TOWARDS IDENTIFYING A CHARACTERISTIC NEUROPSYCHOLOGICAL PROFILE FOR FETAL ALCOHOL SPECTRUM DISORDERS
2. SPECIFIC CAREGIVER- AND TEACHER-RATING

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ABSTRACT

Objectives
This study compares the behavioral profile of children with fetal alcohol spectrum disorder (FASD) who were diagnosed using the Canadian Guidelines with children with prenatal alcohol exposure who did not meet criteria for a FASD diagnosis.

Methods and Procedures
To accomplish this, we used caregiver and teacher questionnaires evaluating different aspects of behavior. Investigated were 170 children, 109 who received a diagnosis of FASD (Diagnosed Group) and 61 who did not (Non-Diagnosed Group). On the caregiver report, children in the Diagnosed Group had more internalizing and externalizing problems on the CBCL, more executive function difficulties on the BRIEF and more attention problems on the Conner's Rating Scale, compared to the Non-Diagnosed Group. On teacher report, children in the Diagnosed Group had more internalizing and externalizing problems on the TRF and more attention problems on the Conner's Rating Scale, compared to the Non-Diagnosed Group. For both informants, more children in the Diagnosed group had scores in the clinically elevated range.

Conclusion
Overall, the present results identify key caregiver- and teacher-rated profiles of children with FASD diagnoses. These profiles will aid in better understanding, diagnosing and providing focused treatment approaches for children with FASD.

Key Words: *Fetal Alcohol Spectrum Disorder, caregiver, teacher, neuropsychological tests, behavior*

Fetal alcohol spectrum disorders (FASD) are a set of developmental conditions that arise from prenatal exposure to alcohol, a powerful teratogen with severe consequences for brain development. As a result of prenatal alcohol exposure (PAE), children with FASD have a variety of significant deficits, particularly within the executive function[1], language[2-3], memory[4-5], attention[6], and social skills domains.[7-9] Deficits are also commonly reported using a variety of caregiver and teacher questionnaires examining behavior, social skills and attention problems.[7,10-11] In particular, children with FASD exhibit high incidence of psychiatric and psychological diagnoses, particularly conduct problems, oppositional defiant disorder and attention deficit hyperactivity disorder (ADHD)[12-14], however their behavior profiles are different from those children with other psychiatric conditions.[15] Importantly, despite the high incidence of behavior and cognitive problems in children with FASD, PAE does not necessarily lead to the observe behavior problems and a diagnosis of FASD.[16-17] It is not known, however, how children with FASD differ from individuals with known PAE but who are not diagnosed with an FASD and whether there exists a syndrome-specific behavior profile in this population.

To address these knowledge gaps, the present study compared caregiver and teacher-rated questionnaires for children assessed in the Motherisk Clinic at the Hospital for Sick Children

in Toronto to determine whether a syndrome-specific behavioral profile of FASD was present. For nearly 20 years, the Motherisk Clinic has been assessing children with prenatal teratogen exposure, including alcohol and other illicit drugs. The majority of children seen in this clinic are brought by foster or adoptive parents who are concerned that their children's learning and/or behavioral problems may have been caused by prenatal alcohol exposure. The overall aim of the current study was to determine whether there is a behavioral profile of children exposed to alcohol prenatally who meet criteria for FASD. Along with our companion paper (Nash et al. J Popul Ther Clin Pharmacol 2013;20(1):e44-e52), the information gained from the present study will be essential for better diagnosis and treatment of children with FASD. Not only will we gain a more thorough understanding of FASD, but we will also have increased knowledge of the differences between children with PAE who meet criteria for FASD and children with PAE who do not meet FASD criteria.

METHODS

Participants

Between 2005 and 2009, 170 children aged 6 to 16 years attended the Motherisk Clinic at the Hospital for Sick Children in Toronto and were included in the present study. Out of the 170 children, 109 received a FASD diagnosis (Diagnosed group, mean age = 10.33, SD = 3.57, 55% male) and 61 did not receive a FASD diagnosis (Non-Diagnosed group, mean age = 8.94, SD = 3.41, 66% male) based on the Canadian Guidelines.

