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Validation of the FASD-Tree as a screening tool for fetal alcohol spectrum disorders

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Abstract

Background—As many as 80% of individuals with fetal alcohol spectrum disorders (FASD) are misdiagnosed or not diagnosed. This study tests the accuracy and validity of a web-based screening tool (the FASD-Tree) for identifying children and adolescents with fetal alcohol spectrum disorders (FASD).

Methods—Children with histories of prenatal alcohol exposure and controls (N=302) were examined for physical signs of fetal alcohol syndrome (FAS), and parents completed behavioral questionnaires. Data were entered into the FASD-Tree, a web-based decision tree application. The FASD-Tree provided two outcomes: a dichotomous indicator (yes/no) and a numeric risk score (0–5), which have been shown separately to identify children with PAE and neurobehavioral impairment and to correlate with neurobehavioral outcomes. Overall accuracy (ACC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the decision tree, risk score, and their combination. Misclassified cases were examined for systematic bias.

Results—The FASD-Tree was successful in accurately identifying youth with histories of prenatal alcohol exposure and the subgroup of individuals with FASD, indicating its validity as an FASD screening tool. Overall accuracy rates for FASD-Tree components ranged from 75.0%–84.1% and both the decision tree outcome and risk score, as well as their combination, resulted in fair to good discrimination (AUC = .722-.862) of youth with histories of prenatal alcohol exposure or FASD. While most participants were correctly classified, those who were misclassified differed in IQ and attention. Race, ethnicity, and sex did not affect the results.

Conclusion—The FASD-Tree is not a biomarker of PAE and does not provide definitive evidence of such exposure. Rather it is an accurate and valid screening tool for FASD and should

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be used by clinicians who suspect that a patient has a history of prenatal alcohol exposure, even if that exposure is unknown.

Keywords

Diagnosis; Screening; Fetal Alcohol Spectrum Disorders (FASD); Behavior; Prenatal Alcohol Exposure

Introduction

While the teratogenicity of alcohol is well-documented, children with prenatal alcohol exposure (PAE) and neurobehavioral differences including those who qualify for a diagnosis of fetal alcohol spectrum disorders (FASD) remain unidentified or misdiagnosed (Chasnoff et al., 2015). The subgroup of children with PAE who have fetal alcohol syndrome (FAS) is readily identifiable by clinicians with adequate training (Jones et al., 2006); however, this subgroup is the minority of individuals with FASD. The remaining majority present with significant neurobehavioral impairments without sufficient growth deficits and/or dysmorphology to merit FAS diagnosis. Instead, they are included under the diagnostic umbrella of FASD, which includes FAS, partial FAS, and alcohol-related neurodevelopmental disorder (ARND). Although multiple diagnostic systems are used in the U.S (Coles et al., 2016), there is agreement that (1) physical differences (e.g., growth deficit, microcephaly, short palpebral fissures, thin vermilion border, smooth philtrum) and neurobehavior or cognitive differences characterize FAS and (2) individuals with FASD may present with or without physical differences (Hoyme et al., 2016, Jones et al., 2006, Mattson et al., 2019, Mattson and Riley, 2011). FASD occurs in as many as 5% of school-age children (May et al., 2018) although heterogeneity of physical presentation (i.e., FAS vs. FASD) coupled with an overlap in clinical phenotype with other neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder (ADHD), results in under-identification, misdiagnosis, and misunderstanding of the etiology of difficulties faced by children with FASD (Chasnoff et al., 2015). Failure to identify children with FASD or to differentiate children with neurobehavioral differences due to PAE from those with similar behavioral concerns without PAE can impede access to tailored intervention (Coles et al., 2015, Petrenko et al., 2020) and affect prognosis, as early identification is related to more positive outcomes (Streissguth et al., 1996). While efforts to identify individuals with FASD have been moderately successful in research settings, including those using active case ascertainment (May et al., 2018), they have not translated easily to clinical settings, likely due to the extensive neuropsychological testing and dysmorphology expertise required. We previously described two indicators of FASD. The first was a hierarchical decision tree (Goh et al., 2016) which was developed by testing over 1,000 variables collected from 434 children with or without prenatal alcohol exposure and with or without clinical behavioral problems. The model was validated in an independent sample of 454 children. Four domains that maximized discrimination between exposed and unexposed participants were selected from the larger set of variables, including specific physical measurements, problem behaviors, adaptive behavior, and IQ. Accuracy rates were ≥80%. The second tool was a risk score ranging from 0–5 that was developed using the same clinical data. We previously showed the risk score accurately identified youth

with PAE (overall classification accuracy rates of 67–79%) and correlated with the critical outcomes of overall ability (measured by IQ score) and executive functioning (Bernes et al., 2022). The goal of this study was to test the accuracy of the FASD-Tree, a web-based tool that incorporates both an updated version of the decision tree and the risk score from our previous studies, as a screening tool for FASD.

