfunction and language deficits in children with FASD. Voxel-based morphometry data show anomalies in the left-hemisphere temporoparietal cortices, areas critical for language processing (Sowell et al., 2001).

A number of limitations of the present study should be noted. First, given that this sample of children diagnosed with FASD is small, limiting the generalizability. Second, some of the tests were not clinically sensitive enough to differentiate between the wide spectrum of abilities among children diagnosed with FASD and children who were not. For example, although statistically significant, the Raven CPM and the Rustioni scores ranged from average to high average, with many of the FASD children scoring within the average range. There was not as much variance between the groups as would be expected and also would be necessary to accurately describe this population. Therefore, we conclude that the Raven may not be the best test for discriminating or measuring nonverbal reasoning for the Italian population, particularly for individual children with FASD. In addition, although the PBCL-36 was translated and back-translated, this test was not representative of the types of questions to which Italian parents are accustomed to responding about their children. It seems that the PBCL-36 does not relate well to Italian culture and performed differently than in an American cultural setting, which seems to be more problem oriented in approach to child rearing. Perhaps Italian parents have a different interpretation of problem behaviors than the United States population in which the PBCL-36 was developed. Essentially, there was great variance from U.S.-published data. Anecdotally, several Italian parents became defensive while completing the PBCL-36 questionnaire. It is also possible that symptoms such as hyperactivity and impulsivity, as measured by the PBCL-36 and the DBD Rating Scale should be viewed as a relative cultural construct. These behaviors are perhaps more expected or tolerated by Italians than by Americans.

Third, because this study of neurobehavioral functioning was carried out in the context of a larger epidemiological inquiry that was limited in time to no more than 12 months, the range of tests utilized and developmental traits measured was more limited than we desired. Fourth, although control mothers matriculated further in school, maternal verbal and intellectual functioning was not assessed. But correlation analysis showed no significant difference in correlations between child behavior problems and maternal education. Fifth, only 51% of parents consented to participate, and therefore, it is unknown if a systematic bias entered into subject selection. And finally, it is possible that some children in the control group may have met the criteria for ARND but were not identified using this particular population-based screening and the revised IOM methodology of diagnosis.

Despite the above limitations, the present study is the first to demonstrate population-based neurobehavioral impairments in a cohort of Italian children diagnosed with FASD. This is also the first report indicating the association between inattentive behaviors and measures of academic functioning in a group of children with FASD. If this finding is replicated, it will have significant implications for developing intervention programs for children with FASD.

#### ACKNOWLEDGMENTS

All research methods, procedures, and consent forms were approved by the Ethics Committee of the regional Italian health department and the Human Research Review Committee (HRRC) of the University of New Mexico Health Sciences Center, approval # 03-089.

We gratefully acknowledge the support and assistance of some of the many people who have made this research possible. Drs. Faye Calhoun, Kenneth Warren, and Ting Kai Li of NIAAA were instrumental in bringing the binational research team together and funded the initial collaboration to make this study possible. NIAAA also funded travel for the Italian team to journey to the United States for training and to prepare for and carry out the final case conference, data consolidation, and analyses. In Italy many people have assisted in getting the project started. Luca Deiana, B.A., Luciana Chessa, M.D., Michele Stegagno, M.D., Agostino Battaglia, M.D., and Luigi Tarani, M.D., were all instrumental in hosting members of the project and participating in the early training and screening of children. Psychological testing to finalize the diagnoses of the children was carried out by 2 of the authors of the paper (Giovanna Coriale and Daniela Fiorentino) with assistance from Francesca De Rosa and Corinna Ceoldo. We are also grateful for the support and assistance of various managers, school physicians, and psychologists from A.S.L. R.M.G. and R.M.H.: dott. P. Trecca, dott. Carapellese, dott. Di Giovanni, dott. G. Versace, dott. De Carolis, dott. N. Roma, dott. C. D'Anna, dott.ssa L. Asci, G. Gironda, S. Gagliardi, and A. Pontecorvi. Finally, we thank various individuals from the school office of

the Lazio region and Rome Province: dott.ssa M.T. Silani, and dott.ssa R. Massacesi and dott. F. Valeriani from SIFIP.

## REFERENCES

- Abkarian GG (1992) Communication effects of prenatal alcohol exposure. *J Commun Disord* 25:221–240.
- Adnams CM, Kodituwaku PW, Hay A, Molteno CD, Viljoen D, May PA (2001) Patterns of cognitive-motor development in children with fetal alcohol syndrome from a community in South Africa. *Alcohol Clin Exp Res* 25:557–562.
- Alderton DL, Larson GE (1990) Dimensionality of Raven's advanced progressive matrices items. *Educ Psychol Meas* 50:887–900.
- Alvik A, Haldorsen T, Groholt B, Lindemann R (2006) Alcohol consumption before and during pregnancy comparing concurrent and retrospective reports. *Alcohol Clin Exp Res* 30:510–515.
- Aronson M, Hagberg B (1998) Neuropsychological disorders in children exposed to alcohol during pregnancy: a follow-up study of 24 children to alcoholic mothers in Goteborg, Sweden. *Alcohol Clin Exp Res* 22:321–324.
- Autti-Ramo I (2000) Twelve-year follow-up of children exposed to alcohol in utero. *Dev Med Child Neurol* 42:406–411.
- Baddeley AD, Wilson BA, Kopelman M (2002) *Handbook of Memory Disorders*, 2nd ed. Psychology Press, Hove, East Sussex.
- Bailey BN, Delaney-Black V, Covington CY, Ager J, Janisse J, Hannigan JH, Sokol RJ (2004) Prenatal exposure to binge drinking and cognitive and behavioral outcomes at age 7 years. *Am J Obstet Gynecol* 191:1037–1043.
- Bishop DVM (1989) *Test for the Reception of Grammar*. Medical Research Council, London.
- Burden MJ, Jacobson SW, Jacobson JL (2005) Relation of prenatal alcohol exposure to cognitive processing speed and efficiency in childhood. *Alcohol Clin Exp Res* 29:443–452.
- Carmichael Olson H, Feldman JJ, Streissguth AP, Sampson PD, Bookstein FL (1998) Neuropsychological deficits in adolescents with fetal alcohol syndrome: clinical findings. *Alcohol Clin Exp Res* 22:1998–2012.
- Church MW, Kaltenbach JA (1997) Effects of fetal alcohol exposure on the auditory and vestibular systems. *Alcohol Clin Exp Res* 21:495–512.
- Clarren SK, Randels SP, Sanderson M, Fineman RM (2001) Screening for fetal alcohol syndrome in primary schools: a feasibility study. *Teratology* 63:3–10.
- Coles CD, Platzman KA, Raskind-Hood CL, Brown RT, Falek A, Smith IE (1997) A comparison of children affected by prenatal alcohol exposure and attention deficit, hyperactivity disorder. *Alcohol Clin Exp Res* 21:150–161.
- Czarnecki DM, Russell M, Cooper ML, Salter D (1990) Five-year reliability of self-reported alcohol consumption. *J Stud Alcohol* 51:68–76.
- EUROMAC (1992) A European concerted action: maternal alcohol consumption and its relation to the outcome of the pregnancy and child development at 18 months. *Int J Epidemiol* 2 (suppl 1): S72–S78.
- Graves K, Kaskutas LA (2002) Beverage choice among Native American and African American urban women. *Alcohol Clin Exp Res* 26:218–222.
- Howell DC (2002) *Statistical Methods for Psychology*, 5th ed. Wadsworth, Belmont, CA.
- Hoyme HE, May PA, Kalberg WO, Kodituwaku P, Gossage JP, Trujillo PM, Buckley DG, Miller JH, Aragon AS, Khaole N, Viljoen DL, Jones KL, Robinson LK (2005) A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 institute of medicine criteria. *Pediatrics* 115:39–47.
- Huttenlocher J (1998) Language input and language growth. *Prev Med* 27:195–199.
- Jacobson SW (1998) Specificity of neurobehavioral outcomes associated with prenatal alcohol exposure. *Alcohol Clin Exp Res* 22:313–320.
- Jacobson SW, Chiodo LM, Sokol RJ, Jacobson JL (2002) Validity of maternal report of prenatal alcohol, cocaine, and smoking in relation to neurobehavioral outcome. *Pediatrics* 109:815–825.
- Jacobson SW, Jacobson JL, Sokol RJ, Martier SS, Ager JW, Kaplan MG (1991) Maternal recall of alcohol, cocaine, and marijuana use during pregnancy. *Neurotoxicol Teratol* 13:535–540.
- Kaskutas LA, Graves K (2000) An alternative to standard drinks as a measure of alcohol consumption. *J Subst Abuse* 12:67–78.
- Kaskutas LA, Graves K (2001) Pre-pregnancy drinking: how drink size affects risk assessment. *Addiction* 96:1199–1209.
- Kelly SA, Day N, Streissguth AP (2000) Effects of prenatal alcohol exposure on social behavior in humans and other species. *Neurotoxicol Teratol* 22:143–149.
- King AC (1994) Enhancing the self-report of alcohol consumption in the community: two questionnaire format. *Am J Public Health* 84:294–296.
- Kodituwaku PW, Kalberg W, May PA (2001) The effects of prenatal alcohol exposure on executive functioning. *Alcohol Res Health* 25:192–198.
- Kopera-Frye K, Dehaene S, Streissguth AP (1996) Impairments of number processing induced by prenatal alcohol exposure. *Neuropsychologia* 34:1187–1196.
- Larroque B, Kaminski M (1998) Prenatal alcohol exposure and development at preschool age: main results of a French study. *Alcohol Clin Exp Res* 22:295–303.
- Lemoine P, Harosuseau H, Borteyru JP, Menuet JC (1968) Les enfants des parents alcooliques: anomalies observees a propos de 127 cas. *Quest Medical* 21:476–482.
- Lemoine P, Lemoine P (1992) Outcome of children of alcoholic mothers (study of 105 cases followed to adult age) and various prophylactic findings. *Ann Pediatr (Paris)* 39:226–235.
- Mattson SN, Riley EP, Delis DC, Stern C, Jones KL (1996) Verbal learning and memory in children with fetal alcohol syndrome. *Alcohol Clin Exp Res* 20:810–816.
- Mattson SN, Riley EP, Gramling L, Delis DC, Jones KL (1997) Heavy prenatal alcohol exposure with or without physical features of fetal alcohol syndrome leads to IQ deficits. *J Pediatr* 131:718–721.
- May PA, Brooke L, Gossage JP, Croxford J, Adnams C, Jones KL, Robinson L, Viljoen D (2000) Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. *Am J Public Health* 90:1905–1912.
- May PA, Brooke LE, Gossage JP, Snell C, Hendricks L, Croxford J, Marais AS, Viljoen DL (2005) Maternal risk factors for fetal alcohol syndrome in the Western cape province of South Africa: a population-based study. *Am J Public Health* 95:1190–1199.
- O'Brien G, Yule W (1995) *Behavioural Phenotypes*. MacKeith Press, London, UK.
- Pelham Jr WE, Gnagy EM, Greenslade KE, Milich R (1992) Teacher ratings of DSM-III-R symptoms for the disruptive behavior disorders. *J Am Acad Child Adolesc Psychiatry* 31:210–218.
- Raven JC, Court JH, Raven J (1947) *Manual for Raven's Progressive Matrices and Vocabulary Scales Section 1, General Overview and Section 2, Coloured Progressive Matrices*. H.K. Lewis, London, UK.
- Raven JC, Court JH, Raven J (1985) *Manual for Raven's Progressive Matrices and Vocabulary Scales*. H. K. Lewis, London, UK.
- Riley EP, Mattson SN, Li TK, Jacobson SW, Coles CD, Kodituwaku PW, Adnams CM, Korkman MI (2003) Neurobehavioral consequences of prenatal alcohol exposure: an international perspective. *Alcohol Clin Exp Res* 27:362–373.
- Roccella M, Testa D (2003) Fetal alcohol syndrome in developmental age: neuropsychiatric aspects. *Minerva Pediatr* 55:63–74.
- Roebuck TM, Simmons RW, Richardson C, Mattson SN, Riley EP (1998) Neuromuscular responses to disturbance of balance in children with prenatal exposure to alcohol. *Alcohol Clin Exp Res* 22:1992–1997.
- Room R (2005) Public health policy on alcohol: an international perspective. *Addiction* 100:1562–1563.

