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# **Identifying Fetal Alcohol Spectrum Disorder Among South African Children at Aged 1 and 5 years**

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## **ABSTRACT**

Background. Fetal Alcohol Spectrum Disorders (FASD) are a global health concern. Early intervention mitigates deficits, yet early diagnosis remains challenging. We examine whether children can be screened and meet diagnoses for FASD at 1.5 years compared to 5 years post-birth.

Methods. A population cohort of pregnant women in 24 neighborhoods (N=1258) was recruited and 84.5%-96% were reassessed at two weeks post-birth, 0.5 years, 1.5 years, 3 years, and 5 years later. A two-step process was followed to diagnose FASD; first, a paraprofessional screened the children and then a physician evaluated the child. Logistic regression models examined differences in children receiving a positive FASD screening (n=160) at 1.5 years vs. 5 years and maternal predictors of the FASD positive screening and diagnosis.

Results. Screening positive for FASD more than doubled from 1.5 years to 5 years (from 6.8% to 14.8%). About one quarter of children who screened positive and were evaluated by a physician, were diagnosed as having a FASD. However, half did not complete second stage screening. Mothers without Stage 2 screening were more likely to live in informal housing than those who did (81.3% vs. 62.5%,  $p=0.014$ ).

Conclusions. We found that children can be screened and diagnosed for FASD at 1.5 and 5 years. As FASD characteristics develop over time, repeated screenings are necessary to identify all affected children and launch preventive interventions. Referrals for children to see a physician to confirm diagnosis and link children to care

remains a challenge. Integration with the primary healthcare system might mitigate some of those difficulties.

Key Words. Fetal Alcohol Spectrum Disorders, Alcohol Misuse, Community Health Workers, Prenatal Alcohol Exposure, Child Development

## **INTRODUCTION**

Alcohol use during pregnancy and fetal alcohol spectrum disorders (FASD) are global health concerns (Popova, Lange, Probst, Gmel, & Rehm, 2017) and a recent meta-analysis found the global prevalence of FASD among children and youth to be 7.7 per 1000 population (95% CI, 4.9-11.7) (Lange, Probst, et al., 2017). FASD causes deficits in height and weight, immune system development, executive functioning, problem solving ability, short- and long-term memory, communication skills, and attention (Brown et al., 2018; Gauthier, 2015; Lange, Rovet, Rehm, & Popova, 2017). FASD can result in reduced quality of life and significant economic impacts by reducing productivity due to morbidity and mortality and by increasing burdens on the health care, special education, residential care, and criminal justice systems (Greenmyer, Klug, Kambeitz, Popova, & Burd, 2018).

There is substantial and unequivocal evidence that prenatal alcohol exposure is associated with the serious and long term effects of FASD (Lange, Rovet, et al., 2017; Philip A May et al., 2016). The quantity, frequency, and timing of maternal drinking determines the manifestation of FASD symptoms, with mothers who drink more, more often, and earlier during pregnancy giving birth to children with the most severe outcomes (Philip A May et al., 2013; Rehm et al., 2017). However, even light to moderate levels of alcohol exposure in utero can result in increased risks, including diminished cognitive capacity in children (Willford, Leech, & Day, 2006).

The highest rates of prenatal alcohol use and FASDs globally have been documented in South Africa. South Africa has one of the highest rates of alcohol consumption in the world, and alcohol consumption per capita has increased in the last decade (World Health Organization, 2014). Although about 40% of the population

does not drink alcohol, national surveys show that those who drink are likely to binge drink (Peltzer, Davids, & Njuho, 2011; Ramsoomar & Morojele, 2012; . World Health Organization, 2016). When reporting anonymously, about 25% of mothers report alcohol consumption while pregnant (Davis, Rotheram-Borus, Weichle, Rezai, & Tomlinson, 2017; O'Connor et al., 2011). In selected peri-urban communities in South Africa, about 11% of children entering first grade have been diagnosed with FAS (Roozen et al., 2016).

