Drug and Alcohol Dependence 177 (2017) 258–267

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Who is most affected by prenatal alcohol exposure: Boys or girls?

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ARTICLE INFO

Keywords:
Prenatal alcohol exposure
Fetal alcohol spectrum disorders
Boys and girls
Sex ratio
Dysmorphology
Neurobehavior

ABSTRACT

Objective: To examine outcomes among boys and girls that are associated with prenatal alcohol exposure.
Methods: Boys and girls with fetal alcohol spectrum disorders (FASD) and randomly-selected controls were compared on a variety of physical and neurobehavioral traits.
Results: Sex ratios indicated that heavy maternal binge drinking may have significantly diminished viability to birth and survival of boys postpartum more than girls by age seven. Case control comparisons of a variety of physical and neurobehavioral traits at age seven indicate that both sexes were affected similarly for a majority of variables. However, alcohol-exposed girls had significantly more dysmorphology overall than boys and performed significantly worse on non-verbal IQ tests than males. A three-step sequential regression analysis, controlling for multiple covariates, further indicated that dysmorphology among girls was significantly more associated with five maternal drinking variables and three distal maternal risk factors. However, the overall model, which included five associated neurobehavioral measures at step three, was not significant ($p = 0.09$, two-tailed test). A separate sequential logistic regression analysis of predictors of a FASD diagnosis, however, indicated significantly more negative outcomes overall for girls than boys (Nagelkerke $R^2 = 0.42$ for boys and 0.54 for girls, $z = -2.9$, $p = 0.004$).
Conclusion: Boys and girls had mostly similar outcomes when prenatal alcohol exposure was linked to poor physical and neurocognitive development. Nevertheless, sex ratios implicate lower viability and survival of males by first grade, and girls have more dysmorphology and neurocognitive impairment than boys resulting in a higher probability of a FASD diagnosis.

1. Introduction

Ethyl alcohol is teratogenic when consumed by women in the prenatal period and frequently causes fetal alcohol spectrum disorders (FASD) in offspring. Binge drinking is defined by the National Institute on Alcohol Abuse and Alcoholism as 4 drinks or more per occasion for women (NIAAA, 2004). In clinical epidemiology studies in South Africa (SA), the definition of binge drinking was lowered to 3 or more drinks per occasion, because negative effects on the offspring have been observed repeatedly at this level. Binge drinking produces high

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http://dx.doi.org/10.1016/j.drugalcdep.2017.04.010
Received 6 December 2016; Received in revised form 29 March 2017; Accepted 25 April 2017

concentrations of ethanol in the vulnerable fetus and causes more harm than other patterns of consumption. Children and their mothers residing in five communities of the Western Cape Province (WCP) of SA were studied over two decades yielding a large epidemiology database. FASD prevalence in these communities has been the highest reported in the world. Thirty-four percent to 51% of women in these communities report drinking (3+) during pregnancy, many drinkers binge drink regularly, and rates of total FASD are as high as 18–26% (Croxford and Viljoen, 1999; May et al., 2013a, 2016a,b).

1.1. Male and female survival

Biology dictates that survival rates of male and female embryos and fetuses are different. Female survival is lower in the prenatal period overall, even though there are particular gestational stages when male embryos and fetuses are less robust (Austad, 2015; Orzack et al., 2015). Perinatal, early infant and child mortality is generally higher among males (Badari et al., 1991), particularly in the neonatal period (Hadar et al., 2012; Imaizumi, 1994). In addition, male fetuses and newborns are more negatively affected by maternal stressors (e.g., low gestational weight, advanced maternal age, and higher gravidity) compared to females (Navara, 2014; Mathews and Hamilton, 2005; Rueness et al., 2012). Furthermore, males and females are differentially affected in a variety of birth defects such as hypertrophic pyloric stenosis (Vermes et al., 2016), trisomy 18, trisomy 13 (Baty et al., 1994), and neural tube defects (Pei et al., 2003).

1.2. Sex differences in the presence of alcohol

In a review of human and animal studies, offspring who were prenatally-exposed to alcohol frequently demonstrated enhanced responses to stressors such as intermittent footshock, noise sensitivity, and shake. Similar responses occurred in female rats with prenatal exposure to cocaine and morphine (Weinberg et al., 2008). Heavy prenatal alcohol consumption increases risk for spontaneous abortion, stillbirth, sudden infant death syndrome, and small for gestational age, especially in women 30 years and older (Cavallo et al., 1995; Chiaffarino et al., 2006; Iyasu et al., 2002; Windham et al., 1992). Some researchers asked whether differential sex mortality from prenatal alcohol exposure alters sex ratios in humans (Qazi and Masakawa, 1976). Others found no evidence to support an altered sex ratio in small clinical samples (Abel, 1979). Regarding auditory response to stimuli and other neurophysiological activation in frontal and medial temporal cortex, prenatal alcohol exposure has been reported to produce widespread, differential responses in males and females (Abel, 1989; Tesche et al., 2014).

1.3. Purpose of this paper

This paper examined differences in outcomes between boys and girls exposed to various amounts of alcohol prenatally. Is there a differential susceptibility to the negative effects of alcohol based on sex as measured by sex ratios, case control analyses, and multiple correlation models? General population data were used to explore whether six and seven year-old boys exhibit more negative prenatal alcohol-induced outcomes than girls or vice versa.

2. Methods

2.1. Diagnostic categories for FASD: inclusion in the sample

To receive a diagnosis within the FASD spectrum, a child had to meet criteria as defined by one of four specific diagnoses described in 1996 by the U.S. Institute of Medicine (Stratton et al., 1996) and revised and published in 2005 (Hoyme et al., 2005). Children with FAS have growth deficiencies, facial and other dysmorphology, cognitive delay, and often significant behavioral problems. Children with partial FAS (PFAS) have similar problems to those with FAS but with less growth deficiency. Children with alcohol-related neurodevelopmental disorders (ARND) have little dysmorphology, but have significant cognitive and behavioral problems (Hoyme et al., 2005, 2016). Children with alcohol-related birth defects (ARBD) have a major structural/physiological anomaly that was likely caused by prenatal alcohol exposure, but no significant cognitive/behavioral problems. Final diagnoses in the data set were made by a pediatric dysmorphologist in a multidisciplinary case conference of team members reviewing data collected in the physical, neurocognitive, behavioral, and maternal risk domains.