The diagnostic assessments were conducted by a multidisciplinary team consisting of a psychologist, psychometrist, and neurologist, who used a combination of standardized and non-standardized measures, rating scales, interviews, clinical observations, and developmental history. Diagnoses were made using the Canadian Guidelines and children were classified using the 4-Digit Coding system developed at the University of Washington.[18] Diagnostic expression is classified using a 4-point Likert scale with 1 representing no evidence of the FASD profile and 4 reflecting the "classic" FAS profile. All participants in our clinic were required to have a confirmed history of prenatal exposure to alcohol either via Children's Aid's records, reported alcohol withdrawal at birth, or report from the biological mother.

With regards to the "brain" rankings used in diagnosis, Brain 1 refers to no evidence of brain damage caused by prenatal exposure to alcohol as evidenced on psychometric measures, Brain 2 refers to suspected damage, Brain 3 refers to probable brain dysfunction evidenced by psychometric measures, and Brain 4 is evidenced by damage confirmed by physical characteristics through medical examination. Children categorized by Brain 3 were required to show impairment (as classified by the Canadian Guidelines) in three or more of the following domains: sensory/motor, communication, attention, intellectual functioning, executive functioning, memory, and academic achievement. It is important to note that a Brain 4 ranking only occurs when there are "hard" medical criteria met, such as microcephly, structural abnormalities, and/or other hard neurological signs.

For the purposes of data analysis, children in the Brain 3 and 4 groups were considered the Diagnosed Group and those children who received a brain score of 1 and 2 comprised the Non-Diagnosed Group. As is importantly highlighted in the literature[19-20], several diagnostic centres use different nomenclature to refer to different diagnostic categories on the FASD spectrum. Therefore for clarification, a 'brain' score of 3 is similar to either an ARND or p/FAS diagnosis, while a 'brain' score of 4 similar to an FAS diagnosis. 'Brain' scores of 1 and 2 are indicative of PAE, without meeting diagnostic criteria based on the Canadian guidelines. Table 1 indicates the breakdown by brain classification and diagnosis for the sample. A subset of these data is presented in a companion paper (Nash et al., J Popul Ther Clin Pharmacol 2013;20(1):e44-e52).

TABLE 1 Brain Score Distributions for Diagnosed and Non-Diagnosed Groups

	Diagnosed Group	Non-Diagnosed
Brain 1 (%)	0	34.9
Brain 2 (%)	0	62.8
Brain 3 (%)	92.9	2.3
Brain 4 (%)	7.1	0

Materials and Procedures

Prior to testing, all parents or guardians provided signed informed consent and all children gave assent. Parents/guardians completed a structured case history form providing information on demographics and the child's prenatal, birth and developmental history. The Hollingshead scale was used to determine family socioeconomic status (SES) based on caregiver education and occupation data[21]. Although all 170 children were administered the majority of standardized tests, not all caregivers and teachers completed all of the questionnaires. Therefore, only a subset of the total number of children will be analyzed depending on the number of caregiver and teacher questionnaires that were completed and returned to the clinic.

Child Behavior Checklist (CBCL) and Teacher Report Form (TRF)[22]. The CBCL was completed for 148 of the total 170 children (98 Diagnosed and 50 Non-Diagnosed). The TRF was completed for 140 children (95 Diagnosed and 45 Non-Diagnosed). The CBCL is a widely used questionnaire for 4 to 18 years old children. It contains 118 items requiring caregivers to rate their child using a 3-point scale. The TRF, which is comparable to the CBCL, seeks similar information as the CBCL but from a teacher's perspective. Both the CBCL and TRF are divided into three different scales; (a) three Broad Band scales including Internalizing, Externalizing and Total problems; (b) seven Narrow Band scales including Anxiety/Depression, Withdrawal, Somatic, Social, Thought, Attention, Rule Breaking and Aggressive Behavior Problems; and (c) several scales which reflect the degree of similarity of the child's profile to children receiving specific DMS-IV diagnoses. Analyses for the present paper will be conducted on the broad Band scores. For both caregiver and teacher questionnaires, scores are provided as T-scores (mean=50, standard deviation=10) based on normative data of Achenbach and Rescorla (2001). T-scores of 65 and above are considered in the clinically impaired range.

