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E-mail	sylvia.roozen@maastrichtuniversity.nl		
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Neonatal Diagnosis of Fetal Alcohol Syndrome: Not Necessarily a Hopeless Prognosis

Claire B. Ernhart, Tom Greene, Robert J. Sokol, Susan Martier, Thomas A. Boyd, and Joel Ager

A neonatal examination for fetal alcohol syndrome (FAS) should promote the guidance of parents, the planning of remediation for affected children, and the collection of prevalence data. A blinded examination of FAS characteristics conducted as part of a large prospective study of disadvantaged alcohol-exposed infants identified eight neonates who met the published criteria for FAS. These children were followed through the preschool years with a blinded assessment protocol. Seven of these children were found to have no impairment in cognitive and language development, when compared with their peers, and to be of average size. The one child who was mentally and growth retarded at follow-up who had been diagnosed as FAS might not have been diagnosed FAS using clinical criteria (as opposed to blinded research criteria), because his mother provided in-pregnancy reports of only low alcohol intake; she later acknowledged drinking an average of over 21 drinks/week during the pregnancy. The findings are positive in that they provide hope for children who present FAS at birth, although concern with adverse outcomes is certainly not dispelled. In particular, the possibility of later-emerging impairment in more complex tasks is not ruled out.
Key Words: FAS, Alcoholism, Intelligence, Teratology, Growth.

FETAL ALCOHOL syndrome (FAS) is defined by published Research Society on Alcoholism criteria.[1–3] These include positive findings in three areas: intrauterine growth retardation, neurological abnormalities (including mental retardation), and the presence of a characteristic pattern of anomalies, including specific craniofacial anomalies. Maternal alcohol abuse in pregnancy is necessary, but not sufficient, for the occurrence of FAS, although it is not a criterion for diagnosis in this study. Alcohol-related birth defects (ARBDs) and/or fetal alcohol effects (FAEs) refer to partial presentations (usually under a research protocol). These effects might include small stature, relatively mino anomalies, as hirsutism, or, more importantly, a small def icit in intelligence. Because these attributes are not specifi to alcohol exposure, ARBDs may be difficult to identify i individuals, but are supported by group statistics and ani mal research.

Diagnosis of FAS or ARBDs is not routine in man nurseries, nor are indicators of FAS always recorded i medical records.[4] Clinicians may be unfamiliar with th dysmorphology of FAS and/or reluctant to record informa tion that may be stigmatizing. Because immediate attentio is not indicated for most symptoms and the prognosis fo individual cases is unclear and therefore not clinically com pelling, a suspected diagnosis may not be made explici Conversely, a diagnosis of FAS may be entered for a abnormality related to a confounding factor, such as use o cigarettes or marijuana.[5] The diagnosis of FAS has eve been reported to be entered into medical records to in crease payments by health insurers.[6]

Clinical diagnosis usually depends on knowledge of ma ternal alcohol use. This information is difficult to obtai because both laboratory and self-report methods are o limited sensitivity. Biochemical traces of alcohol do no persist long enough for laboratory diagnosis. Maternal re port, seldom volunteered, is susceptible to underreport ing.[7,8]

Despite the difficulties in diagnosis, some investigator have identified and followed infants who present with FA A most interesting report is the 10-year description[9] of th 11 children first diagnosed with FAS. Of these, 2 died, was lost to follow-up, and 8 continued to be dysmorphi and deficient in size. Four were severely impaired and had borderline to dull normal IQs. The histories of number of these children included death of the alcoholi mother, neglect, physical abuse, failure to thrive, and othe tumultuous circumstances. The possible confounding effe of these risk factors is difficult to tease out.

In a medical record review[4] of 5602 women, six instance of FAS were identified among 38 children of alcoho abusing women. Although 22 of the 38 children were trace at follow-up, the outcome for the 6 FAS cases per se wa not specified. Nevertheless, 18 of the 22 children of thes alcohol-abusing women were found to be in state hospital The authors assumed them to be mentally retarded. Da were not collected on other variables that might have a fected this remarkable outcome. Although this study

From the Department of Psychiatry (C.B.E.), Case Western Reserve University; the Department of Biostatistics and Epidemiology (T.G.), Cleveland Clinic; the School of Medicine (R.J.S.) and the Departments of Obstetrics (S.M.) and Psychology (J.A.), Wayne State University; and the Rehabilitation Hospital at Heather Hill (T.A.B.), Cleveland, Ohio.

