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The influence of maternal weight and alcohol exposure on infant physical characteristics and neurodevelopmental outcomes

Julie M. Hasken [a,b,*], Linda S. Adair [b], Stephanie L. Martin [b], Amanda L. Thompson [b,c], Anna-Susan Marais [d], Marlene M. de Vries [d], Wendy O. Kalberg [e], David Buckley [e], H. Eugene Hoyme [f], Soraya Seedat [d], Charles D.H. Parry [d,g], Philip A. May [a,b,d,e]

[a] The University of North Carolina at Chapel Hill, Nutrition Research Institute, 500 Laureate Way, Kannapolis, NC 28081, United States
[b] The University of North Carolina at Chapel Hill, Department of Nutrition, 135 Dauer Dr, Chapel Hill, NC 27599, United States
[c] The University of North Carolina, Department of Anthropology, Alumni Hall, Chapel Hill, NC 27599, United States
[d] Stellenbosch University, Faculty of Medicine and Health Sciences, Clinical Building, Francie van Zijl Drive, Tygerberg, 7505, Cape Town, South Africa
[e] The University of New Mexico, Center on Alcohol, Substance Abuse and Addictions, 2650 Yale SE, Albuquerque, NM 87106, United States
[f] Sanford Children's Genomic Medicine Consortium, Sanford Health, and the University of South Dakota Sanford School of Medicine, Department of Pediatrics, Sioux Falls, SD 57117, United States
[g] South African Medical Research Council, Cape Town 7505, South Africa

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ABSTRACT

Background: Mothers of children with fetal alcohol spectrum disorders tend to have lower weight compared to other mothers. Yet how alcohol and maternal weight may predispose infants to poorer physical growth and neurodevelopmental trajectories is relatively unexplained.
Methods: South African mothers (n = 406) were recruited prenatally and their offspring were provided standardized dysmorphology and neurodevelopment examinations at 6 weeks and 9 months of age. Maternal weight was obtained postpartum, and linear mixed modeling determined whether postpartum maternal weight and prenatal alcohol exposure significantly influenced infant growth, dysmorphology, and neurodevelopment within the first year of life.
Results: Postpartum maternal weight was positively associated with birth length, weight, and head circumference centile, but the rate of growth from birth to nine months was similar among all infants. Maternal weight was inversely associated with dysmorphology. Many infants in this population were performing within the borderline or extremely low range. Higher maternal weight was associated with significantly better cognitive and motor performance at 6 weeks; however, the rate of developmental growth was similar among all infants, regardless of postpartum maternal weight.
Conclusion: Higher postpartum maternal weight may be a protective factor but does not eliminate the adverse effects of alcohol on infant growth and dysmorphology. Regardless of maternal weight, alcohol remains a powerful teratogen and moderate to high use prenatally can result in adverse infant physical and neurocognitive development.

Introduction

Individual variation within the fetal alcohol spectrum disorders (FASD) continuum

Fetal alcohol spectrum disorders (FASD) is an umbrella term for physical and neurocognitive delays and deficits associated with prenatal alcohol exposure. In the general US population, it is estimated that 5% of all children fall within the FASD continuum (May et al., 2018). The Western Cape Province of South Africa has the highest reported FASD prevalence in the world with an estimated 17–31% of children having an FASD (May et al., 2000; Viljoen et al., 2005; May et al., 2007; May et al., 2013; May et al., 2016; May et al., 2016; May et al., 2017; May et al., 2021; Roozen et al., 2016). The individual variation in child growth,

* Corresponding author at: Nutrition Research Institute, Department of Nutrition, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, 500 Laureate Way, Kannapolis, NC 28081, United States.
E-mail address: julie_hasken@unc.edu (J.M. Hasken).

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facial dysmorphology, and neurocognitive impairments among children with prenatal alcohol exposure is not fully explained by the quantity, frequency, or gestational timing of prenatal alcohol consumption or other known risk factors (May et al., 2013). This results in some children developing within the normal range, while others have severe impairments despite similar exposure to alcohol in utero. Yet within each FASD diagnostic category, there is individual variation in growth, dysmorphology, and cognitive and behavioral performance, especially over time. Other distal and environmental factors, such as maternal size, age, gravidity, and socioeconomic status have been identified in case control studies as contributing to risk for FASD (Abel, 1998).