Behavioral Rating Inventory of Executive Function (BRIEF)[23]. The BRIEF caregiver was completed on 149 of the total 170 children (100 Diagnosed and 49 Non-Diagnosed) and the teacher BRIEF was completed on 96 children (65 Diagnosed and 31 Non-Diagnosed). The BRIEF is a measure of executive function behaviors that include scores in the domains of inhibition, set shifting, emotional control, working memory, planning, organizational skills, and monitoring. Analyses will be conducted on the overall Index scores including the Behavioral Regulation Index (BRI), Metacognition Index (MI), and Global Executive Composite (GEC). For both the caregiver and teacher version of the BRIEF scores have a mean of 50 and a standard deviation of 10, with higher scoring indicating more difficulties. T-scores of 65 and above are considered in the clinically impaired range.

Conners' Rating Scale (CRS)[24]. The CRS-Caregiver was completed on 169 children (108 Diagnosed and 61 Non-Diagnosed) and the CRS-Teacher was completed on 102 children (65 Diagnosed and 37 Non-Diagnosed). The subscales on the CRS rating scale provide measures for various behavioral characteristics including oppositionality, cognitive problems, inattention, hyperactivity, anxiety, perfectionism, social problems, and psychosomatic tendencies. Analyses were conducted on the ADHD, Global, and DSM Total scores. Scores on the CRS have a mean of 50 and a standard deviation of 10, with

higher score indicating more difficulty. Again, clinically elevated scores are indicated by T-score of 65 or greater.

Data Management and Statistical Plan

Demographic characteristics were compared between groups using one-way analyses of variance (ANOVA) for continuous variables and chi-square analyses for binary variables. Groups were directly compared on caregiver and teacher questionnaires using multivariate analyses of variance (MANOVA) for each measure. Separate MANOVAs were conducted for the CBCL, TRF, BRIEF-Caregiver, BRIEF-Teacher, CRS-Caregiver, and CRS-Teacher. Wilks Lambda values were used to indicate significance. Odds ratios and 95 percent confidence intervals (CI) were also calculated on the caregiver and teacher questionnaires to determine the likelihood of scores within each group to be in the clinical range.

RESULTS

Demographics

The distribution of Brain diagnoses for the Diagnosed and Non-Diagnosed groups are presented in Table 1. The remaining demographic information is presented in Table 2. Overall there was a significant age difference between groups ($p < 0.05$), with the Diagnosed group being older than the Non-Diagnosed group. Furthermore, compared to Non-Diagnosed group, children in the Diagnosed group were two times more likely to have a previous ADHD diagnosis [$p < 0.01$, odds ratio = 2.32, 95% CI = 1.21 to 4.43], two times more likely to be in a special education placement [$p < 0.01$, odds ratio = 2.48, 95% CI = 1.30 to 4.73], two times more likely to have a biological mother with a mental health issue [$p < 0.05$, odds ratio = 2.21, 95% CI = 0.99 to 4.94], and five times more likely to have a biological father diagnosed with a mental health disorder [$p < 0.03$, odds ratio = 4.68, 95% CI = 1.02 to 21.35]. Odds ratios were only calculated on demographic variables that were significantly different between groups.

TABLE 2 Demographic Information for children with PAE diagnosed with FASD (Diagnosed Group) and children with PAE not diagnosed with FASD (Non-Diagnosed Group)

	Diagnosed Group Mean (SD)	**Non-Diagnosed Mean (SD)**	***p* value**
Age	10.3 (3.6)	8.9 (3.4)	< .01
Number of placements	3.1 (2.0)	2.7 (1.5)	ns
SES	3.0 (1.2)	3.1 (1.1)	ns
Birth weight (kilograms)	8.37(4.9)	12.2(6.4)	ns
Male	n=60	n=40	ns
Cigarette Exposure	88(%)	87(%)	ns
Cocaine Exposure	29(%)	22(%)	ns
Marijuana Exposure	40(%)	27(%)	ns
ADHD Diagnosis	61(%)	40(%)	< .01
ODD Diagnosis	8(%)	2(%)	ns
Special Education Placement	64(%)	42(%)	< .01
Maternal Mental Health Concerns	32(%)	18(%)	< .05
Maternal Learning Disorder	22(%)	18(%)	ns
Paternal Substance Abuse	54(%)	56(%)	ns
Paternal Learning Disorder	19(%)	15(%)	ns
Paternal Mental Health Concerns	<10(%)	15(%)	< .03
Medication Status			
Risperidol	12(%)	9(%)	
Zoloft	2(%)	0	
Dexedrine	4(%)	0	

