Title: Prenatal alcohol exposure is associated with early motor, but not language development in a South African cohort

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Abstract

Objective: To investigate the association of prenatal alcohol exposure (PAE) and early neurodevelopment in the first 2 years of life, adjusting for maternal sociodemographic and psychosocial factors, in the Drakenstein Child Health Study (DCHS), a South African birth cohort study.

Methods: The DCHS comprises a population-based birth cohort of 1143 children, of which, a subsample completed the Bayley Scales of Infant Development-III (BSID-III) at 6 (n = 260) and 24 months of age (n = 734). A subset of alcohol exposed, and unexposed children was included in this analysis at age 6 months (n = 52 exposed; n = 104 unexposed) and 24 months (n = 92 exposed; n=184 unexposed). Multiple hierarchical regression was used to explore the associations of PAE with motor and language development.

Results: PAE was significantly associated with decreased gross motor (OR = 0.16, 95%CI 0.06-0.44, p = 0.001) or fine motor (OR = 0.16, 95%CI 0.06-0.46, p = 0.001) functioning after adjusting for maternal sociodemographic and psychosocial factors at 6 months of age only. No significant effects were found in either receptive or expressive communication and cognitive outcomes at either time point.

Conclusion: PAE has potentially important consequences for motor development in the first 2 years of life, a period during which the most rapid growth and maturation occurs. These findings highlight the importance of identifying high-risk families in order to provide preventive interventions, particularly in antenatal clinics and early intervention services.

Keywords

Prenatal Alcohol Exposure$_1$, Motor Development$_2$, Language Development$_3$, Neurodevelopment$_4$,

Significant outcomes
Prenatal alcohol exposure (PAE) had a significant impact on motor functioning after adjusting for variety of sociodemographic and psychosocial factors at 6 months of age, but not on cognitive or language development.
The findings of this study highlight the importance of identifying psychosocial risk factors, particularly in antenatal clinics and early intervention services in a South African context.

Limitations
The Bayley Scales of Infant Development-III tool assesses general ability of a given task but may have low sensitivity for detecting minor developmental impairments especially during infancy.
Language impairments are very subtle in the early years and may be more difficult to identify impairments than in other domains.
A small sample size may have reduced the power of the study and findings may not be generalizable to other populations.

Introduction

Prenatal alcohol exposure (PAE) has been recognized as a major global public health concern. A recent study estimated 9.8% of mothers consumed alcohol during pregnancy and 4.3% were heavy drinkers (defined as an average of two or more drinks per day; Popova et al., 2017). Estimated global prevalence rates of fetal alcohol spectrum disorders (FASDs) have been reported at 7.7 (4.9 - 11.7) per 1000 children (Olivier et al., 2016). In low and middle-income countries (LMICs), such as South Africa, the estimated prevalence of FASDs is as high as 111.1 per 1,000 children in some communities (Olivier et al., 2016). The majority of previous studies exploring the impact of PAE on child development in the context of psychobiological and psychosocial factors have been performed in high-income countries, even though higher rates of PAE, poverty, post-traumatic stress disorder (PTSD) and depression exist in LMICs (Flak et al., 2014; Keen et al., 2010; May et al., 2008). The research taking into account contextual factors such as those cited above, underscores the importance of examining the adverse effects of PAE in young children (Flak et al., 2014; May et al., 2008), within the broader context of psychosocial and environmental risk factors that may additionally influence not only early neurodevelopmental outcomes, but also lifelong health trajectories.

