Vol. 30, No. 9
September 2006

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

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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 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,

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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.

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DOI: 10.1111/j.1530-0277.2006.00187.x

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 administrated 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 Aprendimento" (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 Aprendimento" (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).

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

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

[a] *t*-test.
[b] χ^2 test of data.
[c] Estimated number of drinks consumed on a typical day during pregnancy.
NS, not significant; FASD, fetal alcohol spectrum disorders.

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 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.

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

	Behavioral problems (PBCL)			
Variables	r	r^2	F statistic	p 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
Inattention (DBD)				
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
Maternal education				
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.

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, and 0.04, respectively). These data reflect 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, 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 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 ($n = 22$)		Controls ($n = 60$)				
	Mean	SD	Mean	SD	*df*	*t*	*p* Value
Nonverbal IQ and language comprehension							
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[a]	3.41	21.25[b]	5.60	58.15[c]	–4.16	<0.001
Behavioral symptoms							
Teacher DBD rating of attention	4.32	3.46	0.65	1.31	23.25[c]	4.85	<0.001
Teacher DBD rating of hyperactivity/impulsivity	2.14	2.78	0.70	1.76	27.39[c]	2.26	0.032
Parent DBD rating of attention	2.18	2.97	0.45	0.98	22.70[c]	2.68	0.013
Parent DBD rating of hyperactivity/impulsivity	1.59	1.74	0.57	1.09	27.36[c]	2.58	0.015
PBCL-36	9.14[a]	5.72	3.92[b]	3.70	54	3.94	<0.001

[a]Not all *n*'s = 22 due to incomplete data.
[b]Not all *n*'s = 60 due to incomplete data.
[c]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 ρ -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 ρ -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
Nonverbal IQ and language comprehension							
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[a]	(6.01)	21.21[b]	(5.48)	57	0.071	*ns* .943
Behavioral symptoms							
Teacher DBD rating of attention	0.21	(0.63)	0.85	(1.49)	57.71[c]	−2.34	.023
Teacher DBD rating of hyperactivity/impulsivity	0.16	(0.76)	0.95	(2.02)	56.51[c]	−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[a]	(3.86)	4.06[b]	3.70	40	−0.415	*ns* .680

[a]Not all *n*'s = 19 due to incomplete data.
[b]Not all *n*'s = 41 due to incomplete data.
[c]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
Nonverbal IQ and language comprehension							
Raven CPM	17.86	(3.59)	20.63	(5.11)	39	−2.02	0.049
Raven CPM %-itle 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[a]	(3.41)	21.33[b]	(6.01)	26.01[c]	−2.76	0.010
Behavioral symptoms							
Teacher DBD rating of attention	4.32	(3.46)	0.21	(0.63)	22.61[c]	5.47	<0.001
Teacher DBD rating of hyperactivity/impulsivity	2.14	(2.78)	0.16	(0.76)	24.61[c]	3.19	0.004
Parent DBD rating of attention	2.18	(2.97)	0.58	(1.26)	29.19[c]	2.32	0.029
Parent DBD rating of hyperactivity/impulsivity	1.59	(1.74)	0.37	(0.83)	31.06[c]	2.93	0.006
PBCL-36	9.14[a]	(5.72)	3.50[b]	(3.86)	22	2.70	0.013

[a]Not all *n*' s = 22 due to incomplete data.
[b]Not all *n*'s = 19 due to incomplete data.
[c]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.

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