2.2. Sample and sampling procedures – a three tier process

The sample originates from six active case ascertainment, general population studies collected for a larger epidemiological investigation of prevalence and characteristics of FASD in a major agricultural region of the WCP (May et al., 2000, 2005, 2007, 2013a, 2016a,b). Parents and guardians of all children enrolled in first-grade classes in all schools of these regions provided consent for 77% of the children to participate in the studies.

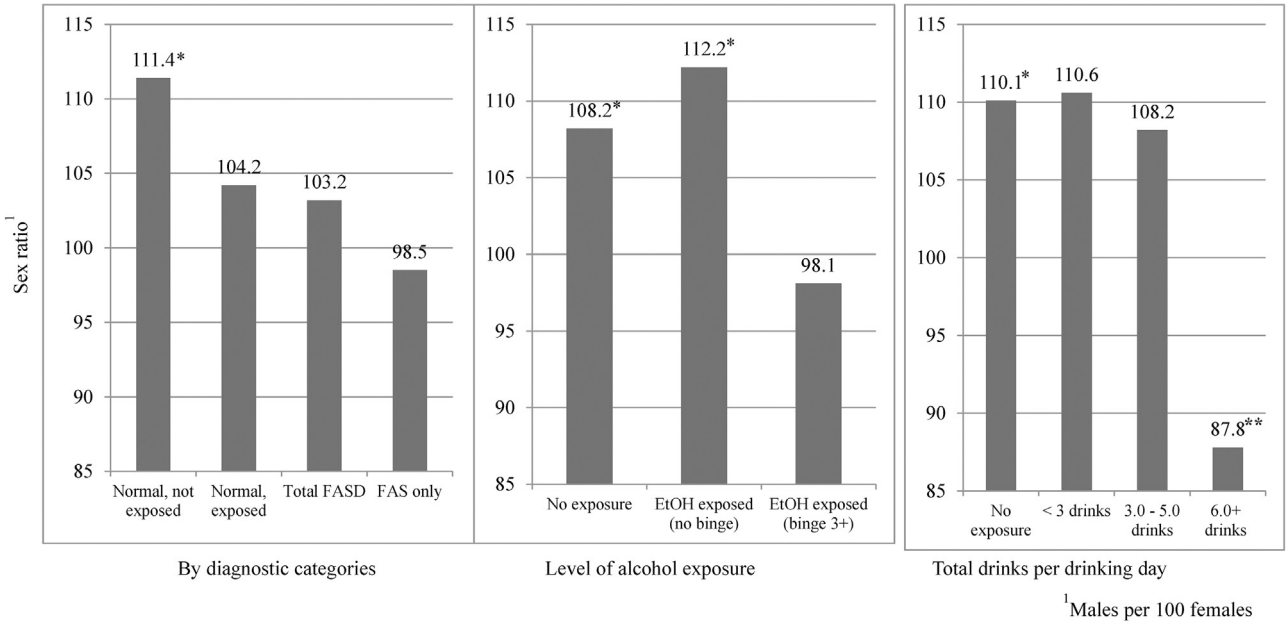
Children were assessed for features of FASD and alcohol-exposure in a three-tier process. In Tier I, all consented first-grade learners were measured for height, weight, and occipitofrontal (head) circumference (OFC). Children who were ≤25th centile on height, weight, and/or OFC were advanced to Tier II, along with children chosen randomly from school roles as potential controls.

In Tier II, each child received a dysmorphology examination by pediatric dysmorphologists blinded from any prior information about the children. Once exams were completed, all children suspected of having a FASD, and all randomly-selected, potential controls were advanced to Tier III.

All children in Tier III participated in cognitive and behavioral testing. Cognitive traits were assessed with: Tests of the Reception of Grammar (TROG) (Bishop, 1989), a measure of verbal IQ, Colored Progressive Matrices for nonverbal IQ (Raven, 1981), and the Weschler Intelligence Scales for Children (WISC-IV) Digit-Span Scaled Score for executive functioning (Wechsler, 2003). The Achenbach Teacher Report Form (Achenbach and Rescorla, 2001) assessed inattention and total problem behaviors.

2.3. Maternal questionnaire and measurement of alcohol use

Mothers of all study children in Tier III participated in maternal interviews of prenatal risk similar to many previous SA studies by the authors and others (Jacobson et al., 2008; May et al., 2005, 2008, 2013b; Viljoen et al., 2002). All interviews were administered in the field by experienced, Afrikaans-speaking staff. Items were carefully sequenced to enhance sensitivity and accuracy, covering variables on general health, reproduction, nutrition, alcohol and other drug use, and socioeconomic status (SES). Drinking questions followed a timeline, follow-back sequence (Sobell et al., 1998, 2001), and used vessels methodology pictures tailored to the common, local alcohol products and drinking practices (Kaskutas, 2000, 2001; Kaskutas and Kerr, 2008). A seven-day, retrospective drinking log of alcohol consumption during the week preceding the interview was embedded into nutrition questions. Current drinking data establish a baseline understanding of alcohol use and aid accurate calibration of drinking quantity, frequency, and gestational timing for subsequent questions regarding alcohol consumption 3 months prior to the index pregnancy and by trimester during pregnancy (May et al., 2000, 2005, 2008; Viljoen et al., 2002). Such sequencing minimizes under-reporting (Alvik et al., 2006). Retrospective reports of alcohol use during pregnancy are considered more accurate for determining prenatal drinking experience than those reported prenatally (Czarnecki et al., 1990; Hannigan et al., 2010). These methods work well, especially embedded within a dietary inventory (King, 1994).



*z-test of proportions (boys vs. girls) significant with a one-tailed test at $p<.05$; more males than females. (Left to right: z=2.26, $p=.012$; z=1.89, $p=.029$; z= 1.91, $p=.028$; z=2.09, $p=.018$)

**z-test of proportions (boys vs. girls) significant with a one-tailed test at $p<.05$; more females than males (z=1.65, $p=.0466$).

Fig. 1. Sex Ratios by alcohol exposure and FASD, level of alcohol exposure, and total drinks per drinking day.

2.4. Sample composition

Included here in all analyses, except Fig. 1, are data on 1545 children (791 boys and 754 girls) from community studies of the prevalence and characteristics of FASD in five communities. Fig. 1, which analyzes sex ratios, utilizes additional cases and random controls from a sixth study where the diagnoses had been finalized, but the detailed trait database was not ready for other analyses. Average age of the participants was 6.8 years (SD = 8.7 months). Fifty-four percent of the children (n = 841) were diagnosed with one of three FASD specific diagnoses: FAS, PFAS, and ARND. For this paper, all FASD diagnoses are grouped. Additionally, there are 704 normally-functioning children that were randomly-selected for entry into the studies. Some of these controls (27%) were exposed to alcohol prenatally. For most variables there were complete data on 430 boys with FASD and 97 alcohol-exposed and 264 unexposed control boys. There were 411 girls with FASD, 95 alcohol-exposed and 248 unexposed control girls.