Maternal weight as a risk factor for FASD

Maternal weight has long been suggested as a contributing factor to the risk and severity of an FASD diagnosis. Because women with higher weight have more body tissue to which alcohol is distributed, their blood alcohol concentration may be lower, and the quantity of alcohol that crosses the placenta may be reduced, resulting in less severe growth deficiencies, dysmorphology, and neurobehavioral impairment. In South African longitudinal studies, mothers of children with FASD had, on average, significantly lower maternal weight and body mass index (BMI) when measured at 42 to 60 months postpartum (Kalberg et al., 2019). This is consistent with previous findings from 5 separate cross-sectional studies in the Western Cape Province where maternal weight and BMI (measured 7–8 years postpartum) were significantly lower among mothers of children with FASD. This is especially true for children with fetal alcohol syndrome (FAS) when compared to mothers of children with typical development (May et al., 2016; May et al., 2016; May et al., 2017; May et al., 2005; May et al., 2008).

Among alcohol-exposed pregnancies, higher maternal weight, whether measured prenatally or postpartum, may be protective against some of the adverse effects of prenatal alcohol exposure. However, in non-alcohol-exposed pregnancies, increased pre-pregnancy maternal weight and/or excessive weight gain during pregnancy, may increase the risk of obesity during early childhood and may place the child at risk for delay in neurocognitive and motor development (Adane et al., 2018; Álvarez-Bueno et al., 2017). Because both alcohol exposure and maternal obesity may independently predispose a child to poorer physical and/or neurodevelopmental trajectories, it is necessary to understand how prenatal alcohol exposure and maternal weight influence the developmental trajectories of children. The purpose of this study was to determine the role of postpartum maternal weight (as a proxy for pre-pregnancy weight) and prenatal alcohol exposure on infant physical and neurocognitive outcomes from birth to 9 months.

Methods

Study design and sample

All women seeking prenatal care in five communities in the predominately agricultural region of the Western Cape Province of South Africa were invited to consent to, and participate in, a brief alcohol-screening, demographic, and health indicators questionnaire during the pregnancy. The brief questionnaire included the Alcohol Use Disorder Identification Test (AUDIT) (Babor et al., 2001), the Tolerance, Annoyed, Cut-back, and Eyeopener (TACE) screen (National Institute of Alcoholism and Alcohol Abuse, 2003), and alcohol consumption in the previous 30 days of the pregnancy.

Of the 1,370 women who completed the brief questionnaire, 680 were visited by study staff following the birth of the index children with 419 of these visits occurring within ten days postpartum among term (gestational age $\geq$ 37 weeks) and singleton births. Maternal weight was measured, and additional information about the pregnancy was obtained within ten days of delivery. Weight was measured with electronic scales with 0.01 kg precision. Four hundred and six (406) mothers and their infants were followed until 9 months postpartum.

Infant length, weight, and occipital frontal (head) circumference (OFC) measurements were collected by the attending physician or nurse immediately following the birth and recorded on the infant's medical card. At 6 weeks and 9 months postpartum, study staff completed a dysmorphology exam for each infant, and infants were administered a neurodevelopmental assessment. The dysmorphology exam measured a child's length, weight, and OFC and assessed the presence or absence of 12 other minor anomalies (Hoyme et al., 2016). Following each dysmorphology exam, centiles were calculated for each growth measure. For children under the age of 2, the Centers for Disease Control and Prevention (CDC) has adopted the World Health Organization (WHO) growth curves (Centers for Disease Control and Prevention, 2019). The sex-specific CDC/WHO growth curves were used to determine each infant's growth centile for length and weight. OFC measurements were plotted against growth charts developed by Nellhaus (Nellhaus, 1968). Palpebral fissure length (PFL) measurements were plotted on curves developed by Thomas et al. with $\leq$ 10th centile considered short (Thomas et al., 1987). The total dysmorphology score, a weighted summary measure, was determined for each infant following the dysmorphology exam (Hoyme et al., 2005, 2016) with a higher score indicating more dysmorphology. The Bayley Scales of Infant and Toddler Development, 3rd Edition, was used to assess an infant's abilities in cognitive, language, motor, and social/emotional domains. The Bayley has been widely used internationally and has been shown to be a reliable tool, specifically with South African populations (Kalberg et al., 2019; Rademeyer and Jacklin, 2013; Rodriguez et al., 2020; Ballot et al., 2017). The examiners were blinded to alcohol exposure history and any previous study assessments.

Statistical analysis

Postpartum maternal weight was divided into tertiles. One-way analysis of variance (ANOVA) tests were then employed to compare maternal demographic variables, alcohol consumption patterns, and infant physical and neurodevelopmental characteristics. To control for Type I error, post-hoc analyses were performed using Dunnett's C pairwise comparisons with alpha = 0.05 (Tabachnick and Fidell, 2019). Categorical variables were examined using chi-square. Consistent with the Revised Institute of Medicine diagnostic guidelines for FASD, developmental delay was defined as a composite score $\leq$ 1.5 SD below the reference population mean (Hoyme et al., 2016).