- Rustioni DML (1994) *Prove di valutazione della comprensione linguistica*. Organizzazione Speciali, Firenze, Italy.
- Sobell LC, Agrawal S, Annis H, Ayala-Velazquez H, Echeverria L, Leo GI, Rybakowski JK, Sandahl C, Saunders B, Thomas S, Zioikowski M (2001) Cross-cultural evaluation of two drinking assessment instruments: alcohol timeline followback and inventory of drinking situations. *Subst Use Misuse* 36:313–331.
- Sobell LC, Sobell MB (1995) Alcohol consumption measures, in *Assessing Alcohol Problems* (Allen JP, Columbus M eds), p. 55. NIAAA, Bethesda, MD.
- Sowell ER, Mattson SN, Thompson PM, Jernigan TL, Riley EP, Toga AW (2001) Mapping callosal morphology and cognitive correlates. *Neurology* 57:235–244.
- Spohr HL, Willms J, Steinhausen HC (1993) Prenatal alcohol exposure and long-term developmental consequences. *Lancet* 341:907–910.
- Steinhausen HC (1995) Children of alcoholic mothers: a review. *Eur Child Adolesc Psychol* 4:143–145.
- Steinhausen HC, Spohr HL (1998) Long-term outcome of children with fetal alcohol syndrome: psychopathology, behavior, and intelligence. *Alcohol Clin Exp Res* 22:334–338.
- Stratton K, Howe C, Battaglia F (1996) *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment*. National Academy Press, Washington, DC.
- Streissguth AP, Barr HM, Olson HC, Sampson PD, Bookstein FL, Burgess DM (1994) Drinking during pregnancy decreases word attack and arithmetic scores on standardized tests: adolescent data from a population-based prospective study. *Alcohol Clin Exp Res* 18:248–254.
- Streissguth AP, Barr HM, Sampson PD (1990) Moderate prenatal alcohol exposure: effects on child IQ and learning problems at age 7 1/2 years. *Alcohol Clin Exp Res* 14:662–669.
- Streissguth AP, Bookstein FL, Barr HM, Press S, Sampson PD (1998) A fetal alcohol behavior scale. *Alcohol Clin Exp Res* 22:325–333.
- Terreni A, Tretti ML, Corcella PR, Cornoldi C, Tressoldi PE (2002) *Questionario osservativo per l'identificazione precoce delle difficoltà di apprendimento (IPDA)*. Erickson, Trento.
- Uecker A, Nadel L (1996) Spatial locations gone awry: object and spatial memory deficits in children with fetal alcohol syndrome. *Neuropsychologia* 34:209–223.
- Viljoen DL, Gossage JP, Adnams CM, Jones KL, Robinson LK, Hoyme HE, Snell C, Khaole N, Asante KK, Findlay R, Quinton B, Brooke LE, May PA (2005) Fetal alcohol syndrome epidemiology in a South African community: a second study of a very high prevalence area. *J. Stud Alcohol* 5:593–604.
- Wilson BA, Alderman N, Burgess P, Emslie H, Evans J (1996) *Behavioral Assessment of the Dysexecutive Syndrome*. Thames Valley Test Company, Bury St., Edmunds.
- Zaidel E, Zaidel DW, Sperry RW (1981) Left and right intelligence: case studies of Raven's progressive matrices following brain bisection and hemidecortation. *Cortex* 17:167–186.

# Epidemiology of FASD in a Province in Italy: Prevalence and Characteristics of Children in a Random Sample of Schools

Philip A. May, Daniela Fiorentino, J. Phillip Gossage, Wendy O. Kalberg, H. Eugene Hoyme, Luther K. Robinson, Giovanna Coriale, Kenneth Lyons Jones, Miguel del Campo, Luigi Tarani, Marina Romeo, Piyadasa W. Kodituwakku, Luca Deiana, David Buckley, and Mauro Ceccanti

**Background:** Accurate estimates of the prevalence and characteristics of fetal alcohol syndrome (FAS) and fetal alcohol spectrum disorders (FASD) in a Western European population are lacking and are of particular interest in settings where the usual pattern of alcohol consumption is thought to be daily drinking with meals. To address these issues, an epidemiology study of FAS and other FASD was undertaken in Italian schools.

**Methods:** Primary schools ( $n = 25$ ) in 2 health districts of the Lazio region were randomly selected and recruited for the study. Five hundred forty-three children, 50% of those enrolled in first-grade classes, received parental permission to participate in a 2-tiered, active case ascertainment screening process. Detailed evaluation of children selected in a preliminary screening phase was carried out on those who were small for height, weight, and head circumference and/or referred by teachers for suspected learning and behavioral problems. Detailed evaluation was carried out on each child's: (1) physical growth and dysmorphology, (2) psychological development and behavior, and (3) prenatal exposure to alcohol and other risk factors for FASD via maternal interviews. A group of 67 randomly selected children without FASD from the same classes was utilized as a comparison group.

**Results:** Using 2 denominators for prevalence estimation, a conservative one and a strict sample-based estimate, the prevalence of FAS in this province of Italy was 3.7 to 7.4 per 1,000 children. When cases of partial FAS (PFAS) and a case of alcohol-related neurodevelopmental deficits (ARND) were added to FAS cases, the rate of FASD was 20.3 to 40.5 per 1,000 and estimated at 35 per 1,000 overall or between 2.3 and 4.1% of all children. This exceeds previously published estimates of both FAS and FASD for the western world. Detailed data are presented that demonstrate the utility of the guidelines of the revised Institute of Medicine diagnostic criteria for FASD. Children with FASD are significantly more impaired/affected ( $p < 0.05$ ) than randomly selected comparison children on all measures of growth deficiency, key facial features of FASD, overall dysmorphology scores, language comprehension, non-verbal IQ, and behavior. Maternal reports of current drinking were significantly higher for mothers of FASD children than comparison mothers, but reported rates of overall drinking during pregnancy were not significantly different. In contrast to expectations, daily drinking among mothers of the comparison group was not common. However, dysmorphology scores of the children were significantly correlated with drinking in the second and third trimesters, drinks per current drinking day, and current drinks per month. Finally, children with the physical features of FASD had lower IQs; nonverbal IQ was significantly correlated with head circumference and negatively correlated with overall dysmorphology score, smooth philtrum, and several other facial and physical anomalies characteristic of FAS.

**Conclusions:** Using careful measures of ascertainment in a primary school setting, these results provide relatively high estimates of the prevalence of FASD and raise the question of whether FASD is more common in the western world than previously estimated.

**Keywords:** Fetal Alcohol Syndrome (FAS), Fetal Alcohol Spectrum Disorder (FAD), Epidemiology, Prevalence, Italy.

From The University of New Mexico, Albuquerque, New Mexico (PAM, JPG, WOK, PWK, DB); The University of Rome, "La Sapienza," Rome, Italy (DF, GC, LT, MR, LD, MC); Stanford University, Stanford, California (HEH); The State University of New York at Buffalo, Buffalo, New York (LKR); The University of California, San Diego, California (KLJ); and the Universitat Pompeu Fabra, Barcelona, Spain (MC).

Received for publication November 1, 2005; accepted April 26, 2006.

This project was funded in part by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (pilot project subcontract # 53257A-P1660-780211CSM from San Diego State University) as part of the International Consortium for the Study of FASD [(CIFASD)—AA014811 and AA014828]. In Italy, it was supported by a grant from the health department of the regional government of the Lazio Region, Assessorato alla Sanita della Regione Lazio (ASL RMG), and a grant by SITAC Oulus.

Reprint requests: Philip A. May, PhD, Center on Alcoholism, Substance Abuse and Addictions (CASAA), The University of New Mexico, 2650 Yale Boulevard, S.E., Albuquerque, NM 87106; Fax: 505-925-2313; E-mail: pmay@unm.edu

Copyright © 2006 by the Research Society on Alcoholism.

DOI: 10.1111/j.1530-0277.2006.00188.x

**T**HE EPIDEMIOLOGY OF fetal alcohol syndrome (FAS), or fetal alcohol spectrum disorders (FASD) of any kind, had not been researched from a population-based perspective in a Western European population. However, in 2003, a collaborative plan between researchers from the United States and Italy was finalized with officials of the U.S. National Institute on Alcohol Abuse and Alcoholism (NIAAA) and several governmental agencies in Italy to determine the nature and extent of FASD in Italy. While most population-based epidemiology studies of FASD have been carried out in populations where heavy episodic drinking (e.g., “binge drinking”) is common, in much of Western Europe alcohol consumption is commonly believed to be moderate, daily, and with meals.

#### RELEVANT LITERATURE ON FASD AND MATERNAL DRINKING IN ITALY

Only a few cases of children with FAS in Italy have been described in the published literature (Calvani et al., 1985a, 1985b; Moretti and Montali, 1982; Roccella and Testa, 2003; Scianaro et al., 1978; Scotto et al., 1993). These articles present data on 24 cases where the physical and behavioral characteristics are described as similar to those FASD children in U.S. studies.

In Italy, where daily, moderate drinking is believed to be the predominant pattern, some studies have shown no relationship between maternal alcohol consumption, reduced birth weight, or pregnancy loss (De Nigris et al., 1981; Parazzini et al., 1994, 1996; Primatesta et al., 1993). Other studies, however, have linked prenatal alcohol use and smoking with low birth weight. Nonsmokers in Italy who drank 10 g (0.35 oz) or more absolute alcohol a day were at the highest risk for having low-birth-weight infants (<2,500 g), and maternal alcohol consumption of 20 g (0.75 oz or 1.5 drinks) per day significantly increased the risk of preterm delivery (Lazzaroni et al., 1993a). Bonati and Fellin (1991) found that more than one-third of 4,966 women delivering in Italian hospitals were daily drinkers, and that nearly all of these women continued drinking after recognition of pregnancy. The authors distinguished between women who “drank between meals” and those who did not, with slightly less than 1% falling into the former category. Overall, maternal drinking was not associated with lower birth weight, but the authors concluded that birth weight is affected only by abusive drinking (Bonati and Fellin, 1991), the small proportion who drank between meals. Primatesta et al. (1993) also reported low rates of binge drinking (1.4%) among prepregnant women in Milan. However, in this same study, 9% of the women reported risky to very risky average weekly consumption of alcohol, with 29% continuing to drink daily during pregnancy.

#### STUDIES OF FASD PREVALENCE AND OTHER EPIDEMIOLOGICAL CHARACTERISTICS

Our review of the literature revealed no major epidemiologic studies of FAS or FASD previously undertaken in Italy or in Western Europe that utilized extensive outreach or other methods of active case ascertainment.

Most studies in the United States that have attempted to define the prevalence and other epidemiological characteristics of FASD have used clinic- (Astley et al., 2004; Sampson et al., 1997) or record-based systems (Chavez et al., 1988; Egeland et al., 1995, 1998) without active recruitment in defined populations. Such methods are likely to underreport the extent and specific characteristics of the problem in any population (Leversha and Marks, 1995). Without active case ascertainment, many children with FAS and other FASD are neither detected (Clarren et al., 2001; Egeland et al., 1998; Little et al., 1990; Stratton et al., 1996) nor referred for a diagnosis (see reviews in Abel, 1995, 1996, 1998; Abel and Sokol, 1987, 1991; May and Gossage, 2002; Stratton et al., 1996). Comparing studies of mainstream populations that utilize different methods (e.g., passive vs active) is perilous if taken literally.