2.5. Statistical analysis

Statistical analyses were performed by SPSS 24 (IBM, 2015). Boys and girls were compared, segregated by sex, across diagnostic groups for statistical analyses using chi-square tests for categorical variables, and one-way analysis of variance (ANOVA) for continuous variables. Dunnett's C tests were used to compare pairwise differences between groups.

Advanced multiple correlation analysis was performed via sequential regression models utilizing identical independent variables and two different dependent variables: 1.) physical traits and dysmorphology and 2.) children diagnosed FASD vs. not-FASD. Specific applications of these techniques are described in detail in the results section.

2.6. Sex ratio analysis

Sex ratio is a standard, descriptive measure of sex distribution, expressed as the ratio of males to 100 females (Barclay, 1958; Yusuf et al., 2014). Used routinely by demographers, sex ratio is a single measure summarizing sex composition in large samples or entire populations such as census and vital statistic reports. Sex ratio at birth in developed societies is generally 104–106, for an excess of males is born under supportive and stable social and environmental conditions. In SA the overall the sex ratio at birth has been 101 in recent years (Statistics South Africa, 2016). Among the majority (Coloured) population in this sample, it is 101.8 at birth and 101 for children 5–9 years old. In order to show a significant statistical difference with sex ratios, very large samples are generally required.

3. Results

3.1. Sex ratios by alcohol exposure and FASD diagnoses

Fig. 1 presents sex ratios by diagnoses and two measures of prenatal alcohol exposure. The sex ratio is lowest for children with FAS (98.5 boys per 100 females) in the diagnostic breakdown and significantly highest (more boys than girls) for unexposed controls. For the second comparison, alcohol exposure, there are again significantly more males than females in least alcohol-exposed groups (108.2 and 112.2), and the sex ratio is lowest (fewer males) for children exposed to alcohol levels from three drinks or more (3+) per occasion (103.2). The third comparison indicates that children exposed prenatally to six or more (6+) drinks per drinking day (heavy binge drinking) have a significantly lower sex ratio (87.8). Therefore, the trend is for the highest sex ratios (more males) in the no or low alcohol exposure categories, and lower ratios (fewer males) in the alcohol-exposed categories. Significant statistical differences are found for more males where alcohol exposure is low and significantly fewer males when exposed to 6+ drinks per drinking day (z = 1.65, p = 0.05, one-tailed). Boys are significantly less prevalent than girls at 6–7 years of age when born to mothers who were heavy prenatal binge drinkers.

3.2. Case control comparisons of FASD traits within each sex

For separate comparisons of boys vs. boys and girls vs. girls, there were significant categorical differences between children with FASD

Table 1
Child Physical Characteristics the Cardinal Facial Features of FAS for Boys and Girls by FASD Diagnosis and Alcohol Exposure for Randomly-Selected Normal Controls.

	Children with FASD	Alcohol-exposed children[1]	Unexposed children[1]	F-Score	*p*-value[2]
A. Physical and Dysmorphology Variables					
Boys	(n = 430) Mean (SD)	(n = 97) Mean (SD)	(n = 264) Mean (SD)		
Height (cm)	112.6 (6.0)	116.0 (5.8)	117.9 (6.3)	64.15	< 0.001[abc]
Weight (kg)	18.2 (3.1)	20.8 (3.6)	21.6 (4.2)	48.31	< 0.001[ab]
Child's Body Mass Index (BMI)	14.2 (1.2)	15.3 (1.8)	15.3 (1.7)	52.271	< 0.001[ab]
Head Circumference (OFC in cm)	49.5 (2.1)	51.4 (1.1)	51.5 (1.5)	100.530	< 0.001[ab]
Palpebral Fissure Length (cm)	2.3 (0.1)	2.4 (0.1)	2.5 (0.1)	152.538	< 0.001[abc]
Maxillary Arc (cm)	23.4 (1.5)	24.1 (0.8)	24.1 (0.8)	23.703	< 0.001[ab]
Mandibular Arc (cm)	24.3 (1.5)	25.2 (1.0)	25.2 (1.0)	29.613	< 0.001[ab]
Vermilion Border Ranking[3]	3.8 (0.6)	3.1 (0.7)	3.1 (0.8)	77.616	< 0.001[ab]
Philtrum Ranking[3]	3.8 (0.7)	3.2 (0.7)	3.3 (0.7)	49.663	< 0.001[ab]
Total Dysmorphology Score	15.8 (4.7)	6.8 (3.8)	6.8 (4.2)	394.479	< 0.001[ab]
Girls	(n = 411)	(n = 95)	(n = 248)		
Height (cm)	112.3 (5.8)	116.2 (7.6)	117.8 (6.4)	62.959	< 0.001[ab]
Weight (kg)	17.5 (2.9)	19.8 (3.5)	21.6 (4.1)	106.484	< 0.001[abc]
Child's BMI	13.8 (1.4)	14.7 (1.6)	15.5 (2.0)	72.739	< 0.001[abc]
Head Circumference (OFC in cm)	48.6 (3.7)	50.5 (1.6)	51.0 (2.1)	49.872	< 0.001[ab]
Palpebral Fissure Length (cm)	2.3 (0.1)	2.4 (0.1)	2.5 (0.4)	156.227	< 0.001[abc]
Maxillary Arc (cm)	23.1 (1.9)	23.8 (0.9)	24.0 (2.1)	13.449	< 0.001[ab]
Mandibular Arc (cm)	24.3 (1.0)	24.9 (1.1)	25.3 (1.0)	51.263	< 0.001[abc]
Vermilion Border Ranking[3]	3.9 (0.6)	3.2 (0.7)	3.0 (0.7)	110.075	< 0.001[ab]
Philtrum Ranking[3]	3.7 (0.7)	3.2 (0.7)	3.1 (0.7)	51.934	< 0.001[ab]
Total Dysmorphology Score	15.6 (4.4)	8.5 (4.0)	6.3 (4.1)	397.906	< 0.001[abc]
B. Cognitive and Behavioral Outcome Measures					
Boys	(n = 421)	(n = 97)	(n = 248)		
Non-verbal IQ: Raven progressive matrices centile	13.2 (12.6)	24.0 (20.0)	24.3 (19.8)	43.389	< 0.001[ab]
Verbal: TROG (test of reception of grammar)	13.4 (17.5)	31.6 (25.2)	24.3 (22.5)	38.616	< 0.001[ab]
Digit Span: WISC working memory scaled score	3.8 (2.5)	5.2 (2.3)	5.0 (2.6)	18.793	< 0.001[ab]
Behavior Problems: Achenbach TRF total behavior T-score	43.5 (33.0)	27.6 (27.5)	29.6 (26.2)	15.85	< 0.001[ab]
Attention Problems: Achenbach TRF inattention T-score	17.1 (12.1)	11.3 (11.2)	11.5 (10.7)	16.576	< 0.001[ab]
Girls	(n = 400)	(n = 95)	(n = 237)		
Non-verbal IQ: Raven progressive matrices centile	12.9 (11.9)	19.7 (13.5)	25.5 (20.8)	49.483	< 0.001[abc]
Verbal: TROG (test of reception of grammar)	12.6 (15.9)	29.8 (23.1)	31.1 (25.0)	65.036	< 0.001[ab]
Digit Span: WISC working memory scaled score	3.9 (2.6)	6.1 (2.7)	6.4 (2.9)	53.068	< 0.001[ab]
Behavior Problems: Achenbach TRF total behavior T-score	39.6 (35.4)	17.9 (16.8)	20.1 (22.5)	29.281	< 0.001[ab]
Attention Problems: Achenbach TRF inattention T-score	14.3 (11.9)	8.0 (8.8)	7.9 (9.5)	22.479	< 0.001[ab]

