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

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**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, nonverbal 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.

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THE 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 Difficota' 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

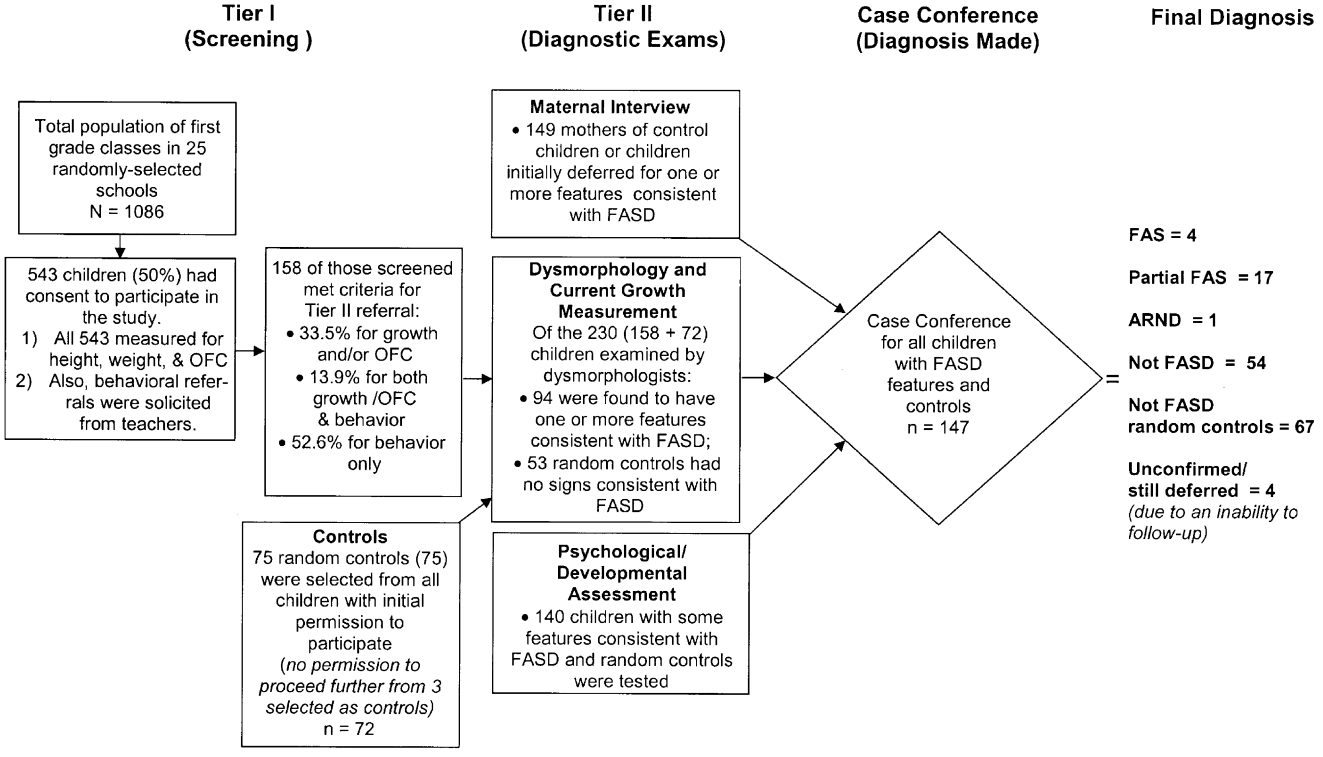


**Fig. 1.** Methodological flow of the fetal alcohol spectrum disorders Study in Italy. Wave I. 2004.

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 ($\leq$ 10th percentile), and microcephaly ($\leq$ 10th 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 ($\leq$ 10th percentile), evidence of abnormal brain structure or growth (e.g., microcephaly $\leq$ 10th 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 anteverted 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 FAS 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 $2\times2$ 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, camptodactly, 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 ($n = 22$)[a] | Control children ($n = 67$) | $p$ Value, OR (95%CI)[b] |
|---|---|---|---|---|
| *Sex (%)* | | | | |
| Males | 51.0 | 50.0 | 44.8 | |
| Females | 49.0 | 50.0 | 55.2 | NS (0.670)[c] OR = 1.23 (0.42–3.63) |
| Age (mo) Mean (SD) | 80.4 (4.4) | 80.1 (4.3) | 79.9 (3.4) | NS (0.801)[d] |
| Height (cm)[e], Mean (SD) | 121.5 (5.4) | 116.2 (5.2) | 121.4 (4.5)[f] | $<0.001$[d] |
| Weight (kg)[e], Mean (SD) | 25.3 (5.3) | 22.0 (4.4) | 25.5 (4.5)[f] | 0.002[d] |
| Children's BMI[e], Mean (SD) | 16.9 (2.8) | 16.2 (2.4) | 17.3 (2.5) | NS (0.077)[d] |
| BMI percentile[e], Mean (SD) | 61.8 (31.4) | 52.2 (33.9) | 69.6 (28.4) | 0.020[d] |