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Reprint requests: Claire B. Ernhart, Ph.D., Department of Psychiatry, Case Western Reserve University and MetroHealth Medical Center, 2500 MetroHealth Drive, Cleveland, OH 44109-1998.

suggestive, drawbacks of study design limit the conclusions that can be drawn.

Six prospective studies[10] of FAEs have focused on the risk of any effect (i.e., ARBDs). FAS was not, per se, a central feature of the studies, but FAS cases were not excluded from study protocols. The few cases that were identified have been followed with the same methodological rigor as other members of the cohorts. A major advantage of following these cases within a cohort is that the data of the cohort are available for comparison and adjustment of results for confounding. Two groups of investigators have reported neonatal diagnosis of FAS in their cohorts.

In the Seattle study, a subgroup of infants was identified at birth as having exposure histories >1.5 oz/day (average of 3 drinks/day during pregnancy).[11] These infants were examined by a dysmorphologist who was blinded to the history of fetal alcohol exposure. Of the examined infants, 33 were followed to age 4 years. Of these, 10 had been identified in the neonatal examination as presenting FAEs (growth deficiency and specific morphologic features). Two of these had enough features for a clear diagnosis of FAS. The 10 cases had a mean IQ at age 4 years that was 10.5 points below the mean for the 23 non-FAE offspring of heavy drinking mothers.[12] Individual data for the two FAS cases were not published.

A number of children in the Cleveland prospective study were positive for ARBDs, including cranio-facial anomalies and low birth weight,[13,14] but no evidence of persisting adverse effects of fetal alcohol exposure for the cohort with respect to intelligence,[15] language,[16] size,[17] and performance on a vigilance task[18] was found. This present study describes the later development of eight children who were identified at birth as having FAS.

METHODS

Subjects

During the period from September 1978 to December 1981, the Michigan Alcoholism Screening Test (MAST)[19] was used to screen 7764 women at their initial antenatal visits at Cleveland Metropolitan General Hospital (now MetroHealth Medical Center). Protocols were approved by the Hospital's Institutional Review Board. Approximately 11% (852) of these women were identified as alcoholic or at risk for alcoholism (MAST scores ≥ 5). Of these, 698 women were followed through pregnancy. The remaining 18% of the identified cases were lost to study during gestation caused by noncompliance, moving, changes in caregiving arrangements, and fetal loss. At the same time, 668 MAST-negative women with concurrent pregnancies were selected by matching on the following variables: ethnicity, date of first antenatal visit, smoking, drug abuse, parity, prepregnancy weight, and weeks of gestation at registration. This process produced a pregnancy cohort of 1366 women who were followed until delivery. (The number of controls is slightly lower because these women were necessarily recruited later in gestation, and it was not always possible to find a MAST− match before the time of delivery of the MAST+ case.) Twenty-five infants of the women followed through pregnancy were identified as having FAS by trained clinicians who were blinded to prenatal exposure to alcohol.

All infants born to women in the pregnancy cohort from January 1, 1981 to March 31, 1982 were considered for recruitment into the prospective study of child development. (Grant support was not awarded for the child development portion of the study until 1981.) Informed consent was obtained. Exclusion criteria, applied without knowledge of alcohol exposure or the results of neonatal examination were: weekend delivery and discharge, gestational age < 37 weeks, neonatal intensive care, parental refusal, primary language other than English, plans to move from the area, maternal narcotic use, maternal psychosis, or placement for adoption. The initial child development cohort, after exclusion, consisted of 359 children. Eight of these children were among the 25 FAS infants identified in the pregnancy study. The remaining 17 FAS cases had been born before January 1, 1981 and thus were not included in the developmental study. To minimize loss caused by exclusion and attrition, yoked matching was not continued into the developmental study.

Study Variables

Alcohol Indices. During each antenatal visit, each woman was interviewed using a carefully structured format[20] to determine ongoing alcohol use. An index of drinking through pregnancy, in-pregnancy AA/day, described the average ounces of absolute alcohol consumed per day based on maternal reports of the numbers of drinks of each beverage consumed.