[1] Data presented for normal controls is only for those who entered the study via random selection.
[2] Post-hoc Dunnett's C were significantly different ($p < 0.05$) for: [a]FASD & Exposed; [b]FASD & Unexposed; [c]Exposed & Unexposed.
[3] Rating on the Astley/Clarren lip-philtrum guide.

and the two normal comparison groups for the majority of physical traits and growth measures (see Table 1, part A). This is expected given that these are variables that are dictated by the FASD diagnostic criteria (Hoyme et al., 2005). Virtually all traits formed a linear pattern for each sex: children with FASD were most affected, followed by exposed controls, and unexposed controls. For boys there was a statistically significant post-hoc, pairwise difference across all three groups (FASD and exposed, FASD and unexposed, and exposed and unexposed) for two variables: height and palpebral fissure length (PFL). There was post-hoc significance between two of the groups among boys (FASD and exposed and FASD and unexposed) for the remaining eight variables: weight, OFC, body mass index (BMI), maxillary arc, mandibular arc, vermilion border rating, philtrum rating, and total dysmorphology score. Alcohol exerts a significant, measureable negative effect on even the exposed boys found to be in the normal range.

For girls, there were significant pairwise differences across all three groups (FASD and exposed, FASD and unexposed, and exposed and unexposed) for five variables: weight, BMI, PFL, mandibular arc, and total dysmorphology score (Table 1). Furthermore, there were significant pairwise differences between two groups (FASD and exposed and FASD and unexposed) for the remaining variables: height, OFC, maxillary arc, vermilion border rating, and philtrum rating. Alcohol exposure had a more significant effect on girls which separated the categorical diagnostic and alcohol-exposure groups more clearly than in boys.

Comparing between sexes (boys to girls) in Table 1, the mean total dysmorphology score for alcohol-exposed, normal girls was 8.5 ± 4.0, which is significantly higher than boys, 6.8 ± 3.8 ($t = 2.91$, $p = 0.004$). In the other two diagnostic categories, children with FASD and unexposed children, boy vs. girl dysmorphology score averages are statistically similar.

The second section (B) of Table 1 contains means and standard deviations of cognitive and behavioral measures for boys and girls. Children with FASD performed significantly worse than either group of comparison children on each measure as dictated by FASD diagnostic criteria. Boys had significant, mean, pairwise differences in post-hoc analyses between two of the diagnostic groups on cognitive and behavioral measures: FASD and exposed controls and FASD and unexposed control boys. The FASD group was most cognitively impaired and behaviorally more problematic than control groups, but the pattern was not consistent in the predicted direction with alcohol exposure in the control groups. None of the five neurobehavioral measures differentiated between exposed and unexposed boy control groups in the expected direction.

For girls, there was a significant difference between FASD and exposed and FASD and unexposed girls for all measures. Notably, nonverbal IQ significantly differentiated across all female diagnostic groups.

3.3. Sequential logistic and multiple regression of variables associated with FASD physical traits and dysmorphology

Sex differences in the relationship between physical traits and dysmorphology scores were examined through separate sequential, regression analyses for boys and girls. There were 1533 children (776 boys and 757 girls) who had at least one measure within the following array of neuropsychological measures in those data collection sites in which these measures were administered. Sequential logistic and multiple regression analyses were adjusted for the following covariates: paternal drinking (number of drinks per occasion during pregnancy), weekly drinking (maternal drinks per week during pregnancy), daily drinking (maternal drinks per drinking day during pregnancy) at step 1, and income (total weekly household income), maternal education (years), and maternal BMI at step 2. In step 3 the neurobehavioral variables were entered. The dependent variable was total dysmorphology score.

Data preprocessing and assumptions were made, as almost all of the covariates and neurobehavioral variables had serious positive skewness. Logarithmic transformations were applied to all three continuous drinking variables and both IQ measures. Square root transformations were applied to behavior and attention problems as well as Digit Span. Weekly household income was trichotomized (1 = 0 to 490 Rands, 2 = 500 to 1200 Rands, 3 = 1055–15,000 Rands).

Missing values were found for all neuropsychological variables and covariates, ranging from less than 1% for the neuropsychological measures to 37% for paternal drinking. The pattern of missing values indicated they were not missing at random. The approach taken to deal with missing data was multiple imputation with $m = 25$. Dependent variables and sex were omitted from the imputation process to avoid overfitting. Relative efficiency for all variables in the final model exceeded 0.98.

A three-step sequential multiple regression examined (1) the relationship between a set of drinking variables and total dysmorphology score; (2) the additional predictability of dysmorphology offered by household income, maternal BMI, and maternal education; and (3) the association between dysmorphology and the child's neuropsychological functioning after adjusting for maternal drinking and demographic covariates. At each step variables entered were adjusted for each other and for variables entered at a previous step. Table 2 summarizes average (over 25 imputations) R^2, adjusted R^2, and statistics demonstrating change over the sequential steps. Table 3 provides pooled results of sequential multiple regression where Models 1 and 2 include only covariates and Model 3 includes neuropsychological variables as well as covariates.

