Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

Drug Alcohol Depend. 2016 November 1; 168: 274–286. doi:10.1016/j.drugalcdep.2016.09.025.

THE CONTINUUM OF FETAL ALCOHOL SPECTRUM DISORDERS IN A COMMUNITY IN SOUTH AFRICA: PREVALENCE AND CHARACTERISTICS IN A FIFTH SAMPLE

Philip A. May[1,2], **Anna-Susan Marais**[2], **Marlene M. de Vries**[2], **Wendy O. Kalberg**[3], **David Buckley**[3], **Julie M. Hasken**[1], **Colleen M. Adnams**[4], **Ronel Barnard**[2], **Belinda Joubert**[2], **Marise Cloete**[2], **Barbara Tabachnick**[5], **Luther K. Robinson**[6], **Melanie A. Manning**[7], **Kenneth Lyons Jones**[8], **Heidre Bezuidenhout**[2], **Soraya Seedat**[2], **Charles D.H. Parry**[2,9], and **H. Eugene Hoyme**[10,11]

[1]The University of North Carolina at Chapel Hill, Nutrition Research Institute

[2]Stellenbosch University, Faculty of Medicine and Health Sciences

[3]The University of New Mexico, Center on Alcoholism, Substance Abuse and Addictions

[4]University of Cape Town, Department of Psychiatry and Mental Health

[5]California State University, Northridge

[6]State University of New York, Buffalo, Department of Pediatrics

[7]Stanford University School of Medicine, Departments of Pathology and Pediatrics

[8]University of California San Diego School of Medicine, Department of Pediatrics

[9]South African Medical Research Council

Corresponding Author: Philip A. May, Nutrition Research Institute, Department of Nutrition, Gillings School of Global Public Health, University of North Carolina – Chapel Hill, 500 Laureate Way, Kannapolis, NC, 28081. philip_may@unc.edu Phone: (704) 250-5002.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of interests

None of the authors have any conflicts of interest to declare.

Contributors

Philip May was the principal investigator of the NIH-funded FASD epidemiology studies in South Africa over the past two decades and the grant that funded this research. He, with assistance from Julie Hasken and Barbara Tabachnick on final data analysis and table and figure preparation, was the major writer and final editor of all drafts. Anna-Susan Marais served as program manager and supervised all data collection and protocols in the main office at the Faculty of Medicine and Health Sciences of Stellenbosch University. Ronel Barnard was the program officer in the field office of the study community; she, along with Marlene de Vries, oversaw all final data compilation in the field program office, including data quality. Belinda Joubert and Marise Cloete were the lead maternal interviewers. Wendy Kalberg and David Buckley supervised data entry, files, and data sets in the United States. Colleen Adnams and Wendy Kalberg designed and oversaw the cognitive testing and behavioral checklist component and interpreted the analysis of neurobehavioral results for diagnosis and manuscript preparation. Eugene Hoyme, Luther Robinson, Melanie Manning, Heidre Bezuidenhout, and Kenneth Jones generated all dysmorphology data for the team in the field and made the final diagnoses of the children in multidisciplinary case conferences. Soraya Seedat and Charles Parry are the South African co-investigators who participated in the study design, oversaw and facilitated all study activities in South Africa both in the field and at Stellenbosch University, Faculty of Medicine and Health Sciences. Each author contributed to, read, edited, and approved various drafts of the manuscript.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

[10]Sanford Research, University of South Dakota Sanford School of Medicine, Department of Pediatrics

[11]The University of Arizona College of Medicine, Department of Pediatrics and the Center for Applied Genetics and Genomic Medicine

Abstract

Background—The prevalence and characteristics of the continuum of diagnoses within fetal alcohol spectrum disorders (FASD) were researched in a fifth sample in a South African community.

Methods—An active case ascertainment approach was employed among all first grade learners in this community (n=862). Following individual examination by clinical geneticists/ dysmorphologists, cognitive/behavioral testing, and maternal interviews, final diagnoses were made in multidisciplinary case conferences.

Results—Physical measurements, cardinal facial features of FAS, and total dysmorphology scores clearly differentiated diagnostic categories in a consistent, linear fashion, from severe to mild. Neurodevelopmental delays and behavioral problems were significantly worse for each of the FASD diagnostic categories, although not as consistently linear across diagnostic groups. Alcohol use was documented by direct report from the mother in 71% to 100% of cases in specific diagnostic groups. Significant distal maternal risk factors in this population are: advanced maternal age at pregnancy; low height, weight, and body mass index (BMI); small head circumference; low education; low income; and rural residence. Even when controlling for socioeconomic status, prenatal drinking correlates significantly with total dysmorphology score, head circumference, and five cognitive and behavioral measures. In this community, FAS occurs in 59 – 79 per 1,000 children, and total FASD in 170 – 233 per 1,000 children, or 17% to 23%.

Conclusions—Very high rates of FASD continue in this community where entrenched practices of regular binge drinking co-exist with challenging conditions for childbearing and child development in a significant portion of the population.

Keywords

fetal alcohol spectrum disorders (FASD); prenatal alcohol use; microcephaly; alcohol abuse; binge drinking; maternal risk for FASD; prevalence; children with FASD; South Africa

1. INTRODUCTION

1.1 Diagnosing a continuum

The diagnosis of a continuum of disabilities associated with prenatal alcohol exposure has evolved since fetal alcohol syndrome (FAS) was first defined by Jones and Smith (1973). Children with significant dysmorphia and cognitive/behavioral impairments were identified as FAS. Soon thereafter, less consistent, less severe patterns of dysmorphia and neurobehavioral impairment were recognized in animal and human studies and referred to as fetal alcohol effects (Aase, 1994; Aase et al., 1995; Clarren et al., 1978). Four specific diagnostic categories were later created by a committee of the Institute of Medicine (IOM):

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

FAS, partial FAS (PFAS), alcohol-related birth defects (ARBD), and alcohol-related neurodevelopmental disorder (ARND; Stratton et al., 1996). These four diagnoses form a continuum from the most dysmorphic to least dysmorphic and were later referred to as fetal alcohol spectrum disorders (FASD; Streissguth and O'Malley, 2000; Warren et al., 2004). FASD are rarely diagnosed or diagnosed properly even within advanced health care institutions which colors the understanding of the full continuum of FASD. For example, in one study in the United States (USA) 80% of children with FASD had not been diagnosed at all, and 7% were misdiagnosed (Chasnoff et al., 2015). Because of this, FASD epidemiology information gathered through registries or summarized from clinic data of diagnosed cases are inaccurate for understanding prevalence and characteristics of FASD in general populations (Fox et al., 2015). Epidemiologic studies of FASD are difficult to pursue and expensive (Stratton et al., 1996). Few studies have documented the prevalence and characteristics of the continuum of FASD in general populations, especially in the USA and Europe (May and Gossage, 2001; Sampson et al., 1997). But recent studies indicate that FASD prevalence is approximately 2 to 5% in general populations of the USA, Italy, Poland, and Croatia (May et al., 2009, 2011a, 2014a, 2015; Okulicz-Kozaryn, Borkowska, Brzozka, 2015; Petković and Barišić, 2010, 2013).

1.2 FASD epidemiology studies in South Africa

Some communities in South Africa (ZA) have a higher prevalence of FASD than any other general populations studied to date. From an epidemiologic perspective, ZA has proven an excellent venue for implementing active case ascertainment methods for understanding general population patterns and the diagnosis, prevalence, characteristics, and etiology of FASD. Many characteristics of FASD have been described in four previous studies of the single municipality and surrounding rural areas in the Western Cape Province (WCP) studied here (May et al., 2000, 2007, 2013a; Viljoen et al., 2005). Other researchers have independently completed FASD studies in other ZA communities with similar patterns and rates (Olivier et al., 2013; Urban et al., 2008, 2015; Viljoen et al., 2003). From previous studies in ZA communities, research evolved from an exclusive focus on FAS to delineating and understanding all diagnoses of FASD. In recent publications from this community, FAS affected 59 – 91 per 1,000 children, and total FASD rates were 135 – 208 per 1,000 (13.5 to 20.8%; May et al., 2013a). Norms and practices of regular, consistent, weekend binge drinking, low socioeconomic status (SES), insufficient nutrition, high fertility, and challenging conditions for prenatal and postnatal development combine to elevate prevalence and severity of FASD (May et al., 2005, 2008, 2013b, 2014b, 2016a; Viljoen et al., 2002).

1.3 The current study

As before, active case ascertainment methodology was employed by a multidisciplinary field research team with offices in the community and dysmorphologists from the USA. The approach and methods of general population research on FASD have been pioneered and fully developed in this locale (population = 50,000) characterized by small industries and multiple farms producing vegetables, poultry, grapes and other fruits, and wine.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

2. METHODS

2.1 Sampling and recruitment

Active, written consent for children to participate in the study was obtained from parents/guardians of 862 (73.5%) first grade pupils enrolled in all 13 primary schools of the community; and assent forms were obtained from children seven years and older. As in Figure 1, a three-tier process of screening, data collection, and diagnosis was instituted. In Tier I all consented children were measured for height, weight, and head circumference. If a child was ≤ 25th centile on height, weight, and/or occipitofrontal (head) circumference (OFC), he/she was advanced to Tier II. In addition, 450 child enrollment numbers were picked randomly as potential controls (typically developing/not FASD comparison children) from all children on the school roles, and 353 had consent to participate. Each qualifying child (small and/or randomly-selected) was advanced to Tier II where he/she received a standardized, blinded physical examination by a dysmorphologist. Of those advanced to Tier III, the racial composition mirrored the community: 83% Coloured (mixed race), 11% Black, and 6% White.

2.2 IOM diagnostic categories

The IOM criteria for the specific diagnoses in the FASD continuum are presented in Figure 2 and described in more detail elsewhere (Hoyme et al., 2005, 2015). Significant growth restriction and marked dysmorphia are present in children with FAS, and less growth restriction and dysmorphia in children with PFAS; however, at least two of three cardinal facial features and a constellation of other minor anomalies are present with both FAS and PFAS. The clinical traits of FAS and PFAS have been clearly linked with prenatal alcohol exposure in thousands of cases and multiple correlation studies (May et al., 2011b, 2013b, 2016b); and these two diagnoses can be made by experienced physicians without direct documentation of alcohol exposure, after ruling out other malformation syndromes with similar phenotypes. In previous studies in WCP communities, it has rarely been necessary to diagnose a child with FAS or PFAS without strong evidence of prenatal alcohol use (May et al., 2008, 2013b). Women in this population are candid, the interviewing format and contexts are effective, and our staff interviewers are experienced and long-term residents of the region. Children with ARND do not have a characteristic pattern of facial characteristics; therefore, direct evidence of prenatal alcohol exposure and significant cognitive impairment are required.