Fortunately, early interventions that address cognitive functioning in children with FASD have been successful in reducing developmental deficits (Matzopoulos, Truen, Bowman, & Corrigall, 2014; Parry, Rehm, Poznyak, & Room, 2009; Reid et al., 2015). However, it can be difficult to diagnose FASD early and to link children to the care and the early intervention they need (Burd, Cotsonas-Hassler, Martsolf, & Kerbeshian, 2003). Only a small portion of children with a FASD are receiving appropriate early diagnosis (Chamberlain, Reid, Warner, Shelton, & Dawe, 2017). Because early intervention is so important for children with FASD, we evaluated FASD symptoms at 1.5 and 5 years to examine the earliest age in this sample at which a reliable diagnosis of FASD could be made. We also examined the characteristics of mothers who followed-up to complete a second diagnostic interview and assessment, which required visiting a physician.

## **METHODS**

The study was approved by the Institutional Review Boards of the University of California, Los Angeles, and Stellenbosch University (IRB#10-000386). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the

1964 Helsinki declaration and its later amendments or comparable ethical standards. This study is registered with ClinicalTrials.gov (NCT00996528).

## **Participants**

Cape Town has a network of townships with both formal homes and informal shacks. Most families (70%) earn 0-800 ZAR per month (about 60 USD). We identified 24 neighborhoods of similar size (450-600 households) that were within five kilometers of health clinics, were non-contiguous and/or separated by natural barriers (e.g., a highway), with similar patterns of migration among residents, and had five to seven alcohol bars (shebeens). Shebeens are informal public drinking venues typically that serve both home brew, beer, and wine and whiskey, and are important community-based gathering places in South Africa.

Recruiters (local women from nearby neighborhoods) were trained to conduct house-to-house visits from May 2009 to September 2010 to invite all pregnant women ages 18 years or older to participate in the study (Rotheram-Borus et al., 2011). Pregnant women were recruited at an average 26 weeks of pregnancy (range, 3-40 weeks); only 2% of women (n=25/1283) refused participation. Recruiters identified pregnant women, obtained consent to contact, and referred to the assessment team. A driver took potential participants to a centralized assessment center located at the intersection of three townships. Among all participants, 91.9% were reassessed at two weeks post-birth, 85.6% at six months, 91.7% at 1.5 years, 84.7% at 3 years and 84.5% at 5 years post-birth. During the study period, a total of 105 children died, 7 of which were screened for FASD at either time point. Children with FASD were no more likely to die compared to those without FASD. Multiple births were removed (n=13), reducing the total sample (n=1225). With the remaining

singleton children, 977 children (79.8%); (n=809) were screened for FASD at 1.5 years and/or 5 years (n=858).

## **Measures**

Mothers. All women in the sample were of Black African (e.g. Xhosa) ethnicity. Mothers reported their age, education, income, and housing characteristics. Food insecurity was measured with the US Household Food Security Survey Module (Carlson, Andrews, & Bickel, 1999): an 8-item food insecurity scale, which measured the frequency of running out of food, being unable to afford balanced meals, and skipping meals because of lack of food over six months (Carlson et al., 1999; Tsai, Hung, & Weiser, 2012; Tsai, Tomlinson, Comulada, & Rotheram-Borus, 2016). This module has been used in a variety of populations and countries, including in South Africa (Abrahams, Lund, Field, & Honikman, 2018; Tsai et al., 2012; Ukegbu, Nwofia, Ndudiri, Uwakwe, & Uwaegbute, 2019). To screen for depression, we administered the Edinburgh Postnatal Depression Scale (EPDS) with a cut-off of  $\geq 13$  to indicate depressed mood (Lawrie, Hofmeyr, de Jager, & Berk, 1998). Interpersonal partner violence was captured by asking whether the woman had been slapped, pushed or shoved, and/or threatened with a weapon by a current partner in the past 12 months (Straus, 1979).