NOTE: available information varies for each variable

Caregiver Questionnaires

CBCL

For the CBCL Broad Band scales, a MANOVA was conducted on 98 children in the Diagnosed Group and 50 in the Non-Diagnosed Group. The omnibus effect of Group was significant [F (3, 144) = 6.80, $p < 0.001$, $\eta p^2 = 0.12$). Univariate analyses indicated significant effects of Group on the Internalizing ($p < 0.02$, $\eta p^2 = 0.04$), Externalizing ($p < 0.001$, $\eta p^2 = 0.12$), and Total Problems scales ($p < 0.001$, $\eta p^2 = 0.11$). These results are presented in Table 3.

Odds ratio and 95% confidence intervals were calculated for the CBCL Broad Band scales. Results indicated children in the Diagnosed group are two times more likely to have Internalizing Problem scores ($p < 0.02$, odds ratio = 2.52, 95% CI = 1.19 to 5.31), four times more likely to have Externalizing Problem scores ($p < 0.001$, odds ratio = 4.58, 95% CI = 2.18 to 9.62), and three times more likely to have Total Problem scores ($p < 0.01$, odds ratio = 2.94; 95% CI = 1.42 to 6.11) in the clinical range, compared to children in the Non-Diagnosed group.

TABLE 3 Means (SD) of the CBCL for the Diagnosed and Non-Diagnosed Group

	Diagnosed Group n=98 Mean (SD)	**Non-Diagnosed Group n=50 Mean (SD)**	**F value**	***p* value**
Internalizing	62.02 (10.16)	57.60 (10.89)	5.97	0.016
Externalizing	71.15 (8.93)*	63.62 (11.63)	19.10	0.001
Total Problems	70.32 (7.34)*	63. 70 (11.41)	18.23	0.001

Note: * indicates T scores in the clinically significant range (65+).

BRIEF-Caregiver

For the BRIEF-Caregiver Index scores, a MANOVA was conducted on 100 children in the Diagnosed Group and 49 in the Non-Diagnosed Group. The omnibus effect of Group was significant [F (3, 145) = 4.70, $p < 0.01$, $\eta p^2 = 0.09$). Univariate analyses revealed significant effects of Group on all of the BRI ($p < 0.01$, $\eta p^2 = 0.06$), MI ($p < 0.01$, $\eta p^2 = 0.07$) and GEC ($p < 0.001$, $\eta p^2 = 0.08$). These results are presented in Table 4. Odds ratio and 95% confidence intervals were calculated for the BRIEF Index scores. The results indicate that children in the Diagnosed group are four times more likely to have BRI score ($p < 0.001$, odds ratio = 3.84; 95% CI = 1.82 to 8.08), three times more likely to have MI scores ($p < 0.01$, odds ratio = 2,80; 95% CI = 1.36 to 5.78) and two times more likely to have GEC scores ($p < 0.05$, odds ratio = 2.45; 95% CI = 1.17 to 5.13) in the clinically significant range, compared to children in the Non-Diagnosed group.

TABLE 4 Means (SD) of the BRIEF-Caregiver for the Diagnosed and Non-Diagnosed

	Diagnosed Group n=100 Mean (SD)	**Non Diagnosed Group n=49 Mean (SD)**	**F value**	***p* value**
BRI	73.83 (12.07)*	66.57 (15.21)*	9.97	0.002
MI	71.32 (10.76)*	64.90 (11.79)	10.99	0.001
GEC	73.76 (10.25)*	66.63 (13.03)*	13.25	0.001

Note: * indicates T scores in the clinically significant range (65+).

CRS-Caregiver

For the CRS-Caregiver ADHD, Global and DSM Total scores, a MANOVA was conducted on 108 in the Diagnosed Group and 61 in the Non-Diagnosed Group. The omnibus effect of Group was significant [F (3, 165) = 9.94, $p < 0.001$, $\eta p^2 = 0.15$]. Univariate analyses revealed significant effects of Group on the ADHD ($p < 0.001$, $\eta p^2 = 0.14$), Global ($p < 0.001$, $\eta p^2 = 0.14$), and DSM Total ($p < 0.001$, $\eta p^2 = 0.13$) scores. These results are presented in Table 5.