The adverse effects of PAE manifest a continuum of disorders, namely, FASDs. Fetal alcohol syndrome (FAS) is a pattern of often irreversible physical and mental birth deficiencies (Nayak & Murthy, 2008; Safe et al., 2018), while alcohol related neurodevelopmental disorder (ARND) and alcohol related birth defects (ARBDs) are described as conditions in which the exposed child demonstrates some but not all features of FAS (Sokol, 2003). Previous studies have shown that FAS and ARND are associated with a range of impairments in motor functioning, reading comprehension or executive functioning in the early school years (Adnams et al., 2001; Comasco

et al., 2018; Cone-Wesson, 2005). Safe et al. (2018), for example, have reported that children with FAS displayed both motor function and language impairments at 12 years of age, while Coggins et al. (2007) found that school-aged children with FASDs often exhibit clinically meaningful deficits in language and social communication between 6-12 years of age. Previous work by Viholainen et al. (2006) reported that impaired language development has also been found to be precursor of problems with motor functioning in the school years.

While there is a rapidly growing literature detailing the effects of PAE on neurodevelopmental outcomes in school-going children, comparable data across motor and language functioning are limited in very young children. A previous cross-sectional study assessed specific developmental domains and found PAE deficits at 12 months of age: motor coordination and gross motor functioning (Hutchinson et al., 2019). Other cross-sectional analyses found that FAS was associated with abnormal walking and balance (Henderson et al., 2007; Kalberg et al., 2006; Kaplan-Estrin et al., 1999; Mattson et al., 2011; O'leary, 2004), and deficits in receptive and expressive communication through 2 years (Kodituwakku, 2007; Kodituwakku et al., 2011; O'leary et al., 2009). However, very few studies included data at different timepoints in the first two years of life (see Hendricks et al., 2019). Of the few studies exploring developmental impairments over time, heavy alcohol exposure was significantly associated with delayed motor functioning in toddlers between 12-17 months but not at 24 months of age (Davies et al., 2011; Fried & Watkinson, 1988; Jacobson & Jacobson, 2002). However, the heterogeneity in designs and methodologies of previous studies limit the ability to interpret results across different age cohorts. For example, the impact of maternal alcohol consumption on child outcomes using a clinical diagnosis of FAS without focus on children who do not meet the FASD criteria was reported in only one study (Davies et al., 2011).

Much of the longitudinal research describing the developmental outcomes in early childhood has been conducted in well-resourced settings (Fried & Watkinson, 1990; Fried et al., 1992; Kaplan-Estrin et al., 1999), less is known about the effects of PAE on early neurodevelopmental outcomes at different time timepoints in LMICs, and much of the work published to date has lacked control groups and or has adjusted for very few confounders (maternal age, gestation, birth weight and parity; Fried & Watkinson, 1988; 1990; Fried et al., 1992; Jacobson & Jacobson, 2002). Few studies have adjusted for additional psychosocial factors, such as maternal PTSD, which frequently co-occurs with PAE and which may have detrimental effects on young children's' neurodevelopmental outcomes.

Aim of the study

This study aimed to investigate the association of PAE and early neurodevelopment through two years of age, adjusting for sociodemographic and psychosocial factors in the Drakenstein Child Health Study (DCHS), a South African birth cohort study.

Materials and methods

Design and setting

This study formed part of the DCHS, a multidisciplinary birth cohort study investigating the early determinants of child health (Donald et al., 2018; Stein et al., 2015; Zar et al., 2016). The DCHS enrolled pregnant women (20 to 28 weeks' gestation) from two primary health care clinics, Mbekweni (a predominantly black African community) and TC Newman (a mixed-ancestry community) in the Western Cape, South Africa. Both communities are characterized by low SES and a high prevalence of multiple psychosocial risk factors (Zar et al., 2016). Pregnant women were eligible to participate if they were 18 years or older, had access to one of the two

primary health care clinics for antenatal care and had stated no intention to move out of the district within the following year. Mother-child dyads were followed longitudinally until children were at least 6 years of age.

