### Title

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### Journal

Alcoholism: Clinical and Experimental Research, 48(1)



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### Publication Date

2024

### DOI

10.1111/acer.15233

Peer reviewed

HHS Public Access

Author manuscript

*Alcohol Clin Exp Res (Hoboken)*. Author manuscript; available in PMC 2025 January 01.

Published in final edited form as:

*Alcohol Clin Exp Res (Hoboken)*. 2024 January ; 48(1): 122–131. doi:10.1111/acer.15233.

# Predicting fetal alcohol spectrum disorders in preschool-aged children from early life factors

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## Abstract

**Background:** Early life factors, including parental sociodemographic characteristics, pregnancy exposures, and physical and neurodevelopmental features measured in infancy are associated with fetal alcohol spectrum disorders (FASD). The objective of this study was to evaluate the performance of a classifier model for FASD diagnosed in preschool-aged children from pregnancy and infancy-related characteristics.

**Methods:** We analyzed a prospective pregnancy cohort in Western Ukraine enrolled between 2008 and 2014. Maternal and paternal sociodemographic factors, maternal prenatal alcohol use and smoking behaviors, reproductive characteristics, birth outcomes, infant alcohol-related dysmorphic and physical features, and infant neurodevelopmental outcomes were used to predict FASD. Data were split into separate training (80%: n=245) and test (20%: n=58; 11 FASD, 47 no FASD) datasets. Training data was balanced using data augmentation through synthetic minority oversampling technique. Four classifier models (random forest, extreme gradient boosting (XGBoost), logistic regression (full model) and backwards stepwise logistic regression) were evaluated for accuracy, sensitivity, and specificity in the hold-out sample.

**Results:** From 306 children evaluated for FASD, 61 had a diagnosis. Random forest models had the highest sensitivity (0.54), with accuracy of 0.86 (95% CI 0.74, 0.94) in hold-out data. Boosted gradient models performed similarly, however, sensitivity was less than 50%. The full logistic regression model performed poorly (sensitivity=0.18, accuracy=0.65), while stepwise logistic regression had performance similar to the boosted gradient model with lower specificity. In a

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hold-out sample, the best performing algorithm correctly classified 6 of 11 children with FASD, and 44 of 47 children without FASD.

**Conclusions:** As early identification and treatment optimizes outcomes of children with FASD, classifier models from early life characteristics show promise. Models may be improved through inclusion of physiologic markers of prenatal alcohol exposure and should be tested in different samples.

### Keywords

prenatal alcohol exposure; fetal alcohol spectrum disorders; predictive modeling

## Introduction

Fetal alcohol spectrum disorders (FASD), which are caused by prenatal alcohol exposure, affect approximately 8 of 1000 people in the general population (Lange et al., 2017). There are multiple difficulties in obtaining an accurate diagnosis of FASD, including subtlety of the physical features, lack of available data or under-reporting of prenatal alcohol exposure, and non-specific or variable expression of the alcohol-related neurobehavioral and growth abnormalities. Further, the diagnosis of children affected by prenatal alcohol exposure is a complex medical process requiring expertise in dysmorphology and neuropsychology, greatly limiting the number that can be evaluated (Popova et al., 2023). Consequently, FASD is grossly under-recognized (Chasnoff et al., 2015). Further, although fetal alcohol syndrome can be diagnosed from dysmorphic features at birth, diagnosis often occurs later. In data from electronic health record surveillance systems in 8 U.S states, the mean age of FAS diagnosis was 48 months (range 0–94 months). Other diagnoses on the spectrum require evidence of neurocognitive or neurobehavioral impairments. While severe impairments can be assessed early in life using standardized measures of infant development, less severe impairments are not able to be assessed using standard instruments until later in childhood (Gomez and Abdul-Rahman, 2021), which contributes to delayed diagnosis. Early diagnosis is associated with more positive outcomes for children with FASD, highlighting the need to support screening and evaluation efforts (Olson and Montague, 2011).

With the goal of expanding early identification and diagnosis of FASD, many researchers (Bandoli et al., 2022; Ehrig et al., 2023; Goh et al., 2016; Kalberg et al., 2019; Lussier et al., 2018; Mattson et al., 2012; Mesa et al., 2017; Suttie et al., 2017) are incorporating predictive modeling techniques into FASD research, creating statistical models that can separate subjects into two or more classes based on attributes measured in each subject. The goals of these models, typically termed classifier models, differ. Some attempt to screen school-aged children based on a limited set of features, flagging children who would benefit from formal evaluations (Ehrig et al., 2023; Goh et al., 2016; Mattson et al., 2012). Others focus on classifying children affected by prenatal alcohol exposure based on physiologic markers of exposure (Lussier et al., 2018; Mesa et al., 2017; Suttie et al., 2017). Finally, our group and others have tested whether features of pregnancy and infancy, data which are available years prior to a diagnosis, may identify children who are likely to later receive an FASD diagnosis (Bandoli et al., 2022; Kalberg et al., 2019; Oh et al., 2023). Our initial work created classifier models for neurodevelopmental delay, primarily from infant

alcohol-related dysmorphic features (Bandoli et al., 2022). Although the features had modest predictive ability, other pregnancy and infant related factors, including socioeconomic status, cigarette smoking, breastfeeding, domestic violence, have been previously associated with FASD (Bandoli et al., 2023; May et al., 2021; May and Gossage, 2011; Ward et al., 2021). Thus, the objective of this study was to expand the inputs to include a broad range of pregnancy and infancy characteristics to best predict FASD in preschool aged children.