2.3 Assessment of cognitive and behavioral traits

In Tier III, all randomly-selected control candidates and all children with features of a diagnosis within FASD were advanced to cognitive testing and teachers completed Achenbach Teacher Report Forms (TRF; Achenbach and Rescorla, 2001) to evaluate inattention and behavioral issues. Tests administered to all children in Tier III were: Test of Reception of Grammar (TROG; Bishop, 1989) for verbal abilities; Raven Coloured Progressive Matrices (Raven, 1981) for nonverbal, fluid intelligence; and the Digit Span subtest of the Wechsler Intelligence Scales for Children, Third Edition (WISC-III; Wechsler, 1997) for working memory. Tests were administered by blinded psychometrists, mostly in Afrikaans, although 5% were in English, and 5% were in Xhosa for the Black African

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

children. Although centile scores were referenced from the standard charts of the Raven and the TROG, in addition, a normal curve was calculated for the cohort prior to the final case conference, so that the team had a true sense of the cohort's abilities compared to the norms for each instrument used. This was undertaken for two reasons: 1) this population is significantly disadvantaged and 2) this population was not included in normative samples for any of the tests used. Any scores falling at the 7th percentile or below were 1.5 standard deviations below the mean and were considered impaired. The score reported for the Digit Span is scaled with a mean of 10 and standard deviation of +3. The two scores of the Achenbach (total problems and inattention) were scored as follows: total problem T score ≥ 64 and an inattention T score of ≥ 22 were in the clinical range.

2.4 Maternal risk factor assessment: proximal and distal variables

Also, every Tier III child's mother that consented (n=491; 87.5%) was interviewed in person (96% in Afrikaans) regarding maternal risk for FASD in the index pregnancy. The interviews used time-line follow back methods (Sobel et al., 1988, 2001) adapted to a specific medical history format. Similar questions have been used effectively and successfully in other ZA studies by our team and other experienced researchers (Jacobson et al., 2008; Viljoen et al., 2002). Proximal variables assessed included alcohol use by quantity, frequency, and timing during pregnancy and when breastfeeding (May et al., 2016c). Distal variables of maternal risk were addressed, including: maternal height, weight, and OFC; childbearing history; and demographic variables. All questions were contextual to medical history and dietary intake (King, 1994). In previous ZA community studies, direct, substantially accurate maternal reports of prenatal alcohol use were obtained from most mothers, and in this sample consultation with knowledgeable collateral informants about the index pregnancy was necessary in only a few instances. Overall, 89.7%, 70.6%, 100%, and 41% of the mothers of FAS, PFAS, ARND, and controls, respectively, reported drinking alcohol during the index pregnancy. Death, moving from the study area, multiple missed appointments, and a few outright refusals accounted for no interviews with 70 mothers (12.5%).

2.5 Case conference for final diagnosis

Final diagnoses were made for each child in a multidisciplinary case conference where data and findings from each domain (growth, dysmorphology, cognitive/behavioral performance, and maternal risk) were reviewed and assessed by research team members who had performed the exams, testing, and maternal interviews. After review and discussion for each child, final diagnoses were made by the dysmorphologists.

2.6 Statistical analysis

Data were processed with Excel (Microsoft, 2010) and analyzed with SPSS 23 (IBM, 2014). Case control analysis compares results across FASD diagnostic groups and controls. Statistical significance was determined using chi-square and one-way analysis of variance (ANOVA) using Bonferroni-adjusted values for interpretation as indicated on each table (Tabachnick and Fidel, 2013). With statistically significant ANOVAs, post-hoc analyses were performed using Dunnett's pairwise comparisons ($\alpha = .05$). Table 5 employs partial correlation analysis of associations between prenatal drinking and select child outcomes, after adjusting for two SES measures. Even though optimizing SES conditions has not been

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

found to significantly affect functioning and development in many severely-affected children with FAS in adoption studies (Landgren et al., 2010), SES has been demonstrated to have a significant independent effect on physical growth and neurodevelopment in community studies in ZA (May et al., 2011, 2013c).

3. RESULTS

3.1 Child physical growth and physical development and dysmorphology

In Table 1, mean values are presented for demographic, growth, and the three cardinal facial variables for the FASD diagnostic continuum and controls. Children with FASD were properly classified by the revised IOM criteria and therefore were significantly different from controls on height, weight, BMI, OFC, and cardinal facial features of FAS (palpebral fissure length (PFL), smooth philtrum, and narrow vermilion). Age differed among groups in the sample; FASD children were slightly older because poor performance kept some from advancing to 2nd grade. Only the proportion of male and female subjects was similar across groups. Pairwise differences for weight, BMI, and OFC were significantly different for the majority of comparisons among groups. Most importantly, head circumference was the single trait that most distinguished each group from one another in Dunnett comparisons: 76.8% of the children with FAS had a head circumference < 3rd centile (< 2 standard deviations below the mean), while 8.8% of those with PFAS, and 43.6% with ARND were < 3rd centile. These head circumference data are best explained by the diagnostic criteria employed which require a small OFC for the assignment of a diagnosis of FAS, as opposed to its being optional in PFAS. In addition, in the current study any child with an OFC < 10th centile who lacked the requisite facial dysmorphology was deferred to rule out ARND.

Also in Table 1, total dysmorphology score means summarize the total of all FASD-relevant minor anomalies found in children of each group (see Hoyme et al., 2005). Scores were significantly different across groups: the FAS group was the highest (18.3), then PFAS (13.2), ARND (11.1), and controls (6.7). Variance within each group was relatively equal (SD=3.2–3.8). Mean dysmorphology scores form a linear continuum across FASD groups and controls (Figure 3). Head circumference is not as linear due to a small OFC being optional in PFAS. In the post-hoc analyses, each diagnostic group was significantly differentiated from the other by total dysmorphology.

3.2 Other minor anomalies

Table 2 details other minor anomalies by diagnostic group. Maxillary and mandibular arcs, inner canthal distance, and inter-pupillary distance, hypoplastic midface, epicanthal folds, ptosis, camptodactyly, flat nasal bridge, altered palmar creases, and prognathism are significantly different across groups. The PFAS group is sometimes an exception, indicating greater variability in this group.

3.3 Cognitive and behavioral traits

Cognitive testing and behavior checklist results (Table 3) indicate low average achievement levels for all community children and significant statistical differences between diagnostic groups with Bonferroni-adjusted values. Controls performed best on each measure. FASD

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

groups performed significantly worse on each cognitive measure: verbal and non-verbal ability and working memory. Children with FAS performed most poorly on cognitive measures, followed by those with ARND and then PFAS. Those with ARND had the most behavior problems, followed by PFAS and FAS and inattention was also worst for children with ARND, followed by FAS and PFAS. Post-hoc analysis indicated that all tests/checklists distinguished each FASD diagnostic groups from controls. Notably, PFAS and ARND groups were significantly different from one another on verbal IQ and the Digit Span, with PFAS performing better than ARND. Working memory (Digit Span) was the only measure where each group was significantly different from one another (Figure 4).

3.4 Proximal maternal risk– alcohol use in the index pregnancy

Among mothers of normal controls, 59% abstained and 41% drank during the index pregnancy. The children of the latter mothers were neither significantly dysmorphic nor neurobehaviorally impaired enough to qualify for a FASD diagnosis. Drinking levels of mothers of controls who drank were lower than mothers of children with ARND and substantially lower than mothers of children with FAS or PFAS, especially during trimesters 2 and 3. Mothers of children with FAS drank the most: 90% reported drinking an average of 16.5 drinks per week during the index pregnancy mostly on Fridays and Saturdays, 7.5 drinks per drinking day, and bingeing three or more drinks per occasion (74%) or five or more drinks per occasion (66%). Drinking frequency and quantities were less than FAS levels among mothers of children with PFAS, ARND, and controls; however, mothers of children with ARND drank twice as frequently during pregnancy than did mothers of children with PFAS (0.8 vs 1.6 days per week).

3.5 Correlating alcohol use with outcomes

Partial correlation analysis measured associations between maternal drinking and seven child outcomes after adjusting for a confounder, SES (household income and mother's education). Transformations were undertaken for most measures due to positive skewness. Logarithmic transformations were applied to number of drinks per drinking day, average number of drinks per week, verbal and non-verbal IQ, and digit span performance. Square root transformations were applied to behavior and inattention problems, income, and education. Although highly unbalanced, transformations could not be applied to "yes/no" items: reported drinking and the two measures of binge drinking. A criterion of $p < .012$ was set to control for Type I familywise error rate.

Drank during pregnancy, drinks per drinking day, and drinks per week correlated significantly with virtually all cognitive scores using Bonferroni-adjusted values. Verbal and nonverbal IQ and Digit Span performance were also significantly lower with drinking during pregnancy. Several relationships between drinking during pregnancy and behavior problems were positive and statistically significant, including behavior problems and inattention. Drinking during pregnancy and inattention correlated with the number of drinks per drinking day, drinks per week, and binges of 5 or more drinks. However, none of the above partial correlations were particularly strong once adjusted for SES measures, with r ranging from −.143 to −.250. Thus, each of the latter drinking variables accounts for only about 3% of the

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

variance in the child's cognitive or behavioral scores. The remaining behavioral measures also indicate positive relationships but fail to meet strict statistical criterion.

The binge drinking measure of 3+ drinks per occasion correlated significantly with two of the cognitive and behavioral measures in the expected direction. Five or more drinks per occasion was significantly related to all cognitive/behavioral measures; all were in the expected direction, but were not particularly strong.

Maternal drinking measures correlated most highly with total dysmorphology score after adjusting for SES, with drinks per drinking day (r =.302) and drinks per week (r =.313) having the highest coefficients. Child's head circumference was also significantly correlated with every drinking measure (r = −.216 to −.306, p<.001).

3.6 Tobacco and other drug use

A significantly higher percentage of FASD mothers reported smoking during the index pregnancy (Table 4). A high percentage of women smoked, but average quantity was relatively low, 20 to 29 cigarettes per week, and did not differ across groups. Use of other drugs was very low and not significantly different among groups in lifetime or pregnancy (0.0 to .05% in the FASD groups, and 1.3% for control groups).

3.7 Distal maternal risk– physical, childbearing, and demographic

Mothers of children with FASD were significantly older at the birth of index child, shorter, lower in weight, and had lower BMI, smaller OFC, higher parity, and lower educational achievement and income. Ninety-four percent (94%) of the mothers of FAS children breastfed for a duration of 26.4 months. More children with FASD underwent gestation in rural areas.