| Occipital circumference (cm)[e], Mean (SD) | 52.0 (1.5) | 50.7 (1.8) | 51.9 (1.1)[f] | $<0.001$[d] |
| Palpebral fissure length (cm), Mean (SD) | | 2.4 (0.1) | 2.5 (0.1) | 0.004[d] |
| Philtrum length (cm), Mean (SD) | | 1.5 (0.2) | 1.4 (0.2) | 0.001[d] |
| Short innercanthal distance ($\leq$ 25%) | | 18.2 | 7.5 | NS (0.148)[c] OR = 2.76 (0.54–13.85) |
| Fine motor dysfunction (%) | | 0.0 | 0.0 | NS[c,g] |
| Hypoplastic midface (%) | | 27.3 | 11.9 | NS (0.087[c] OR = 2.77 (0.71–10.72) |
| "Railroad track" ears (%) | | 22.7 | 6.0 | 0.024[c] OR = 4.63 (0.93–24.04) |
| Strabismus (%) | | 9.1 | 3.0 | NS (0.230)[c] OR = 2.30 (0.30–35.78) |
| Ptosis (%) | | 13.6 | 0.0 | 0.002[c,g] |
| Epicanthal folds (%) | | 40.9 | 14.9 | 0.010[c] OR = 3.95 (1.16–13.55) |
| Flat nasal bridge (%) | | 0.0 | 0.0 | NS[c,g] |
| Anteverted nostrils (%) | | 36.4 | 9.0 | 0.002[c] OR = 5.81 (1.49–23.36) |
| Long philtrum (%) | | 68.2 | 40.3 | 0.023[c] OR = 3.17 (1.02–10.13) |
| Smooth philtrum (%) | | 90.9 | 10.4 | $<0.001$[c] OR = 85.71 (14.10–689.60) |
| Narrow vermillion border (%) | | 86.4 | 25.4 | $<0.001$[c] OR = 18.63 (4.34–92.35) |
| Prognathism (%) | | 0.0 | 0.0 | NS[c,g] |
| Heart murmur (%) | | 0.0 | 1.5 | NS (0.564)[c] (0.00 55.88) |
| Heart malformations (%) | | 0.0 | 0.0 | NS[c,g] |
| Hypoplastic nails | | 0.0 | 0.0 | NS[c,g] |
| Limited elbow supination (%) | | 13.6 | 3.0 | NS (0.060)[c] OR = 5.13 (0.62–48.90) |
| Clinodactyly (%) | | 31.8 | 26.9 | NS (0.654)[c] OR = 1.27 (0.39–4.09) |
| Camptodactyly (%) | | 22.7 | 7.5 | 0.05[c] OR = 3.65 (0.78–17.19) |
| Palmar crease alteration (%) | | 45.5 | 19.4 | 0.015[c] OR = 3.46 (1.08–11.19) |
| Hypertrichosis (%) | | 0.0 | 0.0 | NS[c,g] |
| Other features (%) | | 4.5 | 9.0 | NS (0.505)[c] OR = 0.48 (0.02–4.59) |
| Dysmorphology score[h], Mean (SD) | | 12.5 (3.89) | 3.3 (3.03) | $<0.001$[d] |