In population-based, active case ascertainment studies of FASD cases are actively sought for examination and diagnosis through outreach in a defined population through an organized network of training and communication (Stratton et al., 1996). All previously published, active case ascertainment, population-based studies of FAS, except one, were carried out in predominantly minority (usually American Indian) and low-socioeconomic-status (SES) communities in the United States and South Africa (Duimstra et al., 1993; May and Hymbaugh, 1982; May et al., 1983, 2002; Quaid et al., 1993). While most population-based studies have used active referral systems, in South Africa in-school screening of first-grade children has been pursued successfully in several waves (May et al., 2000, 2005; Viljoen et al., 2002, 2005). This study in Italy utilizes methods similar to those used in South Africa.

Only one in-school study has been completed in any population in the United States. Clarren et al. (2001) used methods of passive parental consent (all children were included unless parents took special measures to withdraw them), which yielded very high participation in 1 county in Washington State. In another Washington county, active consent for children to participate was required, which yielded low participation (<25%). In the high-participation county, the rate of FAS was determined to be 3.1 per 1,000, substantially higher than estimates of FAS derived from passive ascertainment methods.

Recent clinic- and registry-based estimates of the prevalence of FAS in the mainstream United States population have varied between 0.33 per 1,000 births and 2.0 (Abel and Sokol, 1991; May and Gossage, 2002; Stratton et al., 1996). Furthermore, the combined rate of FAS and ARND (similar to FASD) has been estimated from

clinical studies at 9 per 1,000 or approximately 1% (Sampson et al., 1997).

Owing to a lack of studies utilizing active case ascertainment, and also because of recent advancements in the clarification of the Institute of Medicine (IOM) categories for FASD (Hoyme et al., 2005), we believe that the overall rate of FASD may be higher in both the United States and Western Europe than current estimates suggest. To develop more accurate estimates of the prevalence and characteristics of FAS and FASD in Western Europe, specifically in a setting in which binge drinking is thought to be uncommon, a team of U.S. and Italian investigators carried out this active case ascertainment, population-based study.

## METHODS

### Sample

The data originate from in-school, first-grade samples from 2 health districts of the Lazio region that lie outside of the large metropolitan area of Rome. The study area is characterized by a number of small towns and municipalities, some with suburban economies (e.g., bedroom communities somewhat dependent on Rome) and others that are relatively to completely self-sufficient, rural, and agricultural in nature.

The study is a cross-sectional, observational, case-control design with retrospective collection of maternal exposure information. Using a random-number table, 25 schools were selected from the 68 schools in the 2 districts with first-grade classes. Italian research team members approached the regional school administrators and each of the selected schools to explain the study and gain permission to proceed. All parents and guardians of first-grade children were then

contacted via normal school communication channels, including parent organization meetings in the evenings. The total number of children enrolled as first graders in the randomly selected schools was 1,086. Consent forms were signed and returned by slightly over half (51%) of the parents. After the first tier of screening was completed, exactly half of the children, 543, were present and participated in the first tier of screening. The children with consent to participate in this study are believed to be representative of all children enrolled in first grade at the randomly selected schools. All research procedures were approved by both the Ethics Committee of the regional health district in Italy (ASL RMG) and the University of New Mexico Health Sciences Human Research Review Committee (approval #03 089).

### Initial Data Collection—Tier I Screening

Data collection for the diagnoses occurred via 2 tiers of screening. In Tier I, height, weight, and head circumference [occipitofrontal circumference (OFC)] were measured for each child by the local school physicians. Percentiles for growth for each measure were assigned by study staff using recently revised U.S. National Center for Health Statistics growth charts (Kuczmarski et al., 2000). Children at or below the 10th percentile on height, or weight, or OFC were advanced to Tier II of the study (see Fig. 1). In addition to growth, teachers were asked to refer any child with learning or behavior problems. Referrals were made on the basis of a questionnaire that included items on inattention, hyperactivity, and learning problems derived from the Questionario Osservativo per l'Identificazione Percoce delle Difficoltà di Apprendimento (IPDA; Terreni et al., 2002) and a translation of the Pelham Disruptive Behavior Disorder rating scale (Pelham et al., 1992). Of the 543 children in the study, 158 met one or both of the above criteria for Tier II of the study. Overall, 33.5% of the 158 children who entered Tier II (the diagnostic phase) of the study solely because of size and/or OFC, 13.9% entered by referrals for both poor growth and

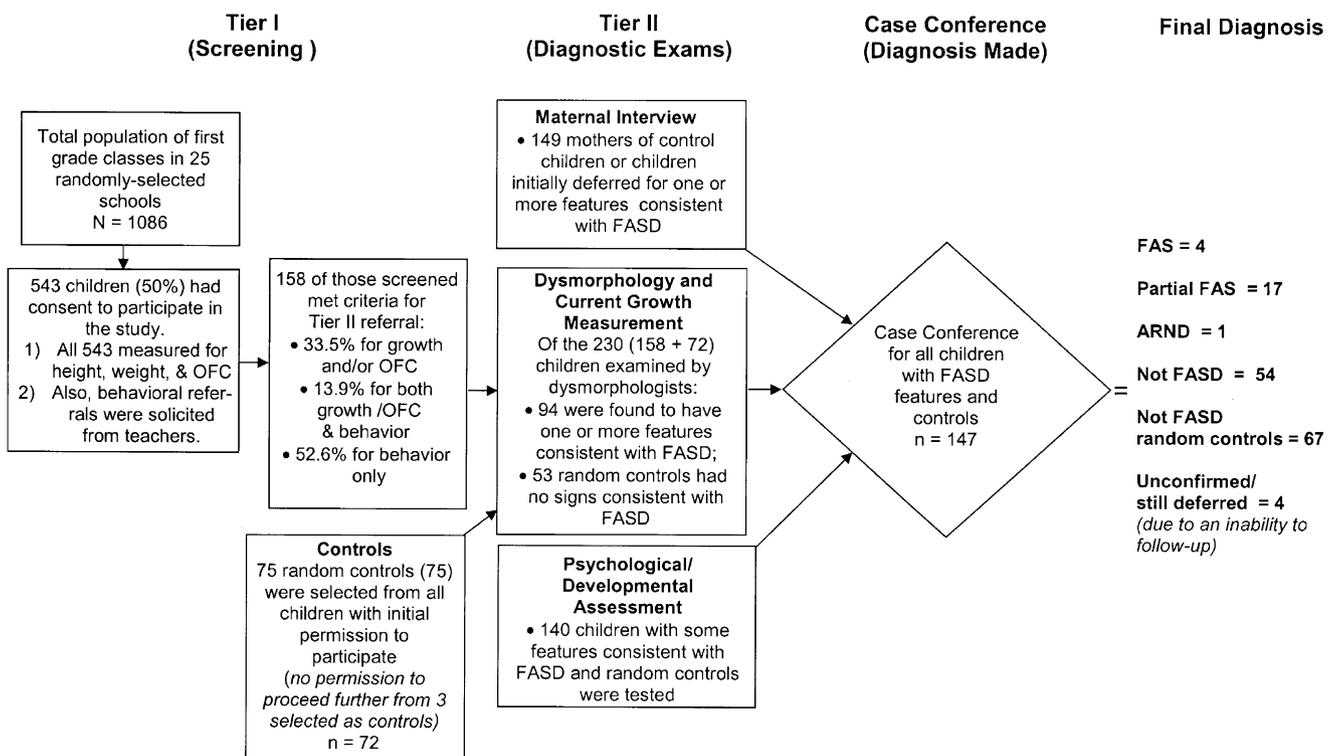


Fig. 1. Methodological flow of the fetal alcohol spectrum disorders Study in Italy. Wave I. 2004.

behavioral/learning, and 52.6% of the children entered solely for learning and/or behavior problems. Additional children were also entered into Tier II screening as controls.

### *Tier II—Diagnostic Procedures*

In Tier II, 3 domains of assessment were explored for each child: (1) dysmorphology, physical growth, and development; (2) psychological development (intelligence and behavior); and (3) maternal risk factors. A standardized examination, by 4 dysmorphologists working together in 2 teams, was carried out over a period of 2 weeks, followed immediately by the psychological testing.

*Physical Exam—Dysmorphology, Physical Growth, and Development.* Physical assessment followed the revised IOM criteria (Hoyme et al., 2005), a diagnostic schema that has also been published in Italy (Spagnolo et al., 2005) and used in other countries: South Africa, Russia, and Finland (Autti-Rämö et al., 2005). With IOM criteria, a child who displays all of the following characteristics meets criteria for the diagnosis of FAS: 2 or 3 of the cardinal facial anomalies (short palpebral fissures, thin vermilion border, and/or smooth philtrum), prenatal and/or postnatal growth retardation ( $\leq 10$ th percentile), and microcephaly ( $\leq 10$ th percentile) or other evidence of structural brain abnormalities, with or without confirmation of maternal drinking. For partial FAS (PFAS), a child must exhibit 2 or more facial features and 1 or more of the following characteristics: prenatal and/or postnatal growth retardation ( $\leq 10$ th percentile), evidence of abnormal brain structure or growth (e.g., microcephaly  $\leq 10$ th percentile), or evidence of characteristic behavioral or cognitive abnormalities, with or without evidence of maternal drinking. For a diagnosis of alcohol-related neurodevelopmental disorder (ARND), a child must have a solid documentation of significant prenatal alcohol exposure, display neurological or structural brain abnormalities (e.g., microcephaly), or manifest evidence of a complex and characteristic pattern of behavioral or cognitive abnormalities inconsistent with developmental level and not explained by genetic predisposition, family background, or environment alone (Hoyme et al., 2005). Diagnosis of FAS or PFAS without a confirmed history of alcohol exposure must be viewed as tentative, but IOM criteria allow diagnosis of these categories without definite direct reports of exposure (Stratton et al., 1996).

*The Dysmorphology Scoring System.* Each child was examined by 1 of 2 teams of dysmorphologists working blinded from any knowledge of the child and family. Interrater reliability for the lead dysmorphologists of the teams in similar studies was found to be 0.82 to 0.92 in independent assessments of key facial measurements (May et al., 2000; Viljoen et al., 2005). The data from each child were recorded (in English) by a member of the research team working one on one with the examining physicians. Each of the over 40 features examined are features linked by research with FASD. Based on the standardized assessment, a total dysmorphology score was calculated for each child. In the scoring system, some key features of FASD are weighed more heavily than others. Small head circumference, short palpebral fissures, smooth philtrum, and thin vermilion border of the upper lip are all assigned a 3. Features assigned a score of 2 are low weight for age, midfacial hypoplasia, ptosis, and antverted nares. Most features carry a weight of 1 or 0. The highest possible score is 36. Higher scores indicate more features consistent with FASD (see Hoyme et al., 2005).

*Preliminary Classification of FAS and Deferred.* In the study, the term “deferred” is used merely as a “holding” diagnosis pending gathering of additional information for a final diagnosis. When a child is examined by dysmorphologists in the first part of Tier II of the study, he/she is assigned a diagnosis of probable FAS, deferred as possible FASD, or not FASD. Probable FAS, deferred children, and controls are then administered the battery of neuropsychological tests. A final diagnosis is assigned later in case conference: FAS, partial FAS, ARND, or not FASD. Four children left the study as still

deferred because of secondary refusals of consent or multiple absences resulting in noncompletion of testing.