3.8 Prevalence estimates by three methods and final estimates

Final diagnoses of the children with FASD in the consented sample are presented in Table 6, section 1. No cases of ARBD were found. Sixty-nine children were diagnosed with FAS, 91 with PFAS, and 39 with ARND.

The first estimation technique using two different denominators is summarized in the left section of Table 6: number of children enrolled in 1st grade (n=1,172) and total number of consented study participants (n=862). The assumption is that oversampling small children provides the greatest inclusion of children with FAS or PFAS. The rate of FAS with this technique is 58.9 – 79.4 per 1,000, and total FASD is 169.8 – 230.9 per 1,000.

A second rate was calculated from the 83 cases of FASD found within the 347 fully examined and tested randomly-selected children (middle section). From this technique the rates are: 77.8 FAS cases per 1,000 (95% CI = 49.6 to 105.9) and total FASD of 239.2 per 1,000 (95% CI = 194.3 to 284.1).

The third rate (Table 6, right section) estimates the total number of cases likely to be found in the unconsented children ("b") and adds these cases to those diagnosed among consented children ("a"). The proportions of FASD diagnoses in the random sample (middle section,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

column 2) were used to estimate the number of cases among unconsented children (column 3, “b”) which were then added to cases diagnosed in the consented children (a+b =273). The rate of FAS is therefore estimated as 79.4 per 1,000 and total FASD as 232.9 per 1,000 or 23%.

Convergence is substantial among the rates from the three techniques (Figure 5). The final range of rates that most accurately characterizes FASD prevalence in this sample is 170 per 1,000 (total cases diagnosed among examined children over the total school enrollment-technique 1) and the high estimate of 233 of all enrolled students from technique 3.

4. DISCUSSION

4.1 Summary findings for the community

The physical, cognitive, and behavioral traits of the children with FASD and the controls in this general population sample are very similar to those found previously over a 15-year period and especially in sample 4 (May et al., 2013a). Child physical growth and development and many minor anomalies in this sample most often followed a linear fashion by the diagnostic categories of the revised IOM criteria. No cases of isolated ARBD were found, which has been a common experience with population-based and clinical studies. Major structural anomalies associated with heavy prenatal alcohol exposure are rarely found in isolation from cognitive and behavioral problems in most populations; when prenatal alcohol use is sufficient to cause major malformations, alcohol exposure has been sufficient to also cause other physical anomalies and cognitive/behavioral problems that qualify for another FASD diagnosis. This research has again linked specific child traits, especially dysmorphology, to detailed maternal reports of prenatal alcohol use. Such links to specific quantity, frequency, and gestational timing are rare in other studies due to inaccurate reporting of alcohol use. An exception is that prospective longitudinal studies have effectively documented the dose-dependent effects of alcohol on development (Alvik et al., 2013; Burden et al., 2005; Day et al., 2013; Jacobson and Jacobson, 2002; Jacobson et al., 2013; Streissguth et al., 1994).

Additionally, many distal variables of maternal risk were similar in this study to previous studies in the WCP. Less than optimal maternal health (e.g., low BMI from inadequate nutrition), SES, and other challenges for child growth and development were associated with a higher prevalence of the more severe forms of FASD. In similar studies in the USA, we have found more cases of ARND per number of children with FAS and PFAS, most likely due to less prevalent and more sporadic binge drinking coupled with more favorable health, nutrition, and SES conditions (May et al., 2014b, 2016a).

4.2 Prevalence estimates

The prevalence estimates from the three techniques are convergent. The highest prevalence rate that we report corrected for estimated cases in the non-consented children (technique 2). The final range of total FASD reported is 170 to 233 per 1,000 or 17 – 23%.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

4.3 Linking findings to prenatal alcohol use

Since all parts of the study were performed blinded by professionals from several disciplines, linking of the different domains for final diagnosis is important. Furthermore, the traits and diagnoses of the children are linked to reports of maternal prenatal use of alcohol in over 87% of the FASD cases, and remaining cases were frequently linked by collateral reports from relatives, neighbors, and other propinqutous and knowledgeable individuals. Correlation analysis further associates drinking to child traits. More drinking during pregnancy, especially binge drinking, yields more minor anomalies and poorer performance on cognitive/behavioral measures. The association of drinking and neurobehavioral performance, however, was not as strong as correlations with dysmorphology. As demonstrated elsewhere (May et al., 2011b, 2013c), dysmorphology correlates most highly with drinking even after controlling for multiple confounders. Distal maternal risk variables differ across the maternal groups and are associated with additional individual variation in child outcomes over and above that caused by differing alcohol use patterns alone. Mothers who exhibit more distal risk factors often bear children with poorer outcomes and abilities.

4.4 FASD as a cause of microcephaly and public health implications

This sample again indicates that prenatal exposure to alcohol is a major cause of deficient brain growth measured by OFC. Furthermore, microcephaly is an important indicator of risk for cognitive and behavioral problems as illustrated by the high prevalence of microcephaly in the poorly performing children with FAS and ARND. Alcohol as a cause of microcephaly has existed in the shadow of other teratogens like mercury, rubella, thalidomide, and now zika virus. The prevalence of microcephaly in children with FASD can and should be compared with microcephaly rates caused by other teratogens. Alcohol is left out from discussions of microcephaly, and more attention is needed to the fact that prolonged and heavy prenatal exposure to alcohol is a major cause of poor brain and cerebral development which is significantly associated with poor cognitive/behavioral performance.

4.5 Why are more children diagnosed with FAS and PFAS than ARND?

In this sample, there were far more children diagnosed with FAS and PFAS than with ARND. This raises some questions regarding how to interpret the lower prevalence of ARND in this sample and other studies in ZA communities. There are four major influences on the number of PFAS and ARND children diagnosed. First, our methods lead with preliminary assessment of poor growth and dysmorphology making it likely that we will identify most every child with FAS and PFAS in the population, but less likely that we will capture most children with ARND. Second, except for a few children with ARND picked up from those who were randomly-selected, the vast majority were diagnosed because our clinical team deferred every child with an OFC $<10^{th}$ centile for testing and their mothers for a maternal interview. Third, in this predominantly low SES population with undernutrition for most vital nutrients (May et al., 2014b, 2016a) and much drinking in the first two trimesters (May et al., 2013b), physical traits (dysmorphology) are obviously and most severely affected (May et al., 2011, 2013c). Fourth, the cognitive tests and behavioral checklists used in ZA epidemiology studies are, by necessity, not extensive or sophisticated

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

enough to detect a broad range of specific and particular deficits (e.g., multiple executive functioning traits) that might qualify more children for ARND.

4.6 Why did children with ARND perform worse on neurobehavioral measures than children with PFAS?

Mothers of children with PFAS and those with ARND differ in drinking pattern in ways that may produce more dysmorphia in children with PFAS; yet these drinking patterns may provide a relative advantage for children with PFAS in cognitive and behavioral performance. First, while mothers of children with PFAS report more drinks per prenatal drinking day overall than those of children with ARND, they report a significantly lower average number of drinking days per week during pregnancy overall (0.8 vs. 1.6 days) and in 1st (2.0 vs. 2.2 days) and 2nd (2.0 vs. 2.3 days) trimesters than mothers of ARND children. Second, mothers of children with PFAS are more likely to abstain in the third trimester (77% vs 59%) than mothers of children with ARND. Therefore, children with ARND have been exposed to prenatal alcohol more frequently than those with PFAS. Third, children with PFAS also have significantly shorter PFL than children with ARND, an indicator of compromised brain development in the 1st trimester. Fourth, average head circumference of PFAS children is significantly larger than children with ARND (50.8 cm vs. 49.5 cm), likely due to fewer drinking days and less drinking in the 3rd trimester by the mothers of children with PFAS. This is further explained by the procedures in our study; the great majority of children with ARND were ascertained because of a referral to testing because of small OFC: 87.2% of ARND cases had OFC < 10th centile. For children with PFAS, in which a small OFC is optional, only 25.3% had OFC < 10th. Fifth, mothers of children with PFAS reported more protective distal factors for neurodevelopment (May et al., 2008, 2013) than mothers of children with ARND. They have significantly higher income and higher educational achievement and are taller, heavier, and lower parity. Therefore, children with PFAS may be performing better on the cognitive/behavioral measures as a relative benefit from: lower frequency of prenatal exposure, lack of 3rd trimester exposure, a larger head size, and distal maternal protective factors. While children with PFAS are more dysmorphic, possibly due to more binge-induced alcohol exposure in the first trimester, they performed better than children with ARND who were alcohol-exposed more frequently throughout pregnancy.

4.7 Strengths and limitations

The strengths of this study are substantial. 1) It benefited from a high participation rate among children (73.5%) and their mothers (over 87.5%), and few cases lost to incomplete follow-up. 2) The study utilized a randomly-selected, fully screened, normal comparison/control group from the same community ensuring relevant and accurate comparisons of child groups who were all living in similar community conditions. 3) Complete dysmorphology exams were coupled with cognitive/behavioral assessments for all children in the final sample. 4) Detailed, direct reports of prenatal alcohol use by quantity, frequency, and gestational timing of consumption were linked to child outcomes. 5) Distal maternal risk factors were determined from direct, in-person interviews and linked to specific child outcomes. 6) Three standard demographic/epidemiologic techniques were used to estimate prevalence, and convergence of estimated rates provides substantial support for the final estimates.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Limitations of this study are as follows. 1) Since this community is rather unique in the world in racial, ethnic, and cultural traits, extrapolating the exact values and findings directly to non-ZA populations might be difficult and perilous for some variables (e.g., precise amounts of alcohol that pose risk in another population). But general relationships and patterns established are robust and may be identifiable in most populations. 2) Maternal interviews were administered 7 years post-partum, and poor recall may have negatively affected some maternal risk measures. 3) Without accurate alcohol biomarker samples administered to the interviewed mothers, it is impossible to know exactly how precise and accurate reporting was. 4) Basing much of the initial study sample on child growth and dysmorphology, prevalence of ARND is likely under-estimated. However, an exception to a low ARND rate may be found in the isolated random-selection rates (technique #2 in Table 6) where the rate of ARND is indeed higher than that in other rate estimation techniques. 5) Finally, administering a more extensive battery of cognitive/behavioral instruments is desirable, but time and monetary resources made this impossible. The battery used was somewhat comprehensive and yet economical as is required in a large epidemiologic study.

4.8. Conclusions

FASD prevalence has remained high in this community. A historically-common pattern of recreational drinking on weekends, coupled with poverty conditions, combine for high prevalence of FASD. The traits of children with FAS, PFAS, and ARND in this population are clearly different from one another and from normal controls on multiple child traits and multiple risk variables for their mothers. The rate of FAS of 59 to 79 per 1,000 is extremely high, as are rates of PFAS and ARND. Total FASD of 17 to 23% is much higher than any of the research team initially thought likely in a general population when work commenced in this community in 1997. High prevalence again raises the need for prevention and intervention.