[a]There was 1 set of twins among the FASD cases.
[b]95% CIs calculated via the Cornfield technique.
[c]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 $<5$.
[d]*t*-Test of data comparing children with FASD and controls.
[e]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.
[f]Measurements at time of Tier I screen; therefore, they are directly comparable to all other groups.
[g]Calculations of ORs not possible for indicated variable.
[h]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[a] 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

| | Final Dx FASD | | | | | |
|---|---|---|---|---|---|---|
| Child variables | Preliminary Dx FAS mean score (SD) ($n = 11$) | Preliminary Dx deferred mean score (SD) ($n = 11$) | Controls mean score (SD) ($n = 67$) | Test statistic[b] | df | $p$ Value |
| *Developmental traits* | | | | | | |
| Language comprehension[c] | 3.2 (2.3)[4] | 3.5 (2.1)[3] | 4.9 (1.8) | $F = 5.03$ | 2/85 | 0.009 |
| Nonverbal IQ[d] | 51.8 (19.7)[4] | 58.2 (21.5)[3] | 72.3 (21.7) | $F = 5.62$ | 2/85 | 0.005 |
| Behavior[e] | 5.3 (3.8)[1] | 11.7 (6.1)[4] | 3.9 (3.7) | $F = 15.43$ | 2/73 | $< 0.001$ |
| Total dysmorphology score | 14.5 (3.3)[2,4] | 10.4 (3.4)[4] | 3.3 (3.0) | $F = 77.35$ | 2/88 | $< 0.001$ |
| *Maternal variables* | ($n = 9$) | ($n = 8$) | ($n = 63$) | | | |
| 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 | $X^2 = 0.08$ | 2 | NS (0.962) |
| Mean drinks per current week[f] (SD) | 16.2 (26.6)[4] | 7.5 (8.7)[4] | 1.5 (2.1) | $F = 6.01$ | 2/38 | 0.006 |
| Mean drinks per current drinking day[f] (SD) | 2.6 (3.6)[4] | 1.5 (0.9)[4] | 0.8 (0.4) | $F = 5.01$ | 2/38 | 0.012 |

[1] $t$-Test significantly different ($< 0.05$) from preliminarily deferred.
[2] $t$-Test significantly different ($< 0.01$) from preliminarily deferred.
[3] $t$-Test significantly different ($< 0.05$) from controls.
[4] $t$-Test significantly different ($< 0.01$) from controls.
[a] All scores standardized for age of child at the time of testing.
[b] One-way analysis of variance ($F$) or chi-square.
[c] Rustioni Qualitative Test.
[d] Raven Colored Progressive Matrices.
[e] Personal Behaviors Checklist (PBCL-36).
[f] 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 preliminary 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 |
|---|---|---|---|
| *Demographic and socioeconomic variables* | | | |
| Mean Age (y) on day of interview (SD) | 37.9 (5.3) | 36.6 (5.8) | NS (0.636)[a] |
| Residence during index pregnancy (%) | | | |
| Urban | 23.5 | 23.8 | |
| Suburban | 47.1 | 55.6 | |
| Rural | 29.4 | 20.6 | NS (0.727)[b] |
| 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[b,c] |
| Religiosity Index—Mean (SD) | 3.9 (1.7) | 2.4 (1.7) | 0.001[a] |
| Currently employed, % | 58.8 | 59.7 | NS (0.949)[b] 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)[b,c] |
| Among those employed, hours of work per week—Mean (SD) | 30.8 (11.6) | 27.1 (9.5) | NS (0.305)[a] |
| | Mothers of children with FASD ($n = 12$) | Mothers of control children ($n = 48$) | $p$ Value, OR (95% CI)[d] |
| *Substance use variables* | | | |
| Current drinker[f] (of ever drinkers) (%) | 91.7 | 100.0 | 0.046[e] |
| Mean number of drinks last month (current drinkers[f]) (SD) | 41.9 (73.7) | 8.0 (8.8) | 0.007[a] |
| Percent drinking 3 mo before index pregnancy (ever drinkers) | 91.7 | 87.5 | NS (0.688)[b], OR = 1.57 (0.15–38.97) |
| Percent drinking during index pregnancy (ever drinkers) | 69.2 | 64.6 | NS (0.754)[b], 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)[b], OR = 1.19 (0.27–5.15) |
| Second and third trimester of pregnancy with index child (%) | 50.0 | 33.3 | NS (0.284)[b], OR = 2.00 (0.46–8.71) |
| Current smoker (of those who ever smoked) (%) | 36.4 | 59.4 | NS (0.187)[b], 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 | NS (0.372)[b,c] |
| 11 to 19 | 0.0 | 27.8 | |
| 20 (1 pack) | 25.0 | 5.6 | |
| Percent smoked 3 mo before index pregnancy (among ever smokers) | 90.9 | 65.6 | NS (0.107)[b], OR = 5.24 (0.53–125.85) |
| Percent used tobacco during index pregnancy (ever smokers) | 40.0 | 37.5 | NS (0.887)[b], OR = 1.11 (0.20–5.94) |