*Psychological and Behavioral Measures.* Psychological and developmental evaluations utilized a battery of tests that included measures of perceptual and nonverbal reasoning ability, a language comprehension measure, and 2 measures of behavior. The Raven Colored Progressive Matrices (CPM; Raven et al., 1976) is a perceptual test instrument for assessing nonverbal reasoning ability. The CPM version of the Raven is used with young children and the elderly. Coupled with a standardized test of language ability, the Raven can provide a single test of intelligence that is not culturally biased. The Rustioni Test of Language Comprehension (Rustioni, 1994) is an Italian test of linguistic understanding developed and normed on the Italian population to provide an assessment of one’s understanding of Italian grammar. The Parent/Teacher Descriptive Behavior Disorder (DBD) ratio scale (Pelham et al., 1992) and the Personal Behaviors Checklist (PBCL-3; Streissguth et al., 1998) measure behavior and provided Italian parental and teacher perceptions of the child’s behavior. These tests provided a battery that was brief, yet culturally appropriate, to assess the functioning of the children on general intelligence, language, and behavior. The Raven, Pelham, and PBCL have been used with school children in other FASD studies in other countries (Adnams et al., 2001; Stromland et al., 2005). Children performing poorly on most of these tests (generally 1.5 or more standard deviations below the mean) were candidates for a diagnosis of FAS, PFAS, or ARND when other problems of growth, dysmorphology, and maternal exposure to alcohol are present. Ninety children with 1 or more features of FASD and 50 of the random controls received the full battery of psychological tests (Fig. 1).

*Maternal Interviews and Maternal Body Mass Index.* All but 2 of the maternal interviews were carried out at the schools. They were initiated as soon as consent forms were received. The questionnaire consisted of 175 items, many of which were drawn from questionnaires used elsewhere in FASD epidemiology projects (May et al., 2005; Viljoen et al., 2002). Items were reviewed by the binational research team and chosen for sensitivity and substantive and cultural relevance. Translated from English to Italian, they were checked via back-translation techniques. Domains covered by the instrument are as follows: demographic and socioeconomic; reproductive history; nutrition and eating pattern; drinking by quantity, frequency, and timing of the alcohol exposure before, during, and after the index pregnancy; and family and home environment. Body mass index (BMI) scores were calculated with the following metric formula: weight in kilograms/(height in meters). Low maternal BMI has recently been linked to an increased likelihood for FAS births (May et al., 2005; Khaole et al., 2004).

The mothers of all students were contacted for interviews to gather information on maternal risk and protective factors in this population and the specific exposure to alcohol. If a mother was not available, collateral information was discretely sought whenever possible. Maternal interviewers were blinded to all information on the children. All 519 mothers who consented to have their children examined, who were located, who consented, and who showed up for an interview were interviewed. This was done so as not to single out for stigma any particular women in the communities.

Eighty-six of the 94 mothers of children with one or more features consistent with FASD (91.5%) were interviewed. Sixty-three of the 67 (94%) mothers of children ultimately retained as controls were interviewed (Fig. 1). This paper reports primarily the data from 18 of the 21 (85.7%) mothers of the 22 FASD children (there was 1 set of twins) compared with the 63 control mothers for whom data were most complete.

*Case Conference for Final Diagnosis.* In revised IOM diagnostic methodology, the 3 separate data sets (a, d, and e above) are independently collected and maintained by 3 separate groups of professionals on the research team: (1) child growth, physical development, and dysmorphology; (2) psychological and behavioral

assessments; and (3) maternal risk and protective data. During the data collection phase, there is no sharing of findings across disciplines. Once all data are collected and filed electronically in a centralized data bank, then summary findings are prepared on each child via a case conference form. At case conferences, all of the research team, representing each of the 3 substantive/data domains, comes together over several days to review and discuss Tier II findings on a case-by-case basis. A final diagnosis for each child and control (to confirm that randomly selected controls do not have an FASD) is assigned. Representatives of each discipline/data domain present data for each child still blinded as to the reason the child entered Tier II of the study. The diagnosis is then made by consensus or, if necessary and very rarely, by vote.

*Selection of the Control Children.* Controls attending the same first-grade classes were chosen ( $n = 75$ ) via a random-number table from all 543 children for whom there were signed consent forms, regardless of the child's size or a referral for behavioral/learning problems. They are believed to be representative of the average or modal child enrolled in these first-grade classes. Control children underwent the screening and testing simultaneously with the index cases. Examiners in all of the substantive domains and parents and teachers were blinded throughout the research as to the reason for examining or testing any of the children, subjects, or controls. The general public and the schools knew it was a study of "development." Nineteen of the randomly selected controls were originally deferred upon dysmorphological examination because of one or more physical features consistent with FASD.

Early in the study, 3 of the 75 picked controls were not included because of withdrawn permission, and later 3 were not provided a second permission for psychological testing. Two of the randomly selected children were found to have an FASD as a final diagnosis and removed as controls, but all others chosen in the original control selection are included in the control group of 67 (Fig. 1).

*Mothers of FASD Children.* The data reported in this paper represent only the mothers of children with an FASD diagnosis and mothers of 63 controls. There were 22 children diagnosed with an FASD, but because a set of twins was included, there were only 21 possible mothers to interview. Up to 5 biological mothers of FASD children are not included in some analyses, because 2 were unavailable due to adoption or foster placement, 1 could not be located, 1 refused an interview repeatedly, and 1 terminated the interview prematurely. Four of the mothers of FASD children denied drinking at all; yet, all but one of them who did deny drinking were known informally to reliable collateral informants (teachers, community members, and social service workers) as drinkers and/or as having alcohol, other substance abuse, or comorbidity problems.

#### Data Analysis

All data were entered and processed by EPI Info (version 6) software of the U.S. Centers for Disease Control and Prevention (Dean et al., 1994). Analyses primarily include tests of significance for both discrete [chi-square, Fisher's exact tests, and odds ratios (ORs) for  $2 \times 2$  comparisons with 95% confidence intervals calculated by the Cornfield technique] and continuous variables ( $t$ -tests and Blalock difference of proportions tests) (Blalock, 1972) that compare subjects with controls. Zero-order Pearson correlations are provided in Tables 4 and 5. No adjustments were made for multiple comparisons. One-way analysis of variance was used to test relationships between 3 groups in Table 2, and for correlation significance in Tables 4 and 5. Pairwise post hoc analyses of between-group differences were used utilizing  $t$ -tests.

## RESULTS

In Table 1, the demographic and growth parameters for study children are presented for 3 categories: all 543

children in the overall sample, the 22 children diagnosed with an FASD, and the 67 randomly selected controls. The exact diagnoses of the FASD children are indicated in Fig. 1: 4 children had FAS, 17 had partial FAS, and 1 with ARND. The 3 aggregates presented in Table 1 are similar in sex composition and age, as 45 to 51% of all groups were male, and the mean age for the 3 groups was 80 months (6.7 years). Furthermore, there was no appreciable difference between total sample measures of growth and the control group, indicating that random selection of controls produced a representative sample. Owing to adherence to screening criteria, there are significant differences between the children with FASD and controls in the following parameters: height, weight, BMI percentile, and head circumference (OFC). In the diagnostic process, poor growth, small head circumference, short palpebral fissures, and/or features of a hypoplastic midface serve to differentiate FASD subjects from non-FASD children and indicate risk of mental deficiency. Individual facial features were also found to be significantly different between groups. Palpebral fissure length, philtral length, ptosis, epicanthal folds, anteverted nostrils, long philtrum, smooth philtrum, and narrow vermilion border are all significantly different between the FASD group and controls. The highest ORs for facial feature differences were upper lip features: smooth philtrum (OR = 85.7) and narrow vermilion border (OR = 18.6). Other minor structural anomalies that differentiate the 2 groups are as follows: railroad track ear configuration, camptodactyly, and alteration of palmar creases in the children with FASD. Nonstatistically significant differences between FASD subjects and controls were as follows: strabismus, heart murmur, limited elbow supination ( $p = 0.06$ ), clinodactyly, and general clinical observations of poor fine motor coordination, hypoplastic midface, and prognathic chin. The mean total dysmorphology score was significantly different ( $p < 0.001$ ) for the FASD group ( $12.5 \pm 3.9$ ) and controls ( $3.3 \pm 3.0$ ), indicating, as predicted by the diagnostic process, substantially more dysmorphic features in the FASD group. Overall, 36.4% of the children diagnosed with an FASD had all 3 of the key facial features commonly seen with FAS (50% of the FAS and 35.3% of the PFAS children).

#### Development and Behavior

In Table 2, developmental and behavioral test findings are summarized, in addition to a summary of maternal age and selected maternal drinking variables. The study children were divided into 3 groups: 2 FASD groups, (1) those first preliminarily diagnosed as FAS and (2) those in whom diagnosis was initially deferred but who later converted to a diagnosis of FASD, and (3) the controls. Of those children with a preliminary diagnosis of FAS, 54.5% were referred into the study because of deficient growth or small head size, another 36.4% of this group were referred for

**Table 1.** Demographic and Growth Parameters for All Study Children, Children with a Final Diagnosis of FASD, and Randomly Selected Controls: Lazio Region, Italy

Variable	Children in study (n = 543)	Children with FASD (n = 22) <sup>a</sup>	Control children (n = 67)	p Value, OR (95%CI) <sup>b</sup>
<b>Sex (%)</b>				
Males	51.0	50.0	44.8	NS (0.670) <sup>c</sup> OR = 1.23 (0.42–3.63)
Females	49.0	50.0	55.2	
Age (mo) Mean (SD)	80.4 (4.4)	80.1 (4.3)	79.9 (3.4)	NS (0.801) <sup>d</sup>
Height (cm) <sup>e</sup> , Mean (SD)	121.5 (5.4)	116.2 (5.2)	121.4 (4.5) <sup>f</sup>	< 0.001 <sup>d</sup>
Weight (kg) <sup>e</sup> , Mean (SD)	25.3 (5.3)	22.0 (4.4)	25.5 (4.5) <sup>f</sup>	0.002 <sup>d</sup>
Children's BMI <sup>e</sup> , Mean (SD)	16.9 (2.8)	16.2 (2.4)	17.3 (2.5)	NS (0.077) <sup>d</sup>
BMI percentile <sup>e</sup> , Mean (SD)	61.8 (31.4)	52.2 (33.9)	69.6 (28.4)	0.020 <sup>d</sup>
Occipital circumference (cm) <sup>e</sup> , Mean (SD)	52.0 (1.5)	50.7 (1.8)	51.9 (1.1) <sup>f</sup>	< 0.001 <sup>d</sup>
Palpebral fissure length (cm), Mean (SD)		2.4 (0.1)	2.5 (0.1)	0.004 <sup>d</sup>
Philtrum length (cm), Mean (SD)		1.5 (0.2)	1.4 (0.2)	0.001 <sup>d</sup>
Short innercanthal distance (≤ 25%)		18.2	7.5	NS (0.148) <sup>c</sup> OR = 2.76 (0.54–13.85)
Fine motor dysfunction (%)		0.0	0.0	NS <sup>c,g</sup>
Hypoplastic midface (%)		27.3	11.9	NS (0.087) <sup>c</sup> OR = 2.77 (0.71–10.72)
“Railroad track” ears (%)		22.7	6.0	0.024 <sup>c</sup> OR = 4.63 (0.93–24.04)
Strabismus (%)		9.1	3.0	NS (0.230) <sup>c</sup> OR = 2.30 (0.30–35.78)
Ptosis (%)		13.6	0.0	0.002 <sup>c,g</sup>
Epicanthal folds (%)		40.9	14.9	0.010 <sup>c</sup> OR = 3.95 (1.16–13.55)
Flat nasal bridge (%)		0.0	0.0	NS <sup>c,g</sup>
Anteverted nostrils (%)		36.4	9.0	0.002 <sup>c</sup> OR = 5.81 (1.49–23.36)
Long philtrum (%)		68.2	40.3	0.023 <sup>c</sup> OR = 3.17 (1.02–10.13)
Smooth philtrum (%)		90.9	10.4	< 0.001 <sup>c</sup> OR = 85.71 (14.10–689.60)
Narrow vermillion border (%)		86.4	25.4	< 0.001 <sup>c</sup> OR = 18.63 (4.34–92.35)
Prognathism (%)		0.0	0.0	NS <sup>c,g</sup>
Heart murmur (%)		0.0	1.5	NS (0.564) <sup>c</sup> (0.00 55.88)
Heart malformations (%)		0.0	0.0	NS <sup>c,g</sup>
Hypoplastic nails		0.0	0.0	NS <sup>c,g</sup>
Limited elbow supination (%)		13.6	3.0	NS (0.060) <sup>c</sup> OR = 5.13 (0.62–48.90)
Clinodactyly (%)		31.8	26.9	NS (0.654) <sup>c</sup> OR = 1.27 (0.39–4.09)
Camptodactyly (%)		22.7	7.5	0.05 <sup>c</sup> OR = 3.65 (0.78–17.19)
Palmar crease alteration (%)		45.5	19.4	0.015 <sup>c</sup> OR = 3.46 (1.08–11.19)
Hypertrichosis (%)		0.0	0.0	NS <sup>c,g</sup>
Other features (%)		4.5	9.0	NS (0.505) <sup>c</sup> OR = 0.48 (0.02–4.59)
Dysmorphology score <sup>h</sup> , Mean (SD)		12.5 (3.89)	3.3 (3.03)	< 0.001 <sup>d</sup>