Acknowledgments

The authors thank the South African, Western Cape Province, Department of Education administrators and teachers who approved and facilitated the study, the parents who consented for their children to participate in the study, all children who participated in the study at each of the schools, and each of the mothers who provided information for the maternal risk portion this study. We are especially indebted to the fantastic field work staff for this study: Teresa Alexander, Romena Ferreira, and others whose skill in locating, transporting, and accommodating subjects was invaluable. Joanna Janse van Rensburg, Hildegard Daniels, and Teboho Linda completed the psychological testing under a contract to the University of Cape Town.

Protocols and consent forms used were approved by the University of New Mexico (Medical School HRRC 96–209 and 00–422, and Main Campus IRB 9625), the Ethics Committee of Stellenbosch University, Faculty of Health Sciences, and the University of Cape Town.

Role of the funding source

Funding was provided by the National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism (NIAAA) (UO1 AA15134).

REFERENCES

Aase JM. Clinical recognition of FAS: difficulties of detection and diagnosis. Alcohol Health Res. 1994; 18:5–9.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Aase JM, Jones KL, Clarren SK. Do we need the term “FAE”? Pediatrics. 1995; 95:428–430. [PubMed: 7862486]

Achenbach, TM.; Rescorla, LA. Manual For The ASEBA School-Age Forms And Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth and Families; 2001.

Alvik A, Aalen OO, Lindermann R. Early fetal binge alcohol exposure predicts high behavioral symptom scores in 5.5 year-old children. Alcohol. Clin. Exp. Res. 2013; 37:1954–1962. [PubMed: 23888929]

Bishop, DVM. Test of Reception of Grammar (TROG). 2nd. Manchester: University of Manchester; 1989.

Burden MJ, Jacobson SW, Sokol RJ, Jacobson JL. Effects of prenatal alcohol exposure on attention and working memory at 7.5 years of age. Alcohol. Clin. Exp. Res. 2005; 29:443–452. [PubMed: 15770121]

Chasnoff IJ, Wells AM, King L. Misdiagnosis and missed diagnoses in foster and adopted children with prenatal alcohol exposure. Pediatrics. 2015; 135:264–270. [PubMed: 25583914]

Clarren SK, Smith DW. The fetal alcohol syndrome. N. Engl. J. Med. 1978; 11:1063–1067.

Day N, Helsel A, Sonon K, Goldschmidt L. The association between prenatal alcohol exposure and behavior at 22 years of age. Alcohol. Clin Exp Res. 2013; 37:1171–1178. [PubMed: 23442183]

Fox DJ, Pettygrove S, Cunniff C, O’Leary LA, Gilboa SM, Bertrand J, Druschel CM, Breen A, Robinson L, Ortiz L, Frias JL, Ruttenber M, Klumb D, Meaney J. Fetal alcohol syndrome among children aged 7–9 years – Arizona, Colorado, and New York, 2010. MMWR. 2015; 64:54–57. [PubMed: 25632951]

Hoyme HE, Hoyme DB, Elliott AJ, Blankenship J, Kalberg WO, Buckley D, Abdul-Rahman O, Adam MP, Robinson LK, Manning MA, Bezuidenhout H, Jones KL, May PA. A South African mixed race lip/philtrum guide for diagnosis of fetal alcohol spectrum disorders. Am. J. Med. Genet. A. 2015; 167A:752–755. [PubMed: 25711340]

Hoyme HE, May PA, Kalberg WO, Kodituwakku P, Gossage JP, Trujillo PM, Buckley DG, Miller J, Khaole N, Viljoen DL, Jones KL, Robinson LK. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 Institute of Medicine criteria. Pediatrics. 2005; 115:39–47. [PubMed: 15629980]

IBM SPSS Statistics for Windows. Version 23.0. IBM Corp. Armonk, NY: 2014.

Jacobson JL, Jacobson SW. Effects of prenatal alcohol exposure on child development. Alcohol. Res Health. 2002; 26:282–286. [PubMed: 12875038]

Jacobson SW, Carter RC, Jacobson JL. Commentary on Day and colleagues: the association between prenatal alcohol exposure and behavior at 22 years of age—adverse effects of risky patterns of drinking among low to moderate alcohol-using pregnant women. Alcohol. Clin. Exp. Res. 2013; 37:1069–1073. [PubMed: 23822873]

Jacobson SW, Stanton ME, Molteno CD, Burden MJ, Fuller DS, Hoyme HE, Robinson LK, Khaole N, Jacobson JL. Impaired eyeblink conditioning in children with fetal alcohol syndrome. Alcohol. Clin. Exp. Res. 2008; 32:365–372. [PubMed: 18162064]

Jones KJ, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. Lancet. 1973; 302:999–1001. [PubMed: 4127281]

King AC. Enhancing the self-report of alcohol consumption in the community: two questionnaire formats. Am. J. Public Health. 1994; 84:294–296. [PubMed: 8296958]

Landgren M, Svensson L, Stromland K, Andersson Gronlund M. Prenatal alcohol exposure and neurodevelopmental disorder in children adopted from Eastern Europe. Pediatrics. 2010; 125:e1178–e1185. [PubMed: 20385628]

May PA, Hamrick KJ, Corbin KD, Hasken JM, Marais AS, Blankenship J, Hoyme HE, Gossage JP. Maternal nutritional status as a contributing factor for the risk of fetal alcohol spectrum disorders. Reprod. Toxicol. 2016a; 59:101–108. [PubMed: 26656914]

May PA, de Vries MM, Marais AS, Kalberg WO, Adnams CM, Hasken JM, Tabachnick BG, Robinson LK, Manning MA, Jones KL, Hoyme D, Seedat S, Parry CDH, Hoyme HE. The continuum of fetal alcohol spectrum disorders in four rural communities in South Africa: prevalence and characteristic. Drug Alcohol Depend. 2016b; 159:207–218. [PubMed: 26774945]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

May PA, Hasken JM, Blankenship J, Marais A-S, Jourbert B, Cloete M, de Vries MM, Barnard R, Botha I, Roux S, Dom C, Gossage JP, Kalberg WO, Buckley D, Robinson LK, Adnams CM, Manning MA, Parry CHD, Hoyme HE, Tabachnick BG, Seedat S. Breastfeeding and maternal alcohol use: prevalence and effects on child outcomes and fetal alcohol spectrum disorders. Reprod. Toxicol. 2016c; 63:13–21. [PubMed: 27174445]

May PA, Keaster C, Bozeman R, Goodover J, Blankenship J, Kalberg WO, Buckley D, Brooks M, Hasken J, Gossage JP, Robinson LK, Manning M, Hoyme HE. Prevalence and characteristics of fetal alcohol syndrome and partial fetal alcohol syndrome in a Rocky Mountain Region City. Drug Alcohol Depend. 2015; 155:229–127.

May PA, Baete A, Russo J, Elliott AJ, Blankenship J, Kalberg WO, Buckley D, Brooks M, Hasken J, Abdul-Rahman O, Adam MP, Robinson LK, Manning M, Hoyme HE. Prevalence and characteristics of fetal alcohol spectrum disorders. Pediatrics. 2014a; 134:855–866. [PubMed: 25349310]

May PA, Hamrick KJ, Corbin KD, Hasken J, Marais AS, Brooke LE, Blankenship J, Hoyme HE, Gossage JP. Dietary intake, nutrition, and fetal alcohol spectrum disorders in the Western Cape Province of South Africa. Reprod. Toxicol. 2014b; 46:31–39. [PubMed: 24568797]

May PA, Blankenship J, Marais AS, Gossage JP, Kalberg WO, Barnard R, De Vries M, Robinson LK, Adnams CM, Buckley D, Manning M, Jones KL, Parry CDH, Hoyme HE, Seedat S. Approaching the prevalence of the full spectrum of fetal alcohol spectrum disorders in a South African population-based study. Alcohol. Clin. Exp. Res. 2013a; 37:818–830. [PubMed: 23241076]

May PA, Blankenship J, Marais AS, Gossage JP, Kalberg WO, Joubert B, Cloete M, Barnard R, de Vries M, Hasken J, Robinson LK, Adnams CM, Buckley D, Manning M, Parry CD, Hoyme HE, Tabachnick BG, Seedat S. Maternal alcohol consumption producing fetal alcohol spectrum disorders (FASD): quantity, frequency, and timing of drinking. Drug Alcohol Depend. 2013b; 133:502–512. [PubMed: 23932841]

May PA, Tabachnick B, Gossage JP, Kalberg WO, Marais AS, Robinson LK, Manning M, Blankenship J, Buckley D, Hoyme HE, Adnams C. Maternal factors predicting cognitive and behavioral characteristics of children with fetal alcohol spectrums disorders. J. Dev. Behav. Pediatr. 2013c; 34:314–325. [PubMed: 23751886]

May PA, Fiorentino D, Coriale G, Kalberg WO, Hoyme HE, Aragon AS, Buckley D, Stellavato C, Gossage JP, Robinson LK, Jones KL, Manning M, Ceccanti M. Prevalence of children with severe fetal alcohol spectrum disorders in communities near Rome, Italy: new estimated rates are higher than previous estimates. Int. J. Env. Res. Public Health. 2011a; 8:2331–2351. [PubMed: 21776233]

May PA, Tabachnick BG, Gossage JP, Kalberg WO, Marais AS, Robinson LK, Manning M, Buckley D, Hoyme HE. Maternal risk factors predicting child physical characteristics and dysmorphology in fetal alcohol syndrome and partial fetal alcohol syndrome. Drug Alcohol Depend. 2011; 119:18–27. [PubMed: 21658862]

May PA, Gossage JP, Kalberg WO, Robinson LK, Buckley D, Manning M, Hoyme HE. Prevalence and epidemiologic characteristics of FASD from various research methods with an emphasis on recent in-school studies. Dev. Disabil. Res. Rev. 2009; 15:176–192. [PubMed: 19731384]

May PA, Gossage JP, Marais AS, Hendricks LS, Snell CL, Tabachnick BG, Stellavato C, Buckley DG, Brooke LE, Viljoen DL. Maternal risk factors for fetal alcohol syndrome and partial fetal alcohol syndrome in South Africa: a third study. Alcohol. Clin. Exp. Res. 2008; 32:738–753. [PubMed: 18336634]

May PA, Gossage JP, Marais AS, Adnams C, Hoyme HE, Jones KL, Robinson LK, Khaole NC, Snell C, Kalberg WO, Hendricks L, Brooke L, Stellavato C, Viljoen DL. The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. Drug Alcohol Depend. 2007; 88:259–271. [PubMed: 17127017]

May PA, Brooke LE, Gossage JP, Snell C, Hendricks L, Croxford J, Marais AS, Viljoen DL. Maternal risk factors for fetal alcohol syndrome in the Western Cape Province of South Africa: a population-based study. Am. J. Public Health. 2005; 95:1190–1199. [PubMed: 15933241]

May PA, Brooke LE, Gossage JP, Croxford J, Adnams C, Jones KL, Robinson LK, Viljoen D. The epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. Am. J. Public Health. 2000; 90:1905–1912. [PubMed: 11111264]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Microsoft Excel. Microsoft. Redmond, WA: 2010.