TABLE 5 Means (SD) of the CRS-Caregiver for the Diagnosed and Non-Diagnosed Group

	Diagnosed Group n=108 Mean (SD)	Non Diagnosed Group n=61 Mean (SD)	F value	*p* value
ADHD	74.53 (11.19)*	65.46 (10.80)*	26.26	0.001
Global	75.75 (11.69)*	65.75 (12.39)*	27.28	0.001
DSM Total	76.92 (11.29)*	67.21 (13.27)*	25.34	0.001

Note: * indicates T scores in the clinically significant range (65+).

Odds ratios and 95% confidence intervals were calculated for these scores. Results revealed children in the Diagnosed group were four times more likely to have ADHD scores ($p < 0.001$, odds ratio = 4.28; 95% CI = 2.14 to 8.55), four times more likely to have Global scores ($p < 0.001$, odds ratio = 4.53; 95% CI = 2.22 to 9.25), and three times more likely to have DSM Total scores ($p < 0.01$, odds ratio = 3.06, 95% CI = 1.51 to 6.18) in the clinically significant range, compared to children in the Non-Diagnosed group.

Teacher Questionnaires

TRF

For the TRF Broad Band scales, a MANOVA was conducted on 95 children in the Diagnosed Group and 45 in the Non-Diagnosed Group. The omnibus effect of Group was significant [F (3,136) = 4.01, $p < 0.01$, $\eta p^2 = 0.08$]. Univariate analyses revealed significant effects of Group on the Internalizing Problems ($p < 0.05$, $\eta p^2 = 0.04$), Externalizing Problems ($p < 0.01$, $\eta p^2 = 0.07$), and Total Problems ($p < 0.01$, $\eta p^2 = 0.08$). These results are presented in Table 6.

TABLE 6 Means (SD) of the TRF for the Diagnosed and Non-Diagnosed Group

	Diagnosed Group n=95 Mean (SD)	Non Diagnosed Group n=45 Mean (SD)	F value	*p* value
Internalizing	58.06 (9.57)	54.00 (10.18)	5.28	0.023
Externalizing	64.54 (9.44)	59.31 (8.69)	9.84	0.002
Total Problems	64.83 (8.51)*	59.62 (8.12)	11.77	0.001

Note: * indicates T scores in the clinically significant range (65+).

Odds ratio and 95% confidence intervals were calculated for the Broad Band scales. Results indicated children in the Diagnosed group are four times more likely to have Internalizing Problems scores ($p < 0.01$, odds ratio = 4.07, 95% CI = 1.33 to 12.47), three times more likely to have Externalizing Problems scores ($p < 0.01$, odds ratio = 3,24, 95% CI = 1.51 to 6.95), and four times more likely to have Total Problems scores ($p < 0.01$, odds ratio = 3.74; 95% CI = 1.70 to 8.24) in the clinically significant range, compared to children in the Non-Diagnosed group.

BRIEF-Teacher

For the BRIEF-Teacher Index scores, a MANOVA was conducted on 65 children in the Diagnosed Group and 31 in the Non-Diagnosed Group. There were no significant omnibus or univariate effects of Group, indicating no differences between the Diagnosed and Non-Diagnosed group on any scales from the BRIEF teacher. No odds ratios were calculated for the BRIEF teacher scales.

CRS-Teacher

A MANOVA was conducted on 65 Diagnosed Group and 37 Non-Diagnosed Group for the CRS-Teacher ADHD, Global and DSM Total scores. There was no omnibus effect of Group. Univariate analyses revealed significant effects of Group on the ADHD ($p < 0.05$, $\eta p^2 = 0.04$), Global ($p < 0.05$, $\eta p^2 = 0.05$), and DSM Total ($p < 0.2$, $\eta p^2 = 0.06$) scales. These results were presented in Table 7.

TABLE 7 Means (SD) of the CRS-Teacher for the Diagnosed and Non-Diagnosed Group

	Diagnosed Group n=65 Mean (SD)	Non Diagnosed Group n=37 Mean (SD)	F value	*p* value
ADHD	72.69 (13.44)*	66.76 (14.01)*	4.44	0.038
Global	73.89 (13.40)*	67.35 (14.27)*	5.36	0.023
Total	73.29 (13.37)*	66.22 (14.49)*	6.22	0.014

Note: * indicates T scores in the clinically significant range (65+).