A second AA/day was obtained retrospectively by interview at the 4-year, 10-month assessment. Retrospective AA/day was markedly higher than in-pregnancy AA/day for many of the women. Because overreporting of alcohol use in the retrospective interview seems doubtful, the discrepancies are interpreted as reflecting underreporting during pregnancy.[9]

Neonatal Examination. Research nurse practitioners who were experienced in the evaluation of neonates were trained by a developmental pediatrician who followed a detailed protocol describing the characteristics of FAEs. The examiners were blinded to prenatal alcohol exposure. The examination was made in conjunction with the administration of the Brazelton Neonatal Behavior Assessment Scale and a portion of the Graham/Rosenblith Behavioral Examination of the Neonate. Inter-observer consistency for all scores and ratings was maintained under pediatric supervision throughout the study.

The criteria for the research diagnosis were: birthweight <10th percentile for gestational age on the basis of hospital norms, at least four anomalies, including at least one neurological anomaly (jitteriness, tremor, poor muscle tone, etc.) and at least one FAS-linked craniofacial anomaly. The criteria used were those established by the Fetal Alcohol Study Group of the Research Society on Alcoholism.[1,2] The features associated with FAS have been demonstrated to be identifiable by trained medical providers and by biomedical scientists.[21] One additional case, without other neurological signs observed by the research nurse but with macrocephaly and a clinical diagnosis of FAS, was included.* The research diagnosis of FAS was made by staff, blinded to alcohol exposure variables, after all perinatal data had been collected and coded.

Outcome Measures. Aside from the neonatal data, all outcome measures were obtained in the home. This strategy was used to minimize attrition and to facilitate the assessment of the home environment.

Cognitive development was evaluated with the Mental Development Index (MDI) of the Bayley Scales of Infant Development[23] at 6 months, 1 and 2 years, the Stanford-Binet Intelligence Scale[24] at 3 years, and the Wechsler Preschool and Primary Scales of Intelligence (WPPSI)[25] at 4 years, 10 months. One child (FAS8), who was retarded, was tested with the Bayley Scales at 3 years and the Stanford-Binet at 4 years, 10 months. Because his performance was appreciably below tabled values, scores were estimated at 50 through age 3 years and 25 at age 4 years, 10 months. These assigned scores probably represent the upper bounds of the child's true functioning level.

Language development was measured at ages 1, 2, and 3 years[16] using measures derived from the Receptive and Expressive Scales of the Se-

* *It might be argued that this case should be excluded because the designated neurological signs were not observed. Macrocephaly, however, has been reported in one study of two cases.[22] It may thus be an occasionally occurring central nervous system indicator of FAS. With this caveat, the case is included in the series.*

quenced Inventory of Language Development [Sequenced Inventory of Communication Development (SCID)].[26] At age 2 years, additional measures of speech production were obtained from two 10-minute standardized play periods. These indices were: (1) the Mean Length of Utterance, which reflects the child's ability to move beyond single words; (2) Intelligibility, an index of the ability to produce comprehensible sounds; and (3) Spontaneity, which describes initiative in speech as opposed to repetition. Intercoder reliability for each production measure was at least 0.90 (Pearson's r).

Behavior was assessed with the Child Behavior Checklist (CBCL)[27] that was orally administered to the primary caretaker when the children were about 6–7 years old. Results for total behavior problems, internalizing and externalizing behavior, and hyperactivity were analyzed. The latter is of interest because fetal alcohol exposure has previously been linked to hyperactivity.[28] Standardized t scores are reported to increase interpretability.

Newborn weight, length, and head circumference were measured by trained nurse practitioners. Subsequent size measurements were taken by trained examiners in the home at ages 6 months, 1 year, 2 years, 3 years, and 4 years, 10 months.