Okulicz-Kozaryn K, Borkowska M, Brzozka K. FASD prevalence among schoolchildren in Poland. J. App. Res. Intellect. Disabil. Epub ahead of print. 2015

Olivier L, Urban M, Chersich M, Temmerman M, Vijoen D. Burden of fetal alcohol syndrome in a rural West Coast area of South Africa. S. Afr. Med. J. 2013; 103:402–405. [PubMed: 23725961]

Petković G, Barišić I. FAS prevalence in a sample of urban schoolchildren in Croatia. Reprod. Toxicol. 2010; 29:237–272. [PubMed: 19922788]

Petković G, Barišić I. Prevalence of fetal alcohol syndrome and maternal characteristics in a sample of schoolchildren from a rural province of Croatia. Int. J. Environ. Res. Public Health. 2013; 10:1547–1561. [PubMed: 23591786]

Raven, J. Research Supplement No.1: the 1979 British Standardisation Of The Standard Progressive Matrices And Mill Hill Vocabulary Scales, Together With Comparative Data From Earlier Studies In The UK, US, Canada, Germany and Ireland. San Antonio, TX: Harcourt Assessment; 1981. Manual for Raven's Progressive Matrices and Vocabulary Scales.

Sampson PD, Streissguth AP, Bookstein FL, Little RE, Clarren SK, Dehaene P, Hanson JW, Graham JM. Incidence of fetal alcohol syndrome and prevalence of alcohol-related neurodevelopmental disorder. Teratology. 1997; 56:317–326. [PubMed: 9451756]

Stratton, KR.; Howe, CJ.; Battaglia, FC. Institute Of Medicine. Washington, DC: National Academy Press; 1996. Fetal Alcohol Syndrome Diagnosis, Epidemiology, Prevention, And Treatment.

Streissguth AP, O'Malley K. Neuropsychiatric implications and long-term consequences of fetal alcohol spectrum disorders. Sem. Clin. Neuropsychol. 2000; 47:177–190.

Streissguth AP, Barr HM, Sampson PD, Bookstien FL. Prenatal alcohol and offspring development: the first fourteen years. Drug Alcohol Depend. 1994; 36:89–99. [PubMed: 7851285]

Sobell LC, Agrawal S, Annis H, Ayala-Velazquez H, Echeverria L, Leo GI, Rybakowski JK, Sandahl C, Saunders B, Thomas S, Zioikowski M. Cross-cultural evaluation of two drinking assessment instruments: alcohol timeline followback and inventory of drinking situations. Subst. Use Misuse. 2001; 36:313–331. [PubMed: 11325169]

Sobell LC, Sobell MB, Leo GI, Cancilla A. Reliability of a timeline method: assessing normal drinker's reports of recent drinking and a comparative evaluation across several populations. Br. J. Addict. 1998; 83:393–402.

Tabachnick, BG.; Fidell, LS. Using Multivariate Statistics. 6th. New York: Pearson; 2013.

Urban M, Chersich F, Fourie LA, Chetty C, Olivier L, Viljoen D. Fetal alcohol syndrome among Grade 1 schoolchildren in Northern Cape Province: prevalence and risk factors. S. Afr. Med. J. 2008; 98:877–880. [PubMed: 19177895]

Urban MF, Olivier L, Viljoen D, Lombard C, Louw JG, Drotsky LM, Temmerman M, Chersich MF. Prevalence of fetal alcohol syndrome in a South African city with a predominantly Black African population. Alcohol. Clin. Exp. Res. 2015; 39:1016–1026. [PubMed: 25941030]

Viljoen DL, Gossage JP, Adnams C, Jones KL, Robinson LKHE, Snell C, Khaole N, Asante KK, Findlay R, Quinton B, Brooke LE, May PA. Fetal alcohol syndrome epidemiology in a South African community: a second study of a very high prevalence area. J. Stud. Alcohol. 2005; 66:593–604. [PubMed: 16331845]

Viljoen D, Hymbaugh K. Fetal alcohol syndrome---South Africa, 2001. MMWR. 2003; 52:660–662. [PubMed: 12869904]

Viljoen D, Croxford J, Gossage JP, Kodituwakku PW, May PA. Characteristics of mothers of children with fetal alcohol syndrome in the Western Cape Province of South Africa: a case control study. J. Stud. Alcohol. 2002; 63:6–17. [PubMed: 11925060]

Warren, K.; Floyd, L.; Calhoun, F., et al. Consensus Statement on FASD. Washington, DC: National Organization on Fetal Alcohol Syndrome; 2004.

Wechsler, D. Wechsler Intelligence Scale for Children. Third. San Antonio, TX: Psychological Corporation; 2003.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Research Highlights

- High rates of fetal alcohol spectrum disorders were again found in this community.
- Fetal alcohol syndrome prevalence is 59 – 79 per 1,000 children.
- Total FASD prevalence is 17% – 23%.
- Prenatal alcohol use correlated with poor physical and behavioral outcomes.
- Distal maternal risks include: high parity, low BMI, SES, and head circumference.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

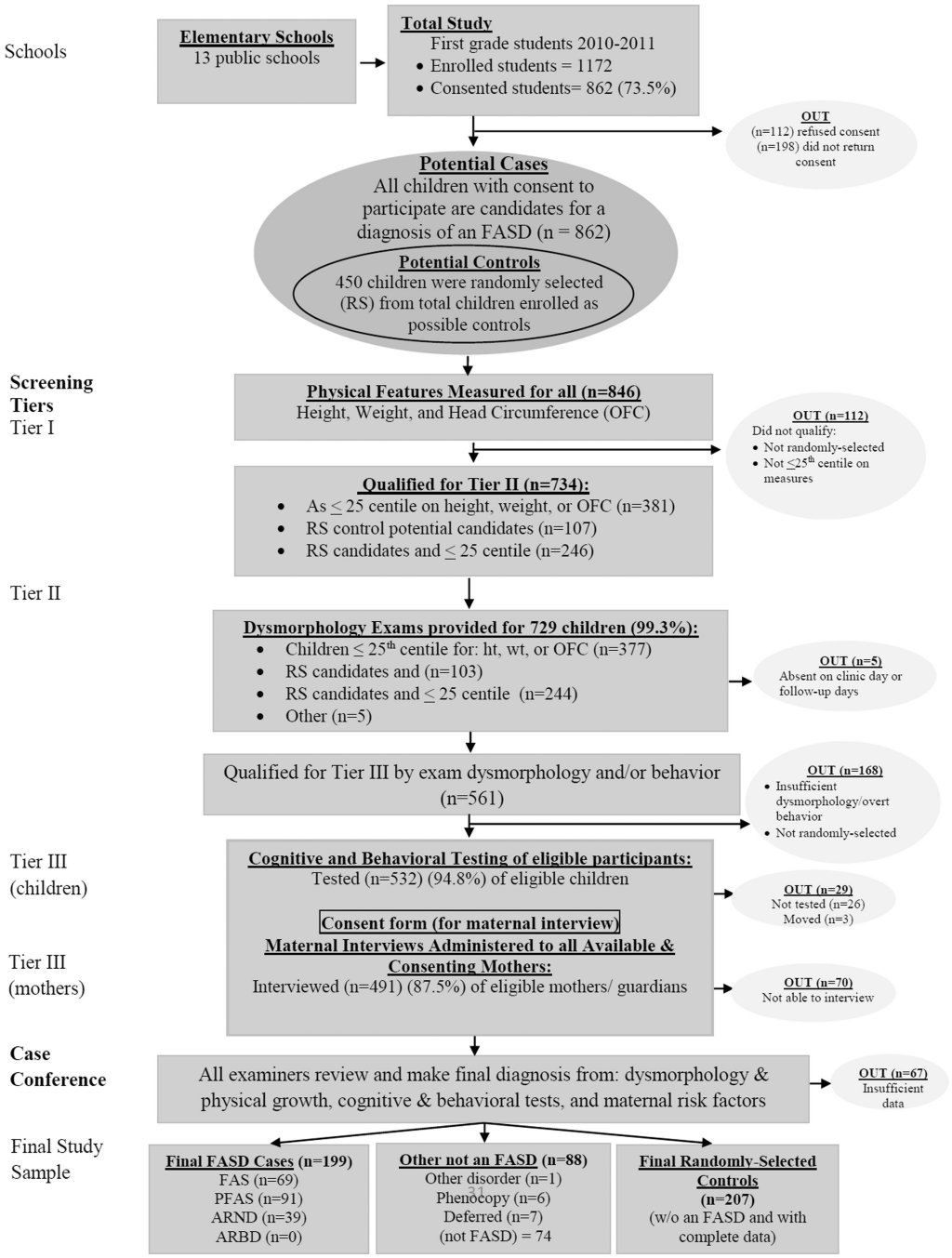

Figure 1.