Maternal alcohol consumption was self-reported at all assessments using the 3-item AUDIT-C, which ranges from 0 points (non-drinking) to 12 (very high-risk drinking). The three questions on the screen include: 1) days of any alcohol use; 2) usual number of drinks per day; and 3) binge episodes of five or more drinks in a single day. Previous research has found high concurrence between AUDIT-C ( $\geq 3/4$ ) and the full AUDIT. Previous research has found high concurrence between the



AUDIT-C ( $\geq 3/4$ ) and the full AUDIT (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993) cut-off score of  $\geq 7/8$  (Morojele et al., 2017). For this study, question 3 was modified to define a binge episode as heavy episodic drinking of four or more drinks in a single day to conform to the National Institute on Alcohol Abuse and Alcoholism definition of hazardous drinking in women (NIAAA, 2005). Five additional questions were from the TWEAK, a measure recommended to assess alcohol misuse in pregnant women (CDC, 2009). An AUDIT-C score of four or more drinks in a single day at least once a month and at least one positive symptom from the TWEAK (e.g., needing alcohol to get up each morning) was used to indicate high risk drinking (Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998). This study focused on maternal alcohol use and binge drinking at two time points during pregnancy; drinking prior to the mother recognizing that she was pregnant and following pregnancy recognition.

Mother's HIV status was obtained by self-reports and examination of their children's health record summarized on the Road-to-Health Card. At an 8-year follow-up assessment, rapid HIV tests were administered to mothers. Comparing maternal self-reports of HIV status, there were 40 potential discrepancies, including both false positives and false negatives, among 1041 mothers (a 3.8% discrepancy rate).

Children. The primary outcome for this paper was whether a child of a participant received a positive FASD screening and diagnosis at 1.5 years and/or 5 years. At the time of this study, FASD diagnostic criteria required that mothers acknowledged drinking alcohol during pregnancy and that a physician assessed and validated the child's status.

A senior U.S.-based senior alcohol researcher personally trained paraprofessional screeners to identify select FASD characteristics based on the U.S.

Institute of Medicine (IOM) criteria (Hoyme et al., 2005; P. A. May et al., 2009). Training methods have been previously described (O'Connor et al., 2014). In brief, screening components consisted of 1) evidence of growth retardation (height or weight  $\leq 10^{\text{th}}$  percentile); 2) evidence of deficient brain growth (occipital frontal circumference (OFC)  $\leq 10^{\text{th}}$  percentile); and 3) evidence of a pattern of facial anomalies characteristic of FAS (flat upper vermillion border (lip) or flat philtrum). The lip and philtrum were assessed using the Lip-Philtrum Guide (Astley, 2004), which is used to objectively measure philtrum smoothness and the flatness of the upper vermillion border of the lip (O'Connor et al., 2014). A child with a rank of 1 has a well-formed upper lip or deeply grooved philtrum, and a rank of 5 reflects an upper lip or philtrum that is smooth (O'Connor et al., 2014). Scores of 4 or greater indicate a positive facial feature. The formal training period included the use of realistic dolls that served as models of black infants with features consistent with FASD. Reliability was assessed between the screeners and a trained clinical psychologist with expertise in FASD, which resulted in 95% agreement on lip and 100% agreement on philtrum. Continued supervision and reliability of screening outcome was overseen by an on-sight alcohol researcher on a weekly basis. Any child meeting criteria of height, weight, or OFC  $\leq 10^{\text{th}}$  percentile; or receiving a philtrum or lip score  $\geq 4$  received a positive FASD screening and referral for further evaluation.

Stage 2, clinical FASD evaluations were performed by a pediatrician employed by the study who was trained to reliability to assess FASD by the senior alcohol researcher. All children were photographed and photos were evaluated by the senior alcohol researcher who was blind to physician diagnoses. FASD diagnoses were based on the IOM criteria (which included growth retardation, facial features of flat

philtrum, flat upper lip, and short palpebral fissures) and included classifications of FAS, partial FAS (pFAS), or alcohol related neurodevelopment disorder (ARND) (Hoyme et al., 2005; O'Connor et al., 2014). For the purpose of this study, we grouped the FASD diagnoses into a dichotomous variable measuring any FASD diagnosis versus none.