Covariates. The variables that were considered for entry as covariates are described herein. (1) *Demographic variables:* Maternal race and parity, and the sex of the child. (2) *Maternal substance abuse during pregnancy:* Maternal cigarettes per day, any use of marijuana, any use of other drugs. (3) *Family background:* Maternal IQ was estimated by the Peabody Picture Vocabulary Test-Revised (PPVT-R).[29] Years of education was the average for the two parents. Maternal size was evaluated by prepregnancy weight and measurements of stature and head circumference determined postpartum. Paternal size was computed by averaging the standardized estimates (Z-scores) of the father's height and weight given by the mother. (4) *Perinatal history:* Gestational age at birth (as estimated by the Ballard examination).[30] (5) *Caretaking environment:* The quality of the caretaking environment was evaluated in the home at ages 1, 2, and 3 years, and at 4 years, 10 months by the Home Observation for the Measurement of the Environment (HOME) Inventory.[31] Interrater reliabilities ranged from 0.98 to 0.99. (6) *Postnatal stressors:* Examiners regularly recorded history of medical problems (primarily otitis media) and psychosocial stressors.[32] (7) *Study-related variables:* Chronological date of first antenatal visit, gestational age at first antenatal visit, and exact age of child at the administration of the WPPSI.

Statistical Analysis

The absolute scores obtained on the tests of cognitive development at each age of examination are of interest and will be presented. We were concerned, however, that scores would be unduly influenced by confounding factors that are often prevalent in research on disadvantaged families. The availability of the cohort data enabled us to assess the data obtained from the eight children while reducing the influence of other factors. Thus, for instance, if the mother of a case was at an extreme of intelligence or childrearing skills, this contribution could be controlled statistically so that that child's performance could be contrasted more objectively with the summary statistics for the remainder of the cohort.

For this reason, the developmental and growth outcomes for the eight cases were compared with those for the remainder of the cohort by regressing the respective outcome measures on eight dummy variables designating the individual FAS cases in conjunction with covariate data. This provided adjusted scores. Fixed covariate sets used in other analyses[15–18] were used; one covariate set was used for all cognitive outcomes, another set for all language outcomes, and so on. The sets are listed in Table 1.

It might be argued that the medical problems index should not be covaried because prenatal alcohol exposure is a possible risk factor for otitis media,[33] which is the most prevalent problem in the index. Similarly, alcohol-related deficits in the child could influence parental caretaking behavior,[34] as measured by the HOME Inventory. For this reason, the regression analyses were repeated with these indices removed from the covariate sets.

Table 1. Covariate Sets Used for Different Groups of Outcome Measures

Covariates considered	Outcome measure groups			
	Cognitive	Language	Size	CBCL
Race	X	X	X	X
Sex	X	X	X	X
Parity	X	X	X	X
Date of first antenatal visit	X	X	X	X
Duration of gestation at first antenatal visit			X	
Maternal age at delivery		X	X	X
Maternal IQ (PPVT-R)	X	X	X	X
Average parental education	X	X		
Maternal drug use		X		
Maternal marijuana use			X	X
Maternal cigarettes/day			X	
Maternal prepregnancy weight			X	
Maternal stature			X	
Maternal head circumference			X	
Average of standardized paternal weight and stature			X	
Gestational age at birth			X	
Age at testing*	X	X	X	
Medical problems*	X	X		
Psychosocial stressors*	X	X		
Home*	X	X	X	X
Primary caretaker at testing*				X
SES at testing*				X
No. of children in household at testing*				X

* Postnatal covariates.

RESULTS

Background Characteristics of FAS Cases

Demographic and other background characteristics for each of the eight FAS cases and group statistics for the non-FAS members of the cohort are listed in Table 2. Six of the eight diagnosed FAS cases were Black; this contrasts with a percentage of 30.5 Blacks among the non-FAS subjects. The low maternal PPVT-R IQ's were generally consistent with those of the remainder of the cohort. Table 3 summarizes the results of the neonatal assessments that contributed to the FAS determination.

Evidence of alcohol use was not used for the diagnosis of FAS. Nevertheless, as shown in Table 4, 6 of the 8 mothers were alcoholic by the criterion of MAST score ≥ 5. In all but one case, retrospective AA/day was greater (by 7 to 61 times) than in-pregnancy AA/day. This is consistent with the underreporting previously described.[7] Based on the retrospective report, mothers of 7 of the 8 diagnosed cases consumed an average of at least 21 drinks/week. (The typical pattern involved heavy drinking on weekends with lesser amounts during the week.) The mother of FAS2 had the highest retrospective AA/day in the entire cohort. She stated that, in the evenings in the first half of her pregnancy, she consumed one-half of a bottle of whiskey (shots), a six-pack of beer, and eight mixed drinks. In the second half of her pregnancy, she cut down slightly. In contrast, the mother of FAS7 reported no problems with