<sup>a</sup>There was 1 set of twins among the FASD cases.

<sup>b</sup>95% CIs calculated via the Cornfield technique.

<sup>c</sup>Chi-squared test of data comparing children with FASD and controls; a Fisher's exact test when there are cells with an expected value of < 5.

<sup>d</sup>t-Test of data comparing children with FASD and controls.

<sup>e</sup>Measurements are actual values at the time of screening and exams. Percentiles were calculated via standardized NCHS growth charts for age and sex and used. (1) When considering inclusion of children in the study, (2) for comparison, and (3) when diagnosis was made.

<sup>f</sup>Measurements at time of Tier I screen; therefore, they are directly comparable to all other groups.

<sup>g</sup>Calculations of ORs not possible for indicated variable.

<sup>h</sup>The dysmorphology score is a weighted measure of dysmorphic features. It is not utilized in diagnostic assessment, but provides a quantitative measure of dysmorphic features for comparison purposes (Hoyme et al., 2005).

NS, not significant; FASD, fetal alcohol spectrum disorder; BMI, body mass index; 95% CI, 95% confidence interval; OR, odds ratio.

both size and behavioral/learning problems, and < 10% were referred for behavioral/learning problems only. In the preliminarily deferred group, only 18.2% were referred

because of growth or OFC deficiency and all the remaining 81.8% were referred by teachers for learning/behavioral problems. On language comprehension ( $p = 0.009$ ),

**Table 2.** General Developmental and Behavioral Indicators<sup>a</sup> of Children with FASD (by Preliminary Diagnosis After Dysmorphology Exam) and Randomly Selected Controls and Comparisons Across Diagnostic Groups by Maternal Age and Various Drinking Measures: Lazio Region, Italy

Child variables	Final Dx FASD			Test statistic <sup>b</sup>	df	p Value
	Preliminary Dx FAS mean score (SD) (n = 11)	Preliminary Dx deferred mean score (SD) (n = 11)	Controls mean score (SD) (n = 67)			
<i>Developmental traits</i>						
Language comprehension <sup>c</sup>	3.2 (2.3) <sup>4</sup>	3.5 (2.1) <sup>3</sup>	4.9 (1.8)	F = 5.03	2/85	0.009
Nonverbal IQ <sup>d</sup>	51.8 (19.7) <sup>4</sup>	58.2 (21.5) <sup>3</sup>	72.3 (21.7)	F = 5.62	2/85	0.005
Behavior <sup>e</sup>	5.3 (3.8) <sup>1</sup>	11.7 (6.1) <sup>4</sup>	3.9 (3.7)	F = 15.43	2/73	< 0.001
Total dysmorphology score	14.5 (3.3) <sup>2,4</sup>	10.4 (3.4) <sup>4</sup>	3.3 (3.0)	F = 77.35	2/88	< 0.001
<i>Maternal variables</i>						
Maternal age during index pregnancy ( $\bar{X}$ ), Mean (SD)	32.4 (5.2)	31.1 (3.2)	29.7 (5.7)	F = 1.105	2/77	NS (0.337)
Report drinking during pregnancy (%)	44.4	50.0	49.2	$\chi^2 = 0.08$	2	NS (0.962)
Mean drinks per current week <sup>f</sup> (SD)	16.2 (26.6) <sup>4</sup>	7.5 (8.7) <sup>4</sup>	1.5 (2.1)	F = 6.01	2/38	0.006
Mean drinks per current drinking day <sup>f</sup> (SD)	2.6 (3.6) <sup>4</sup>	1.5 (0.9) <sup>4</sup>	0.8 (0.4)	F = 5.01	2/38	0.012

<sup>1</sup>t-Test significantly different (<0.05) from preliminarily deferred.

<sup>2</sup>t-Test significantly different (<0.01) from preliminarily deferred.

<sup>3</sup>t-Test significantly different (<0.05) from controls.

<sup>4</sup>t-Test significantly different (<0.01) from controls.

<sup>a</sup>All scores standardized for age of child at the time of testing.

<sup>b</sup>One-way analysis of variance (F) or chi-square.

<sup>c</sup>Rustioni Qualitative Test.

<sup>d</sup>Raven Colored Progressive Matrices.

<sup>e</sup>Personal Behaviors Checklist (PBCL-36).

<sup>f</sup>Among those who reported drinking during pregnancy; includes current nondrinkers.

NS, not statistically significant; FASD, fetal alcohol spectrum disorder; Dx, diagnosis.

nonverbal IQ ( $p = 0.005$ ), and behavioral problems ( $p < 0.001$ ), the 3 groups perform differently. The children preliminarily diagnosed as FAS had the worst scores on language and nonverbal IQ, while the preliminarily deferred FASD children had the most behavioral problems. Overall, the 2 FASD groups performed worse than controls on all standard tests. Post hoc analysis of intergroup differences indicates that the preliminary FAS groups and the initially deferred groups differed on behavior problems, a further indicator that this later group included most of the behavior/learning problem referrals from teachers. Both FASD groups differed significantly from controls on all developmental measures with the exception of behavior. Both the preliminary FAS children and the controls are better behaved than the preliminarily deferred children who were later diagnosed as having an FASD. Total dysmorphology scores for each group form a spectrum ( $14.7 \pm 3.3$ ,  $10.4 \pm 3.4$ , and  $3.3 \pm 3.0$ ) from preliminary FAS to control ( $p < 0.001$ ). Post hoc analyses also indicate significant differences in scores between each group.

In the second part of Table 2, the maternal age of the 3 groups displays a continuum. The mothers of the preliminary group were the oldest ( $\bar{X} = 32.4 \pm 5.2$ ), the preliminarily deferred intermediate ( $\bar{X} = 31.1 \pm 3.2$ ), and the controls the youngest ( $\bar{X} = 29.7 \pm 5.7$ ) at delivery, although the differences were not statistically significant. In general, the current drinking reported by the mothers of the children in these 3 groups also exhibits a spectrum that mirrors the FASD versus control findings. The mean number of drinks currently consumed per week

(at interview) by mothers of children diagnosed as preliminary FAS ( $16.2 \pm 26.6$ ) exceeds that of the preliminarily deferred children ( $7.5 \pm 8.7$ ) and the controls ( $1.5 \pm 2.0$ ), and the standard deviations vary greatly in the 3 groups, being the highest in the mothers of the children eventually diagnosed with an FASD. Binge measures (mean drinks per current drinking day) were the highest for the preliminary FAS group ( $2.6 \pm 3.6$ ). Post hoc *t*-tests indicated that both FASD maternal groups were significantly different than control mothers on both of these variables. But it is interesting to note that only 44% to 50% of the mothers in any of these 3 groups reported drinking at all during pregnancy (once they knew they were pregnant). It was the impression of the interviewers that the veracity of the reporting of prenatal drinking was questionable for some women. For example, in 19% of the interviews of the mothers of FASD children, the blinded interviewers checked a box that indicated suspicion about the truthfulness of responses.

#### Demographic, Socioeconomic, and Maternal Drinking Measures

In Table 3, socioeconomic and drinking indicators for mothers of children with an FASD are compared with those of controls. Demographic and socioeconomic indicators for the 2 maternal groups were analyzed, and the summary in Table 3 indicates very little difference. Mean age, rural/urban residence, frequency of church attendance, religious attitude, and employment were not significantly different in the highlighted analyses or in

**Table 3.** Demographic, Socioeconomic, and Maternity Variables and Substance Use Measures by Mothers of the Children with FASD and Randomly Selected Controls: Lazio Region, Italy

Variable	Mothers of children with FASD (n = 18)	Control mothers (n = 63)	Test statistic p value
<i>Demographic and socioeconomic variables</i>			
Mean Age (y) on day of interview (SD)	37.9 (5.3)	36.6 (5.8)	NS (0.636) <sup>a</sup>
Residence during index pregnancy (%)			
Urban	23.5	23.8	
Suburban	47.1	55.6	
Rural	29.4	20.6	NS (0.727) <sup>b</sup>
Educational attainment (%)			
Elementary	17.6	1.6	
Junior high	41.2	30.2	
Senior high	17.6	49.2	
Degree	23.5	19.0	0.014 <sup>b,c</sup>
Religiosity Index—Mean (SD)	3.9 (1.7)	2.4 (1.7)	0.001 <sup>a</sup>
Currently employed, %	58.8	59.7	NS (0.949) <sup>b</sup> OR = 0.97 (0.28–3.32)
Among those employed, actual job (%)			
Manual worker	40.0	13.5	
Office worker	50.0	67.6	
Manager in an office	0.0	2.7	
Manager	10.0	13.5	
Other	0.0	2.7	NS (0.422) <sup>b,c</sup>
Among those employed, hours of work per week—Mean (SD)	30.8 (11.6)	27.1 (9.5)	NS (0.305) <sup>a</sup>
	Mothers of children with FASD (n = 12)	Mothers of control children (n = 48)	p Value, OR (95% CI) <sup>d</sup>
<i>Substance use variables</i>			
Current drinker <sup>f</sup> (of ever drinkers) (%)	91.7	100.0	0.046 <sup>e</sup>
Mean number of drinks last month (current drinkers <sup>f</sup> ) (SD)	41.9 (73.7)	8.0 (8.8)	0.007 <sup>a</sup>
Percent drinking 3 mo before index pregnancy (ever drinkers)	91.7	87.5	NS (0.688) <sup>b</sup> , OR = 1.57 (0.15–38.97)
Percent drinking during index pregnancy (ever drinkers)	69.2	64.6	NS (0.754) <sup>b</sup> , OR = 1.23 (0.28–5.73)
Among ever drinkers, drinking during:			
First trimester of pregnancy with index child (%)	41.7	37.5	NS (0.791) <sup>b</sup> , OR = 1.19 (0.27–5.15)
Second and third trimester of pregnancy with index child (%)	50.0	33.3	NS (0.284) <sup>b</sup> , OR = 2.00 (0.46–8.71)
Current smoker (of those who ever smoked) (%)	36.4	59.4	NS (0.187) <sup>b</sup> , OR = 0.39 (0.07–1.97)
Cigarettes smoked per day, current smokers (%)			
12	25.0	16.7	
5 to 7	25.0	5.6	
8 to 10	25.0	44.4	
11 to 19	0.0	27.8	NS (0.372) <sup>b,c</sup>
20 (1 pack)	25.0	5.6	
Percent smoked 3 mo before index pregnancy (among ever smokers)	90.9	65.6	NS (0.107) <sup>b</sup> , OR = 5.24 (0.53–125.85)
Percent used tobacco during index pregnancy (ever smokers)	40.0	37.5	NS (0.887) <sup>b</sup> , OR = 1.11 (0.20–5.94)

<sup>a</sup>t-Test.