Sampling Methodology for Prevalence of FASD in a Fifth Sample in a South African Community

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

I. Diagnostic criteria for ***Fetal Alcohol Syndrome (FAS)*** or ***Partial Fetal Alcohol Syndrome (PFAS)*** (with or without confirmed maternal alcohol exposure):

FAS requires all features A–C; PFAS requires A and B or C or evidence of a complex pattern of behavior or cognitive abnormalities inconsistent with developmental level and that cannot be explained by genetic predisposition, family background or environment alone (see Alcohol Related Neurodevelopmental Disorder, ARND in IIB)

A. Evidence of a characteristic pattern of minor facial anomalies, including at least two of the following:

1. Short palpebral fissures (less than or equal to the 10th centile)
2. Thin vermilion border of the upper lip (score 4 or 5 on the lip/philtrum guide)[1]
3. Smooth philtrum (score 4 or 5 on the lip/philtrum guide)[1,2]

B. Evidence of prenatal and/or postnatal growth retardation: height or weight less than or equal to the 10th centile

C. Evidence of deficient brain growth or abnormal morphogenesis, including one or more of the following

1. Structural brain abnormalities
2. Head circumference less than or equal to the 10th centile

II. Diagnostic criteria for alcohol-related effects [***Alcohol Related Birth Defects (ARBD)*** and ***Alcohol Related Neurodevelopmental Disorder (ARND)]:***

(A diagnosis in these categories requires a confirmed history of prenatal alcohol exposure)

A. ARBD requires the characteristic facies as above in IA, plus specific congenital structural defects (including malformations and dysplasias) in at least one organ system (if the patient displays minor anomalies only, at least two must be present). This category assumes the subject to have normal growth and intellectual/behavioral characteristics

B. ARND assumes the subject to have normal growth and structure and at least one of the following

1. Evidence of deficient brain growth or abnormal morphogenesis, including one or more of the following
   a. Structural brain abnormalities
   b. Head circumference less than or equal to the 10th centile
2. Evidence of a complex pattern of behavior or cognitive abnormalities inconsistent with developmental level and that cannot be explained by genetic predisposition, family background or environment alone

---

[1] Astley SJ, Clarren, SK. Diagnosing the full spectrum of fetal alcohol-exposed individuals: introducing the 4-digit diagnostic code. *Alcohol Alcohol.* 2000;35(4):400-10.

[2] For South African children, especially of mixed race: Hoyme, H.E., Hoyme, D.B., Elliott, A.J. et al. A South African mixed race lip/philtrum guide for diagnosis of fetal alcohol spectrum disorders. *Am J Med Genet A*. 2015 167A(4): 752-755.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

a. This pattern includes: marked impairment in the performance of complex tasks (complex problem solving, planning, judgment, abstraction, metacognition, and arithmetic tasks); higher-level receptive and expressive language deficits; and disordered behavior (difficulties in personal manner, emotional lability, motor dysfunction, poor academic performance, and deficient social interaction)

Figure 2.
Institute of Medicine Diagnostic Guidelines for Specific Fetal Alcohol Spectrum Disorders (FASD) as Clarified by Hoyme et al., 2005

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

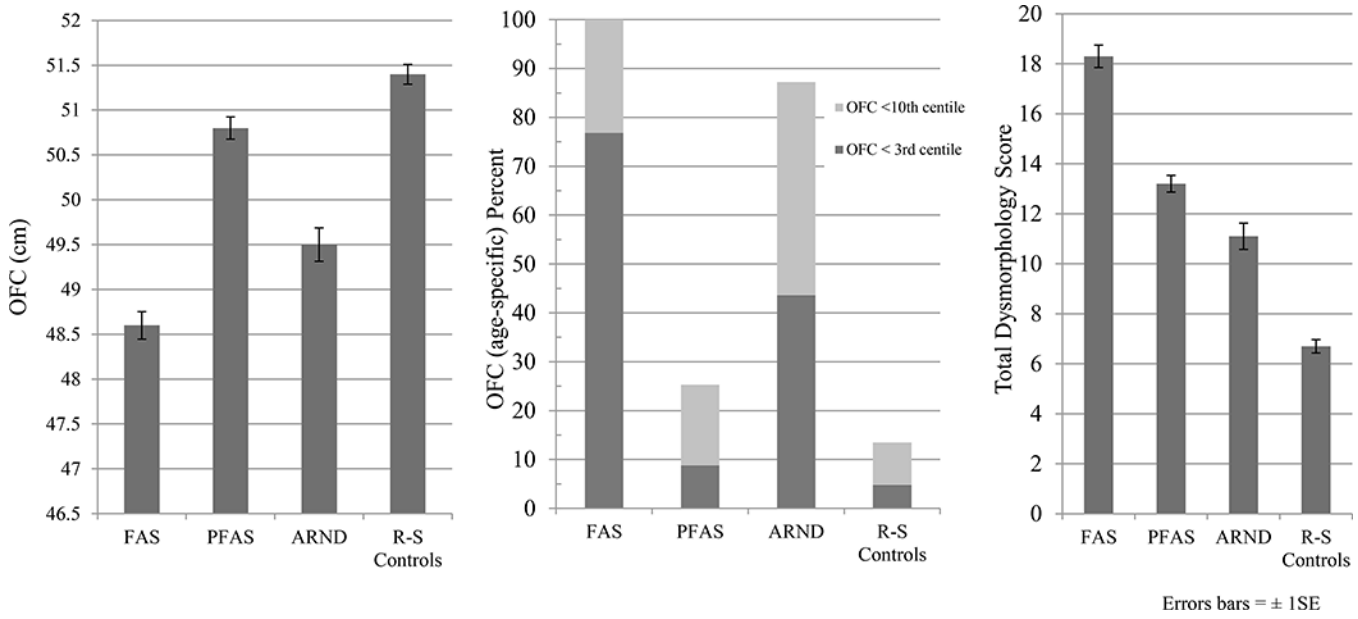

Figure 3.

Occipitofrontal (head) Circumference (OFC) by Measurement (cm) and Age-specific Percentage and Total Dysmorphology Scores by Diagnostic Category for a Fifth Sample in a South African Community

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

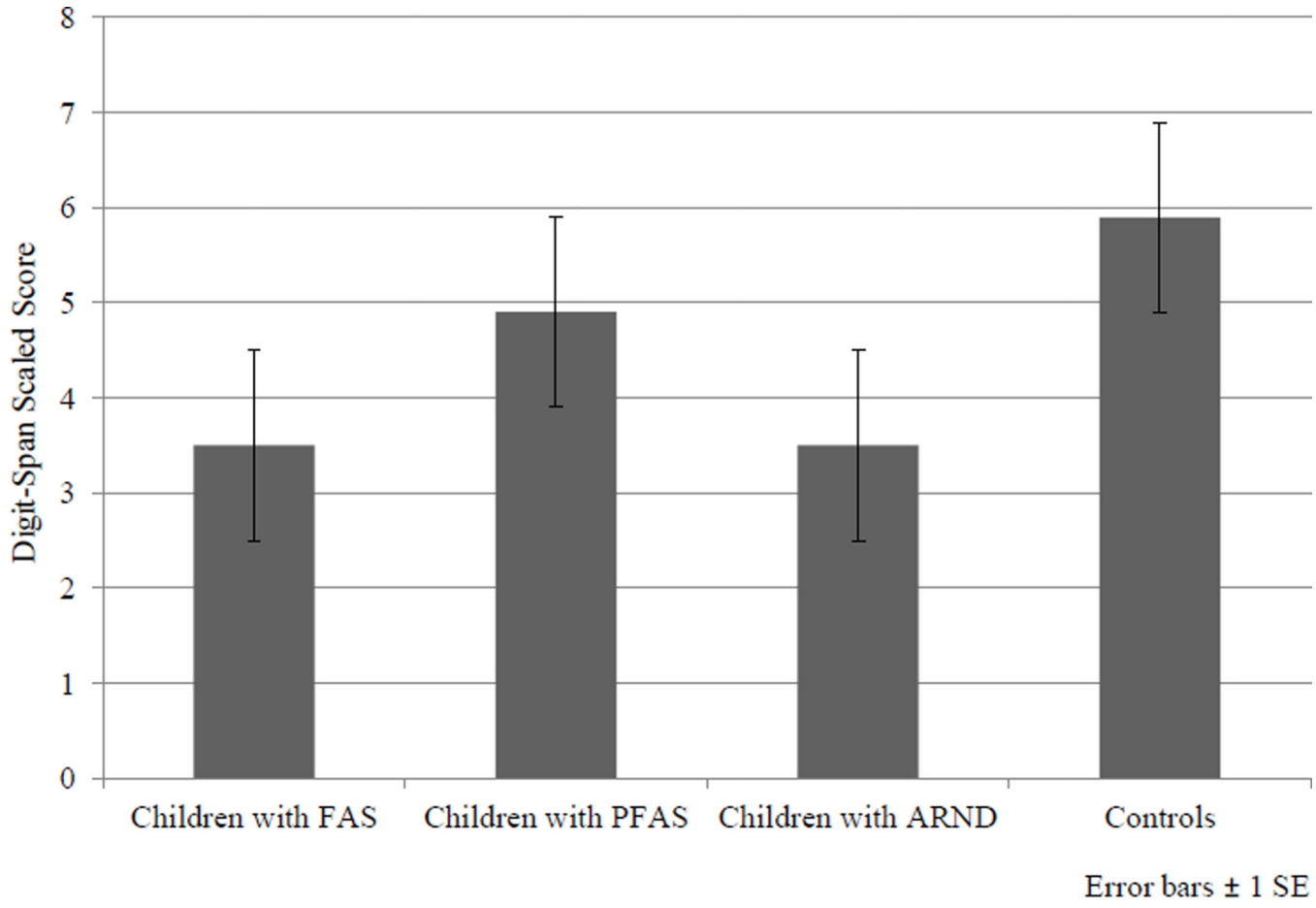

Figure 4.
WISC-IV Digit-Span Scaled Scores by Diagnostic Category for a Fifth Sample in a South African Community