Table 2. Background Characteristics of Diagnosed FAS Cases

Subjects	Race	Sex	Maternal IQ (PPVT-R)	Average parental education	Parity	Maternal marijuana (pregnancy)	Maternal cigarettes/day	Use of other drugs* (pregnancy)	Home score (4 yr)
FAS1	B	F	71	11.0	1	+	20	–	34
FAS2	B	F	68	10.5	1	+	20	+†	32
FAS3	B	M	83	12.0	1	+	17	–	40
FAS4	B	M	66	10.5	2	–	30	–	33
FAS5	W	F	55	8.5	1	–	60	–	41
FAS6	W	F	71	10.0	1	+	20	–	40
FAS7	B	M	66	12.0	0	+	0	–	38
FAS8	B	M	77	12.0	1	+	4	–	30
All non-FAS									
Mean or %	B	M							
	30%	50%	74.7	10.8	1.1	35%+	13.6	9.1%+	39.1
SD			15.0	1.4	1.3	—	12.0	—	7.2

*Cocaine and other stimulants, glue, depressants, and hallucinogens.
†Amphetamines and hallucinogens (T).

Table 3. Criteria Used in FAS Diagnosis

Subjects	Craniofacial anomalies	Neurological anomalies	Other anomalies	Birthweight (g)	Birthweight adjusted for gestational age (K-score)*
FAS1	6	0†	2	2630	−1.16
FAS2	8	2	3	2270	−1.43
FAS3	5	1	1	1830	−2.24
FAS4	4	1	3	2560	−1.32
FAS5	5	1	2	2260	−1.44
FAS6	1	1	2	2600	−1.21
FAS7	2	1	1	2670	−1.09
FAS8	8	1	2	2520	−1.83
All non-FAS					
Mean	2.07	0.31	0.79	3219	−0.02

*A K-score, <-1.00 indicates that birthweight adjusted for gestational age is below the 10th percentile according to norms.
†This infant presented with macrocephaly (i.e., head circumference greater than the 90th percentile).

Table 4. Maternal Drinking Indices for Diagnosed FAS Cases

Subjects	AA/day* (in-pregnancy *p*)	AA/day* (retrospective)	MAST†
FAS1	0.10	2.16	12
FAS2	0.49	10.38	24
FAS3	0.07	1.68	21
FAS4	0.37	2.59	12
FAS5	0.09	7.34	7
FAS6	0.16	1.73	12
FAS7	0.00	0.0	0
FAS8	0.03	1.84	0
All non-FAS	(n = 351)	(n = 231)	(n = 351)
Mean	0.067	0.51	5.44
SD	0.183	1.53	7.62

*AA/day, average ounces of absolute alcohol per day. One drink (12 oz of beer, 4 oz of wine, or 1 oz of liquor) contains 0.5 oz of absolute alcohol.
†A MAST score ≥5 is considered indicative of alcohol-related problems.

Table 5. Summary of Cognitive Scores for FAS Cases

Subjects	MDI (6 months)	MDI (1 yr)	MDI (2 yr)	Binet (3 yr)	Full IQ (4 yr, 10 months)
FAS1	124	133	98	95	94
FAS2	124	121	107	105	87
FAS3	95	93	85	79	95
FAS4	110	126	85	65	79
FAS5	—	110	88	83	87
FAS6	129	119	—	78	101
FAS7	130	106	100	98	87
FAS8	50	50	50	50	25
All non-FAS					
Mean	111.2	111.9	102.6	89.9	87.7
SD	18.3	14.9	17.5	15.3	16.3

alcohol use (MAST score) and, in the in-pregnancy and retrospective interviews, she denied alcohol use. She did report that she smoked marijuana during pregnancy.

Development of FAS Cases

One of the eight children (FAS8) was mentally retarded as determined by cognitive and language assessments (see Tables 5–7). This child also exhibited subnormal physical growth (see Tables 9–11). In weight, stature, and head circumference, he was below the 3rd percentile for the cohort. Supervisors who accompanied the examiners noted the presence of FAS craniofacial anomalies in this child.