<sup>b</sup>Chi-squared test.

<sup>c</sup>Calculations of chi-square-based odds ratio not possible for this variable as it is not a 2×2 configuration.

<sup>d</sup>95% CI calculated via the Cornfield technique.

<sup>e</sup>Difference of proportions test.

<sup>f</sup>Consumed alcohol in 12 months preceding interview.

NS, not statistically significant; 95% CI, 95% confidence interval.

other variable comparisons. There was a significant difference in educational attainment, the mothers of FASD children being somewhat bimodal; yet, overall they are less educated than controls. Also, mothers of FASD children reported significantly higher church attendance and more positive adherence to religion as reflected in the higher religiosity index scores. Direct confirmation of drinking was not available from interviews for 9 of the 21 mothers

of FASD children. Four were judged to be suspect and inaccurate by blinded interviewers, and 5 were missing. Nevertheless, useful data were obtained on the remaining 12 of the mothers of FASD children, and all but 1 of these reported that they were current drinkers. Overall, mothers of children with FASD report drinking 42 drinks in the month before the interview (current drinking) compared with a significantly lower average of 8 for controls

( $p = 0.007$ ). Drinking prevalence reported for the 3 months before the index pregnancy did not differ significantly between groups (91.7% vs 87.5%), nor did reported drinking during pregnancy (69.2% vs 64.6%). Mothers of FASD children were more likely to report consuming alcohol in all trimesters, especially in trimesters 2 and 3, although none of the differences proved significant. Smoking variables did not differ significantly between maternal subjects and controls overall or for any trimester.

#### Developmental and Dysmorphology Measures in Relation to Maternal Drinking

Table 4 presents Pearson correlation coefficients for developmental and dysmorphology traits associated with selected maternal drinking measures. Few of the bivariate correlations of drinking and specific psychological and developmental measures are significant. The one notable exception is the Pelham inattention score, which is significantly associated with all drinking variables except for current drinks per drinking day. However, all of the drinking measures are significantly associated with total dysmorphology score except for drinking during the first trimester. Drinks per month in second and third trimesters and current drinks per drinking day are all positively associated ( $r = 0.25$ – $0.27$ ,  $p < 0.05$ ) with high dysmorphology scores. The highest correlation is between current drinks per month ( $r = 0.32$ ,  $p < 0.01$ ) and dysmorphology score.

#### Maternal and Child Characteristics in Relation to Child's Nonverbal IQ

Further data in Table 5 correlate selected maternal and child physical variables with the child's nonverbal IQ. None of the correlations between selected maternal variables and IQ are significant. However, for the children's variables, head circumference ( $r = 0.25$ ), smooth philtrum ( $r = -0.29$ ), a railroad track ear configuration ( $r = -0.24$ ), ptosis

**Table 5.** Pearson Correlation Coefficients for Child's Nonverbal IQ and Selected Maternal Variables, Child Traits, and Total Dysmorphology Score: Lazio Region, Italy ( $n = 85$ )

Variable	Nonverbal IQ <sup>a</sup>				
	<i>n</i>	<i>r</i>	<i>r</i> <sup>2</sup>	<i>F</i> statistic	<i>p</i> Value
<i>Maternal</i>					
Age when pregnant	77	0.17	0.03	2.35	NS
Height—current	77	-0.07	0.00	0.38	NS
Weight—current	77	-0.07	0.00	0.35	NS
BMI percentile—current	77	-0.08	0.01	0.48	NS
Gravida at index pregnancy	77	-0.01	0.00	0.01	NS
Parity at index pregnancy	77	-0.10	0.01	0.80	NS
<i>Child</i>					
Head circumference	85	0.25	0.06	5.69	<0.05
Inner canthal distance	84	0.06	0.00	0.33	NS
Palbebral fissure length	84	0.04	0.00	0.12	NS
Philtrum length	85	-0.06	0.00	0.29	NS
Smooth philtrum <sup>b</sup>	84	-0.29	0.08	7.45	<0.01
Narrow vermilion border <sup>b</sup>	85	-0.19	0.04	3.06	NS
Hypoplastic midface <sup>c</sup>	85	0.08	0.01	0.59	NS
"Railroad" ears <sup>c</sup>	85	-0.24	0.06	5.10	<0.05
Strabismus <sup>c</sup>	85	-0.18	0.03	2.70	NS
Ptosis <sup>c</sup>	85	-0.24	0.06	5.05	<0.05
Epicanthal folds <sup>c</sup>	85	-0.06	0.00	0.27	NS
Heart murmur <sup>c</sup>	85	0.11	0.01	0.97	NS
Limited supination of elbows <sup>c</sup>	85	-0.22	0.05	4.30	<0.05
Camptodactyly <sup>c</sup>	85	0.07	0.00	0.37	NS
Palmer crease alterations <sup>c</sup>	85	-0.01	0.00	0.01	NS
Other features <sup>c</sup>	85	0.06	0.00	0.27	NS
Dysmorphology score	85	-0.26	0.07	6.32	<0.05

<sup>a</sup>Raven Colored Matrices.

<sup>b</sup>Lip-philtrum guide values ranging from 1 to 5.

<sup>c</sup>Independent variables treated as categorical/dummy variables where the presence of the trait equals 1 and the absence equals 0.

<sup>d</sup>All scores standardized for age at the time of testing.

NS, not statistically significant; FASD, fetal alcohol spectrum disorder; BMI, body mass index.

( $r = -0.24$ ), limited supination of elbows ( $r = -0.22$ ), and total dysmorphology score ( $r = -0.26$ ) are significantly correlated with the child's nonverbal IQ, a key measure in FASD diagnosis. However, none of these traits, when taken individually as zero-order correlations, explain more than

**Table 4.** Pearson Correlation Coefficients for Developmental<sup>a</sup> and Physical Dysmorphology Versus Selected Maternal Drinking Measures: Lazio Region, Italy ( $n = 79$ )

Trait	Drinks per month first trimester	Drinks per month second trimester	Drinks per month third trimester	Drinks per current drinking day	Drinks per current month
Language comprehension <sup>b</sup>	-0.19	-0.18	-0.18	0.04	-0.15
Nonverbal IQ <sup>c</sup>	-0.09	-0.12	-0.12	0.01	-0.08
Behavior <sup>d</sup>	-0.02	0.02	0.02	0.04	0.04
Inattention <sup>e</sup>	0.23*	0.31**	0.31**	0.21	0.24*
Hyperactivity <sup>f</sup>	0.00	0.04	0.04	0.03	0.02
Dysmorphology score	0.20	0.27*	0.27*	0.25*	0.32**

<sup>a</sup>All scores standardized for age at the time of testing.

<sup>b</sup>Rustioni Qualitative Test (number of errors made by each child).

<sup>c</sup>Raven Colored Matrices.

<sup>d</sup>Personal Behaviors Checklist (PBCL-36).

<sup>e</sup>Pelham—inattention subscore.

<sup>f</sup>Pelham—hyperactivity subscore.

\* $p < 0.05$ .

\*\* $p < 0.01$ .

5% to 8% of the variance in a child’s nonverbal IQ. Larger samples would allow multiple correlation studies.

*Prevalence of FAS*

Table 6 presents prevalence estimates for various levels of FASD in the Italian study population. Overall, the rate of FAS and partial FAS exceeded our expectations and also current estimated rates for the United States. Estimated rates of FASD diagnoses are presented in 2 ways in Table 6: rates calculated on the basis of the sample consenting to participate (*n* = 543) and also projected to the total number of children in the first-grade classrooms from which the sample was drawn (*n* = 1,086). Therefore, the rate of FAS overall is between 3.7 and 7.4 per 1,000 children. Partial FAS is between 15.7 and 31.3 per 1,000 children. The overall range of rates of FASD (including the case of ARND) is 20.3 to 40.5 per 1,000 children. If one excludes the cases for which maternal alcohol intake could not be confirmed directly, the observed rates of FASD are slightly more than half (55%) of the above rates: overall, 11.1 to 22.0 per 1,000; 2.8 to 5.5 per 1,000 for FAS; and 7.4 to 14.7 per 1,000 PFAS.

The lower prevalence rates in Table 6 assume that the 2 methods of active recruitment for the sample to be screened (growth or OFC  $\leq$  10% and/or referral for learning or behavioral problems) captured all candidates for an FASD diagnosis among the 543 children who had consented to participate. The higher rates assume the polar opposite: that the active recruitment of cases by the school officials was not at all selective, and a child not in the study was no more or less likely to have FASD as those 543 who did participate. The truth may lie in the middle. Of the 69 randomly selected control/comparison children who had permission to participate, and who were examined by blinded dysmorphology teams, 2 were ultimately diagnosed with an FASD (1 FAS and 1 partial FAS). Therefore, 2.9% of the randomly selected children from the consenting participant pool had an FASD. Projecting this proportion to the 543 children not participating in the study, an additional

16 cases of FASD are estimated to exist among those not screened. This results in an overall estimated FASD rate of 34.9 per 1,000 children, or 3.5%. We believe that this rate is likely to err on the high side for the more severe diagnoses (FAS and PFAS) if one assumes that the active case ascertainment methods, both growth and referrals from teachers, may have recruited a high proportion of the children who were candidates for these diagnoses.

DISCUSSION

One of the greatest limitations to the prevalence calculations of this study, and all active case ascertainment studies, is the consent rate. The fact that consent to participate was obtained for only 50% of the children in the randomly selected schools introduces potential bias for which it is difficult to account. This has been a problem in U.S. studies as well, as there is frequently a reluctance of guardians, especially birth parents, to provide consent for an examination of their child for FASD or other developmental issues. In fact, because of the reluctance of parents and guardians, most active case ascertainment studies have avoided in-school studies of FASD, relying instead on large outreach referral networks within and between public health and educational systems. The one in-school study in the United States, in a county that required active consent from parents, was only able to recruit <25% of the children (Clarren et al., 2001). We have attempted in this study to correct this potential skewing of the data by several methods. First, some children, in addition to those referred for physical growth and development, were referred for academic or behavioral problems. Consent for these specially referred children was high in most schools because of the persistence of teachers, administrators, and research team members. Second, to account for possible selectivity, we have provided a range of rate estimates rather than one definite rate. Finally, the proportion of children found to have an FASD in the randomly selected cases from the participant pool was used to estimate a single rate for the sample. Therefore, we have

**Table 6.** Cases Diagnosed and Estimated Rates of FASD Among First-Grade School Children in Lazio Region, Italy, 2004

	Diagnosis with direct confirmation of EtOH use (from mother’s interview) during pregnancy			Diagnosis without direct confirmation of EtOH use (from mother’s interview) during pregnancy			Total sample		
	<i>n</i>	Rate for sample <sup>a</sup>	Rate for entire class <sup>b</sup>	<i>n</i>	Rate for sample <sup>a</sup>	Rate for entire class <sup>b</sup>	<i>n</i>	Rate for sample <sup>a</sup>	Rate for entire class <sup>b</sup>
FAS	3	5.5	2.8	1	1.8	0.9	4	7.4	3.7
Partial FAS	8	14.7	7.4	9	16.6	8.3	17	31.3	15.7
ARND <sup>c</sup>	1	1.8	0.9	—	—	—	1	1.8	0.9
Total	12	22.0	11.1	10	18.4	9.2	22	40.5	20.3

<sup>a</sup>Rate per 1,000 children based on the sample screened, *n* = 543.