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

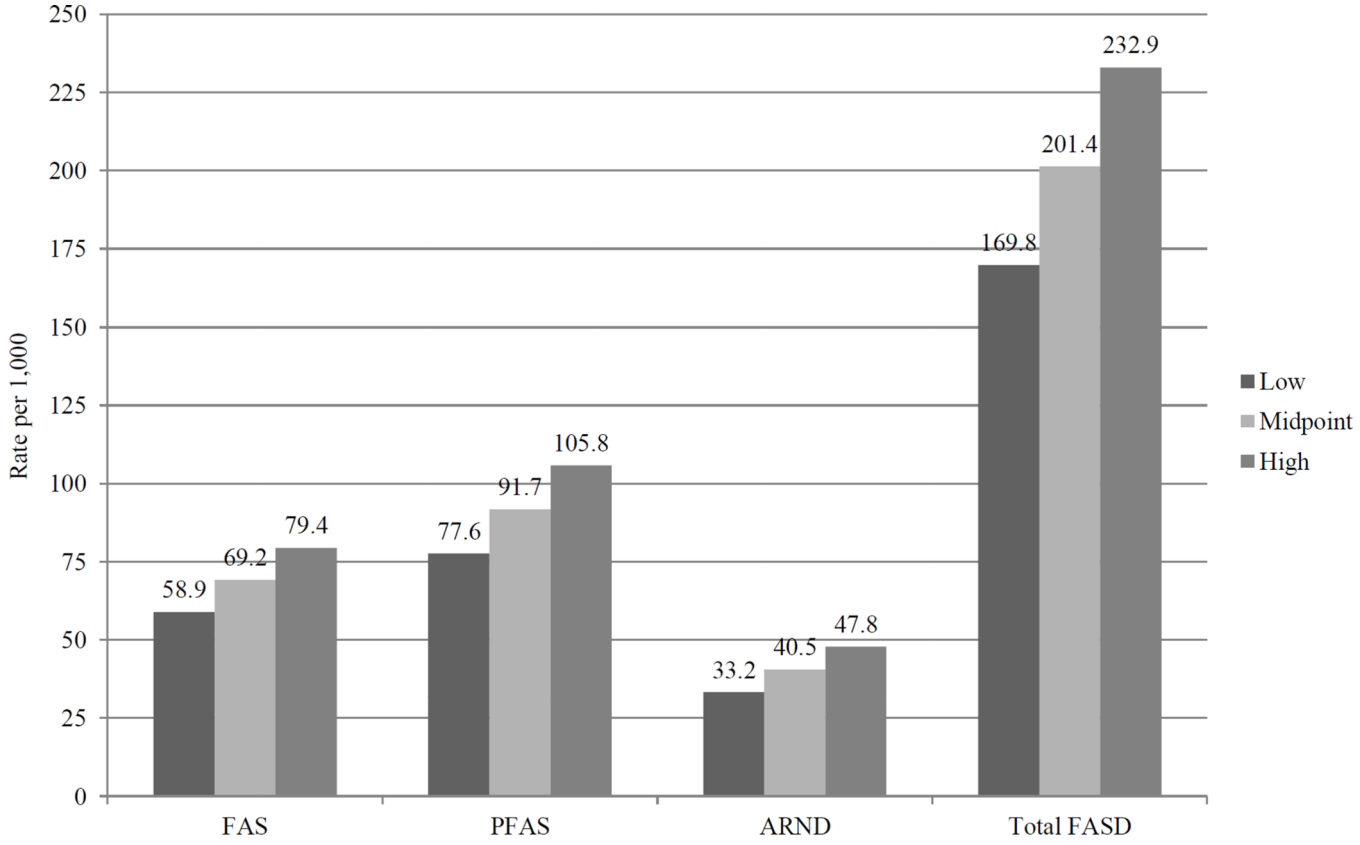

Figure 5.

Final Prevalence Rates (per 1,000) of FASD Diagnostic Groups and Controls in a Fifth Sample in a South African Community

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2017 November 01.

Table 1

Children's Demographic, Growth, Cardinal FASD Variables, and Total Dysmorphology Score from A Fifth Sample with Post Hoc Analysis Summary

	All Children[1] (n=846)	**Children with FAS (n=69)**	**Children with Partial FAS (n=91)**	**Children with ARND (n=39)**	**Randomly-Selected Normal Controls (n=207)**	**Statistical Test Value**	***P***
Sex (% male)	52.9	47.8	53.9	61.5	53.1	χ^2=1.909	.592
Age (months) – Mean (SD)	79.3 (6.6)	83.2 (7.5)	79.8 (6.3)	80.3 (7.7)	78.2 (6.3)	F=10.249	<.001 *a,c*
Height (cm) – Mean (SD)	115.3 (6.1)	110.0 (5.0)	114.1 (5.7)	111.4 (5.4)	116.0 (5.5)	F=24.666	<.001 *a,c,e,f*
Height centile – Mean (SD)	26.2 (25.6)	6.13 (8.9)	21.9 (19.5)	11.1 (14.6)	35.6 (27.4)	F=37.115	<.001 *a,c,d,e,f*
Weight (kg) – Mean (SD)	20.0 (3.9)	16.6 (2.1)	18.8 (2.7)	17.6 (2.1)	20.3 (3.3)	F=33.215	<.001 *a,c,e,f*
Weight centile – Mean (SD)	22.1 (24.6)	3.1 (4.6)	15.7 (17.4)	8.3 (11.7)	31.2 (36.7)	F=39.098	<.001 *a,c, d, e,f*
Child's BMI – Mean (SD)	14.9 (1.9)	13.7 (1.2)	14.3 (1.3)	14.2 (1.1)	15.1 (1.7)	F=18.079	<.001 *a,c,e,f*
BMI Percentile – Mean (SD)	34.3 (29.9)	13.8 (19.4)	24.3 (22.7)	20.3 (20.9)	37.2 (29.1)	F=17.630	<.001 *a,c,e,f*
OFC (cm) - Mean (SD)	50.9 (1.6)	48.6 (1.3)	50.8 (1.2)	49.5 (1.2)	51.4 (1.4)	F=12.556	<.001 *a,b, c,d, e,f*
OFC < 3rd centile (%)	21.7	76.8	8.8	43.6	4.8	χ^2=178.083	<.001
OFC < 10th centile (%)	37.9	100.0	25.3	87.2	13.5	χ^2=211.643	<.001
PFL centile - Mean (SD)	--	7.3 (9.4)	12.1 (14.1)	20.5 (14.0)	26.4 (14.9)	F=43.671	<.001 *b,c,d,e*
Smooth Philtrum[2] (%)	--	82.6	79.1	12.8	16.9	χ^2=165.711	<.001
Narrow Vermilion[3] (%)	--	95.7	89.0	12.8	27.5	<2=176.063	<.001
Total Dysmorphology Score – Mean (SD)	--	18.3 (3.7)	13.2 (3.2)	11.1 (3.3)	6.7 (3.8)	F=204.149	<.001 *a,b, c,d, e,f*

[1] The "All Children" group is not included in any of the Table 1 statistical test analyses.

[2] Scores of 4 or 5 on Astley Lip Philtrum Guide;

[3] Scores of 4 or 5 on Astley Lip Philtrum Guide

Bonferroni-adjusted value =.004

Significant (p<.05) post-hoc Dunnett C comparisons between:

[a] FAS & PFAS;

[b] FAS & ARND;

[c] FAS & Controls;

[d] PFAS & ARND;

[e] PFAS & Controls

[f] ARND & Controls

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2017 November 01.

Table 2

Other Minor Anomalies of Children with FAS, PFAS, and ARND Compared to Controls from A Fifth Sample

	Children with FAS (n=69)	**Children with Partial FAS (n=88)**	**Children with ARND (n=39)**	**Randomly-Selected Normal Controls (n=206)**	**Test score**	**p-value[f]**
Maxillary Arc (cm)	23.1 (.9)	23.7 (.8)	23.3 (.7)	24.2 (.8)	F=17.443	<.001[a,b,c,d,e]
Mandibular Arc (cm)	24.0 (1.2)	24.7 (.9)	24.5 (1.0)	25.4 (.8)	F=17.618	<.001[a,b,d,e]
Inner canthal distance (cm)	2.8 (.3)	2.9 (.2)	2.8 (.3)	2.9 (.3)	F=6.369	<.001[b,c,e]
Inter-pupillary distance (cm)	4.9 (.3)	5.1 (.3)	5.0 (.3)	5.2 (.3)	F=15.270	<.001 [a,b,d,e]
Hypoplastic midface (%)	85.5	69.2	79.5	51.7	χ^2=32.622	<.001
Epicanthal folds (%)	57.4	44.0	69.2	41.1	χ^2=13.922	.003
Ptosis (%)	29.0	15.4	12.8	3.9	χ^2=33.804	<.001
Clinodactyly (%)	47.8	49.5	46.2	36.7	χ^2=5.649	.130
Camptodactyly (%)	21.7	5.5	12.8	6.8	χ^2=15.860	.001
Flat nasal bridge (%)	62.3	56.0	66.7	44.9	χ^2=52.5	.012
Altered palmar creases (%)	44.9	30.8	15.4	28.0	χ^2=11.619	.009
Prognathism (%)	26.1	12.1	7.7	3.9	χ^2=29.549	<.001

Significant (p<.05) post-hoc Dunnett C comparisons between:

[a]FAS & PFAS;

[b]FAS & Controls;

[c]PFAS & ARND;

[d]PFAS & Controls;

[e]ARND & Controls;

[f]Bonferroni-adjusted value for ANOVA comparisons <.004

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2017 November 01.

Table 3

Mean Scores on Developmental and Behavioral Indicators[1] of Children with FAS, PFAS, and ARND Compared to Controls from A Fifth Sample with Post Hoc Analyses

	Children with FAS (n=69)		**Children with Partial FAS (n=88)**		**Children with ARND (n=39)**		**Randomly-Selected Normal Controls (n=206)**			
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**F**	**p-value**
Verbal IQ[^](percentile scores)	20.2	(21.5)	26.4	(23.2)	14.6	(17.2)	38.4	(26.9)	17.563	<.001[b,c,d,e]
Non-verbal IQ[+] (percentile scores)	13.0	(9.0)	20.8	(15.3)	14.3	(11.9)	29.1	(22.3)	17.668	<.001[a,b,d,e]
WISC-IV Digit-Span Scaled Score[†]	3.5	(2.4)	4.9	(2.6)	3.5	(2.4)	5.9	(2.6)	21.371	<.001[a,b,c,d,e]
Achenbach Teacher Report Form (TRF) Total Problem Score	35.9	(34.7)	39.6	(38.2)	46.6	(37.8)	22.9	(24.0)	10.850	<.001[b,d,e]
Achenbach TRF Inattention Score	17.2	(14.1)	16.3	(13.6)	21.0	(11.7)	10.3	(10.8)	13.473	<.001[b,d,e]

[1] All scores standardized for age of child at time of testing.

[^] Test of Reception of Grammar (TROG). A measure of verbal intelligence.

[+] Raven Coloured Progressive Matrices. A measure of nonverbal intelligence. WISC-IV Digit Span Scaled Score - mean of 10 and standard deviation of 3.

[†] Bonferroni-adjusted value < 0.01

Significant (p<05) post-hoc Dunnett C comparisons between:

[a] FAS & PFAS;

[b] FAS & Controls;

[c] PFAS & ARND;

[d] PFAS & Controls;

[e] ARND & Controls

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2017 November 01.