The association of maternal weight with infant length, weight, and OFC centiles were examined from birth to 9 months using linear mixed models. The association of maternal weight with other child physical and neurodevelopmental outcomes were examined from 6 weeks to 9 months. Random effects models, with random intercept and slope for time, with an autoregressive co-variance matrix, were utilized. Gestational age, maternal age, and maternal weight were centered on the sample mean. To aid in the interpretation of parameter estimates, time (in months) was centered, thereby allowing the intercept to reflect the outcome at 6 weeks of age for dysmorphology and neurodevelopmental outcomes. To address whether the association between infant outcomes and maternal risk factors changed over time, a two-way age (time) interaction with each covariate was explored. All analyses were carried out using SPSS 26 (IBM, 2021).

Results

Maternal characteristics

The maternal demographic and alcohol consumption information by maternal weight tertiles are displayed in Table 1. Maternal age significantly distinguished the groups, with women in tertile 3 significantly older than women in tertile 1. Approximately 20–25% of women in each group reported drinking in the previous 30 days of their pregnancy, and

Table 1
Maternal characteristics as reported during pregnancy by maternal weight tertile.

	Tertile 1 (<56.0 kg) (n=135)		Tertile 2 (56.0–67.9 kg) (n=136)		Tertile 3 (≥68 kg) (n=135)		p
Weight within 10 days of birth (kg)	48.5	(5.1)	61.7	(3.4)	80.6	(10.7)	<.001[A, B,C]
Age	26.2	(5.5)	27.1	(6.1)	28.2	(5.5)	.012[B]
Gravidity	2.7	(1.3)	2.8	(1.4)	2.9	(1.2)	.575
Parity	2.1	(1.3)	2.2	(1.2)	2.2	(1.1)	.654
Used tobacco (% Yes)	57.8		47.8		48.9		.197
AUDIT Total	10.4	(8.9)	9.2	(8.7)	8.9	(8.8)	.290
TACE Total	2.7	(0.6)	2.6	(0.7)	2.6	(0.6)	.176
Trimester interviewed (%)							
First	5.9		10.3		8.1		
Second	23.0		22.8		25.2		
Third	71.0		66.9		66.7		.728
Drank in previous 30 days (% Yes)	25.2		23.5		20.0		.585
DDD – previous 30 days[1]	6.3	(5.7)	6.3	(5.2)	6.6	(5.0)	.973
Number of drinking days – previous 30 days[1]	4.3	(3.3)	4.4	(3.8)	3.1	(3.7)	.297
Number of 3+ binges – previous 30 days[1]	4.0	(3.5)	3.6	(3.9)	2.9	(3.8)	.517
AUDIT Total[1]	17.9	(6.2)	17.4	(7.0)	17.0	(6.2)	.887
TACE Total[1]	4.2	(.6)	3.8	(.9)	3.9	(.9)	.072

1. Among those who reported drinking in the previous 30 days.
DDD: Drinks per drinking day Post-hoc Dunnet C comparisons significant difference between: A. Tertile 1 & Tertile 2; B. Tertile 1 & Tertile 3; C. Tertile 2 & Tertile 3.

they consumed a mean of 6.3 to 6.6 drinks per drinking day (DDD) on an average of 3.1 to 4.4 days. There was no significant difference in quantity or frequency of alcohol consumption by maternal weight tertile.

Infant characteristics

Infant physical growth and dysmorphology measurements at birth, 6 weeks, and 9 months by maternal weight tertile are presented in Table 2. Stunting and wasting were present at birth and remained present for a proportion (approximately 20%) of the infants. At birth, children born to mothers in tertile 1 were significantly shorter, lighter, and had a smaller OFC than children born to heavier mothers. By 6 weeks, in post-hoc comparisons, length, weight, and OFC continued to significantly differentiate between infants of mothers in tertile 1 and tertile 3. Significantly more children born to mothers in tertile 1 were stunted (length < 3rd centile), were microcephalic (OFC ≤ 3rd centile), and had shorter inner canthal distance (ICD) at 6 weeks. The total dysmorphology score was significantly higher among infants born to the lightest mothers. By 9 months, children born to mothers in tertile 1 were significantly shorter, lighter, had a smaller OFC, ICD, and inner pupillary distance (IPD). Overall, tertile 1 children had significantly more minor anomalies and a higher mean total dysmorphology score than the other two groups.

Infant neurobehavioral outcomes

At 6 weeks infants in this cohort performed, on average, within the "average" range (composite score 90–109) on all four domains (Table 3). Only the cognitive score approached a significant difference between groups at 6 weeks. By 9 months, the cohort performed in the "high average" range (composite score 110–119) on the cognitive domain and within the average range for language, motor, and social/emotional domains. Infants whose mothers were in tertile 1 performed significantly worse on the motor composite score and social/emotional composite score at 9 months compared to infants whose mothers were heavier. On average, infants in all maternal weight groups were performing within the normal range; however, infants born to lighter women were performing lower than infants born to heavier mothers by 9 months.