<sup>b</sup>Rate per 1,000 children in all first-grade classrooms assuming no children with FASD were missed by the consent and screening process.

<sup>c</sup>ARND cannot be diagnosed without confirmation of EtOH consumption during pregnancy. Direct confirmation in this study means via direct statement from the mother via interview.

FASD, fetal alcohol spectrum disorder; EtOH, ethanol; ARND, alcohol-related neurodevelopmental deficit.

provided high (sample only) and low (total enrollment) rates of prevalence along with a single estimate (35 per 1,000) that may combine the advantages of both probabilistic screening and random selection of control subjects.

While it is difficult to compare the rates of FASD found in this population with other studies in developed countries, the rates of FAS and PFAS were high. Even the most conservative estimated rates from this study far exceed estimates from clinic-based studies from the United States (Abel, 1998; Sampson et al., 1997). For example, Sampson et al. (1997) estimated the rate of FAS and ARND to be 1% in the U.S. population. While we used a different, updated, and likely more sensitive diagnostic scheme (Hoyme et al., 2005) in Italy, we have found that the rate of FASD may be 2.0% to 4.1% (20.3–40.5 per 1,000). The FAS-only (not FASD) rates are, however, somewhat close to the 3.1 per 1,000 reported by Clarren et al. (2001) in the in-school study in Washington State of the United States. Yet, they are much lower than the in-school samples of South African children of 46 to 75 full-blown FAS cases per 1,000 (May et al., 2000; Viljoen et al., 2005), where poor nutrition, poverty, binge drinking, and other factors combine for extremely high rates.

Our findings raise the substantial question as to whether FASD prevalence is accurately reported or estimated in the United States or in any Western European country. The rate of FAS has been estimated recently as 0.5 to 2.0 (Stratton et al., 1996) or 0.5 to 1.5 (May and Gossage, 2002). These estimates may be quite low, as they arise primarily from passive case ascertainment studies. Furthermore, the estimate that FASD may affect 1% of the U.S. population (Sampson et al., 1997) or any developed population may also be substantially low, as this in-school study in Italy provides estimates of 2% to 4%. Many authors have suggested that FAS and other FASD are underreported, and studies have documented high rates of undiagnosed cases in several countries (Clarren et al., 2001; Duimstra et al., 1993; Leversha and Marks, 1995; Little et al., 1990; Kvigne et al., 2003; Square, 1997). Therefore, our conclusion is that FAS and FASD are probably more common in the western, developed world than currently estimated. In support of this conclusion, Clarren et al. wrote after their in-school study: “none of the [FAS] children had been identified in the Washington State Registry. In our opinion, none of these cases of FAS would have been included in any passive surveillance study reporting the prevalence FAS . . . .” Only through additional active case ascertainment studies of FAS and other FASD in the United States and Western Europe can the question of the true prevalence of FASD be answered.

#### *Traits of Children With FASD in Italy Related to Maternal Drinking*

The children in Italy identified as having an FASD meet the revised IOM criteria that we have used to identify

children with substantial prenatal alcohol exposure elsewhere in the world. Their suppressed growth and development, depressed intellectual functioning, and behavior problems are similar to those identified and described in subpopulations of the United States and South Africa. Their height, weight, and BMI percentile were depressed; short palpebral fissures and hypoplastic midfacial features were common, especially the smooth philtrum and a narrow vermilion border. The prevalence of hand defects was also similar to alcohol-using maternal populations studied elsewhere. The intellectual performance and problematic behavior of Italian children with FASD formed a spectrum that was correlated with the level of current drinking reported by the mother and the severity of the child's dysmorphism. Italian children with FASD were significantly more deficient in verbal IQ and nonverbal IQ and more prone to behavioral problems than controls. Once again, the data from this study raise the question of whether high levels of current drinking are proof of a substantial prenatal effect on the child's behavior or whether the postnatal environment is most important. When combined with the dysmorphic features documented in children diagnosed with an FASD, the prenatal effect is evident, but postnatal behavioral influences via household conditions are also important. In this Italian population, there was no significant variation by SES, but social behavior from family to family differed.

As in previous studies in the schools of South Africa, the diagnostic dysmorphism definitely led the blinded research team to children who had behavioral and learning problems and more importantly to mothers who had substantial issues of alcohol use and comorbidity, but once again, an episodic pattern of heavy drinking seems to emerge to differentiate the mothers of FASD children from controls, although evidence of episodic drinking is less in this Italian population than in other populations in which we have worked. Nevertheless, the average number of current drinks per week reported by Italian mothers of FASD children (16.2) is strikingly similar to that reported by South African women who have had FAS children (16.1 and 13.6) (May et al., 2005; Viljoen et al., 2002). In general, even though about three-fourths of maternal controls and 100% of the women who have ever consumed alcohol reported drinking in the past year, daily drinking in this part of Italy seems to be less common than we suspected. But to a greater degree than South African women, Italian subjects reported fewer binges and also seemed more challenging to engage in frank and accurate discussion of drinking during the prenatal period.

While some studies of maternal drinking in Italy have not linked maternal drinking to major adverse fetal outcomes (Lazzaroni et al., 1992, 1993a, 1993b), two other studies of prenatal drinking in Italy have reported substantially higher levels of drinking during pregnancy than we found. In Italian hospitals, 29% of women reported drinking daily throughout pregnancy and 1% were

classified as drinking between meals (Bonati and Fellin, 1991). Another study in Milan indicated that 1.4% of mothers binged, that 29% of the pregnant respondents reported that they continued to drink daily, and that 9% drank more than 11.5 standard drinks per week (Bonati and Fellin, 1991; Primatesta et al., 1993). If our maternal data collected in this wave of research are correct, then the stereotype of daily drinking among Italian women needs to be questioned and begs clarification.

#### *Traits of Mothers of FASD Children Compared With Controls*

We encountered some frustrations with the structure and nature of our questionnaire used in Italy. The translation process and the need for economy of time may have compromised the integrity of the instrument. This may have led to problems of completeness of data and accurate reporting levels of drinking, especially the reporting of drinking during pregnancy. Current drinking measures seemed to be more accurate, valid, and useful to the research in this population than measures associated with pregnancy, which has been reported in other studies in other populations (Alvik et al., 2006; May et al., 2005; Viljoen et al., 2002). Overall, even though virtually all women in the study were current drinkers and we suspect underreporting, there were substantial differences in the current drinking levels reported by mothers of FASD children and controls. It is the gradient of difference, not the absolute values, upon which one must rely. The mothers of FASD children were more likely to report current drinking levels exceeding an average of over 1 standard drink per day (1.4) compared with one-quarter (0.27) of a standard drink per day for controls. Reported drinking and smoking during pregnancy did not vary significantly between the 2 groups; yet, these differences were the greatest in the second and third trimesters, in keeping with other literature on maternal risk factors. Importantly, dysmorphology scores were significantly correlated with second and third trimester drinking, but overall, the inability to obtain complete and detailed drinking data from over 40% of the mothers of FASD children was a problem.

#### *Other Diagnostic Considerations*

We have utilized the IOM-approved option of classifying 1 of the 4 children with FAS (25%) in the absence of detailed alcohol-exposure data, and 9 of the 17 (53%) with partial FAS with less than perfect alcohol exposure data, for in many of these cases it was collateral data. We doubt that we have underdiagnosed FAS or PFAS, because linking detailed dysmorphology and behavioral data provided, in each case, symptomology that is definitely specific to FAS and PFAS. Also, in the diagnostic process most other known causes of these symptoms have been eliminated. However, ARND may be underdiagnosed in this study. A diagnosis of ARND specifically requires detailed

evidence of substantial alcohol exposure. The extent of any bias introduced into this study by inaccurate or missing maternal data is unknown. This study has again demonstrated that using dysmorphology in the first parts of our selective screening methodology, we rarely diagnose alcohol-related learning disability and behavior problems without significant dysmorphology and vice versa. Only one ARND child was identified with the current active case ascertainment methods. If a research project began first with all children with deficient performance on IQ, learning, or behavioral testing (regardless of size or head circumference), and then moved on to assess dysmorphology and maternal risk factors, more cases of ARND would likely emerge. But until we better understand the true and unique behavioral phenotype of FASD children, and find the specific neuropsychological tests that discriminate FASD children from other children with or without other disabilities, such a population-based study is likely to be onerous and impossible.

#### CONCLUSION

Fetal alcohol syndrome and other FASD were found among the first-grade populations of randomly selected schools in the Lazio Region of Italy. The rates of FAS (3.7–7.4 per 1,000 children) and total FASD (20.3–40.5 per 1,000) were high. But as this is one of the first in-school studies of FASD prevalence ever undertaken in a western, highly developed population, there are few similar, active case ascertainment studies with which it can be accurately compared. Overall, the rate of FASD in this Western European population may be 3.5%. Even though the data on maternal drinking among mothers of FASD children were not as complete or informative as desired, and the sample was small, substantial insight has been gained into the implications of the Italian, Western European drinking style associated with FASD. In this part of Italy, maternal drinking may be less regular and universal than previously thought. Fetal alcohol syndrome and other FASD do exist in Italy, as such birth defects are produced by a small minority of heavy drinkers of either a binge or a daily consumption pattern. As children with FASD present substantial challenges to parents, schools, and social service systems, there is a need to identify these children early so that their development can be maximized.

#### ACKNOWLEDGMENTS

We gratefully acknowledge the support and assistance of many people. We can only mention some of the many who have made this research possible. Drs. Faye Calhoun, Kenneth Warren, and Ting Kai Li of NIAAA were instrumental in bringing the binational research team together and sponsoring the initial trip to Italy for collaboration between the 2 countries. NIAAA also funded the Italian team's travel to South Africa and the United States to train, prepare for, and carry out the field research and the

final case conference in which all diagnoses were completed. In Italy, many people have assisted in initiating the project. Luca Deiana, Luciana Chessa, M.D., Michele Stagagno, M.D., and Agatino Battaglia, M.D., were all instrumental in hosting us and participating in the early training and screening of children. Maternal interviewers were outstanding in locating mothers and interviewing them: Lucia Cupelli, Irene Di Stefano, Marcella Scamporrino, Anna Maria Galli, Federica Cereatti, and Francesca De Rosa. We would also like to thank Stefano Giacomelli, who coordinated the organization of maternal interviews and was very supportive during the study in many different ways. We also thank managers, school physicians, and psychologists from ASL RMG\* and RMH\*\* from whom we received assistance: dott. P. Trecca,\* dott. C. Carapellese,\* dott. Di Giovanni, dott. G. Versace,\*\* dott. V.De Carolis,\*\* dott. N. Roma,\*\* dott. C.D'Anna,\*\* dott. ssa L.Asci,\*\* G.Gironda,\*\* S. Gagliardi,\*\* and A. Pontecorvi.\*\* Those who assisted from the School Office of Lazio Region\* and Rome Province\*\* were: dott. ssa L. Signori,\* dott. ssa R. Massacesi,\* and dott. ssa M.T. Silani.\*\* Finally, we thank dott. F. Valeriani from SIFIP. Finally, in addition to 2 of the authors of this paper (Daniela Fiorentino, and Giovanna Coriale), the psychological testing of the children was carried out with assistance from Francesca De Rosa and Corinna Ceoldo.