## Materials and Methods

### Study design

Data are from a prospective cohort study of pregnant women in western Ukraine conducted as part of the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) supported by the National Institute on Alcohol Abuse and Alcoholism (www.CIFASD.org). This randomized clinical trial of micronutrient supplementation has been described elsewhere in detail (Chambers et al., 2014; Coles et al., 2015). Briefly, all pregnant women who presented to one of two centralized prenatal care facilities in western Ukraine, the Rivne Regional Medical Diagnostic Center and the Khmelnytsky Perinatal Center, between April 2008 through August 2014 were eligible for screening about their alcohol consumption around conception and the most recent month of pregnancy. Women who reported at least weekly binge episodes of 4–5 alcoholic drinks/occasion, at least 5 episodes of 3–4 drinks, or at least 10 episodes of 1–2 drinks in the month around conception and/or in the most recent month of pregnancy were recruited. Following identification of a woman meeting these criteria who consented to participate, the next women with minimal or no exposure (no more than 2 drinks per occasion and no more than 2 drinks per week in the month around conception and no alcohol in the most recent month of pregnancy) was recruited for participation. Women were interviewed about demographics, behaviors and pregnancy characteristics using standard questionnaires upon enrollment. Mothers of live born infants were invited back twice in the first year postpartum (~6 and 12 months) at which time neurodevelopmental assessments were conducted along with dysmorphology exams. Neurodevelopmental assessments were administered by one of two Ukrainian psychologists blinded to the mother's alcohol exposure group. These individuals were trained by psychologists on the study team, with periodic review of test administration and scoring carried out in person and via recordings.

Dysmorphology exams were performed by study pediatricians/geneticists at each of the study sites following specialized training and validation on recognition and measurement of all alcohol-related dysmorphic features, using a standard protocol and an examination checklist. A common set of reference standards for dysmorphic features and growth was established for the CIFASD consortium irrespective of the population in which it was applied. These standards were used to assign percentiles for growth measures and dysmorphic features and can be found at CIFASD.org. Exams were completed at a median age of 12 months (range 0–52 months, interquartile range 5 months). Some children had more than one exam performed during infancy. In those situations, we prioritized the exam selected for analysis in the following order: 1) between 9 and 13 months of age, 2) between 4 and 8 months of age, 3) between 14 and 18 months of age, 4) ages from 0–3 months or

>18 months, using the first assessment that met this prioritization. At 3.5–4.5 years of age, children returned for neurodevelopment assessments, at which time FASD evaluations were conducted.

The study was approved by the institutional review board at the University of California, San Diego and the Lviv National Medical University, Lviv, Ukraine.

## FASD evaluations

An FASD evaluation was completed for children with sufficient information, including the preschool-aged neurodevelopmental battery, using the criteria from the CoFASP study (May et al., 2018), which was based on modified Hoyme 2016 criteria (Hoyme et al., 2016). Children were evaluated for fetal alcohol syndrome (FAS), partial FAS, alcohol related neurodevelopmental disorder (ARND), or no FASD diagnosis. Prenatal alcohol exposure was determined by enrollment group; those enrolled into the prenatal alcohol exposure group were considered sufficient exposure, while those recruited as minimal to no exposure were considered not to have sufficient prenatal alcohol exposure. Dysmorphology exams at infant or toddler visits classified children as less than or equal to the $10^{th}$ centile for height, weight, and head circumference, as well as short palpebral fissures ($<10^{th}$ centile), thin vermilion border (rank 4 or 5 on lip-philtrum guide), or smooth philtrum (rank 4 or 5 on lip-philtrum guide). Neurobehavioral status was assessed with the Differential Ability Scales, $2^{nd}$ edition (DAS-II) (Elliott, 2007) and the Child Behavior Checklist (CBCL) (Achenbach and Edelbrock, 1991). Scores at or below 85 on the DAS-II were evidence of cognitive deficit, and the upper quartile of the CBCL was used as the cut-off for behavioral impairment. A full description of criteria as they relate to this cohort are detailed here (Kable et al., 2021) and reproduced in supplementary material.