The drinking covariates at step 1 significantly predicted dysmorphology, as expected, for both boys and girls, with averaged (over 25 imputations) adjusted $R^2 = 0.16$ and 0.20, respectively, $p < 0.001$. Note, however, in Table 3 that only one of the individual drinking variables, number of drinks per drinking day during pregnancy, when adjusted for each other, provided statistically significant prediction, $p > 0.05$, due to high correlations among drinking variables. Only number of drinks per drinking day (a binge measure) was a significant predictor of dysmorphology for both boys and girls. Failure of the other variables to provide significant prediction is due to the high correlations among the drinking variables.

The three maternal variables entered at step 2 added significantly to prediction (Table 2), with average change in $R^2 = 0.07$ and 0.09 for boys and girls, respectively, $p < 0.001$, following the pattern at step 1 of stronger predictability for girls than boys. Table 3 shows that among the three covariates, two offered statistically significant predictability for boys after adjustment for the remaining covariates: maternal BMI with average squared semipartial correlation = 0.018, and maternal education with average squared semipartial correlation = 0.048. For girls, only maternal education offered statistically significant predictability after adjustment for the remaining covariates, with averaged squared semipartial correlations of 0.076.

Change in R^2 at step 3, which measures the enhancement of the model provided by the association between neuropsychological variables and dysmorphology after adjustment for covariates, also was greater for girls, with average change in $R^2 = 0.06$, than for boys, with average change in $R^2 = 0.04$, respectively. The difference in R between girls and boys, however, failed to achieve statistical significance, $p = 0.09$, two-tailed test.

The pattern of neuropsychological associations with dysmorphology was different for males and females. For males, after adjusting for covariates and other predictors, only verbal IQ (squared semipartial correlation = 0.015) was significantly associated with total dysmorphology score; but for females, nonverbal IQ (squared semipartial correlation = 0.018) and Digit Span (squared semipartial correlation = 0.009) were significantly associated with that score. The negative signs of the unstandardized coefficients in Table 3 confirm that, as expected, lower intellectual functioning scores were associated with higher dysmorphology scores. Behavior and attention problems show no statistically significant association with dysmorphology after adjustment for all other variables.

3.4. Regression of variables associated with FASD diagnosis

Sex differences in the relationship between covariates, neuropsychological functioning and a FASD diagnosis were examined through separate sequential logistic regression analyses for boys and girls. The sample utilized was the same as the previous regression. Sequential logistic regression analyses were again adjusted for the same covariates: paternal drinking, weekly drinking, daily drinking at step 1, and income, maternal education, and maternal BMI at step 2. The binary dependent variable was FASD vs randomly-selected control. Data preprocessing and assumptions were also the same as above because of serious positive skewness in many variables. Logarithmic transformations were applied to both IQ measures and all three continuous drinking variables. Square root transformations were applied to behavior and attention problems as well as Digit Span. Weekly household income was trichotomized.

Missing values were found for all predictors and covariates, and again multiple imputation was employed to deal with missing data, with $m = 25$. Relative efficiencies for all variables in the analyses were greater than 0.985. Dependent variables and sex were omitted from the imputation process to avoid overfitting.

Table 2
Summary of Models Averaged over 25 Imputations

Sex	Model	R Square	Adjusted R^2	Std. Error of the Estimate	R^2 Change	F change	df1/df2
male	1	0.16	0.16	5.47	0.16	22.74*	5/580
	2	0.24	0.23	5.23	0.07	18.70*	3/577
	3	0.27	0.26	4.13	0.04	5.55*	5/572
female	1	0.21	0.20	5.23	0.21	29.22*	5/559
	2	0.29	0.28	4.95	0.09	22.78*	3/556
	3	0.35	0.33	4.78	0.06	9.34*	5/551

* $p < 0.001$.

Table 3
Total Dysmorphology Score as Predicted by Eight Drinking, Maternal, and Demographic Covariates and Five Neuropsychological Indicators for Males and Females, Pooled over 25 Imputations.