All mothers were contacted repeatedly and offered transportation and a 20 ZAR (about 8 USD at the time) incentive to complete each evaluation. We were not able to conduct the second stage screening to the 24% of children who had relocated to the Eastern Cape. The Eastern Cape is a deeply rural area with significant distances between households and clinic sites. While mothers and children in the Eastern Cape were reassessed by interviewer teams, there were no physicians available to assess children referred for FASD.

## **Data Analysis**

We estimated the prevalence of positive FASD screening and FASD diagnosis at 1.5 years, 5 years, and the consistency between the two assessments. We compared the characteristics of mothers of children who screened positive with mothers whose children screened negative using t-tests for continuous variables and chi-square tests for discrete variables.

We compared mothers of children with a positive FASD screening who were referred and followed up by visiting the study physician to mothers who did not follow-up with the referral to the physician using t-tests for continuous variables and chi-square tests for discrete variables. We used SAS 9.4 and Stata® SE software version 14.2.

## **RESULTS**

Table 1 summarizes the maternal characteristics of the mothers based on children's FASD diagnostic status: screening negative, screening positive, and diagnosed with a FASD. Overall, the mean age of mothers in our sample was  $26.5 \pm 5.6$  years, a quarter had less than a high school level of education, just over half had a monthly household income  $<R\ 2,001$  (about \$150 USD in 2010), and all were black. Most were informally housed (68.1%), and almost half did not have water and/or a flush toilet on their premises. However, most had electricity. Half of the mothers reported being hungry in the last week. The HIV prevalence in our sample was high at 28.3% in pregnancy. About a third of mothers experienced depressive symptoms (35.3%) or interpersonal partner violence (36.3%) in the last year.

In the bivariate comparisons, mothers of children who received a positive FASD screening were less likely to have a high school education (31.9% vs. 24.2%,  $p=0.043$ ); more likely to have a monthly income  $<R2,000$  (63.9% vs. 50.6%,  $p=0.002$ ), a depressed mood (46.3% vs. 33.2%,  $p=0.002$ ); and to have experienced interpersonal partner violence (45.3% vs. 34.5%,  $p=0.010$ ) compared to mothers whose children were not referred. As would be expected, mothers whose children screened FASD positive were significantly more likely to use alcohol and binge drink during pregnancy compared to mothers whose children screened negative. These general trends held for mothers of children that received an FASD diagnosis at either time point.

Figure 1 shows the diagnostic status of children over time for FASD, including the prevalence of positive FASD screenings and the prevalence of positive FASD diagnoses at both 1.5 years and 5 years of age. Among our sample of 977 children, there were 160 (16.4%) who screened positive for a FASD at the 1.5 year and/or 5

year assessments. Among those who screened positive, 55% (88/160) followed up with the physician, and 25% (22/88) received a FASD diagnosis. Looking across the assessment time points, at 1.5 years, 55 (6.8%) children screened positive, and at 5 years, 127 (14.8%) children screened positive. Among the 45 children referred at 1.5 years and not missing at 5 years, 22 (48.9%) were referred again at 5 years. Furthermore, among the five children diagnosed with a FASD at 1.5 years and not missing at 5 years, four were again diagnosed with a FASD at 5 years. One child, who screened positive, but did not follow up with the physician at 1.5 years, was re-screened and diagnosed with a FASD at 5 years.

In our follow-up comparison of the mothers with children who screened positive for a FASD (80 children who followed up with the study physician and 80 children who did not), we found that mothers who did not see the physician were significantly more likely to live in informal housing (81.3% vs. 62.5%,  $p=0.014$ ). No other covariates were significant.

## **DISCUSSION**

This study conducted FASD paraprofessional screenings and physician diagnoses among children at 1.5 and 5-years post-birth in Cape Town, South Africa. Screenings at 5 years identified more than twice as many children as those at 1.5 years. About one quarter of children who screened positive and were evaluated by a physician, were diagnosed with a FASD. However, half were not evaluated by a physician. Mothers of children who received a positive FASD screening had lower levels of education and income and were more likely to experience the syndemics of interpersonal partner violence and binge drinking during pregnancy compared to

mothers whose children screened negative. Children with positive FASD screenings were shorter and weighed less than those who screened negative.