Participants

This study utilized a subgroup from the DCHS. The PAE group comprised mothers with a minimum score of 11 on the alcohol questions of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST; Humeniuk et al., 2006). A follow-up cohort completed a measure on alcohol questions at 3-6 weeks and 24 months of age. Mothers were asked postpartum to provide a positive history of alcohol use in any of the 3 trimesters of pregnancy at levels consistent with the World Health Organization's (WHOs) moderate-to-severe alcohol use. The unexposed group included children whose mothers had a score less than 11 on the ASSIST antenatally. After birth, infants identified were included for the study unless the mothers had a positive urine screen for any other drug abuse (opiates, marijuana, cocaine, methamphetamine, barbiturates). Infants born prematurely or with any other congenital malformations, as well as sets of twins and triplets were excluded from the study.

In total, there were 1143 live births in the DCHS (see Donald et al., 2018). A subsample of the larger cohort completed the BSID-III at 6 months (n = 260), whereas the full cohort was invited to participate at 24 months (n = 734) making a larger sample available. At 6 and 24 months of age, a subset of infants and toddlers were selected whose mothers reported moderate-to-severe levels of alcohol consumption and for whom Bayley Scales of Infant Development (BSID-III) data were available. Of the 260 infants, 52 were exposed to alcohol at 6 months, and of the 734 toddlers, 92 were exposed to alcohol at 24 months. The unexposed group comprised 104 at 6

months and 184 at 24 months. Unexposed control children were randomly matched for maternal education and clinic site in a 1:2 ratio (Figure 1).

Measures

Participants were asked to complete self-reported and clinician-administered measures at antenatal and postnatal study visits in their preferred language, English, Afrikaans or isiXhosa. At the point of assessments (6 and 24 months of age), every effort was made to ensure a safe, anonymous, confidential and supportive environment. Translation of the measures from English to Afrikaans and isiXhosa included a standard forward and back-translation process (see Stein et al., 2015). Prior to the administration of the measures, adult mothers or legal guardians of the children received enough information about the study and were asked to complete an informed consent form in their preferred language.

Maternal sociodemographic, psychosocial and infant measures for this study have previously been described (Donald et al., 2018, Stein et al., 2015) and included:

Sociodemographic measures. Measures included data on SES (maternal income, education, employment status and asset sum), marital status and HIV status (Myer et al., 2008). Higher scores on this validated composite score indicated higher SES.

Psychosocial measures. Measures included data on composite scores of maternal smoking (cigarette and cannabis use) and psychological variables (PTSD and depression) administered antenatally. Maternal smoking was assessed using the ASSIST (Humeniuk et al., 2006), maternal PTSD was assessed using the Modified Posttraumatic Stress Disorder Symptom Scale (MPSS) (Foa et al., 1993) and maternal depression was assessed using the Beck Depression Inventory (BDI-II) (Beck et al., 1996).

Composite scores were created for maternal smoking and psychological variables. The indicators for SES included maternal income, education, employment status and asset sum; smoking included cigarette and cannabis use; and psychological variables included PTSD and depression. Composite variables were used to combine data into a single score as they are considered more robust than a unidimensional measure (Field, 2013).

*ASSIST***.** As above, the ASSIST assessed alcohol or substance use. This measure includes seven items with scores from 0-10 for alcohol and 0-3 for illicit drugs indicating low risk; 11-26 for alcohol and 4-26 for illicit drugs indicating moderate risk and above 26 as high risk of severe problems, with the likelihood of alcohol dependence (Group, 2002). The higher the score, the greater the alcohol-related risk. The ASSIST has good reliability and validity in several countries including Australia, Brazil, Ireland, India, Israel, the Palestinian Territories, Puerto Rico, the United Kingdom and Zimbabwe (Group, 2002) and in South Africa (Humeniuk et al., 2006).

Bayley-III Scales of Infant Development (BSID-III). The BSID-III was conducted at the 6- and 24-month visits, to assess child development in infants and toddlers between 0-42 months (Bayley, 2006). This is an international, well-validated test that was used to measure language and motor development. The BSID-III has been standardized with a stratified sample of 1000 children ranging from 0-42 months that was representative of the US population with respect to gender, race/ethnicity, geographic region, and parent education level having high reliability and validity (Bayley, 2006). The Bayley-III has been shown to be a reliable tool for use among the South African population (Rademeyer & Jacklin, 2013).