## Predictors

For this analysis, potential predictors of FASD were evaluated from the prenatal and infancy periods. Predictors queried at enrollment included:

**Parental characteristics:** maternal and paternal age, maternal height (centimeters), maternal pre-pregnancy weight (kilograms), maternal and paternal education level (none, <9 years, 9 years, high school diploma, some college, college graduate), maternal and paternal unemployment, paternal alcohol use at enrollment (yes, no), paternal smoking at enrollment (yes, no), maternal marital status (married or living with partner vs. else), electricity in the house, phone in the house, toilet in the house, Hollingshead socioeconomic status (8–66, continuous) (Hollingshead, 2011), and crowding (rooms/people in house).

**Reproductive characteristics:** number of previous miscarriages, number of previous terminations, pregnancy intentions (planned, not planned for now, not planned for any time, refused), gestational week of pregnancy recognition, gestational week of first prenatal care visit, prenatal vitamin use at enrollment (multivitamin or prenatal vitamins, none), prenatal vitamin trial assignment (none, prenatal vitamin, prenatal vitamin plus choline), any medication use in pregnancy, and bleeding during pregnancy.

**Maternal substance use:** maternal (ever) marijuana use, AUDIT score (0–40) (Babor et al., 2001), absolute ounces alcohol (AAoz) per day at conception, AAoz per drinking day at conception, AAoz per day in the two weeks before enrollment, AAoz per drinking day in the two weeks before enrollment, and maternal cigarettes per day at enrollment.

### Predictors queried in the first year of life included:

**Birth outcomes:** infant left hospital with mother (yes, no), infant ever breastfed (yes, no), gestational age at delivery, birth weight (grams), birth length (centimeters), and birth head circumference (centimeters).

**Infant physical features (6–12 months):** infant height percentile, infant weight percentile, infant head circumference percentile, palpebral fissure length percentile, thin vermilion border, smooth philtrum, philtrum length percentile, inner canthal distance, midface hypoplasia, railroad track ears, strabismus, ptosis, epicanthal folds, anteverted nares, clinodactyly, camptodactyly, decreased pronation or supination of the arms, joint problems, hockey stick palmar crease, aberrant creases of the palm, heart murmur, heart defect, maxillary arc (centimeters), mandibular arc (centimeters), and a total dysmorphology score. The score is a linear combination of the dysmorphic features with assigned weights (ranging from 1–3) (Hoyme et al., 2016). From the list of features included in the 2016 May and Hoyme scoring paradigm, flat nasal bridge, hypoplastic fingernails, hypertrichosis and prognathism were not assessed in the Ukraine sample; resulting in a potential dysmorphology scoring range of 0–36.

**Infant neurodevelopmental outcomes (6–12 months):** The Bayley Scales for Infant Development (BSID), Second Edition (Bayley, 1993) Mental Development Index (MDI) and Psychomotor Development Index (PDI), both of which were standardized to a scale with a mean of 100 and a standard deviation of 15.

### Statistical analysis

The analysis aimed at developing and evaluating a prediction model that would differentiate children who would later be diagnosed with FASD from children who would not, based on parental, pregnancy and infancy exposures and characteristics. In cleaning the data, 15 subjects were identified with missing BSID scores, with even split between children with and without an FASD diagnosis (5% each). These were felt to be potentially important predictors for FASD, and thus missing responses we imputed the sample mean BSID score (MDI: 86.5, PDI: 88.0). Very few other data were missing, and thus subjects were allowed to fall out of models in rare circumstances with missing data.

Next, we split the data (n=306; 61 with FASD) into training and test datasets, retaining 80% of the sample (n=245) in the training data and 20% (n=61; 3 with missing data, resulting in 58: 11 with FASD, 47 without FASD) in test data, with an equal proportion of FASD diagnosis in each set. Training data were used to refine the algorithm, while test data (or hold-out data) were only used to evaluate the performance of the final algorithm. The data were imbalanced, with the minority class (FASD diagnosis) consisting of only 20% of the sample. This can result in poor model performance, as there are

not enough cases for the model to learn from. Oversampling techniques can be used to duplicate or create new minority cases to balance the dataset and enhance the ability for the algorithms to differentiate between the groups. To enhance the training algorithm, we performed data augmentation through synthetic minority oversampling technique (SMOTE) (*smotefamily*, R). Specifically, we employed adaptive synthetic sampling, a weighted distribution depending on each minority class according to their degree of learning difficulty. Synthetic sampling creates new cases of the minority class using a nearest neighbor approach to balance the dataset. This was employed on the training dataset only (k=5) to establish a 50:50 balance between classes, resulting in a sample of 368 individuals split evenly between diagnosis (n=184) and no diagnosis (n=184).