Methods

Measures

The FASD-Tree.—We previously described two tools for identifying youth with histories of PAE: (1) a decision tree based on the results of a physical examination and parent questionnaires (Goh et al., 2016) that had ≥80% classification accuracy, and (2) a risk score based on the same data that had 67–79% classification accuracy (Bernes et al., 2022). The risk score and an updated version of the decision tree were combined in an automated web-based screening tool called the FASD-Tree. Completion of the FASD-Tree requires a physical exam and 2 parent questionnaires (see Table 1). The FASD-Tree provides two outcomes: a dichotomous indicator from the decision tree algorithm and a numerical risk score. For this study, we examined results from the two outcomes separately and in combination. As a result, several labels and outcomes are reported. For clarity, we list and define them as follows. For the decision tree component of the FASD-Tree, we use Tree-Positive to refer to decision tree outcomes that are consistent with FASD (positive decision tree) and Tree-Negative to refer to the outcomes that are inconsistent with FASD (negative decision tree). Similarly, for the risk score component of the FASD-Tree, we use “high risk” to refer to risk score outcomes that are consistent with FASD and “low risk” to refer to risk score outcomes that are inconsistent with FASD. Finally, for the combined FASD-Tree, we use FASD-Positive to refer to FASD-Tree outcomes that are consistent with FASD (positive decision tree or a high risk score) and FASD-Negative to refer to the FASD-Tree outcomes that are inconsistent with FASD (negative decision tree or a low risk score). More detail about each component is provided below.

The decision tree indicator included in the FASD-Tree is based on our previous work (Goh et al., 2016) and incorporates specific measures from the physical exam and the Vineland Adaptive Behavior Scales-third edition (VABS-3; Sparrow et al., 2016). To return a response of “Tree-Positive” (the positive indicator of FASD), a child must meet one or more of the following criteria: (1) presence of FAS (defined as 2 or more primary physical features and growth deficiency and/or microcephaly); (2) one or more primary physical features and two VABS-3 scores <86; (3) one or more secondary physical features; or (4) two VABS-3 scores <86 (see Table 1). These criteria and cut-point values were selected statistically from more than 1000 neuropsychological, behavioral, and physical measures based on analysis of overall accuracy, sensitivity, and specificity of the model in a large sample (Goh et al., 2016). The original decision tree algorithm (Goh et al., 2016) also included the Child Behavior Checklist (CBCL) and a “psychologist route”. However, we found this route to be redundant with the “pediatrician route” and thus removed it from the current version of the FASD-Tree. The CBCL is still required for the risk score, as described below.

The risk score (Bernes et al., 2022) requires data from the physical examination and the VABS-3 (Sparrow et al., 2016) and CBCL (Achenbach and Rescorla, 2001) parent questionnaires on child adaptive function and problem behavior, respectively. The risk score algorithm returns a numeric score from 0–5, with higher scores indicating greater likelihood of FASD. The risk score uses similar measures as the decision tree but weighs the relative contribution of the indicators and results in a score from 0–5 which can be considered as a discrete variable or dichotomized to indicate the risk of FASD (i.e., low vs. high risk, see results). Like the decision tree, the risk score was developed and confirmed in large samples of alcohol-exposed children and controls with and without behavioral concerns.

Participants

Participants for this study were recruited from three sources as part of the Collaborative Initiative on FASD (CIFASD), two university-based FASD clinics, and a university-based FASD research program. Inclusion criteria were age (4–17y) and language (English speaking). History of prenatal alcohol exposure was ascertained by maternal report, medical, legal, or social service records and categorized as either (1) known or suspected or (2) denied by parents or guardians. All recruited participants were eligible for this study. We compared participants with histories of prenatal alcohol exposure (the AE group) to controls (the CON group). As in our previous studies, participants with parent-reported behavioral or cognitive concerns were not excluded. Of the 78 participants in the CON group, 5 (6.5%) had IQ scores <78 (i.e., 1.5 SD below the population average) and 14 (17.9%) had elevated (>65) attention scores on the CBCL. See Table 2 for demographic data.

Analyses

Data were analyzed using SPSS v. 28 (IBM Corporation, 2021) and SAS 9.4 (SAS Institute Inc.). Descriptive statistics were used to identify the sample characteristics. Unadjusted analyses were conducted using analysis of variance (ANOVA) for continuous data (e.g., age) and Chi-square ($\mathbf{X}^2$) tests for categorical data (e.g., sex, race, ethnicity). Classification accuracy was determined using $\mathbf{X}^2$ tests and Receiver Operator Curve (ROC) analysis and sensitivity (true positive rate), specificity (true negative rate), and positive predictive values (PPV; the probability that participants with positive decision tree outcomes or high risk scores are in the AE group) and negative predictive values (NPV; the probability that participants with negative decision tree outcomes or low risk scores were controls) were calculated. Two-sided tests with 95% confidence intervals (CIs) that exclude 1.0 or p-values < 0.05 were used to determine the statistical significance for all analyses.