The motor scale evaluated early fine and gross motor development (Bayley, 2006). The gross motor subset included 72 items that assessed movement of the limbs, static positioning (e.g., sitting, standing), dynamic movement, including locomotion, coordination, balance and motor planning. The fine motor subtest included 66 items that assessed prehension, perceptual-motor integration, motor planning, speed, visual tracking, reaching, object grasping, object manipulation, functional hand skills, and responses to tactile information. The motor assessments were administered using directly observed items for the infant and toddler (Bayley, 2006).

The language scale assessed receptive and expressive communication and was directly administered to the infant or toddler (Bayley, 2006). The receptive communication subtest includes 49 items that assessed pre-verbal behaviour, vocabulary development (identifying objects and pictures), understanding morphological development (pronouns and prepositions), morphological markers (e.g. plural, tense markings, the possessive), social referencing and verbal comprehension (Bayley, 2006). The expressive communication subtest included 48 items that assessed pre-verbal communication (babbling, gesturing), vocabulary development (naming objects, pictures or naming attributes) and morpho-syntactic development. Composite scores were based on the composite equivalents of the scaled scores. Scaled scores were based on scores with a mean of 10 and standard deviation of 3 and range from 1-19. At 6 months scaled scores were corrected for prematurity. The assessors were trained by a paediatric neurologist who ensured quality control and scoring precision. A trained paediatric occupational therapist or physiotherapist administered the BSID - III scales in the home language of the infants and toddlers. The assessors had background experience in paediatric clinical and research environments and were blinded to the exposure status of the children.

The DCHS was approved by the Faculty of Health Sciences Human Research Ethics Committees of the University of Cape Town (UCT) and Stellenbosch University in South Africa, and by the Western Cape Department of Health Provincial Research Committee. All study participants provided written informed consent.

Statistical analysis

The data were analyzed using descriptive statistics which included frequencies and percentages for categorical data while means (SD) were presented for normally distributed data. Medians (IQR) were presented for data that were not normally distributed and for all BSID-III scores. For comparisons between alcohol exposed and unexposed children, chi-squared tests were used for categorical variables while t-tests or, in the case of data that were not normally distributed, Mann-Whitney U test were used. Variables that were associated with PAE at an alpha level of 0.05 or less were included in the final model to determine whether the outcome measures that were significantly associated with PAE remained significant after adjusting for potential confounders (see table 5 and 6). Multiple hierarchical regression was used to explore the associations of PAE with motor and language development. The model adjusted for the maternal sociodemographic and psychosocial confounding variables, which are known to be associated with child neurodevelopment (motor, language and cognitive outcomes). Potential confounding variables included composites of SES (Fried & Watkinson, 1988), smoking (cigarette and cannabis) and psychological variables (Fried & Watkinson, 1990), and child body mass index (BMI) z-score, child's nutritional status according to their gender and age. Significance was set at 0.05 and 95% CIs were reported for all estimates, were applicable.

Results

The maternal and child sociodemographic and psychosocial characteristics are presented in table 1. At 6 months, the median maternal age at enrolment was 24 years (IQR 21-30). In the alcohol group, 15.4 % of the mothers were HIV infected, 46.2% were classified as having PTSD and depression and in the unexposed group, 14.4 % of the mothers were HIV infected and 55.8% had PTSD and depression. At 24 months, the median maternal age at enrolment was 26 years (IQR 22-31). In the alcohol-exposed group, 16.3% of the mothers were HIV infected and 44.6% were classified as having PTSD and depression and in the unexposed group, 16.8 % of the mothers were HIV infected and 43.1% had PTSD and depression. There were no differences across the groups in sociodemographic or psychosocial variables, except for smoking, where mothers who consumed alcohol were more likely to smoke at both 6 months (65.4% vs 37.5%, respectively, p = 0.001) and 24 months of age (69.6 vs 37.5 respectively, p = 0.001). There were no significant differences between the exposed and unexposed groups regarding infants' birth weight and BMI.