Model	Variable	Unstandardized Coefficients		t	p	95% CI for B		Squared Semipartial Correlation[a]
		B	Std. Err.			Lower	Upper	
1 (male)	(Constant)	9.320	0.439	21.254	< 0.001	8.459	10.182	
	Binge 3+ during pregnancy	0.273	0.935	0.292	0.770	−1.561	2.107	< 0.001
	Binge 5+ during pregnancy	0.194	0.803	0.242	0.809	−1.380	1.769	< 0.001
	Number of drinks per occasion (father of COI) during pregnancy (log)	−0.275	0.369	−0.745	0.457	−1.003	0.453	0.001
	Number of drinks per drinking day during pregnancy (log)	2.185	0.780	2.800	0.006	0.640	3.730	0.028
	Number of drinks per week during pregnancy (log)	1.066	0.721	1.478	0.140	−0.352	2.484	0.005
2	(Constant)	14.125	3.932	3.592	< 0.001	6.410	21.841	
(male)	Binge 3+ during pregnancy	0.991	0.905	1.094	0.274	−0.785	2.767	0.002
	Binge 5+ during pregnancy	−0.069	0.774	−0.089	0.929	−1.587	1.449	< 0.001
	Number of drinks per occasion (father of COI) during pregnancy (log)	−0.513	0.357	−1.437	0.152	−1.217	0.191	0.006
	Number of drinks per drinking day during pregnancy (log)	1.609	0.736	2.186	0.030	0.154	3.064	0.016
	Number of drinks per week during pregnancy (log)	0.454	0.686	0.661	0.509	−0.894	1.802	0.001
	Weekly household income (trichotomized)	−0.540	0.322	−1.677	0.094	−1.171	0.092	0.006
	Maternal BMI	−7.107	2.328	−3.053	0.002	−11.674	−2.541	0.018
	Maternal Education	2.533	0.497	5.100	< 0.001	1.559	3.508	0.048
3 (male)	(Constant)	18.352	4.098	4.478	< 0.001	10.315	26.390	
	Binge 3+ during pregnancy	0.906	0.886	1.022	0.307	−0.832	2.644	0.002
	Binge 5+ during pregnancy	0.299	0.761	0.393	0.695	−1.193	1.790	< 0.001
	Number of drinks per occasion (father of COI) during pregnancy (log)	−0.505	0.352	−1.434	0.153	−1.198	0.189	0.006
	Number of drinks per drinking day during pregnancy (log)	1.539	0.679	2.266	0.024	0.201	2.877	0.015
	Number of drinks per week during pregnancy (log)	0.198	0.658	0.301	0.764	−1.094	1.489	< 0.001
	Weekly household income (trichotomized)	−0.360	0.318	−1.131	0.258	−0.984	0.264	0.003
	Maternal BMI	−6.590	2.298	−2.868	0.004	−11.098	−2.083	0.016
	Maternal Education	1.975	0.506	3.907	< 0.001	0.984	2.967	0.029
	Nonverbal IQ (log)	−0.954	0.710	−1.345	0.179	−2.345	0.436	0.003
	Verbal IQ (log)	−1.444	0.499	−2.895	0.004	−2.422	−0.466	0.015
	Digit span (sqrt)	−0.461	0.425	−1.086	0.278	−1.294	0.371	0.002
	Behavior problems (sqrt)	−0.043	0.157	−0.276	0.782	−0.351	0.264	< 0.001
	Attention problems (sqrt)	0.035	0.239	0.146	0.884	−0.433	0.503	< 0.001
1	(Constant)	8.960	0.535	16.752	< 0.001	7.900	10.020	
(female)	Binge 3+ during pregnancy	0.184	0.868	0.212	0.832	−1.517	1.885	< 0.001
	Binge 5+ during pregnancy	0.789	0.802	0.983	0.326	−0.785	2.363	0.002
	Number of drinks per occasion (father of COI) during pregnancy (log)	0.293	0.371	0.790	0.431	−0.439	1.024	0.002
	Number of drinks per drinking day during pregnancy (log)	1.817	0.853	2.129	0.037	0.111	3.523	0.027
	Number of drinks per week during pregnancy (log)	1.261	0.748	1.687	0.092	−0.209	2.732	0.007
2	(Constant)	8.109	3.733	2.172	0.030	0.788	15.431	
(female)	Binge 3+ during pregnancy	0.291	0.830	0.351	0.726	−1.337	1.920	< 0.001
	Binge 5+ during pregnancy	0.315	0.761	0.414	0.679	−1.178	1.807	< 0.001
	Number of drinks per occasion (father of COI) during pregnancy (log)	0.111	0.344	0.321	0.748	−0.568	0.789	< 0.001
	Number of drinks per drinking day during pregnancy (log)	1.231	0.735	1.675	0.097	−0.230	2.691	0.014
	Number of drinks per week during pregnancy (log)	1.148	0.681	1.687	0.092	−0.189	2.484	0.006
	Weekly household income (trichotomized)	−0.548	0.324	−1.689	0.092	−1.184	0.089	0.006
	Maternal BMI	−4.194	2.322	−1.806	0.071	−8.749	0.360	0.007
	Maternal Education	3.009	0.484	6.222	< 0.001	2.060	3.958	0.076
3	(Constant)	16.568	3.937	4.208	< 0.001	8.846	24.290	
(female)	Binge 3+ during pregnancy	0.503	0.806	0.624	0.533	−1.078	2.084	0.001
	Binge 5+ during pregnancy	0.508	0.737	0.690	0.490	−0.937	1.953	0.001
	Number of drinks per occasion (father of COI) during pregnancy (log)	0.079	0.332	0.237	0.813	−0.576	0.734	0.000
	Number of drinks per drinking day during pregnancy (log)	0.641	0.709	0.903	0.369	−0.768	2.049	0.004
	Number of drinks per week during pregnancy (log)	1.037	0.661	1.569	0.117	−0.261	2.336	0.006
	Weekly household income (trichotomized)	−0.300	0.316	−0.950	0.342	−0.921	0.320	0.002
	Maternal BMI	−4.666	2.224	−2.098	0.036	−9.027	−0.305	0.009
	Maternal Education	1.908	0.493	3.871	< 0.001	0.941	2.874	0.030
	Nonverbal IQ (log)	−2.205	0.708	−3.115	0.002	−3.593	−0.817	0.018
	Verbal IQ (log)	−0.777	0.519	−1.498	0.134	−1.794	0.240	0.004
	Digit span (sqrt)	−0.838	0.387	−2.165	0.030	−1.596	−0.079	0.009

(continued on next page)

Table 3 *(continued)*

Model	Variable	Unstandardized Coefficients		t	p	95% CI for B		Squared Semipartial Correlation[a]
		B	Std. Err.			Lower	Upper	
	Behavior problems (sqrt)	0.090	0.154	0.583	0.560	−0.212	0.392	0.001
	Attention problems (sqrt)	−0.029	0.236	−0.124	0.901	−0.493	0.434	< 0.001

[a] Squared semipartial correlation is the proportion of variance in Total Dysmorphology Score contributed by the variable after adjusting for all other variables in the model.

Table 4
Summary of Sequential Steps with Means (and Standard Deviations) over 25 Imputations

Gender	Step	Chi-square	df	Chi-square increase	df	Nagelkerke R^2	Classification success (percentage)		
							RS controls	FASD	Overall
Male	1	144.7	5	144.7	5	0.30	72.4	74.4	73.6
		(3.04)		(3.04)		(.005)	(0.32)	(0.62)	(0.34)
	2	168.7	8	24.1	3	0.34	69.3	75.6	73.0
		(4.20)		(2.85)		(.007)	(1.16)	(0.83)	(0.86)
	3	217.4	13	48.6	5	0.42	69.6	80.9	76.3
		(3.60)		(2.08)		(.006)	(1.10)	(0.44)	(0.58)
Female	1	161.5	5	161.5	5	0.34	74.3	74.2	74.2
		(5.21)		(5.21)		(.007)	(0.54)	(0.46)	(0.35)
	2	204.0	8	41.9	3	0.41	71.6	79.1	76.0
		(5.55)		(4.69)		(.009)	(1.13)	(0.91)	(0.75)
	3	291.6	13	87.5	5	0.54	74.8	86.0	81.4
		(5.24)		(3.77)		(.007)	(0.88)	(0.48)	(0.43)

Table 5
Diagnosis of FASD vs RS Control as Predicted by Eight Drinking, Maternal, and Demographic Covariates and Five Neuropsychological Indicators for Males and Females.