We repeated the analyses using two different grouping variables. First, to be consistent with our previous studies, we compared the AE and CON groups in the first set of analyses. Second, because we were interested in the FASD-Tree as a screening tool for FASD, we compared participants with a clinical diagnosis of FASD to those without this diagnosis in the second set of analyses.

Results

Demographic Information

Demographic data are presented in Table 2. The AE and CON groups were similar in terms of sex (X^2 = 0.20, p = .655), gender identity (X^2 = 4.10, p = .129; excluding those with unknown gender identity), and ethnicity (X^2 = 1.07, p = .301) but not race (X^2 = 4.41, p = .036). A larger proportion of participants were white in the CON group (74.4%) than in the AE group (61.2%). The groups also differed in mean age (F(1,300) =12.26, p < .001) and mean IQ score (F(1,264) =63.25, p < .001); the CON group had a higher mean age and IQ score than the AE group. There were also more participants with low IQ scores (<78 [−1.5 SD]) in the AE group (24.3%) than in the CON group (6.5%; X^2 = 11.24, p < .001). Descriptive data for all measures included in analysis are included in a supplemental table (Table S1).

Comparison of AE and CON Groups

Decision Tree.—The decision tree classification by group is presented in Table 3. In the unadjusted bivariate analysis, the AE group was more likely to be classified as Tree-Positive than controls (X^2 = 60.62, OR=8.54, 95% CI = 4.78–15.26, p < .001). ROC analysis resulted in fair discrimination between the AE and CON groups with an AUC of .743. Overall classification accuracy was 76.2% (Sensitivity = 78.1%, Specificity = 70.5%, PPV = 88.4%, NPV = 52.9%) indicating that the decision tree component accurately classified individuals with histories of prenatal alcohol exposure.

Risk Score.—The results of the risk score are presented in Table 3. The AE group had a higher mean risk score (M=3.2; SD=1.30) than the CON group (M=1.1; SD=1.20) (F(1,299) = 151.67, p < .001); the distribution is shown in Table 3. The ROC analysis resulted in good discrimination between the AE and CON groups (AUC = .862) and indicated that scores of 2 and 3 were good candidates for cut-points. Given our previous results (Bernes et al., 2022), we tested these two different cut-points as indicators of high risk of having FASD. Cut-points of ≥2 (i.e., risk score of 2–5) and ≥3 (i.e., risk score of 3–5) were compared to determine which resulted in the best discrimination of the AE and CON groups. With a risk score cut-point of 2, the AE group was more likely to be classified as high risk than controls (X^2 = 109.59, OR=20.77, 95% CI = 10.87–39.70, p < .001). ROC analysis resulted in good discrimination between the AE and CON groups with an AUC of .813. Overall classification accuracy was 84.1% (Sensitivity = 87.0%, Specificity = 75.6%, PPV = 91.1%, NPV = 67.0%). Similarly, with a risk score cut-point of 3, the AE group was more likely to be classified as high risk than controls (X^2 = 75.78, OR=13.58, 95% CI = 6.99–26.41, p < .001). ROC analysis resulted in fair discrimination between the AE and CON groups with an AUC of .782. Overall classification accuracy was 75.7% (Sensitivity = 73.1%, Specificity = 83.3%, PPV = 92.6%, NPV = 52.0%). Overall, based on these metrics, the risk score cut-point of 2 was judged to be a stronger determinant of group membership than the cut-point score of 3.

FASD-Tree: The Combination of the Decision Tree and Risk Score.—Although the risk score is highly correlated with the decision tree outcome (r = .78, p < .001), each

indicator may provide unique information. We tested the combination of the dichotomous decision tree outcome indicator and risk score indicator in one final model to determine whether requiring either or both indicators yielded better accuracy than one indicator alone. Based on the previous analysis, we used the cut-point of ≥2 (i.e., high risk = 2–5) for this analysis. We compared the presence of no indicators (i.e., decision tree result = No AND Risk Score = 0–1) to one or more indicators (i.e., decision tree result = Yes OR Risk Score = 2–5). The AE group was more likely than controls to have one or more positive indicator ($\mathbf{X}^2$ = 76.69, OR=11.77, 95% CI = 6.42–21.58, p < .001). Overall classification accuracy rate was 81.1% (Sensitivity = 87.4%, Specificity = 62.8%, PPV = 87.1%, NPV = 63.6%). ROC analyses resulted in fair discrimination between the AE and CON groups with an AUC of .751.