Early identification and intervention for children with a FASD can minimize associated negative outcomes (Reid et al., 2015). The paraprofessional screeners in this study were able to identify children at-risk children for an FASD diagnosis at both 1.5 years and 5 years after birth. Further, among children who screened positive for FASD characteristics and went on to see a physician for diagnosis, 25% were found to have a FASD at both time points. This number is likely a low estimate for the positive predictive value of their screening, as about half of children screened positive at each assessment did not follow-up with a physician for diagnosis.

Referral to a physician was a major barrier in the diagnosis of FASD. Only half of mothers followed up the referral with a specialist physician, even when transportation was provided. Parental follow-up may be even more difficult outside the context of a research study (O'Connor et al., 2014). Mothers face multiple challenges, potentially feeling guilty for drinking alcohol during pregnancy or fear of FASD diagnosis (O'Connor et al., 2014; Olson, Jirikowic, Kartin, & Astley, 2007). A major issue was family migration to the Eastern Cape of South Africa. We were not able to transport children in rural South Africa to a physician and 25% of households had migrated by the time their children were 5 years of age. In our sample, we looked for differences between the 80 mothers who followed up with the physician and the 80 mothers who did not. We found living in informal housing was significantly associated with failure to follow-up the positive FASD screening; however, other factors (such as low income or education, depression, IPV, or HIV) were not statistically associated with follow-up screening.

Screenings at 5 years identified more than twice as many children with characteristics of a FASD than screenings at 1.5 years. This intuitively makes sense. As children age, facial characteristics – including the philtrum and vermillion border of the lips – become more defined. As they grow, deficits in height, weight, or head circumference become more pronounced. The rate for identifying FASD was low for both paraprofessionals and physicians at 1.5 years; however, the consistent positive predictive value of their screenings over time indicates it is more likely that some children with mild characteristics of a FASD cannot be identified early in childhood. As a result, identification of every child with a FASD may require repeated screenings over time. Yet, waiting for children to enter school before screening for a FASD may miss the opportunity to intervene early in a child’s life.

Ultimately, only about 2% of children in this study were diagnosed with a FASD. This is much lower than previous studies in areas with high levels of alcohol consumption. However, if we take into consideration the 80 children that screened positive for FASD characteristics, but did not follow-up with a physician for diagnosis, and assume that about a quarter of those children also would be diagnosed, the rate is closer to 4% of the child populations -a number is on the low end of the 2-11% reported in other South African studies (P. A. May et al., 2009; Roozen et al., 2016; Urban et al., 2008).

### **Limitations**

At both the 1.5 and 5-year time points we were not able to link all children who screened positive for a FASD to a physician for diagnosis. Those missed physician evaluations decreased the effectiveness of screening, reduced our ability to assess the accuracy of the screen, and restricted the sample size, thus, limiting avenues for

analysis and the generalizability of results related to the FASD diagnoses. In addition, although our screeners were trained to be non-stigmatizing, it is likely that mothers under-reported their alcohol use. At the time of this study, diagnosis required maternal report or documentation of alcohol use; however, this is no longer the case. This change in criteria, is useful since screenings that rely on maternal reports of alcohol use alone may miss 10-20% of children with a FASD. Further, we used two dichotomous variables for alcohol use and were not able to determine associations between more nuanced levels of alcohol use and FASD positive screenings.

### **Next Steps**

Our study identified several challenges in early diagnosis and intervention for children with a FASD. First, self-reported alcohol use during pregnancy may underestimate true behaviors. There is currently no gold standard for an alcohol biomarker (Asiimwe et al., 2015), but a combination of self-report and biomarkers, such as the PEth test (Helander, Péter, & Zheng, 2012; Hoyme et al., 2005), could provide a valuable additional tool for assessing children's risk of a FASD. While the PEth test is relatively simple, the current cost of more than \$100 may not be feasible for use broadly in a low- and middle-income country. Second, as we lack widely accepted standardized criteria for diagnosing FASD, more research is needed to identify valid and reliable biomarkers for detecting fetal effects from different levels of alcohol use during pregnancy. Thus, more research is needed to investigate the pathways and neurochemistry involved in FASD development, which can inform both diagnostic methods and potential treatments (Ehrhart et al., 2019). Finally, despite free transportation and incentives, it was difficult to ensure follow-up of physician referrals over time. For paraprofessional screenings to ensure children receive early