Table 2 compares the median scores of the alcohol exposed and the unexposed groups for motor and language development at both 6 and 24 months of age. At 6 months, alcohol exposed infants had significantly lower median scores for gross and fine motor functioning compared to the unexposed infants [gross: median scores- 9.0 (IQR 7.2-11.0) vs 11.0 (IQR 9.0-12.0), respectively, p = 0.006; fine: median scores- 11.5 (IQR 10.0-13.0) vs 13.0 (IQR 12.0-15.0), respectively, p = 0.001)]. At 24 months, there were no significant differences, although there remained a trend toward impairment for fine motor functioning in exposed children [(median scores- 8.0 (IQR 7.0-11.0) vs 9.0 (IQR 8.0-11.0), respectively, p = 0.068)]. There were no significant differences in language and cognitive functioning at 6 or at 24 months.

Table 3 demonstrates the regression analysis for gross and fine motor functioning. PAE was significantly associated with gross motor functioning (OR = 0.16, 95%CI 0.06-0.44 p = 0.001) and fine motor functioning (OR = 0.16, 95%CI 0.06-0.46, p = 0.001) after controlling for BMI, SES, smoking and psychological variables at 6 months of age. BMI was significantly associated with both gross (OR=0.83, 95%CI 0.57-1.21, p = 0.001) and fine motor functioning (OR = 0.67, 95%CI 0.46-0.97, 0.004) while SES was significantly associated with gross motor functioning (OR = 2.28, 95%CI 1.24-4.19, p = 0.001) at 6 months.

The final model explained a significant amount of variance in gross motor functioning (F (4) =3.98, p = 0.002, adj R^2 = 0.10), and the R^2 showed that the amount of variance increased from 5% (BMI, SES, smoking, PTSD and depression) to 14% after adding PAE into the model (Appendix A). Similarly, the final model explained a significant amount of variation in fine motor functioning, (F (4) = 3.66, p = 0.004, adj R^2 = 0.13), and the R^2 showed that the explained variance accounted for an extra 9% (0.04 to 0.13) in fine motor functioning (Appendix A).

Discussion

This study comprehensively assessed motor, language and cognitive functioning in a population-based cohort over the first 2 years of life. The findings of our study indicated that PAE is associated with both gross and fine motor functioning at 6 months of age, even after adjusting for maternal sociodemographic and psychosocial factors. While PAE was not associated with receptive and expressive communication nor cognitive performance at either time point in this group, there remained a trend towards significance for poorer fine motor functioning at 24 months of age.

Our findings demonstrate that PAE is associated with deficits in motor functioning across the first two years of life. This is consistent with previously reported cohort studies in preschool age (Davies et al., 2011; Fried & Watkinson, 1988; Jacobson & Jacobson, 2002). In particular, Fried and Watkinson (1988) found a significant association between PAE and motor functioning in early infancy (12 months), even after adjusting for maternal age, gestation, birth weight and parity, but found the effect to wane at later ages. These same investigators continued to report a lack of association between PAE and motor outcomes in a follow-up of these children into school age but reported associations between PAE and language comprehension at 36 months (Fried & Watkinson, 1990). Important differences between our study and the cohort in these studies include: middle-to-high income samples, no control groups and the authors adjusted for primarily physical confounders (maternal age, gestation, birth weight and parity), but not psychosocial factors. Our study adds to the growing body of scientific evidence implicating PAE in motor functioning impairment at 6 months of age even after adjusting for important psychosocial factors such as PTSD and depression when compared to a matched control group.