Comparison of Participants with FASD vs. Not FASD

Because the FASD-Tree is designed as a screening tool for FASD and not only the presence of PAE, we repeated the analyses described above with those participants who met clinical criteria for FASD (n=186) compared to participants without FASD (n=114; all the controls plus 36 participants with histories of PAE but who did not have FASD). FASD was defined as having FAS or ARND (see Table 4 for definitions). We recognize that there are multiple definitions of FAS and FASD used clinically (Coles et al. 2016). As in Hoyme et al., 2016, we used ≤10th percentile for palpebral fissure length and 2 rather than 3 cardinal facial features. Given our goal of screening for FASD, it is appropriate that our criteria are perhaps less stringent than others. That is, we are willing to accept a higher false positive/lower negative predictive values in order to capture the maximum number of individuals with FASD. In addition, because of our goal of detecting FASD rather than exposure alone, we included both exposed and unexposed participants in the “without FASD” group. Two participants did not have sufficient test data to determine a clinically-determined FASD status and were excluded from this analysis.

Decision Tree.—Participants with FASD were more likely to be classified as Tree-Positive than those without FASD ($\mathbf{X}^2$ = 63.70, OR=7.95, 95% CI = 4.64–13.60, p < .001). ROC analysis resulted in fair discrimination between clinically-determined FASD and not FASD with an AUC of .725. Overall classification accuracy was 75.0% (Sensitivity = 82.8%, Specificity = 62.3%, PPV = 78.2%, NPV = 68.9%).

Risk Score.—Participants with FASD had a higher mean risk score (M=3.4; SD=1.20) than those without FASD (M=1.4; SD=1.31) (F(1,297) = 177.41, p < .001). The ROC analysis resulted in good discrimination between participants with FASD and those without FASD (AUC = .849). With a risk score cut-point of 2, the group with FASD was more likely to be classified as High Risk than those without FASD ($\mathbf{X}^2$ = 97.63, OR=17.30, 95% CI = 9.14–32.73, p < .001). ROC analysis resulted in fair discrimination between the groups with an AUC of .767. Overall classification accuracy was 80.3% (Sensitivity = 91.4%, Specificity = 61.9%, PPV = 79.8%, NPV = 81.4%). With a risk score cut-point of 3, the FASD group was more likely to be classified as High Risk than those without FASD ($\mathbf{X}^2$ = 96.44, OR=13.94, 95% CI = 7.89–24.64, p < .001). ROC analysis resulted in fair

discrimination between the groups with an AUC of .788. Overall classification accuracy was 79.3% (Sensitivity = 80.6%, Specificity = 77.0%, PPV = 85.2%, NPV = 70.7%).

FASD-Tree.—Finally, we repeated the analysis of the combination of the decision tree and risk score outcomes for the comparison of the participants with FASD (clinically defined, as described above) and those without FASD. Although the cut-points (>2 or >3) resulted in very similar results, we selected to use the cut-point of ≥2 (i.e., high risk = 2–5) to be consistent with the previous analyses. Using this cut-point, we compared the presence of no indicators (i.e., decision tree result = No AND Risk Score = 0–1) to one or more indicators (i.e., decision tree result = Tree-Positive OR Risk Score = 2–5). The participants with FASD were more likely than those without FASD to have one or more positive indicators ($\mathbf{X}^2$ = 73.41, OR=12.03, 95% CI = 6.40–22.63, p < .001). Overall classification accuracy rate was 76.9% (Sensitivity = 91.4%, Specificity = 53.1%, PPV = 76.2%, NPV = 78.9%). ROC analyses resulted in fair discrimination between the groups with an AUC of .722.

Relationship to Demographic Factors and Other Indicators of Prenatal Alcohol Exposure

We tested the relationships between decision tree outcome and risk score with age, sex, race, ethnicity, FSIQ, and score on the Attention Problems scale from the CBCL (Achenbach and Rescorla, 2001) using Pearson correlations. All correlations are presented in Table 6. In addition to being correlated with each other, both the decision tree outcome and the risk score were correlated with FSIQ and Attention Problems score, but not age, sex, race, or ethnicity.

We also tested whether the relationship between decision tree outcome and PAE was affected by age, sex, race, ethnicity, IQ score, or Attention Problems using logistic regression. PAE remained significantly associated with decision tree outcome (OR=4.42, 95% CI = 1.88–10.36, p < .001) while controlling for age (OR=1.19, 95% CI = 1.07–1.31, p = .001), IQ score (OR=0.96, 95% CI = .94-.98, p < .001), and Attention Problems score (OR=1.06, 95% CI = 1.03–1.10, p < .001), which were also significant predictors. Sex (p = .08), race (p = .65), and ethnicity (p = .33) were not significant.