Gender	Variable	*B*	S.E.	*p*	Odds Ratio Exp(*B*)	95% C.I. for EXP(B)	
						Lower	Upper
Male	Binge 3+ during pregnancy	0.800	0.413	0.053	2.226	0.991	5.000
	Binge 5+ during pregnancy	−0.175	0.407	0.667	0.839	0.378	1.864
	Number of drinks per occasion (father of COI) during pregnancy (log)	−0.104	0.270	0.701	0.901	0.529	1.534
	Number of drinks per drinking day during pregnancy (log)	1.255	1.497	0.402	3.506	0.186	66.073
	Number of drinks per week during pregnancy (log)	0.440	1.101	0.690	1.552	0.179	13.438
	Weekly household income (trichotomized)	0.133	0.155	0.391	1.142	0.843	1.549
	Maternal BMI	−0.012	0.021	0.582	0.989	0.949	1.030
	Maternal Education	−0.120	0.041	0.003	0.887	0.818	0.961
	Nonverbal IQ (log)	−1.086	0.361	0.003	0.338	0.166	0.686
	Verbal IQ (log)	−0.631	0.238	0.008	0.532	0.334	0.847
	Digit span (sqrt)	0.007	0.232	0.976	1.007	0.639	1.588
	Behavior problems (sqrt)	−0.017	0.080	0.833	0.983	0.841	1.150
	Attention problems (sqrt)	0.193	0.131	0.141	1.213	0.938	1.568
	Constant	1.876	0.929	0.044	6.528	1.056	40.375
Female	Binge 3+ during pregnancy	1.014	0.438	0.021	2.756	1.167	6.507
	Binge 5+ during pregnancy	−0.441	0.462	0.339	0.643	0.260	1.592
	Number of drinks per occasion (father of COI) during pregnancy (log)	−0.002	0.288	0.995	0.998	0.567	1.758
	Number of drinks per drinking day during pregnancy (log)	−0.952	1.639	0.562	0.386	0.015	9.617
	Number of drinks per week during pregnancy (log)	2.450	1.268	0.053	11.594	0.965	139.347
	Weekly household income (trichotomized)	0.463	0.175	0.008	1.589	1.128	2.239
	Maternal BMI	−0.017	0.022	0.439	0.983	0.942	1.026
	Maternal Education	−0.132	0.047	0.006	0.877	0.799	0.962
	Nonverbal IQ (log)	−0.978	0.426	0.022	0.376	0.163	0.868
	Verbal IQ (log)	−1.027	0.289	< 0.001	0.358	0.203	0.631
	Digit span (sqrt)	−0.736	0.239	0.002	0.479	0.300	0.765
	Behavior problems (sqrt)	0.090	0.099	0.361	1.095	0.902	1.329
	Attention problems (sqrt)	−0.028	0.160	0.862	0.972	0.710	1.332
	Constant	3.500	1.068	0.001	33.121	4.079	268.941

A three-step sequential multiple regression examined (1) the relationship between drinking variables and FASD diagnosis; (2) the additional predictability of FASD diagnosis offered by household income, maternal BMI, and maternal education; and (3) the further predictability of FASD diagnosis provided by the child's neuropsychological functioning. At each step variables entered were adjusted for each other and for variables entered at a previous step. Table 4 summarizes averages (over 25 imputations) of χ^2, increase in χ^2, and classification success over the sequential steps. Table 5 provides pooled results of sequential logistic regression at the last step of the analysis, including covariates from the first two steps and neuropsychological predictors at the final step.

The set of drinking covariates at step 1 significantly predicted FASD diagnosis, as expected, for both boys and girls, with averaged $\chi^2(5)$

= 144.7 and 161.5, respectively, both $p < 0.001$, with Nagelkerke $R^2 = 0.30$ and 0.34, respectively. Note, however, in Table 5 that virtually no individual drinking variables, when adjusted for each other and all other variables, provided statistically significant prediction, $p > 0.05$, due to the high correlation. The only exception was binges of 3+ drinks during pregnancy significantly affected the outcomes for females.

The three maternal variables entered at step 2 added significantly to prediction, with average change in $\chi^2(3) = 24.1$ and 41.9 for boys and girls, respectively, both $p < 0.001$, following the pattern at step 1 of stronger predictability for girls than boys. At this point, Nagelkerke $R^2 = 0.34$ and 0.41 for boys and girls, respectively. Table 5 shows that only maternal education offered statistically significant predictability after adjustment for the remaining variables, odds ratio = 0.887 for both boys and girls, $p = 0.003$ and 0.006 for boys and girls, respectively. The ratio less than 1 indicates that the odds of a FASD diagnosis decreased as maternal education increased.

Change in χ^2 at step 3, which measures the contribution of neuropsychological variables to prediction after adjustment for all covariates, also was greater for girls, with average change in $\chi^2(5) = 87.5$, than for boys, with average change in $\chi^2(5) = 48.6$, both $p < 0.001$, with final Nagelkerke $R^2 = 0.42$ and 0.54 for boys and girls, respectively. The difference in r between boys and girls was statistically significant, $z = -2.9$, $p = 0.004$.

The pattern of neuropsychological predictors was different for males and females. For males, after adjusting for covariates and other predictors, verbal (odds ratio = 0.532) and non-verbal IQ (odds ratio = 0.338) significantly predicted FASD diagnosis; but for females, Digit Span (odds ratio = 0.479) as well as verbal (odds ratio = 0.358) and nonverbal IQ (odds ratio = 0.376) significantly predicted that diagnosis. The negative signs of the unstandardized coefficients in Table 5, as well as the odds ratio values less than 1, confirm that, as expected, lower intellectual functioning scores were associated with greater odds of FASD diagnosis. Behavior and attention problems provide no statistically significant prediction of FASD after adjustment for all other variables.

4. Discussion

4.1. Sex ratio findings – males more susceptible to early demise

Sex ratio analysis in this general population indicated that males were significantly less prevalent in the groups exposed to the heaviest prenatal alcohol use: severe binge drinking (six or more per drinking day) where the highest blood alcohol concentrations are produced in mother and fetus. While this may be due to skewing in a relatively small sample for sex ratio analysis, it seems unlikely, as the trend is clear in each alcohol exposure category. Where there is less alcohol exposure, there are significantly more boys than girls and where there is more alcohol exposure there are fewer boys. Boys seem more susceptible to alcohol exposure from conception through age seven and have a reduction in their overall viability when exposed to alcohol prenatally. Furthermore, the FAS diagnosis group, where alcohol exposure was the greatest (May et al., 2005, 2008, 2013b), has fewer boys per 100 girls than any other diagnostic category. Similarly, binge exposure categories of 3+ or 6+ drinks or more per occasion also had fewer males than the lower exposure categories. Males are more susceptible to prenatal and postpartum mortality from prenatal alcohol exposure, and possibly alcohol exposure via extended breastfeeding in this population (May et al., 2016b). Furthermore, in the regression analysis, dysmorphology in boys (but not in girls) was significantly related to low maternal BMI which in the literature is related to high levels of alcohol delivered to the fetus (Khaole et al., 2004; May et al., 2008, 2013b; Navara, 2014).