diagnosis and linkage to beneficial interventions, better integration with the healthcare system is required. However, South Africa lacks national surveillance, specialist diagnostic and support services, and training on FASD for health professionals. Therefore, we suggest a coordinated and comprehensive plan for this public health problem (Adebiyi, Mukumbang, & Beytell, 2019). Paraprofessionals can offer repeated referrals, information, and support to mothers, but this is not enough, without a healthcare system that is prepared to diagnose and intervene in the lives of children with FASD.

## **Conclusion**

We conducted FASD paraprofessional screenings and physician diagnoses among children at 1.5 and 5 years in South Africa. Screenings at 5 years identified more than twice as many children than those at 1.5 years. One quarter of children who screened positive and were evaluated by a physician, were diagnosed with a FASD. However, referrals for children to see a physician to confirm diagnosis remains a challenge. Integration with the primary healthcare system might mitigate some of those difficulties. As FASD characteristics develop over time, repeated screenings are necessary to identify all affected children and launch preventive interventions.

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**Table 1. Maternal characteristics organized on the basis of the results of Children’s fetal alcohol spectrum disorder (FASD) screening for at 1.5 years and/or 5 years**

Characteristics	Total (N=977)		Negative FASD Screen (N=817)		Positive FASD Screen (N=160)		FASD Diagnosis† (N=18)		P-value
	N	%	N	%	N	%	N	%	
Age, mean (SD)	26.5	(5.6)	26.4	(5.58)	27.1	(5.86)	29.7	(6.97)	0.190
>35 years	74	7.6	58	7.1	16	10.0	6	33.3	0.205
Education level < high school	249	25.5	198	24.2	51	31.9	7	38.9	0.043*
Monthly household income ≤ R2,000	499	52.8	400	50.6	99	63.9	13	72.2	0.002**
Housing									
Informal housing	665	68.1	550	67.3	115	71.9	11	61.1	0.258
No water on site	460	47.1	380	46.5	80	50.0	8	44.4	0.419
No flush toilet	445	45.6	361	44.2	84	52.5	8	44.4	0.053
No electricity	105	10.8	82	10.0	23	14.4	1	5.6	0.105
Food Insecurity	486	49.7	401	49.1	85	53.1	12	66.7	0.350
EPDS score, mean (SD)	10.8	(7.0)	10.5	(6.90)	12.6	(7.00)	14.2	(7.10)	<0.001**
EPDS score ≥ 13	345	35.3	271	33.2	74	46.3	10	55.6	0.002**
Any intimate partner violence	354	36.3	282	34.5	72	45.3	12	66.7	0.010**
Mother living with HIV	276	28.3	227	29.6	49	32.7	9	50.0	0.048*
Alcohol Use									
Drank alcohol during pregnancy (baseline)	258	26.4	205	25.1	53	33.1	16	88.9	0.035*
Binge ≥ once per month during pregnancy (baseline)	131	14.7	100	13.5	31	20.5	12	75.0	0.025*
Drank alcohol during pregnancy (60 month recall)	185	20.7	142	19.1	43	28.5	15	83.3	0.010**
Binge ≥ once per month	152	17.0	120	16.2	32	21.2	12	66.7	0.133

during pregnancy (60 month recall)				
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\* **p<0.05**, \*\* **p<0.01**, \*\*\* **p<0.001** p-values are from chi-squared, Fisher's exact, and t-tests comparing positive and negative FASD screening outcomes. SD: standard deviation; EPDS: Edinburgh Postnatal Depression Scale; HIV: human immunodeficiency virus.

† FASD diagnosis is a subsample of children who received positive FASD screening.

**Figure 1:** Flow of study children from FASD assessment to referral and diagnosis.