This analysis was repeated for the risk score using the ≥2 cut-point. PAE remained significantly associated with risk score (OR=8.6, 95% CI = 3.35–22.09, p < .001) while controlling for IQ score (OR=0.96, 95% CI = 0.94–0.99, p = .003), and Attention Problems score (OR=1.11, 95% CI = 1.07–1.17, p < .001), which were also significant predictors. Age, sex, race, and ethnicity were not significant (p ≥ .20).

Misclassified Participants

Using the combined FASD-Tree, we examined the misclassified participants by alcohol exposure and by FASD for systematic sources of bias. First, we examined the participants with a history of PAE (n=223). In comparison to participants that were correctly classified, those that were misclassified (false negatives, n=28) were significantly (p < .05) more likely to have 0 primary physical features (82% vs. 43%), more likely to have 0 secondary features (100% vs. 73%), and more likely to be Hispanic or Latino (52% vs. 30%). They had fewer problems on the CBCL Attention Problems scale (64 vs. 74). They also had a higher average

IQ score (99 vs. 88) but were equally likely to have an IQ score <78. They did not differ ($p > .05$) on sex, gender identity, race, microcephaly, height, weight, or age.

Next, we examined the participants without a history of PAE (n=78). In comparison to participants that were correctly classified, those that were misclassified (false positives, n=29) were significantly ($p < .05$) more likely to have 1 or more secondary physical features (59% vs. 0%). They had fewer problems on the CBCL Attention Problems scale (53 vs. 64) and were more likely to have an IQ score <78 (2% vs. 14%) although small cell sizes make this difference likely to be unreliable. Only 5 unexposed participants had IQ scores <78. They did not differ on any other variable.

We also examined the participants with a clinical diagnosis of FASD (n=186). In comparison to correctly classified participants, misclassified participants (false negatives, n= 16) were significantly ($p < .05$) more likely to have 0 primary physical features (100% vs. 42%) and less likely to have weight ≤10% (0% vs. 20%). They had fewer problems on the CBCL Attention Problems scale (68 vs. 75). They did not differ on any other variable.

Finally, we examined the participants without a clinical diagnosis of FASD (n=113). In comparison to correctly classified participants, misclassified participants (false positives, n=53) without a clinical diagnosis of FASD were significantly ($p < .05$) more likely to have >1 primary physical feature (15% vs. 2%) and 1 secondary physical feature (40% vs. 0%). They also had lower average IQ scores (99 vs. 109) and more problems on the CBCL Attention Problems scale (64 vs. 55). They did not differ on any other variable.

Discussion

We compared the classification accuracy of the FASD-Tree for identifying youth with PAE and neurobehavioral differences (i.e., those with FASD) using rigorous statistical analyses; we tested the ability of the FASD-Tree to detect both histories of PAE and a clinical diagnosis of FASD. In the first set of analyses, comparing the AE group to the CON group, both the decision tree dichotomous outcome and the risk score resulted in significant and accurate classification ranging from 76%–84% overall accuracy. Requiring either indicator (Tree-Positive OR a high risk score) was also successful, with a classification accuracy of 81%. In the second set of analyses, comparing participants with a diagnosis of FASD to those without the diagnosis, overall accuracy rates ranged from 75–80% and the combination of the two indicators was accurate in 77% of cases. Thus, the FASD-Tree is a valuable clinical tool that is easy to use and inexpensive, requiring only a physical examination and commonly used parent questionnaires. The use of the FASD-Tree can reduce the number of youth with FASD who are misdiagnosed or missed entirely, which is estimated to be as high as 80% (Chasnoff et al., 2015). Identification of FASD is critical and will allow earlier and accurate referral for clinical services. This study provides replication and further validation of both the decision tree (Goh et al., 2016) and risk score (Bernes et al., 2022) as effective tools.