We employed four algorithms to the datasets: random forest, extreme gradient boosting (XGBoost), logistic regression (full model) and backwards stepwise logistic regression. We selected these algorithms because random forest and boosted gradient models (tree algorithms) work well on datasets with large numbers of features. Logistic regression (with and without feature reduction) was selected due to the efficiency in training, particularly with small datasets, and the interpretability of model coefficients. Random forest and boosted gradient models each employed 10-fold cross validation to optimize hyperparameter configuration. Model performance was based on sensitivity (of children who would later receive a diagnosis, what proportion were correctly identified) and accuracy (number of correct predictions/total number of predictions) in the hold-out (test) data. We also reported specificity (of those without an FASD diagnosis, what proportion were correctly identified). All analyses were performed in R.

## Results

Seven hundred and seventy-six women enrolled into the study at a mean gestational age of 18.2 weeks. From this cohort, 566 had infant dysmorphology and BSID testing at either 6 or 12 months of age; an additional 16 children with preschool neurodevelopmental testing did not have infant neurodevelopmental evaluations. From this subset, 306 children had a full evaluation for FASD available at the time of analysis for inclusion in the sample.

From 306 children evaluated for FASD, 61 (20%) had a diagnosis. Evaluations occurred after preschool-aged testing when children were a mean of 3.9 years (range 3.4–5.9; SD=0.3). The most common diagnosis was ARND (n=45 74%), followed by pFAS (n=10, 16%) and FAS (n=6, 10%). Parental and child characteristics of the sample, stratified by FASD diagnosis, are described in Table 1. In general, children with an FASD diagnosis were more likely to be born to parents with fewer years of education and who were unemployed and not married or cohabitating. Fathers of children with FASD were more likely to drink alcohol and smoke cigarettes at study enrollment. Children with FASD were also more likely to live in a house without a phone or indoor toilet. With respect to pregnancy and maternal characteristics, women who delivered a child later diagnosed with FASD were less likely to have planned the pregnancy, and generally became aware of the pregnancy later in gestation. They were more likely to have ever used marijuana, had higher AUDIT scores and alcohol use at conception and at enrollment, and were more likely to smoke cigarettes during pregnancy. Infants later diagnosed with FASD were slightly shorter and weighed

less at birth, and these differences became more marked in infancy. Several alcohol-related dysmorphic features were more common in children with FASD than those without, which was also observed in the higher total dysmorphology score. Finally, children who went on to receive an FASD diagnosis scored lower on both BSID indices in infancy than children who did not.

Four classifier models (random forest, extreme gradient boosting, logistic regression (full model) and backwards stepwise logistic regression) were tested, with the goals of maximizing sensitivity in test data (Table 2). Random forest models had the highest sensitivity (0.54), with accuracy of 0.86 (95% CI 0.74, 0.94). Boosted gradient models performed similarly, however, sensitivity was less than 50%. The full logistic regression model encountered convergence issues and performed poorly (sensitivity=0.18, accuracy=0.65). Stepwise logistic regression had performance similar to the boosted gradient model (sensitivity=0.46), albeit with lower specificity (0.89).

In the hold-out data (n=58, 11 cases of FASD), the random forest classifier correctly predicted 6 of 11 children with FASD, and correctly predicted 44 of 47 children without FASD (Table 3). Four of the five variables with the highest relevance in the training classifier were all alcohol-related: absolute ounces of alcohol (AAoz) per day at conception, AAoz per drinking day at conception, AAoz per day in the two weeks before enrollment, and AAoz per drinking day in the two weeks before enrollment. Infant weight, midface hypoplasia, the AUDIT score, the two BSID indices, and the week of pregnancy recognition rounded out the top 10 variables based on the contribution to the model (Figure 1). The top 10 variables in the boosted gradient model were similar to those selected from the random forest model, with variation on the order of importance (Supplemental Figure 1).

## Discussion

Leveraging data from a well-characterized birth cohort enrolled in Western Ukraine, we tested different classifier models with the goal of using pregnancy and infancy features to predict children that would later meet diagnostic criteria for FASD. Out of four algorithms tested, random forest models had the highest sensitivity (0.54) while maintaining high specificity (0.94). Features with the highest contribution included quantification of prenatal alcohol exposure around conception and mid pregnancy, as well as the two neurodevelopmental indices administered in infancy.

In our previous work from this cohort, we focused prediction efforts on alcohol-related dysmorphic features, as these features are identifiable in infancy and are known to occur more frequently in children with prenatal alcohol exposure (Bandoli et al., 2020; del Campo and Jones, 2017). Using the physical features and growth alone to predict FASD with logistic regression, area under the curve (AUC) was 0.75, but sensitivity was low (0.27). Performance improved when models were limited to children with prenatal alcohol exposure (AUC 0.77, sensitivity=0.62). The interpretability and generalizability of these previous results were limited due to not testing the algorithm performance in a hold-out sample, and not using rebalancing techniques to account for the large class imbalance.