4.2. Case control comparison – more similarities than differences

When individual male and female traits were compared across diagnostic, case control categories, virtually all physical growth, development, and minor anomalies were significantly different among groups. This indicates diagnostic, categorical validity in the sample, and a similar continuum of effects associated with various exposures to alcohol in the prenatal period for both sexes. For the physical traits linked most to FASD (Table 1), both sexes were rather equally affected by prenatal alcohol exposure, with the exception of females who exhibited significantly more total dysmorphology and cardinal features associated with FASD. Regression of predictors of dysmorphology showed the same trend.

In case control comparisons of cognitive and behavioral traits, a similar pattern was displayed by both sexes. Children with FASD and alcohol-exposed controls suffered from more depressed developmental scores than the unexposed controls for every measure. The only major exception was that girls exhibited significantly poorer non-verbal IQ performance than boys, for even the exposed control girls were performing significantly more poorly than the unexposed girls in the post-hoc comparison.

4.3. Multiple correlation analysis – female development negatively associated with prenatal alcohol exposure

Multiple correlation analysis indicated that girls were indeed more affected than boys as predicted by both dysmorphology and FASD diagnosis. The sequential multiple regression indicated that dysmorphology was more strongly associated with girls (adjusted $R^2 = 0.33$) than boys (adjusted $R^2 = 0.26$). But even though dysmorphology was significantly more affected by each set of predictors (drinking, maternal BMI, income, and education) and associated variables (cognitive and behavioral) when each group entered the regression, the overall differences in all traits were not statistically significant between boys and girls.

On the other hand, the sequential logistic regression analysis of the same variables associated with FASD diagnosis indicated a statistically significant difference between boys and girls (Nagelkerke $R^2 = 0.42$ for boys and 0.54 for girls, $z = -2.9$, $p = 0.004$). Girls were more highly affected in each step of the model: drinking, maternal distal risk factors, and cognition variables.

While both boys and girls were significantly affected in the neuropsychological domain, girls were more negatively affected and the pattern was different for each sex. Verbal and non-verbal IQ suppression were the significant predictors of a FASD diagnosis for boys. For girls, Digit Span (executive functioning), verbal IQ, and non-verbal IQ all significantly predicted an FASD diagnosis. Lower intellectual functioning was greatest among the girls with FASD. Behavioral variables did not significantly differentiate boys from girls.

4.4. Patterns from the various analyses – some differences but mainly similarities

Therefore, from the various analyses we conclude that survivability is reduced more for males than females by prenatal alcohol exposure, particularly when the alcohol exposure occurs in a binge pattern. It could be that the most affected males do not survive the prenatal period and that the severely affected males who do survive may be particularly vulnerable in the neonatal, infant, toddler, and early childhood periods of life. Highly alcohol-exposed girls, on the other hand, may survive these same developmental stages in greater numbers, yet suffer more dysmorphology and developmental delays, both physical and cognitive.

This elaborate analysis of differences may however, obscure the most basic findings from these data. Both males and females exposed to alcohol in the prenatal period, particularly those exposed to heavy maternal binge drinking, are consistently and negatively affected in

similar ways, both physical and neurobehavioral. Alcohol exposure in the prenatal period is not good for either sex.

4.5. Strengths and limitations

Unique traits of this SA population, such as drinking style and environmental challenges for child development, produce high rates of alcohol exposure and FASD, and therefore provide a substantial number of cases to study. This has allowed us the opportunity to undertake this rather complex analysis to see if there were differences between boys and girls from prenatal alcohol exposure. There are some differences, but both sexes are generally affected in similar ways.

However, the uniqueness of this alcohol-using subpopulation (e.g., regular binge drinking on weekends by males and females and frequent exposure to alcohol via breastmilk) may render some of these findings less applicable to other populations who drink differently and are less likely to breastfeed for long periods while also drinking. We feel these findings are theoretically and practically applicable to other populations, but the magnitude of effect and degree of applicability may be relative. The reader must be the judge of how applicable the findings are to other populations and clinical applications.

5. Conclusions

Overall, both boys and girls in these SA communities are consistently and similarly affected by prenatal alcohol exposure on most physical and cognitive development associated with brain development and overall functioning. However, sex ratio analysis indicated that survivability of boys may be more negatively affected by alcohol exposure in the prenatal and/or early postpartum periods. Multiple correlation analysis indicated that girls, overall, were more negatively affected by prenatal alcohol exposure than boys by age seven, particularly in cognitive performance and total dysmorphology.

Conflict of interests

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

Contributors

Philip May was the principal investigator of the NIH grant that funded this research, and he, with assistance from Barbara Tabachnick, Julie Hasken, and Zachary Burroughs on final data analysis and table preparation, was the major writer and final editor of all drafts. Anna-Susan Marais was the program manager who supervised all data 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 and, along with Marlene de Vries, oversaw all final data compilation in the field program office, including final data quality and manuscript preparation. Belinda Joubert, Marise Cloete, and Isobel Botha 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 the analysis of results for diagnosis and manuscript preparation. Eugene Hoyme, Luther Robinson, Melanie Manning, and Heidre Bezuidenhout generated all dysmorphology data for the team in the field and made final diagnoses of the children in multidisciplinary case conferences. Soraya Seedat and Charles Parry are the South African co-investigators who participated in the design 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.

Role of the funding source

This project was funded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), Grant RO1/UO1 AA01115134. Mr. Burroughs' participation was funded by the Robert Noyce Scholarship Program of the National Science Foundation at Catawba College.

Acknowledgements

Protocols and consent forms were approved by: The University of New Mexico (UNM); UNM School of Medicine, HRRC; The University of Cape Town, and Stellenbosch University, Faculty of Medicine and Health Sciences. Active consent forms for all children who participated in any phase of this study were completed by parents or other legal guardians. Mothers who were interviewed about maternal risk factors also provided a separate, written consent for the interview process.

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