There are a limited number of screening tools specifically designed to identify individuals with FASD, and many rely on physical features. While assessing physical features such

as short palpebral fissures or smooth philtrum helps provide an etiologic link to certain neurobehavioral outcomes, it is the behavioral and cognitive effects that are the most impairing features of this diagnosis and should be screened. Recent reviews of screening tools for FAS or FASD indicate that more research is needed (Lim et al., 2022) and that the limited available screening tools have limited psychometric support (Grubb et al., 2021). One screening tool that has been tested in individuals with FASD is the Neurobehavioural Screening Tool (NST; Nash et al., 2011, Nash et al., 2006), which is based on items from the CBCL. When applied to a sample of children with FASD, PAE, or typically-developing controls, the NST had 62.5% sensitivity for FASD and 50% for PAE but 100% specificity (LaFrance et al., 2014). Sensitivity was higher among adolescents than children. Another screening tool, a 33-item survey, has been described recently by Burd and colleagues and has good sensitivity and specificity (Klug et al., 2021). Our tool incorporates both physical and behavioral features, and the outcome provides a validated assessment of FASD with fair to good discrimination ability. When comparing the AE and CON groups, sensitivity was 78.1% for the decision tree, 87.0% for the risk score, and 87.4% for the combined FASD-Tree. Specificity was 70.5% for the decision tree, 75.6% for the risk score and 62.8% for the combined FASD-Tree. When individuals with FASD were the target group, sensitivity was comparable though specificity was somewhat lower. Higher sensitivity than specificity may relate to our criteria for FASD, which while consistent with one of the major diagnostic schemes (Hoyme et al., 2016) are more liberal than other criteria in use in the U.S. and elsewhere (e.g., Astley, 2004). However, higher sensitivity than specificity is important for screening tools. A good screening tool should be easy to administer, low cost, safe to use, and identify the maximum number of individuals in the population of interest. The FASD-Tree meets these criteria.

Clinicians in both primary and specialty settings (e.g., pediatrics, psychiatry) can use the FASD-Tree when PAE is suspected or when behaviors consistent with FASD are noted. Youth identified by the FASD-Tree should be referred for additional specialty evaluation if needed, and intervention or other clinical services, including academic support, mental health services, and social skills training. Clinicians should also refer parents to supportive services. For example, recent advances in telemedicine have led to a mobile health intervention for parents who have children with FASD (Petrenko et al., 2020). It is notable that as with any screening tool, care must be taken not to overinterpret the findings. Clinicians should carefully consider the FASD-Tree results and weigh them alongside other clinical data. The FASD-Tree is not a biomarker of PAE. Rather it is a tool that provides the clinician with empirically supported data to guide clinical decision-making.

While our study documents the validity of the FASD-Tree, it was tested using only expert clinicians. Although clinicians can be trained to evaluate the physical features of FASD (Jones et al., 2006), many remain uncomfortable making a diagnosis (Bax et al., 2015). The FASD-Tree requires only recognition of five physical features in addition to height, weight, and head circumference, and the administration of two commonly used parent questionnaires. Thus, the availability of the FASD-Tree may make it easier for clinicians to screen patients for FASD. In addition, screening for FASD in high-risk populations may result in lower overall costs by reducing the number of children who require comprehensive diagnostic testing (Berrigan et al., 2019). Future studies should examine the utility of the

FASD-Tree in other general and specialty clinical settings. One possibility is adjusting the cut-point based on clinical need; using a lower cut-point (risk score of 2 or higher) resulted in higher sensitivity while a higher cut-point (3 or higher) resulted in higher specificity. While we did not explicitly test the FASD-Tree in a sample recruited from other specialty clinics, our non-exposed sample was heterogeneous and did not exclude participants based on factors such as IQ or ADHD. While participants misclassified as alcohol-exposed had more attention problems on the CBCL and lower IQ scores, PAE remained significantly related to FASD-Tree outcomes even when attention and IQ scores were statistically controlled. Thus, our results are robust even in the presence of these commonly co-occurring factors. However, since it has been suggested that FASD is indistinguishable from other similar conditions (Lange et al., 2019), future studies should test the FASD-Tree in clinically referred samples.

Our study was strengthened by a relatively large sample of individuals with PAE recruited from clinical and research samples. However, our samples were not matched on race or age. These are essential factors to consider in the evaluation of FASD. The FASD-Tree outcome was not affected by race, ethnicity, or sex and remained significant even when we controlled for important variables like age and IQ. Less impacted individuals (i.e., those with higher IQ scores, fewer attention problems) were more likely to be misclassified by the FASD-Tree; thus, additional tools may be required for higher functioning patients. Misclassified individuals with prenatal alcohol exposure were more likely to be Hispanic/Latino, a finding that requires additional research to explain. Finally, we only included a limited number of physical and behavioral indicators in our study. The specific measures were selected based on our previous studies including the decision tree (Goh et al., 2016) and risk score (Bernes et al., 2022), which indicated that a selected group of variables best identified youth with histories of PAE from controls. While other studies may indicate similar results with different measurements, the current study validated the use of the FASD-Tree and thus the specific and select group of measures.

Conclusion.