Table 4

Maternal Demographic, Childbearing, Socioeconomic, Drinking, Tobacco, and Other Drug Use from a Fifth Sample: Mothers of Children with FASD and Normal Controls

	Mothers of						
Maternal Variables	**Children with FAS (n=68)**	**Children with Partial FAS (n=89)**	**Children with ARND (n=39)**	**Randomly Selected Normal Controls (n=207)**	**Statistical Test**	***df***	***P***
Alcohol Consumption Variables							
Current drinker (%Yes)	47.1	30.3	48.7	22.7	χ^2 = 20.592	3	<.001
Drank before index pregnancy (% Yes)	90.9	86.6	100.0	60.2	χ^2 = 51.263	3	<.001
Drank during index pregnancy direct report (% Yes)	89.7	70.6	100.0	41.1	χ^2 = 85.912	3	<.001
Avg # drinks per week during pregnancy	16.5 (23.2)	4.5 (8.1)	8.4 (13.5)	2.3 (6.2)	*F= 25.018*	3	<.001*a,c,d,f*
Avg # of drinking days during pregnancy	1.9 (1.9)	.8 (1.1)	1.6 (1.3)	.4 (.8)	F=32.666	3	<.001 *a,c,d,e,f*
Consumed **3 drinks** or more per occasion during pregnancy (%)	73.5	47.2	89.7	27.1	χ^2 = 80.864	3	<.001
Consumed **5 drinks** or more per occasion during pregnancy (%)	66.2	32.6	53.8	17.9	χ^2 = 63.173	3	<.001
Alcohol Use by Trimester						3	
Drank during **1st trimester** (% Yes)	76.5	55.1	92.3	37.2	χ^2 = 60.143	3	<.001
Binged 3+ (%)	73.5	46.1	82.1	26.6	χ^2 = 72.595	3	<.001
Binged 5+ (%)	64.7	315	48.7	17.4	χ^2 = 59.189	3	<.001
Average # of drinks per drinking day[1]	10.4 (11.3)	6.0 (4.0)	5.5 (3.5)	5.2 (3.9)	*F= 7.634*	3	<.001*a,c,e,f*
# of drinking days per week[1]	2.9 (1.8)	2.0 (1.1)	2.2 (1.1)	1.8 (.9)	*F=8.140*	3	<.00 *a,c,d,e,f*
Drank during **2nd trimester** (% Yes)	64.7	38.2	69.2	18.8	χ^2 = 69.871	3	<.001

	Mothers of						
Maternal Variables	**Children with FAS (n=68)**	**Children with Partial FAS (n=89)**	**Children with ARND (n=39)**	**Randomly Selected Normal Controls (n=207)**	**Statistical Test**	***df***	***P***
Binged 3+ (%)	60.3	31.5	61.5	13.0	χ^2 = 79.941	3	<.001
Binged 5+ (%)	55.9	21.3	35.9	9.2	χ^2 = 68.964	3	<.001
Average # of drinks per drinking day[1]	11.0 (12.1)	6.0 (4.4)	5.3 (3.2)	5.7 (4.9)	*F=4.922*	3	.003 *a,c,e,f*
# of drinking days per week[1]	3.1 (1.9)	2.0 (1.3)	2.3 (1.2)	2.0 (1.2)	*F=5.459*	3	.001 *a,c,d,e,f*
Drank during **3rd trimester** (% Yes)	44.1	22.5	41.0	9.2	χ^2 = 48.727	3	<.001
Binged 3+ (%)	44.1	18.0	38.5	5.8	χ^2 = 63.057	3	<.001
Binged 5+ (%)	39.7	12.4	30.8	4.8	χ^2 = 57.786	3	<.001
Average # of drinks per drinking day[1]	13.5 (14.0)	6.7 (5.3)	6.6 (3.8)	5.7 (5.6)	*F=3.898*	3	.012
# of drinking days per week[1]	2.9 (.9)	3.3 (2.6)	2.5 (.6)	2.3 (1.0)	*F=.396*	3	.758
Tobacco and Use of Other Drugs							
Other Drug Use in lifetime (%)	0.8	1.5	0.3	3.3	χ^2 = 1.305	3	.728
Other Drug Use during pregnancy (%)	0.0	0.5	0.0	1.3	χ^2 = 2.560	3	.464
Used tobacco during index pregnancy (%)	71.6	60.7	82.1	41.2	χ^2 = 35.797	3	<.001
Current smoker, smoked within week (%)	62.5	55.4	66.7	42.4	χ^2 = 13.922	3	.003
Total # of grams of tobacco used per week (each cigarette = 1 gram)	26.3 (29.5)	29.0 (38.0)	27.9 (30.3)	19.8 (32.5)	F= *1.903*	3	.129
Demographics						3	
Age at pregnancy (yrs) – Mean (SD)	29.1 (7.3)	25.1 (6.6)	25.5 (6.4)	24.5 (6.3)	F =*8.278*	3	<.001 *a,c*
Height (cm) – Mean (SD)	156. 2(6.0)	158.5(6.2)	157.7(5.4)	160.0 (6.2)	F =*6.719*	3	<.001 *c*
Weight (kg) – Mean (SD)	57.4(14.1)	66.1(16.3)	63.9(16.1)	70.1 (15.9)	*F= 10.772*	3	<.001 *a,c*

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

	Mothers of						
Maternal Variables	**Children with FAS (n=68)**	**Children with Partial FAS (n=89)**	**Children with ARND (n=39)**	**Randomly Selected Normal Controls (n=207)**	**Statistical Test**	***df***	***P***
BMI – Mean (SD)	21.5(8.8)	23.3(10.1)	25.7(6.3)	26.0 (8.3)	F =*5.556*	3	<.001[b,c]
OFC – Mean (SD)	53.9(1.9)	55.0(2.1)	54.7(5.6)	55.7 (2.3)	F =*7.782*	3	.001[a,c]
Gravidity – Mean (SD)	3.4(1.6)	3.2(1.4)	3.3(1.3)	2.8 (1.3)	F = 3.868	3	.010[c]
Parity – Mean (SD)	3.1(1.3)	2.9(1.3)	3.1(1.4)	2.6 (1.2)	F =*4.472*	3	.004[c]
Breastfed index child (% Yes)	94.0	91.6	97.4	90.7	χ^2 = 2.356	3	.502
Duration of breastfeeding (months) – Mean (SD)	26.4(29.4)	18.5(18.3)	18.5(20.4)	18.1 (19.8)	F = 2.488	3	.060
Maternal education (years) – Mean (SD)	7.6(3.0)	8.7(3.0)	7.9(3.0)	10.3 (2.3)	F = 22.676	3	<.001[c,e,f]
Income (Rand per week) – Mean (SD)	731(546)	1450(2182)	658(479)	1471 (1692)	F = 5.338	3	.001[a,c,d,f]

[1] Drinkers only for that trimester

[a] FAS & PFAS;

[b] FAS & ARND;

[c] FAS & Controls;

[d] PFAS & ARND;

[e] PFAS & Controls;

[f] ARND & Controls Bonferroni-adjusted values by Table section: alcohol consumption <.007; alcohol by trimester <.003; tobacco and other drugs <.01; demographics <.0045

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2017 November 01.

Table 5

Partial Correlation Coefficients (Adjusted for Square Root of Household Income and Square Root of Mother's Education) for Developmental[1] and Physical Dysmorphology Variables with Selected Maternal Drinking Measures During Pregnancy and Paternal Drinking from a South African Community

Child Trait		Mothers Reported Drinking During Pregnancy	Drinks Per Drinking Day During Pregnancy (log)	Drinks Per Week During Pregnancy (log)	3 or more Drinks Per Occasion During Pregnancy	5 or more Drinks Per Occasion During Pregnancy
Verbal ability[a] (log)	Partial *r*	**−.115**	**−.143**	**−.250**	**−.094**	**−.185**
	p[e]	.020	<.001	<.001	.058	<.001
	N	408	408	408	408	408
Non-verbal ability[b] (log)	Partial *r*	**−.205**	**−.235**	**−.250**	**−.198**	**−.180**
	p[e]	<.001	<.001	<.001	<.001	<.001
	N	408	408	408	408	408
WISC-IV Digit Span (log)	Partial *r*	**−.180**	**−.238**	**−.248**	**−.164**	**−.180**
	p[e]	<.001	<.001	<.001	.001	.001
	N	406	406	406	406	406
Behavior[c] (sqrt)	Partial *r*	**.106**	**.200**	**.211**	**.097**	**.132**
	p[e]	.031	<.001	<.001	.049	<.001
	N	408	408	408	408	408
Inattention problems[c] (sqrt)	Partial *r*	**.114**	**.202**	**.210**	**.121**	**.134**
	p[e]	.021	<.001	<.001	.014	<.001
	N	409	409	409	409	409
OFC	Partial *r*	**−.216**	**−.293**	**−.306**	**−.261**	**−.227**
	p[e]	<.001	<.001	<.001	<.001	<.001
	N	417	417	417	417	417
Dysmorphology score	Partial *r*	**.244**	**.302**	**.313**	**.258**	**.248**
	p[e]	<.001	<.001	<.001	<.001	<.001
	N	417	417	417	417	417

[a]Tests of the Reception of Grammar (TROG);

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

[b] Raven Coloured Progressive Matrices;

[c] Personal Behavior Checklist (PBCL-36);

[d] Also adjusted for Mothers' Drinks per Week (log);

[e] Bonferroni adjusted value p<.0012

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 6

Prevalence Rates (per 1,000) of Individual Diagnoses within Fetal Alcohol Spectrum Disorders (FASD) and Total FASD by Three Methods of Estimation from a Fifth Sample in a South African Community

	Oversample of children ≤ 25th centile on height, weight, or OFC			Random Sample Rate of FASD Diagnoses and Estimated Cases in the Non-Consented Children					Combined rate from cases in consented sample (n=862) and estimated cases in non-consented sample (n=310)		
Diagnosis	**(a) n**	**School Enrollment rate[1] (n=1172)**	**Consented student rate[2] (n=862)**	**n**	**Proportion of FASD cases in random sample (n=347)**	**(b) Estimated cases in non consented sample (n=310)**	**Rate of FASD from random sample only[3]**	**95% Confidence Interval**	**(a + b) Total estimated cases**	**Estimated rate for all enrolled students[4] (n=1172)**	**95% Conference Intervals**
FAS	69	58.9	80.0	27	.078	24	77.8	49.6 to 105.9	93	79.4	35.6 to 59.9
PFAS	91	77.6	105.6	37	.107	33	106.6	71.2 to 139.1	124	105.8	88.2 to 123.4
ARND	39	33.2	45.2	19	.055	17	54.8	30.8 to 78.7	56	47.8	63.9 to 94.8
Total FASD	199	169.8	230.9	83	.239	74	239.2	194.3 to 284.1	273	232.9	208.7 to 257.1

[1] Denominator is all children attending first grade in local schools. Rate per 1,000 based on the entire enrollment in 1st grade classrooms (n=1172).

[2] Denominator is the total number of children with consent to participate in this study. Rate per 1,000 based on the sample consented and screened (n=862).

[3] Calculated as the FASD cases diagnosed from the randomly-selected control candidates (numerator) over total number of randomly-selected children x 1,000.

[4] Rate per 1,000 children calculated from FASD cases diagnosed in the consented sample (a) added to the estimated cases in the non-consented sample utilizing the proportional diagnostic distribution of FASD cases among randomly-selected children (b), and divided by all 1st grade children enrolled in the schools (n=1172).