There was strong rationale supporting the hypothesis that classifier performance could be improved with the addition of other pregnancy and infancy characteristics. Alcohol-exposure in pregnancy often does not occur in isolation, and at group levels, pregnancies exposed to high or prolonged use of alcohol tend to systematically differ from those that are not. In cohorts in South Africa, Italy and the United States, women who have a child with FASD tended to have lower education, are more likely to be unemployed, and have lower socioeconomic status than women whose children do not have FASD (May and Gossage, 2011). In a community-based sample of first-grade children from the Rocky Mountain region in the United States, mothers with a child with FASD were more likely to have ever used marijuana, were younger, and started prenatal care later in gestation (May et al., 2020). Fathers of children with FASD were also more likely to have disordered drinking, and children with FASD were less likely to live with their biologic parents (May et al., 2020). These characteristics, as well as maternal mental health disorders and other substance use disorders, were further confirmed in two systematic reviews (Esper and Furtado, 2014; Ward et al., 2021). Moreover, the imbalance of these characteristics was apparent in this sample as well. In addition to differences in prenatal alcohol exposure, children in the sample with an FASD diagnosis were more likely to be born to parents with fewer years of education, who were unemployed and not married or cohabitating, and had lower socioeconomic status. Fathers of children with FASD were more likely to drink alcohol and smoke cigarettes during at study enrollment. Women who delivered a child later diagnosed with FASD were less likely to have planned the pregnancy, and generally became aware of the pregnancy later in gestation. They were more likely to have ever used marijuana, had higher AUDIT scores and alcohol use at conception and in early pregnancy, and were more likely to smoke cigarettes during pregnancy. Finally, children who went on to receive an FASD diagnosis scored lower on both BSID indices in infancy than children who did not meet diagnostic criteria for FASD. These associations, while not necessarily causal for FASD and displayed as group-level variables, can be well-suited for individual-level predictive models (Varga et al., 2020). Indeed, while most of these features were not in the top 10 variables with respect to variable importance, which was largely comprised of prenatal alcohol exposure measures and neurodevelopmental outcomes, they were represented in the top 20 features, including week of pregnancy recognition, maternal smoking and maternal education.

A similar study to ours sought to predict FAS from maternal characteristics. The study used data from the CIFASD consortium, including some of the data from this analysis. The variables considered important in FAS prediction were drinking in all trimesters of pregnancy, race, ethnicity, maternal age, preferred alcoholic beverage, prenatal care, and pregnancy complications (Oh et al., 2023). In their study, CatBoost methods had the best performance (area under the precision recall curve=0.51). However, the study was limited by a small sample (20 cases from 595 individuals with prenatal alcohol exposure), which made metrics such as sensitivity and specificity highly variable and unreliable. Further, due to harmonization of data across multiple studies and locations, many of the granular variables available in our analysis were not uniformly captured and thus not analyzed, limiting direct comparisons between the models.

Overall, our classifier correctly classified 6 of 11 cases of FASD in test data, and correctly classified 44 of 47 children without FASD. Thus, while specificity was high (meaning we

didn't incorrectly classify children as having FASD when they did not, sensitivity was only slightly above 50%, even with a uniquely rich dataset. To further improve performance, future models could integrate physiologic markers of prenatal alcohol exposure, including infant circulating miRNA (Mahnke et al., 2021), cardiac orienting response (Mesa et al., 2017), or DNA methylation (Lussier et al., 2018), which have all shown promise in predicting FASD. However, while performance of these predictive models may be improved, datasets containing pregnancy and infant characteristics and physiologic markers are rare, and scalability of models requiring those types of data would be questionable. Thus, to best serve the widest possible audience, models with relatively few, accessible inputs should be prioritized.

While these types of models are becoming more common in FASD research, we are not yet to the point of having broad clinical utility. Even models that appear to have decent performance, such as ours and others previously discussed, tend to be created from highly selected samples, which likely limit their clinical usefulness in the general population. Further, the likelihood of having full dysmorphic exams and clinician administered neuropsychology evaluations is low, thus would not easily translate to general pediatric practices. This is exacerbated by the fact that some features captured in this model, like growth restriction, dysmorphic features, and neurodevelopmental delay, may not be evident in infancy, and conversely, some children who are growth restricted or have delayed development 'catch up'. Either situation would tax models like the ones employed here, likely reducing the accuracy of the algorithm. However, by continuing to refine models like this, we can take successful models and begin to substitute out more common data points and more 'static' features in the hopes of eventually producing scalable screening tools with clinical applicability.

Our work should be viewed considering its limitations. Due to the low prevalence of FASD, we had an imbalanced sample, which can affect model performance. We attempted to address this by using synthetic sampling in the training data, however, larger, more balanced samples would be ideal. Further, we were unable to stratify the predictions into underlying FASD diagnosis. Given that dysmorphic features and growth weigh heavily in the diagnosis for FAS and pFAS, this favors correct identification of those diagnoses. While FAS/pFAS only made up 25% of the FASD cases, future work should attempt to stratify and tailor algorithms to each diagnosis. In addition, this cohort was enrolled to study prenatal alcohol exposure. It is unclear whether our classifier models would have the same performance on other datasets, particularly in data from samples with either higher or lower prenatal alcohol use. Finally, some of the data used in models, particularly around substance use behaviors, were collected from self-report. The fear of stigma can affect the recall of these behaviors, which would add imprecision to models. Although cost-benefit analysis would be necessary, prioritizing biomarkers or data that are not vulnerable to recall bias may improve future predictive models.