The FASD-Tree is an accurate and valid tool for screening for FASD and should be used by clinicians who suspect that a patient with cognitive or behavioral deficits has a history of PAE, even if that exposure is unknown.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

AE	Alcohol-exposed group
CON	Control group
FASD	fetal alcohol spectrum disorders
ROC	Receiver Operator Curve
AUC	area under the curve
ACC	Overall accuracy
PPV	positive predictive value
NPV	negative predictive value
VABS-3	Vineland Adaptive Behavior Scales-third edition

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Table 1.

Measures collected by FASD-Tree

Measure	Variables Recorded in FASD-Tree
Physical Exam (Jones et al., 2006, Mattson et al., 2010)	Primary physical features: Palpebral fissure length ≤10th percentile Philtrum lipometer score 4 or 5 (Astley, 2004) Vermillion lipometer score 4 or 5 (Astley, 2004) Secondary physical features: Incomplete extension of digits Ptosis Growth deficiency (1 or more): Height ≤10th percentile Weight ≤10th percentile Microcephaly: Head circumference ≤10th percentile
Child Behavior Checklist (T-Scores) (Achenbach and Rescorla, 2001)	Thought problems Attention problems Social problems Aggressive behavior Rule-breaking behavior Somatic complaints
Vineland Adaptive Behavior Scales - 3rd edition (Sparrow et al., 2016)	Socialization Communication Daily Living Skills
Demographic Information	Age Sex Gender Identity Race Ethnicity Family Income IQ score (obtained directly or reported) Previous alcohol-related diagnoses (e.g., FAS, pFAS, ARND) Other Diagnoses History of prenatal alcohol exposure

Table 2.

Sample characteristics

	Control Group (n=78)	Alcohol-Exposed Group (n=224)
Age in years [Mn (SD)]	11.7 (3.29)	10.0 (3.52)
Sex (at birth) [n (%)]		
Female	35 (44.9)	94 (42.0)
Male	43 (55.1)	130 (58.0)
Gender Identity [n (%)]		
Female	30 (56.6)	93 (41.5)
Male	23 (43.4)	130 (58.0)
Transgender	0 (0)	0 (0)
Does not identify as male, female or transgender	0 (0)	1 (0.4)
Unknown[a]	25 (29.1)	0 (0)
Race [n (%)]		
American Indian/Alaska Native	1 (1.3)	8 (3.6)
Asian	2 (2.6)	3 (1.3)
Black or African American	1 (1.3)	39 (17.4)
Native Hawaiian or Other Pacific Islander	0 (0)	1 (0.4)
White	58 (74.4)	137 (61.2)
More than One Race	16 (20.5)	36 (16.1)
Unknown/Not Reported	0 (0)	0 (0)
Ethnicity [n (%)]		
Hispanic or Latino	20 (25.6)	70 (31.3)
Not Hispanic or Latino	56 (71.8)	144 (64.3)
Unknown/Not Reported	2 (2.6)	10 (4.5)
IQ [Mn(SD)][b]	106.9 (18.20)	89.1 (15.85)
IQ Score <78 [n (%)]	5 (6.5)	46 (24.3)
CBCL Attention Problems T-Score [Mn(SD)]	57.7 (9.53)	68.5 (8.40)
Attention Problems [n (%)][c]	14 (17.9%)	173 (77.6%)
History of prenatal alcohol exposure [n (%)]		
Confirmed	0 (0)	163 (72.8)
Suspected	0 (0)	61 (27.2)
FASD Diagnosis [n (%)][d]	0 (0)	186 (83.0)

[a]Gender identity was not collected for 25 participants in the control group.

[b]IQ score data were missing for 1 control and 35 alcohol-exposed participants.

[c]Attention problems based on CBCL (Attention Problems T-score > 65 or ADHD T-score >65). CBCL data missing for 1 alcohol-exposed participant.

[d]FASD diagnosis was missing for 2 alcohol-exposed participants.

Table 3.

Results for the comparison of participants with histories of prenatal alcohol exposure and controls

	Group		Statistic		
	Control [n (%)]	**Alcohol-Exposed [n (%)]**	**Odds Ratio (95% CI)**	**X^2**	**p**
FASD-Tree Outcome					
Tree-Negative	55 (70.5)	49 (21.9)	8.54 (4.78–15.26)	60.62	<.001
Tree-Positive	23 (29.5)	175 (78.1)			
Risk Score Distribution[a,b]					
0	28 (35.9)	6 (2.7)	--	--	--
1	31 (39.7)	23 (10.3)			
2	6 (7.7)	31 (13.9)			
3	8 (10.3)	63 (28.3)			
4	5 (6.4)	64 (28.7)			
5	0 (0)	36 (16.1)			
Risk Score Category 1[a,c]					
Low Risk (0–1)	59 (75.6)	29 (13.0)	20.77 (10.87–39.70)	109.59	<.001
High Risk (2–5)	19 (24.4%)	194 (87.0)			
Risk Score Category 2[a,d]					
Low Risk (0–2)	65 (83.3)	60 (26.9)	13.58(6.99–26.41)	75.78	<.001
High Risk (3–5)	13 (16.7)	163 (73.1)			
Combination of FASD-Tree Outcome and Risk Score					
FASD-Negative (0 indicators)	49 (62.8)	28 (12.6)	11.77 (6.42–21.58)	76.69	<.001
FASD-Positive (1–2 indicators)	29 (37.2)	195 (87.4)			