As shown in Table 5, one child obtained a WPPSI Full-Scale IQ of 79 and three received scores of 87. Comparison with the mean (87.7) and standard deviation (16.3) of the full cohort indicates that these are not deviant values in this group of disadvantaged children. As shown in Table 2, the child (FAS4) whose IQ was 79 was born to a woman whose PPVT-R IQ was 66; this and the low score on the HOME

Table 6. Summary of Adjusted Cognitive Scores for FAS Cases

Subjects	MDI (6 months)	MDI (1 yr)	MDI (2 yr)	Binet (3 yr)	Full IQ (4 yr, 10 months)
FAS1	131.4*	148.1*	112.8	107.6*	102.1
FAS2	123.3	127.8*	117.8	107.6*	100.4
FAS3	105.1	88.4†	77.1†	82.2	88.8
FAS4	134.0*	133.0*	103.4	86.3	89.6
FAS5	—	116.8	95.8	92.2	99.2
FAS6	125.5	114.9	—	75.0	103.0
FAS7	121.3	112.0	100.0	106.0*	93.8
FAS8	64.8†	60.6†	66.0†	74.2†	47.4†
All non-FAS					
Mean	111.2	111.9	102.6	89.9	87.7
SD	18.3	14.9	17.5	15.3	16.3

Note: All cognitive scores are adjusted for the covariates specified in Table 1.

* Adjusted cognitive score over 1 standard deviation above mean for non-FAS subjects.

† Adjusted cognitive score over 1 standard deviation below mean for non-FAS subjects.

Inventory suggest that his performance may have been caused by factors other than fetal alcohol exposure.

Except for the one case, adjusted scores (Table 6) on the earlier developmental measures did not differ notably from the means of the remainder of the cohort. For the other seven children, the results were somewhat variable, but not remarkable with respect to the language measures (summarized in Table 7).

The CBCL could be obtained for only 5 of the 8 cases, and the validity of the findings must be qualified by recognition of the low verbal skills of the mothers who completed the questionnaire. (To avoid the possibility of functional illiteracy, administration of the CBCL was oral.) The findings are provided in Table 8. Only one (FAS5) of the five children had scores greater than one standard deviation above the mean on any scale. None had elevated scores on the Hyperactivity Scale.

The results were essentially unchanged when the analyses were repeated without adjustment for the HOME and medical problems indices. With the exception of FAS8, each child again had higher adjusted scores on the WPPSI than the mean for the non-FAS subjects.

By selection, the FAS cases were physically smaller than the remaining subjects at birth (Tables 9–11). In preschool assessments, however, only two cases (including FAS8) were more than one standard deviation below the cohort mean on weight.

DISCUSSION

Children identified as having FAS on the basis of neonatal examination are not necessarily doomed to an adverse course of development. Seven of the eight children to whom we assigned a rigorous research diagnosis of FAS were within normal range on all outcome variables, whereas one case is seriously retarded. Because our results were not as expected, we first review some limitations of the study.

It may be asked whether these seven cases were, in effect, false-positives for FAS. We believe not. These infants wer evaluated by well-trained experienced examiners utilizin the criteria of positive findings in the three areas tha define FAS.[1,2] The first is the presence of characteristi craniofacial anomalies. Data from the full cohort hav shown a dose–response relationship between drinking earl in pregnancy and the anomalies detected in this examin tion.[14] Birthweight was measured objectively. The exam nation was oriented toward the observation of neurologic anomalies. Because behavioral testing was included,[35] th period during which neurological anomalies could be ob served was relatively long. The diagnoses of FAS wer consistent with the finding, for all but one case, of the late report of the consumption of 21 or more drinks/week.

The correspondence of the research diagnosis and clin cal diagnosis merits attention. Whereas the incidence FAS (3/1000) is higher than that reported for some studie of clinically identified cases, the difference may be traced t differences in risk in different populations.[36] The researc protocol was probably more precise and more rigorou than is likely to be the case in a busy nursery. The recordin of observations was standardized to achieve interobserv agreement.

Another difference is that a clinical diagnosis may in volve previous knowledge of maternal alcohol abuse. Wit this requirement, the one impaired case among these eig children would have been missed. The amount this moth reported in the detailed in-pregnancy interviews was le than the mean for all non-FAS cases in the cohort. It w only in retrospect that she reported drinking an average >21 drinks/week. The common tendency to deny or unde report can thus result in unidentified cases. Postpartu interviews may be informative for cases that are otherwi positive in diagnosis.