In summary, pregnancy and infant-related characteristics were useful in predicting children who were later diagnosed with FASD. Future work should evaluate these same features in different samples and determine whether physiologic markers of prenatal alcohol exposure

improve model performance. Early identification and treatment for children with FASD optimizes outcomes, making predictive models from early life factors an appealing prospect.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgement

All or part of this work was done in conjunction with the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), which is funded by grants from the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Additional information about CIFASD can be found at http://cifasd.org/. Research described in this manuscript was supported by Grant #U01AA014835 to Christina Chambers funded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the NIH Office of Dietary Supplements (ODS). Gretchen Bandoli is funded by the National Institutes on Alcohol Abuse and Alcoholism (1 K01 AA027811-01). We wish to acknowledge the contribution of: OMNI-Net, Ukraine, and participating families and staff in Rivne and Khmelnytsky, Ukraine.

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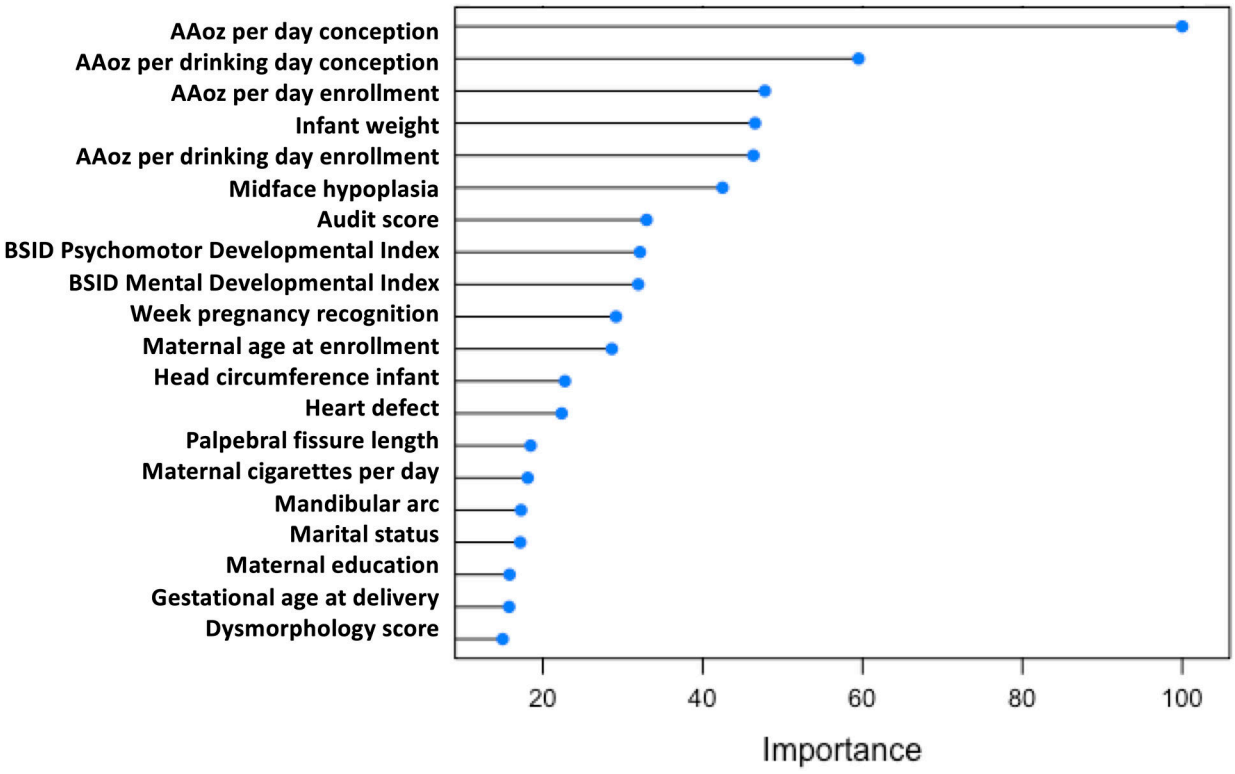