In our cohort, PAE was not found to be associated with receptive or expressive communication or cognitive functioning at the age of 24 months. Previous studies have reported impairments in language and cognitive functioning in toddlers between the ages of 12 and 24 months (Davies et al., 2011; Fried & Watkinson, 1988), however, reports indicated that as children grew into the school years, PAE was not significantly associated with language or cognitive outcomes (Coggins et al., 2007) using standard measures. Lack of associated impact of PAE on early language outcomes in this study may, in part, be a result of language impairments being subtle in infancy and it therefore, being more difficult to identify these outcomes than in other domains. It may be useful for future studies to consider the extent to which specific language outcomes

affect the pragmatic or conversational patterns of children affected by PAE (not just general categories of receptive or expressive communication).

Additional limitations deserve consideration. Firstly, the substudy comprised a small sample size which may have limited the power to detect differences between the groups. Secondly, despite assurances of confidentiality, some women may have chosen not to disclose or minimize reporting alcohol use to the research teams, and the low reported alcohol consumption may therefore represent an element of response bias. Thirdly, the BSID-III tool measures general ability in completing a given task but may have low sensitivity for detecting minor developmental impairments especially during infancy. Further, although this tool has been validated for use in South Africa, this study may not be generalizable to other populations.

A large proportion of very young children in LMICs do not reach their developmental potential due to a wide variety of sociodemographic and psychosocial factors that may impact early developmental outcomes. Our study, reporting the association of PAE and early motor functioning, is one of only a few studies that have additionally addressed important potential psychosocial confounders which frequently co-occur with alcohol use in these communities. These findings highlight the importance of identifying high-risk families in order to provide preventive interventions, particularly in antenatal clinics and early intervention services.

Statement of interest

None.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013.

Authors contribution

HJZ is principal investigator (PI) of the umbrella Drakenstein Child Health Study (DCHS) cohort and played a central role in the design and operational aspects and of the study. DJS is PI of the psychosocial aspects of the DCHS cohort and contributed to the design and decision making involving the psychosocial tools and measures used. KAD, PI of the child psychosocial aspects of the DCHS, was involved in the design of the study and operational aspects of the study and played a key role in the child psychosocial measures used. G.H. and KAD conceived and designed this substudy. GH drafted article, analysed, interpreted findings and discussed the conclusion of the study with input from KAD, SMS and TC. NH and CJW contributed to the operational aspects of the study and in particular the developmental assessment data. All the authors were involved in revising the article, contributed to intellectual content and provided approval of the final version to be published.

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Figure 1: Study sample selection

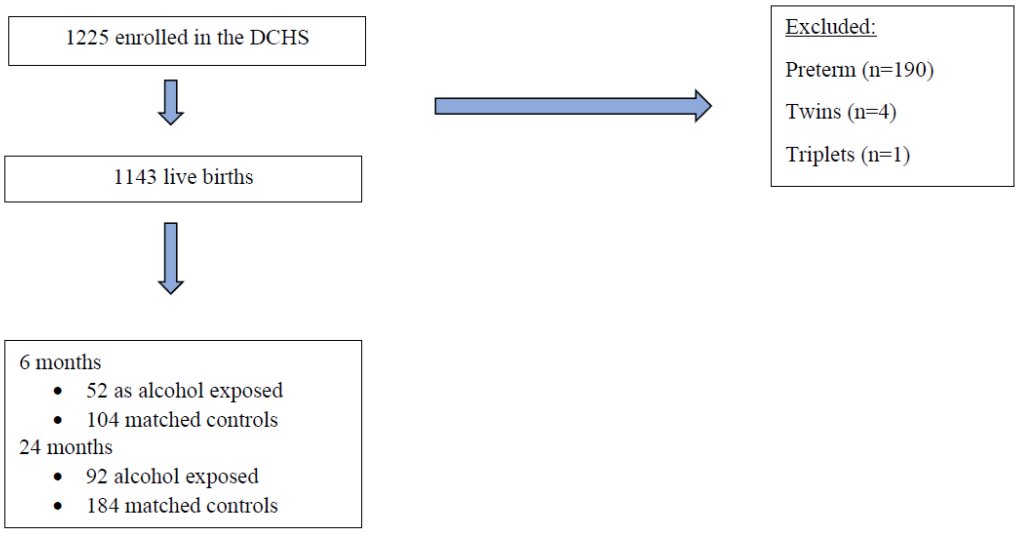

Table 1. Maternal and infant baseline sociodemographic and psychosocial characteristics