Odds ratio analyses were conducted on these scores. Results revealed children in the Diagnosed group were three times more likely to have ADHD scores ($p < 0.01$, odds ratio = 3.45, 95% CI = 1.44 to 8.28), two times more likely to have Global scores ($p < 0.05$, odds ratio = 2.56; 95% CI = 1.11 to 5.90), and three times more likely to have DSM Total scores ($p < 0.05$, odds ratio = 2.68, 95% CI = 1.14 to 6.26) in the clinically significant range, compared to children in the Non-Diagnosed group.

DISCUSSION

The current paper identified a syndrome-specific FASD behavioral profile that distinguishes children with PAE who met criteria for FASD compared to children with PAE who did not meet diagnostic criteria. Children in the Diagnosed group were rated by caregivers and teachers as having more internalizing problems, externalizing problems, and attentional problems compared to the Non-Diagnosed group; whereas only caregivers reported the FASD group as having more executive functioning difficulties. Furthermore, children in the Diagnosed group were more likely to have scores in the clinically elevated range across multiple domains.

Importantly, the findings from the present study highlight that children with FASD have more caregiver- and teacher-rated difficulties in areas of behaviour, attention, and executive

functioning, compared to children who were prenatally exposed to alcohol but did not meet criteria of an FASD diagnosis. However, children in the Non-Diagnosed group did display clinically elevated scores in some of the domains. This is not surprising, given that all children came to the Motherisk Clinic due to complaints and concerns of behavioral and/or cognitive difficulties. Of note, however, results from the odds ratio analyses indicate that children with FASD are more likely to receive scores in the clinical range across multiple domains. In addition, whereas caregivers reported significant differences between the Diagnosed and Non-Diagnosed groups in executive functioning, teachers did not observe these executive function discrepancies. One explanation for these results may be the unique structure of the classroom environment, compared to the home environment. The classroom environment encourages structure and rules, which may help support children's executive functioning (e.g., planning, inhibition). Based on this environment, teachers may have fewer opportunities to observe executive function discrepancies between children with FASD and children with PAE who do not have a diagnosis. In addition, the failure to find significant differences on teacher-rated executive functions may be due to the fact that many children are taking attention medications during school hours. Because caregivers observe children's behavior on and off attention medications, they may provide a more informative perspective on the child's executive and behavioral profiles.

Our results support previous studies that report children with FASD display difficulties in behaviour, executive function and attention, as rated by caregivers and teachers.[7,10-11,15] Importantly, the results from the current study also suggest there may be a syndrome-specific caregiver and teacher-rated profile of FASD. Notably, multiple domains in areas of caregiver-rated externalizing problems, executive function, and attention difficulties were reported to be in the clinically significant range for children in the Diagnosed group. Fewer domains, in comparison, were reported to be in the clinical range for the Non-Diagnosed group. In terms of a diagnostic specific profile, children with FASD were reported to have clinically significant levels of caregiver- and teacher-rated total behaviour problems, and caregiver-rated metacognitive difficulties, compared to children in the Non-Diagnosed group. These findings suggest that the specific FASD profile may be related to increased externalizing behaviour, as well as lower internal monitoring and planning abilities (metacognitive difficulties). In comparison, the caregiver- and teacher-rated CRS ADHD and Global Indices was reported to be in the clinically significant range for children in the Diagnosed and Non-Diagnosed groups, suggesting difficulties with attention and regulation may not be a differential factor following PAE. Taken together, it appears that the combination of exposure to prenatal alcohol and a resulting FASD diagnosis leads to a more clinically significant profile.

Overall, the present study identified a set of behavioral, executive functioning and attention domains that characterize children with PAE who receive a diagnosis of FASD and distinguishes them from children with PAE who do not have FASD. It is clear that including caregiver and teacher perspectives into the diagnostic process, as is done in other developmental disorders such as ADHD[25], is essential to fully understanding the FASD profile. Importantly, not only is this information essential for the diagnostic process of FASD, but also to more thoroughly understand the outcomes following PAE and inform treatment approaches.[26]

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