**Figure 1.**
Variable importance plot (top 20 variables, scaled to range of 0–100) from random forest model.

**Table 1.**

Description of sample from two prenatal clinics in Western Ukraine (N=306)

| | Children without an FASD diagnosis | | Children with an FASD diagnosis | |
|---|---|---|---|---|
| | n=245 | % | n=61 | % |
| *Parental characteristics and SES* | | | | |
| Maternal age (mean, SD) | 26.7 | 4.7 | 26.6 | 6.4 |
| Maternal height (cm) (mean, SD) | 165.3 | 5.6 | 166.1 | 6.7 |
| Maternal pre-pregnancy weight (kg) (mean, SD) | 60.1 | 11.1 | 64.2 | 14.5 |
| Maternal education level | | | | |
| No formal schooling | 0 | 0.0 | 0 | 0.0 |
| <9 years | 0 | 0.0 | 1 | 1.6 |
| 9 years | 4 | 1.6 | 7 | 11.5 |
| Highschool diploma | 98 | 40.0 | 37 | 60.7 |
| Some college | 20 | 8.2 | 5 | 8.2 |
| College graduate | 123 | 50.2 | 11 | 18.0 |
| Maternal unemployment | 88 | 35.9 | 30 | 49.2 |
| Paternal age (mean, SD) | 29.3 | 5.5 | 31.1 | 7.9 |
| Paternal education level | | | | |
| No formal schooling | 8 | 3.3 | 13 | 21.3 |
| <9 years | 3 | 1.2 | 4 | 6.6 |
| 9 years | 0 | 0.0 | 0 | 0.0 |
| Highschool diploma | 129 | 52.7 | 30 | 49.2 |
| Some college | 13 | 5.3 | 2 | 3.3 |
| College graduate | 92 | 37.6 | 12 | 19.7 |
| Paternal unemployment | 20 | 8.2 | 6 | 9.8 |
| Paternal alcohol use at enrollment | | | | |
| Yes | 200 | 81.6 | 57 | 93.4 |
| No | 43 | 17.6 | 2 | 3.3 |
| Refused | 2 | 0.8 | 2 | 3.3 |
| Paternal smoking at enrollment | | | | |
| Yes | 120 | 49.0 | 45 | 73.8 |
| No | 124 | 50.6 | 15 | 24.6 |
| Refused | 1 | 0.4 | 1 | 1.6 |
| Mother married or living with partner | 237 | 96.7 | 47 | 77.0 |
| Electricity in house | 242 | 98.8 | 60 | 98.4 |
| Phone in house | 194 | 79.2 | 42 | 68.9 |
| Toilet inside house | 215 | 87.8 | 37 | 60.7 |
| Socioeconomic status (mean, SD) | 40 | 11.3 | 32.7 | 7.9 |
| Crowding (mean, SD) | 0.8 | 0.4 | 0.9 | 0.4 |
| *Reproductive characteristics* | | | | |
| Mother on birth control to prevent current pregnancy | 18 | 7.3 | 11 | 18.0 |
| Number of previous miscarriages | | | | |

| | | | | |
|---|---|---|---|---|
| 0 | 208 | 84.9 | 48 | 78.7 |
| 1 | 30 | 12.2 | 12 | 19.7 |
| 2 | 7 | 2.9 | 1 | 1.6 |
| Number of previous terminations | | | | |
| 0 | 208 | 84.9 | 42 | 68.9 |
| 1 | 24 | 9.8 | 13 | 21.3 |
| 2 or more | 13 | 5.3 | 6 | 9.8 |
| Was the current pregnancy planned | | | | |
| Yes | 160 | 65.3 | 18 | 29.5 |
| Not now | 64 | 26.1 | 25 | 41.0 |
| Not at any time | 20 | 8.2 | 18 | 29.5 |
| Refused | 1 | 0.4 | 0 | 0.0 |
| Gestational week pregnancy recognition (mean, SD) | 5.0 | 2.6 | 6.4 | 3.8 |
| Gestational week first prenatal care (mean, SD) | 9.5 | 3.7 | 11.6 | 4.7 |
| Prenatal vitamin at enrollment | | | | |
| Multivitamins or prenatal vitamins | 169 | 69.0 | 37 | 60.7 |
| None | 76 | 31.0 | 24 | 39.3 |
| Prenatal vitamin assignment | | | | |
| No prenatal vitamin | 121 | 49.4 | 24 | 39.3 |
| Prenatal vitamin | 60 | 24.5 | 15 | 24.6 |
| Prenatal vitamin plus choline | 64 | 26.1 | 22 | 36.1 |
| Any medication use during pregnancy | 57 | 23.3 | 17 | 27.9 |
| Bleeding during pregnancy | 8 | 3.3 | 1 | 1.6 |
| *Maternal substance use* | | | | |
| Maternal (ever) marijuana use | 8 | 3.3 | 3 | 4.9 |
| Audit score (mean, SD) | 2.8 | 3.3 | 7 | 5.2 |
| Absolute ounces alcohol per day conception (mean, SD) | 0.2 | 0.5 | 0.7 | 0.8 |
| Absolute ounces alcohol per drinking day conception (mean, SD) | 0.5 | 1.1 | 2.1 | 3.1 |
| Absolute ounces alcohol per day in the two weeks before enrollment (mean, SD) | 0 | 0.2 | 0.1 | 0.3 |
| Absolute ounces alcohol per drinking day in the two weeks before enrollment (mean, SD) | 0.2 | 0.6 | 0.7 | 1 |
| Maternal cigarettes per day enrollment (mean, SD) | 0.4 | 1.9 | 2.9 | 6.3 |
| *Birth outcomes* | | | | |
| Infant left hospital with mother | 231 | 94.3 | 56 | 91.8 |
| Infant ever breastfed | | | | |
| Yes | 214 | 87.3 | 54 | 88.5 |
| No | 21 | 8.6 | 7 | 11.5 |
| Refused | 10 | 4.1 | 0 | 0.0 |
| Gestational age at delivery (mean, SD) | 39.5 | 1.4 | 38.9 | 2.1 |
| Birth weight (mean, SD) | 3379.1 | 462.5 | 3123.1 | 570.6 |
| Birth length (mean, SD) | 52.0 | 2.2 | 50.8 | 3.2 |
| Birth head circumference (mean, SD) | 34.6 | 1.5 | 34.2 | 1.9 |