[a] *t*-Test.
[b] Chi-squared test.
[c] Calculations of chi-square-based odds ratio not possible for this variable as it is not a 2×2 configuration.
[d] 95% CI calculated via the Cornfield technique.
[e] Difference of proportions test.
[f] 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 ($r = -0.24$), 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 5.** Pearson Correlation Coefficients for Child's Nonverbal IQ and Selected Maternal Variables, Child Traits, and Total Dysmorphology Score: Lazio Region, Italy ($n = 85$)

| | Nonverbal IQ[a] | | | | |
|---|---|---|---|---|---|
| Variable | *n* | *r* | $r^2$ | *F* statistic | *p* Value |
| *Maternal* | | | | | |
| 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 |
| *Child* | | | | | |
| 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[b] | 84 | −0.29 | 0.08 | 7.45 | <0.01 |
| Narrow vermillion border[b] | 85 | −0.19 | 0.04 | 3.06 | NS |
| Hypoplastic midface[c] | 85 | 0.08 | 0.01 | 0.59 | NS |
| "Railroad" ears[c] | 85 | −0.24 | 0.06 | 5.10 | <0.05 |
| Strabismus[c] | 85 | −0.18 | 0.03 | 2.70 | NS |
| Ptosis[c] | 85 | −0.24 | 0.06 | 5.05 | <0.05 |
| Epicanthal folds[c] | 85 | −0.06 | 0.00 | 0.27 | NS |
| Heart murmur[c] | 85 | 0.11 | 0.01 | 0.97 | NS |
| Limited supination of elbows[c] | 85 | −0.22 | 0.05 | 4.30 | <0.05 |
| Camptodactyly[c] | 85 | 0.07 | 0.00 | 0.37 | NS |
| Palmer crease alterations[c] | 85 | −0.01 | 0.00 | 0.01 | NS |
| Other features[c] | 85 | 0.06 | 0.00 | 0.27 | NS |
| Dysmorphology score | 85 | −0.26 | 0.07 | 6.32 | <0.05 |

[a]Raven Colored Matrices.
[b]Lip-philtrum guide values ranging from 1 to 5.
[c]Independent variables treated as categorical/dummy variables where the presence of the trait equals 1 and the absence equals 0.
[d]All scores standardized for age at the time of testing.
NS, not statistically significant; FASD, fetal alcohol spectrum disorder; BMI, body mass index.

**Table 4.** Pearson Correlation Coefficients for Developmental[a] 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[b] | −0.19 | −0.18 | −0.18 | 0.04 | −0.15 |
| Nonverbal IQ[c] | −0.09 | −0.12 | −0.12 | 0.01 | −0.08 |
| Behavior[d] | −0.02 | 0.02 | 0.02 | 0.04 | 0.04 |
| Inattention[e] | 0.23* | 0.31** | 0.31** | 0.21 | 0.24* |
| Hyperactivity[f] | 0.00 | 0.04 | 0.04 | 0.03 | 0.02 |
| Dysmorphology score | 0.20 | 0.27* | 0.27* | 0.25* | 0.32** |

[a]All scores standardized for age at the time of testing.
[b]Rustioni Qualitative Test (number of errors made by each child).
[c]Raven Colored Matrices.
[d]Personal Behaviors Checklist (PBCL-36).
[e]Pelham–inattention subscore.
[f]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 | | |
|---|---|---|---|---|---|---|---|---|---|
| | *n* | Rate for sample[a] | Rate for entire class[b] | *n* | Rate for sample[a] | Rate for entire class[b] | *n* | Rate for sample[a] | Rate for entire class[b] |
| 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[c] | 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 |

[a]Rate per 1,000 children based on the sample screened, $n = 543$.
[b]Rate per 1,000 children in all first-grade classrooms assuming no children with FASD were missed by the consent and screening process.
[c]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 dysmorphology. 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 dysmorphology 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.

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