It might be argued that *neonatal* diagnosis is more dif cult and hence less valid than diagnosis at a later ag Although this is true, the most clearly differentiating cor ponent, the neonatal anomalies examination, is clearly r lated to alcoholism and alcohol use.[14] Regardless, this not pertinent to this study, because all of the examinatio were performed neonatally.

The mothers of the children in this study were disadva taged and had relatively low verbal skills. It might be a gued that the failure to find impairment, relative to th remainder of the cohort, for seven FAS children is caus by effect modification (i.e., that the effects of FAS may n be observed in children already impaired by other factors their lives). The argument is similar to one made to expla an apparent interaction of socioeconomic status (SES) a lead exposure. It has been suggested that low SES childr have had their higher order functioning disturbed by oth factors and that they have been reduced to a lower, mo basic level that is resilient to lead exposure.[37] A review the literature, however, indicates that such interactive synergistic findings are not widely replicated.[38] For one ri factor, low birthweight, the direction of interaction may

Table 7. Summary of Adjusted Language Scores

	Language outcomes derived from SICD						Speech production measures		
	1 yr		2 yr		3 yr		2 yr		
Subjects	EXP	REC	EXP	REC	EXP	REC	MLU	INTELL	SPON
FAS1	31.5*	32.3*	37.9	47.6*	39.4	38.6*	1.64	33.7†	79.9
FAS2	30.0*	22.3	38.2*	42.6	38.5	27.6	1.58	49.9	74.9
FAS3	25.9	22.8	16.8†	29.9†	19.9†	14.7†	1.65	15.8†	72.5
FAS4	24.2	22.1	28.4	37.5	35.2	24.4	1.45	73.3	90.9*
FAS5	31.1*	23.3	31.8	43.9	40.0	30.1	1.27	57.3	61.4
FAS6	26.9	27.3	—	—	4.8†	25.5	—	—	—
FAS7	21.7†	20.4	38.5*	45.6	43.0*	39.7*	1.61	76.7*	80.7
FAS8	18.5†	10.7†	22.2	17.6†	19.1†	12.1†	0.31	13.1†	22.8†
All non-FAS									
Mean	26.1	24.0	30.0	39.2	30.9	24.9	1.47	56.8	70.1
SD	3.9	5.3	8.0	7.8	10.1	8.8	0.48	19.4	19.7

Note: All language scores are adjusted for the covariates specified in Table 1. EXP, expressive; REC, receptive; MLU, mean length of utterance; INTELL, intelligibility; SPON, spontaneity.

* Adjusted language score over 1 standard deviation above mean for non-FAS subjects.

† Adjusted language score over 1 standard deviation below mean for non-FAS subjects.

Table 8. Adjusted T-Scores on the CBCL

Subjects	Total behavior problems	Internal problems	External problems	Hyperactivity scale
FAS1	58.0	58.2	55.9	54.6*
FAS5	77.8†	75.1†	75.8†	64.3
FAS6	58.9	50.0*	59.9	68.1
FAS7	53.0*	47.3*	53.8	56.3
FAS8	68.7	65.1	71.6	65.0
All non-FAS (n = 221)				
Mean	63.3	60.9	62.9	62.7
SD	9.2	9.1	9.4	6.7

Note: All T-scores are adjusted for the covariates specified in Table 1.

* Adjusted T-score over 1 standard deviation below mean for non-FAS subjects.

† Adjusted T-score over 1 standard deviation above mean for non-FAS subjects.

Table 9. Summary of Adjusted Stature Values for FAS Cases (in cm)

Subjects	Birth	6 Months	1 Year	2 Years	3 Years	4 Years, 10 months
FAS1	51.6	70.1	76.2	84.6	94.0	111.1
FAS2	46.2*	68.3	71.9	88.4	93.3	111.2
FAS3	45.9*	68.4	76.2	87.8	94.7	108.8
FAS4	48.1	69.8	71.2*	85.9	95.3	109.1
FAS5	49.3	—	69.8*	83.4	92.3	104.7
FAS6	47.9	67.3	74.0	—	91.5*	100.4*
FAS7	49.2	64.7	78.0†	87.5	100.3†	132.6†
FAS8b	42.4*	56.9*	65.9*	73.2*	81.1*	93.1*
All non-FAS						
Mean	49.7	67.3	74.2	86.8	95.8	109.0
SD	2.5	3.8	2.9	3.5	4.1	5.6

Note: All data are adjusted for the covariates shown in Table 1.