## REFERENCES

- Abel EL (1995) An update on incidence of FAS: FAS is not an equal opportunity birth defect. *Neurotoxicol Teratol* 17:437-443.
- Abel EL (1996) *Fetal Alcohol Syndrome from Mechanism to Prevention*. CRC Press, Boca Raton, FL.
- Abel EL (1998) *Fetal Alcohol Abuse Syndrome*. Plenum Press, New York.
- Abel EL, Sokol RJ (1987) Incidence of fetal alcohol syndrome and economic impact of FAS-related anomalies. *Drug Alcohol Depend* 19: 51-70.
- Abel EL, Sokol RJ (1991) A revised conservative estimate of the incidence of FAS and its economic impact. *Alcohol Clin Exp Res* 15: 514-524.
- Adnams CM, Kodituwakku PW, Hay A, Molteno CD, Viljoen D, May PA (2001) Patterns of cognitive-motor development in children with fetal alcohol syndrome from a community in South Africa. *Alcohol Clin Exp Res* 25:557-562.
- Alvik A, Haldorsen T, Groholt B, Lindemann R (2006) Alcohol consumption before and during pregnancy comparing concurrent and retrospective reports. *Alcohol Clin Exp Res* 30:510-515.
- Astley SJ (2004) Fetal alcohol syndrome prevention in Washington State: evidence of success. *Paediatr Perinat Epidemiol* 18:344-351.
- Autti-Rämö I, Fagerlund A, Ervalahti N, Loimu L, Korkman M, Hoyme HE (2005) *Am J Med Genet* 140A:137-143.
- Blalock HM (1972) *Social Statistics*. McGraw-Hill Book Company, New York.
- Bonati M, Fellin G (1991) Changes in smoking and drinking behaviour before and during pregnancy in Italian mothers: implications for public health intervention. *Int J Epidemiology* 20:927-932.
- Calvani M, Ghirelli D, Calvani M (1985a) Fetal alcohol syndrome. *Recent Prog Med* 76:476-486.
- Calvani M, Ghirelli D, Calvani M, Fortuna C, Lalli F, Marcolini P (1985b) Fetal alcohol syndrome: clinical, metabolic and immunologic follow-up in 14 cases. *Minerva Pediatr* 37:77-88.
- Chavez GF, Corderro JF, Becerra JE (1988) Leading major congenital malformations among minority groups in the United States, 1981-1986. *Morb Mortal Wkly Rep* 37:17-24.
- Clarren SK, Randels SP, Sanderson M, Fineman RM (2001) Screening for fetal alcohol syndrome in primary schools: a feasibility study. *Teratology* 63:3-10.
- Dean AG, Dean JA, Coulombier D, Brendel KA, Smith DC, Burton AH, Dickers RC, Sullivan K, Fagan RF, Arner TG (1994) *Epi Info Version 6: A Word Processing, Data Base, and Statistics Program for Epidemiology on Microcomputers*. Centers for Disease Control and Prevention, Atlanta, GA.
- De Nigris C, Awabdeh F, Tomassini A, Remotti G (1981) Alcool e gravidanza: incidenza del fenomeno ed effetti sul neonato nella popolazione utente di un ospedale di Varese. *Ann Ost Gin Med Perin* CII:419-430.
- Duimstra C, Johnson D, Kutsch C, Wang B, Zentner M, Kellerman S, Welty TA (1993) Fetal alcohol syndrome surveillance pilot project in American Indian communities in the Northern Plains. *Public Health Rep* 108:225-229.
- Egeland GM, Perham-Hester KA, Gessner BD, Ingle D, Berner JE, Middaugh JP (1998) Fetal alcohol syndrome in Alaska, 1977 through 1992: an administrative prevalence derived from multiple data sources. *Am J Public Health* 88:781-786.
- Egeland GM, Perham-Hester KA, Hook EB (1995) Use of capture-recapture analyses in fetal alcohol syndrome surveillance in Alaska. *Am J Epidemiol* 141:341.
- Hoyme HE, May PA, Kalberg WO, Kodituwakku P, Gossage JP, Trujillo PM, Buckley DG, Miller JH, Aragon AS, Khaole N, Viljoen DL, Jones KL, Robinson LK (2005) A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 institute of medicine criteria. *Pediatrics* 115:39-47.
- Khaole NC, Ramchandani VA, Viljoen DL, Li TK (2004) A pilot study of alcohol exposure and pharmacokinetics in women with or without children with fetal alcohol syndrome. *Alcohol Alcohol* 39:503-508.
- Kuczmariski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF, Johnson CL (2000) *CDC Growth Charts, United States Advance Data from Vital Statistics No 314*. National Center for Health Statistics, Hyattsville, MD.
- Kvigne VL, Leonardson GR, Borzelleca J, Brock E, Neff-Smith M, Welty TK (2003) Characteristics of mothers who have children with fetal alcohol syndrome or some characteristics of fetal alcohol syndrome. *J Am Board Fam Pract* 16:296-303.
- Lazzaroni F, Bonassi S, Magnani M, Calvi A, Repetto E, Serra F, Podesta F, Pearce N (1993a) Moderate maternal drinking and outcome of pregnancy. *Eur J Epidemiol* 9:599-606.
- Lazzaroni F, Bonassi S, Magnani M, Puglisi P, Salomone P, Pantarotto F, Mazzeo P, Cotelessa G, Norelli MT, Santi F (1992) Effects of moderate maternal drinking on some neonatal parameters. *Minerva Pediatr* 44:511-517.
- Lazzaroni F, Bonassi S, Magnani M, Puglisi P, Salomone P, Pantarotto F, Mazzeo P, Cotelessa G, Norelli MT, Santi F (1993b) Alcohol in pregnancy and fetal health. *Minerva Pediatr* 45:47-53.
- Leversha AM, Marks RE (1995) The prevalence of fetal alcohol syndrome in New Zealand. *N Z Med J* 108:502-505.
- Little BB, Snell LM, Rosenfeld CR, Gilstrap LC, Gant NF (1990) Failure to recognize fetal alcohol syndrome in newborn infants. *Am J Dis Child* 144:1142-1146.
- May PA, Brooke L, Gossage JP, Croxford J, Adnams C, Jones KL, Robinson L, Viljoen D (2000) Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. *Am J Public Health* 90:1905-1912.
- May PA, Brooke LE, Gossage JP, Snell C, Hendricks L, Croxford J, Marais AS, Viljoen DL (2005) Maternal risk factors for fetal alcohol syndrome in the Western Cape Province of South Africa: a population-based study. *Am J Public Health* 95:1190-1199.
- May PA, Gossage JP (2002) *The Prevalence of Fetal Alcohol Syndrome Within three New Mexico Indian Communities*. The University of New

- Mexico Center on Alcoholism, Substance Abuse, and Addictions, Albuquerque, NM.
- May PA, Hymbaugh KJ (1982) A pilot project on fetal alcohol syndrome among American Indians. *Alcohol Health Res World* 7:3–9.
- May PA, Hymbaugh KJ, Aase JM, Samet JM (1983) Epidemiology of fetal alcohol syndrome among American Indians of the Southwest. *Soc Biol* 30:374–387.
- May PA, McCloskey J, Gossage JP (2002) Fetal alcohol syndrome among American Indians: epidemiology, issues, and research review, in *Alcohol Use Among American Indians and Alaska Natives: Multiple Perspectives on a Complex Problem. NIAAA Monograph No. 37*, Vol. 13 (Mail PD, Heurtin-Roberts S, Martin SE, Howard J eds), pp 321–369. US Dept of Health and Human Services, Bethesda, MD.
- Moretti M, Montali S (1982) Fetal defects caused by the passive consumption of drugs. *Pediatr Med Chir* 4:481–490.
- Parazzini F, Chatenoud L, Benzi G, Di Cintio E, Dal Pino D, Tozzi L, Fedele L (1996) Coffee and alcohol intake, smoking and risk of multiples pregnancy. *Hum Reprod* 11:2306–2309.
- Parazzini F, Tozzi L, Chatenoud L, Restelli S, Luchini L, La Vecchia C (1994) Alcohol and risk of spontaneous abortion. *Hum Reprod* 9:1950–1953.
- Pelham WE Jr, Gnagy EM, Greenslade KE, Milich R (1992) Teacher ratings of DSM-III-R symptoms for the disruptive behavior disorders. *J Am Acad Child Adolesc Psychiatry* 31:210–218.
- Primatesta P, Del Corno G, Bonazzi MC, Waters WE (1993) Alcohol and pregnancy: an international comparison. *J Public Health Med* 15:69–76.
- Quaid J, Kirkpatrick J, Nakamura R, Aase JM (1993) Establishing the occurrence of FAS/FAE in a rural community. *The Provider* 18:71–75.
- Raven JC, Court JH, Raven J (1976) *Manual for Raven's Progressive Matrices and Vocabulary Scales*. HK Lewis and Co Ltd, London.
- Roccella M, Testa D (2003) Fetal alcohol syndrome in developmental age. *Neuropsychiatric aspects*. *Minerva Pediatr* 55:63–74.
- Rustioni DML (1994) Prove di valutazione della comprensione linguistica. *Organizzazione Speciali, Firenze (Italy)*.
- Sampson PD, Streissguth AP, Bookstein FL, Little RE, Clarren SK, Dehaene P, Hanson JW, Graham JM Jr (1997) Incidence of fetal alcohol syndrome and prevalence of alcohol-related neurodevelopmental disorder. *Teratology* 56:317–326.
- Scianaro L, Prusek W, Liodice G (1978) The fetal alcohol syndrome: clinical observations. *Minerva Pediatr* 30:1585–1588.
- Scotto DT, Venturino G, Sorrentino I, Infuso D, D'Amiano G, Palmieri G (1993) Fetal alcoholic syndrome: a clinical case. *Pediatr Med Chir* 15:525–529.
- Spagnolo PA, Ceccanti M, Hoyme HE (2005) Fetal alcohol spectrum disorders: practical clinical evaluation and diagnosis. *Spettro dei disordini della sindrome feto alcolica: valutazione e diagnosi nella pratica clinica*. *Ital J Pediatr* 31:244–253.
- Square D (1997) Fetal alcoholic epidemic on Manitoba reserve. *Can Med Assoc* 157:5960.
- Stratton K, Howe C, Battaglia F (1996) *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment*. National Academy Press, Washington, DC.
- Streissguth AP, Bookstein FL, Barr HM, Press S, Sampson PD (1998) A fetal alcohol behavior scale. *Alcohol Clin Exp Res* 22:325–333.
- Stromland K, Mattson SN, Adnams CM, Auti-Ramo I, Riley EP, Warren KR (2005) Fetal alcohol spectrum disorders: an international perspective. *Alcohol Clin Exp Res* 29:1121–1126.
- Terreni A, Tretti ML, Corcella PR, Cornoldi C, resoldi PE (2002) *Questionario osservativo per l'identificazione precoce delle difficoltà di apprendimento (IPDA)*. Trento, Erickson.
- Viljoen D, Croxford J, Gossage JP, Kodituwakku PW, May PA (2002) Characteristics of mothers of children with fetal alcohol syndrome in the Western Cape Province of South Africa: a case control study. *J Stud Alcohol* 63:6–17.
- Viljoen DL, Gossage JP, Adnams CM, Jones KL, Robinson LK, Hoyme HE, Snell C, Khaole N, Asante KK, Findlay R, Quinton B, Brooke LE, May PA (2005) Fetal alcohol syndrome epidemiology in a South African community: a second study of a very high prevalence area. *J Stud Alcohol* 5:593–604.