	6 months			24 months		
	Alcohol exposed	**Unexposed**	**p-value**	**Alcohol exposed**	**Unexposed**	**p-value**
Maternal variables	52 (33.3)	104 (66.7)		92 (33.3)	184 (66.7)	
Age n(%)						
18-29	36 (69.2)	79 (76.0)	0.185	59 (64.1)	126 (68.5)	0.837
30-39	15 (28.8)	22 (24.0)		30 (32.6)	51 (27.7)	
40-49	1 (1.9)	0 (0)		3 (3.3)	1 (3.8)	
Study site n(%)						
Mbkweni	19 (36.5)	38 (36.5)	1.000	32 (34.8)	66 (35.9)	0.484
TC Newman	33 (63.5)	66 (63.5)		60 (65.2)	118 (64.1)	
SES n(%)						
Low levels of SES	16 (31.4)	34 (33.3)	0.448	29 (31.9)	65 (35.7)	0.601
Low-medium levels SES	14 (27.5)	31 (30.4)		29 (31.9)	54 (29.7)	
Medium-to-high levels of SES	16 (31.4)	21 (20.6)		22 (24.2)	34 (18.7)	
High SES	5 (9.8)	16 (15.7)		11 (12.1)	29 (15.9)	
Education n(%)						
Primary	4 (7.7)	7(6.7)	0.952	13 (14.1)	24 (13.0)	0.968
Secondary	61 (92.3)	97 (93.3)		79 (85.9)	160 (87.0)	
Tertiary	0 (0)	0 (0)		0 (0)	0 (0)	

Marital status n(%)						
Married or cohabiting	22 (42.3)	33 (31.7)	0.192	54 (58.7)	107 (58.2)	0.518
Other	30 (57.7)	71 (68.3)		38 (41.3)	77 (41.8)	
HIV status n(%)						
Uninfected	44 (84.6)	89 (85.6)	0.873	77 (83.7)	153 (83.2)	0.528
Infected	8 (15.4)	15 (14.4)		15 (16.3)	31 (16.8)	
Smoking (cigarette and cannibas use) n(%)						
No	18 (34.6)	65 (62.5)	0.001*	28 (30.4)	115 (62.5)	0.001 **
Yes	34 (65.4)	39 (37.5)		64 (69.6)	69 (37.5)	
Psychological variables (PTSD and depression) n(%)						
Absent	28 (53.8)	46 (44.2)	0.257	51 (55.4)	103 (56.9)	0.458
Present	24 (46.2)	58 (55.8)		41 (44.6)	78 (43.1)	
Child variables						
Sex n(%)						
Male	26 (50.0)	60 (57.7)	0.362	50 (54.3)	102 (55.4)	0.482
Female	26 (50.0)	44 (42.3)		42 (45.7)	82 (44.6)	
Birth weight n(%)						
>1500	1 (1.9)	0 (0.0)	0.405	3 (3.3)	2 (1.1)	0.089
1500>2500	8 (15.4)	11 (10.6)		14 (15.2)	29 (15.8)	
2500>3500	36 (69.2)	76 (73.1)		66 (71.7)	117 (63.6)	
<3500	7 (13.5)	17 (16.3)		9 (9.8)	36 (19.6)	

BMI z-score, Median (IQR)	-0.005 (-0.75-0.77)	0.22 (-0.533.30)	0.118	0.18 (-0.48-0.97)	0.50 (-0.42-1.38)	0.113
Maternal age, years Median (IQR)	25 (21-31)	24 (21-29)	0.326	26 (22-31)	26 (22-31)	0.594
Gestational age, weeks Median (IQR)	39 (37-39)	39 (38-40)	0.138	39 (37-40)	39 (37-40)	0.811