* Adjusted stature over 1 standard deviation below mean for non-FAS subjects.

† Adjusted stature over 1 standard deviation above mean for non-FAS subjects.

Table 10. Summary of Adjusted Weights for FAS Cases (in kg)

Subjects	Birth	6 Months	1 Year	2 Years	3 Years	4 Years, 10 months
FAS1	2.99	8.99*	10.15	11.78	14.93	19.16
FAS2	2.53†	8.11	9.94	12.68	14.36	18.72
FAS3	2.36†	8.02	10.29	12.86	14.83	20.36
FAS4	2.57†	—	9.79	11.79	13.68	19.45
FAS5	2.55†	—	7.50†	9.72†	11.11†	13.52†
FAS6	2.96	8.52	9.87	—	12.86	16.61
FAS7	2.59†	7.26	—	11.82	13.61	17.11
FAS8	2.58†	4.13	—	8.14†	—	12.54†
All non-FAS						
Mean	3.22	7.87	10.06	12.25	14.20	18.78
SD	0.45	0.99	1.23	1.57	1.93	2.85

Note: All weights are adjusted for the covariates specified in Table 1.

* Adjusted weight over 1 standard deviation above mean for non-FAS subjects.

† Adjusted weight over 1 standard deviation below mean for non-FAS subjects.

Table 11. Summary of Adjusted Head Circumference for FAS Cases (in cm)

Subjects	Birth	6 Months	1 Year	2 Years	3 Years	4 Years, 10 months
FAS1	36.8*	47.4*	49.1*	51.0*	51.2	55.3*
FAS2	32.8	43.4	46.1	49.4	49.7	52.2
FAS3	30.6†	44.6	46.9	49.5	49.9	51.2
FAS4	33.7	44.7	45.5	47.7	49.3	50.5
FAS5	33.0	—	44.3†	46.5†	48.6	49.6
FAS6	32.8	44.4	47.2	—	50.7	51.7
FAS7	30.9†	41.0†	44.0†	48.9	48.9	49.4†
FAS8	32.9	38.7†	41.3†	43.9†	45.6†	46.6†
All non-FAS						
Mean	34.1	43.7	46.1	48.6	50.1	51.1
SD	1.3	1.4	1.4	1.4	1.7	1.7

Note: All head circumference are adjusted for the covariates specified in Table 1.

* Adjusted head circumference over 1 standard deviation above mean for non-FAS subjects.

† Adjusted head circumference over 1 standard deviation below mean for non-FAS subjects.

reversed; children of disadvantaged backgrounds seem to be more vulnerable to birthweight effects.[39]

We looked for evidence of dose–response relationship among these eight children. With respect to "dose," the mother of one child (FAS2) had the highest retrospective AA/day index in the cohort and had very high in-pregnancy AA/day and MAST indices, yet her child scored above the cohort means on the cognitive and language scales. The largest, actually the only, "response" was observed for

FAS8, whose mother was not at the extreme of alcohol consumption and who denied problems related to alcohol use. No relationship between the amount of alcohol consumed and outcome could be discerned among these cases. It must be noted, however, that detection of a dose–response relationship in only eight cases would have been surprising indeed.

One mother (FAS7) reported no use of alcohol and no history of alcohol-related problems. She did report smoking marijuana, which is illegal. Alpert and Zuckerman,[5] basing their opinion on the work of Hingson et al.,[40] have suggested that the FAS dysmorphology may be a common result of numerous agents rather than a specific teratogenic effect of alcohol; this may explain this case. This explanation, however, seems less likely than false denial of drinking by this mother.

It must be noted that the outcome measures used in this study did not sample all possible adverse effects of fetal alcohol exposure. We included no direct measures of several school-age problems seen with some FAS children. These include learning disabilities[41] and limited success in social interactions.[42] Nevertheless, our finding of mental retardation in only one of these eight children provides some hope, although it certainly cannot dispel concern for those faced with a diagnosis of FAS in the newborn.

With this small number of cases, it was not possible to identify characteristics of these children that were related to vulnerability for effect. Clearly, the next areas of research include the identification of such characteristics and the evaluation of remedial interventions so that these children may achieve optimal development.

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