[a] Risk score data were missing for one participant in the alcohol-exposed group

[b] Odds Ratio not reported for risk score due to cell sizes < 5

[c] Risk Score category 1 used the ≥ 2 cut-point for determining high risk

[d] Risk Score category 2 used the ≥ 3 cut-point for determining high risk

Table 4.

Definition of diagnostic labels used to determine clinical diagnosis of FASD

Variable	Definition
Fetal Alcohol Syndrome (FAS)	Requires A and B (A) 2 or more of the following primary physical features: (1) Palpebral fissure length ≤10th percentile (2) Philtrum lipometer score 4 or 5 (3) Vermillion lipometer score 4 or 5 (B) 1 or more of the following indicators of growth deficiency or deficient brain growth (1) Microcephaly (head circumference ≤10th percentile) (2) Growth deficiency (height and/or weight ≤10th percentile)
Alcohol-Related Neurodevelopmental Disorder (ARND)	Requires history of prenatal alcohol exposure and either A or B (A) Behavioral impairment, as indicated by evidence of impairment * in at least one of the following domains: (1) Mood or behavioral regulation (2) Attention deficit (3) Impulse control (B) Cognitive impairment, as indicated by evidence of at least one of the following (1) Global impairment [IQ<78] (2) Impairment * in at least 2 neurobehavioral domains (a) Executive function (b) Learning (c) Memory (d) Visual-spatial function
Fetal Alcohol Spectrum Disorders (FASD)	Presence of FAS or ARND

* Impairment was defined as a score at least 1.5 standard deviations below population norms for all measures (i.e., standard score of <78, T-score >65, or z-score of -1.5).

Table 5.

Results for the comparison of participants with and without clinically-determined FASD

	Group		Statistic		
	Not FASD [n (%)]	**FASD [n (%)]**	**Odds Ratio (95% CI)**	**X2**	**p**
FASD-Tree Outcome					
Tree-Negative	71 (62.3)	32 (17.2)	7.95 (4.64–13.60)	63.70	<.001
Tree-Positive	43 (37.7)	154 (82.8)			
Risk Score Distribution[a,b]					
0	32 (28.3)	2 (1.1)	--	--	--
1	38 (33.6)	14 (7.5)			
2	17 (15.0)	20 (10.8)			
3	14 (12.4)	57 (30.6)			
4	12 (10.6)	57 (30.6)			
5	0 (0)	36 (19.4)			
Risk Score Category 1[a,c]					
Low Risk (0–1)	70 (61.9)	16 (8.6)	17.30 (9.14–32.73)	97.63	<.001
High Risk (2–5)	43 (38.1)	170 (91.4)			
Risk Score Category 2[a,d]					
Low Risk (0–2)	87 (77.0)	36 (19.4)	13.94 (7.89–24.64)	96.44	<.001
High Risk (3–5)	26 (23.0)	150 (80.6)			
Combination of FASD-Tree Outcome and Risk Score					
FASD-Negative (0 indicators)	60 (53.1)	16 (8.6)	12.03 (6.40–22.63)	73.41	<.001
FASD-Positive (1–2 indicators)	53 (46.9)	170 (91.4)			

[a] Risk score data were missing for one participant in the alcohol-exposed group

[b] Odds Ratio not reported for risk score due to cell sizes < 5

[c] Risk Score category 1 used the > 2 cut-point for determining high risk

[d] Risk Score category 2 used the > 3 cut-point for determining high risk

Two participants were excluded from this analyses due to missing data

Table 6.

Correlations between FASD-Tree outcomes and demographic variables

	Decision Tree		Risk Score		Decision Tree OR Risk Score[a]	
	r	**p**	**r**	**p**	**r**	**p**
Age	.100	.083	−.019	.745	−.003	.962
Sex	−.022	.701	.065	.262	.042	.465
Race	.056	.332	.070	.228	.101	.079
Ethnicity	−.010	.862	.051	.389	−.038	.520
FSIQ Score	**−.422**	**<.001**	**−.498**	**<.001**	**−.398**	**<.001**
CBCL Attention Problems T-Score	**.478**	**<.001**	**.599**	**<.001**	**.512**	**<.001**

[a]Risk Score using the > 2 cut-point for determining high risk