| | | | | |
|---|---|---|---|---|
| *Infant physical outcomes (6–12 months)* | | | | |
| Infant height (percentile) (mean, SD) | 59.9 | 27.4 | 50.6 | 3.2 |
| Infant weight (percentile) (mean, SD) | 55.3 | 27.2 | 48.0 | 29 |
| Infant head circumference (percentile) (mean, SD) | 56.3 | 25.7 | 34.2 | 1.9 |
| Thin vermillion border | 31 | 12.7 | 13 | 21.3 |
| Palpebral fissure percentile (mean, SD) | 39.1 | 19.4 | 28.8 | 21.7 |
| Smooth Philtrum | 17 | 6.9 | 10 | 16.4 |
| Philtrum length percentile (mean, SD) | 60 | 18.7 | 59.3 | 21.9 |
| Inner canthal distance percentile (mean, SD) | 58.2 | 20.2 | 55.2 | 23.8 |
| Midface hypoplasia | 2 | 0.8 | 2 | 3.3 |
| Railroad ears | 13 | 5.3 | 5 | 8.2 |
| Strabismus | 8 | 3.3 | 3 | 4.9 |
| Ptosis | 1 | 0.4 | 3 | 4.9 |
| Epicanthal folds | 139 | 56.7 | 41 | 67.2 |
| Anteverted Nares | 44 | 18.0 | 9 | 14.8 |
| Fifth finger clinodactyly | 35 | 14.3 | 7 | 11.5 |
| Camptodactyly | 4 | 1.6 | 1 | 1.6 |
| Decreased pronation/supination of arms | 1 | 0.4 | 1 | 1.6 |
| Other joint problems | 0 | 0.0 | 1 | 1.6 |
| Hockey stick crease | 16 | 6.5 | 7 | 11.5 |
| Other altered palmar creases | 10 | 4.1 | 6 | 9.8 |
| Heart murmur | 19 | 7.8 | 12 | 19.7 |
| Heart defect | 9 | 3.7 | 6 | 9.8 |
| Maxillary arc (mean, SD) | 20.4 | 1.2 | 20.3 | 1.1 |
| Mandibular arc (mean, SD) | 20.5 | 1.3 | 20.3 | 1.4 |
| Dysmorphology score (mean, SD) | 3.6 | 3.1 | 6.4 | 5.3 |
| *Infant neurodevelopment outcomes* | | | | |
| Bayley Scales Infant Development: Mental Developmental Index (mean, SD) | 87.5 | 7.6 | 82.6 | 9.1 |
| Bayley Scales Infant Development: Psychomotor Developmental Index (mean, SD) | 89.0 | 9.7 | 84.9 | 11.9 |

**Table 2.**

Evaluation results from four tested classifier models

| Algorithm | Sensitivity | Specificity | Accuracy (95% CI) |
|---|---|---|---|
| Random forest | 0.54 | 0.94 | 0.86 (0.74, 0.94) |
| Boosted gradient | 0.45 | 0.96 | 0.86 (0.75, 0.94) |
| Logistic regression | 0.18 | 0.77 | 0.65 (0.52, 0.77) |
| Logistic regression (stepwise variable selection) | 0.46 | 0.89 | 0.81 (0.68, 0.90) |

**Table 3.**

Confusion matrix for random forest model on test data (N=58)

| **Prediction/Truth** | **Truth: Diagnosis (n=11)** | **Truth: No Diagnosis (n=47)** |
|---|---|---|
| Pred: Diagnosis | 6 | 3 |
| Pred: No Diagnosis | 5 | 44 |
| Sensitivity/specificity | 54.5% | 93.6% |
| Accuracy (95% CI) | 0.86 | 0.74, 0.94 |