* $p<0.05$

** $p<0.01$

Table 2. Motor, language and cognitive development in the exposed and unexposed group at 6 and 24 months of age

	6 months				24 months			
BSID-III Sub-domains	**Alcohol exposed Median (IQR) N = 52**	**Unexposed Median (IQR) N = 104**	**95% CI**	**p-value**	**Alcohol exposed Median (IQR) N = 92**	**Unexposed Median (IQR) N = 184**	**95% CI**	**p-value**
Gross motor	9.0 (7.2-11.0)	11.0 (9.0-12.0)	0.003-0.006	0.006**	8.0 (7.0 - 9.8)	9.0 (7.0-10.0)	0.20-0.19	0.196
Fine motor	11.5 (10.0-13.0)	13.0 (12.0-15.0)	0.001-0.001	0.001**	8.0 (7.0 -11.0)	9.0 (8.0-11.0)	0.06-0.07	0.068
Receptive communication	9.0 (8.0-11.0)	10.0 (8.3-12.0)	0.60-0.62	0.608	7.0 (5.0 - 8.0)	7.0 (6.0-9.0)	0.85-0.84	0.843
Expressive communication	10.0 (7.0-13.0)	10.0 (8.0-13.0)	0.99-0.99	0.991	7.0 (6.0 - 9.0)	7.0 (6.0-9.0)	0.74-0.75	0.743
Cognitive functioning	9.0 (7.0-11.0)	10.0 (8.0-11.0)	0.23-0.24	0.239	7.0 (6.0-8.0)	8.0 (6.0-8.0)	0.52-0.51	0.518

* $p<0.05$

** $p<0.01$

Table 3. Coefficients for predictors in final model of gross motor functioning at 6 months of age (after adjusting for SES, smoking, PTSD and depression)

	Gross motor functioning			Fine motor functioning		
Variables	**Odds ratio**	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
BMI	0.83	0.57-1.21	0.001**	0.67	0.46-0.97	0.035*
SES	2.28	1.24-4.19	0.009**	0.99	0.54-1.80	0.971
Smoking	1.35	0.49-3.74	0.566	0.69	0.25-1.88	0.473
Psychological variables	0.71	0.27-1.87	0.493	0.48	0.18-1.25	0.134
PAE	0.16	0.06-0.44	0.001**	0.16	0.06-0.46	0.001**

* $p<0.05$

** $p<0.01$

Appendix A.

Table 1. Summary of regression analysis: Regressing gross motor functioning onto BMI, SES, smoking, psychological variables risk, PAE at 6 months of age

Model	R	R Square	Adjusted R Square	F	p-value
1	0.03	0.001	0.04	1.55	0.695
2	0.23	0.05	0.34	3.45	0.035
3	0.23	0.05	0.03	230	0.80
4	0.23	0.05	0.02	1.75	0.14
5	0.37	0.14	0.100	3.98	0.002**

1. Predictors; BMI
2. Predictors: BMI, SES
3. Predictors: BMI, SES, smoking
4. Predictors: BMI, SES, Smoking, Psychological variables
5. Predictors: BMI, SES, Smoking, Psychological variables, *PAE*

* $p<0.05$
** $p<0.01$

Table 2: Summary of regression analysis: Regressing fine motor functioning onto SES, smoking, psychological variables risk, PAE at 6 months of age

Model	R	R Square	Adjusted R Square	F	p-value
1	0.07	0.005	-0.001	0.79	0.375
2	0.12	0.01	0.001	0.99	0.371
3	0.18	0.03	0.01	1.46	0.229
4	0.21	0.04	0.01	1.44	0.225
5	0.36	0.13	0.09	3.66	0.004**

1. Predictors: BMI

2. BMI, SES

3. Predictors: BMI, SES, Smoking

4. Predictors: BMI, SES, Smoking, SES, Psychological variables

5. Predictors: BMI, SES, Smoking, SES, Psychological variables, *PAE*