Individual performance: Percent below the mean

The percent of infants who scored ≤ 2 SD (composite score < 70, "extremely low") and ≤1.5 SD (composite score ≤ 78, "borderline") below the mean is presented in Table 4. By 9 months of age among all infants, 2.5% were borderline on cognitive, 9.9% on language, 11.6% on motor, and 7.5% on social/emotional domains. Significantly more infants in tertile 1 than infants in tertile 3 performed in the borderline range (17.9% vs 11.6%) and in the extremely low range (7.7% vs 3.3%) on motor development. In this population overall, many children had challenges. At 9 months, a quarter (25.6%) of all infants fell within the borderline range and 6.7% were in the extremely low range.

Longitudinal effect of DDD and maternal weight

Table 5 contains a summary of the significant relationships between infant outcomes and the two maternal characteristics of most interest in this analysis (DDD and maternal weight) using linear mixed modeling. The full models and coefficients are presented in the Appendix. In summary, DDD was significantly and negatively associated with infant length centile, weight centile, and weight-for-length at birth. The Bayley social/emotional percentile rank was also significantly and inversely related at 6 weeks of age. DDD was significantly and positively associated with the number of minor anomalies and total dysmorphology at 6 weeks of age, indicating more minor anomalies and higher total dysmorphology scores. The DDD by time interaction was significant indicating that as infants aged from 6 weeks to 9 months, the total dysmorphology score increased. As seen in Fig. 1, infants of non-drinkers had significantly lower total dysmorphology scores at 6 weeks compared to infants of women who consumed alcohol, and the trajectory (slope) was significantly different for infants of mothers who drank and those who did not drink.

Maternal weight was significantly and positively associated with infant length centile, weight centile, and weight-for-length, and OFC centile at birth, and the Bayley cognitive percentile rank and motor percentile rank at 6 weeks of age. Higher maternal weight was also significantly associated with weight-for-length over time indicating that infants born to mothers in tertile 1 were leaner (less weight relative to length) at birth and did not gain weight (relative to length) at the same rate when compared to infants born to heavier mothers (Fig. 2). Higher maternal weight was associated with a significant reduction in the number of minor anomalies and total dysmorphology score at 6 weeks (Fig. 3).

As seen in the Appendix tables, several covariates were also significantly associated with various infant outcomes. In general, when significantly associated with infant outcomes, gestational age was positively associated with the outcome and tobacco use, gravidity, and trimester interviewed (a proxy for when first sought prenatal care) were negatively associated with the infant outcome. Time was also a significant independent predictor of cognitive percentile rank, motor percentile rank, and social/emotional percentile rank indicating infants were following a downward trajectory in neurodevelopmental abilities as they aged.

Except for the interaction term DDD by time for total dysmorphology score and the interaction term for maternal weight by time for weight-for-length, there were no significant DDD by time or maternal weight by time interaction terms. This indicates there were no other significant

Table 2
Child physical characteristics at birth, 6 weeks, and 9 months by maternal weight tertile.

	Tertile 1 (≤53.0 kg) Mean	(SD)	Tertile 2 (53.1–64.0 kg) Mean	(SD)	Tertile 3 (≥64.1 kg) Mean	(SD)	p
Birth	(n=135)		(n=136)		(n=135)		
Sex (% Male)	51.1		52.2		48.1		.788
Gestational Age	39.2	(1.1)	39.1	(1.1)	39.3	(1.0)	.354
Length Centile	26.8	(30.0)	36.0	(33.0)	41.8	(32.0)	<.001[A,B]
<3rd Centile (%)	27.4		16.2		13.3		.008
Weight Centile	14.9	(18.0)	22.5	(22.9)	28.4	(26.2)	<.001[A,B]
<3rd Centile (%)	36.3		21.3		8.1		<.001
Weight-for-Length	58.1	(7.4)	59.9	(7.8)	62.7	(8.7)	<.001[B,C]
Weight-for-Length Centile	26.8	(31.6)	26.0	(31.7)	31.5	(33.6)	.343
OFC Centile	15.6	(22.0)	22.9	(26.5)	26.9	(26.5)	.001[A,B]
6 weeks	(n=123)		(n=126)		(n=126)		
Age (in days)	44.3	(5.0)	43.5	(4.4)	44.6	(5.4)	.184
Length Centile	19.5	(23.7)	26.4	(26.3)	33.0	(27.9)	<.001[B]
<3rd Centile (%)	30.9		23.0		12.7		.002
Weight Centile	30.1	(24.4)	41.0	(30.8)	48.5	(29.3)	<.001[A,B]
<3rd Centile (%)	14.6		9.4		5.6		.055
Weight-for-Length	80.2	(9.7)	83.3	(11.8)	86.2	(10.4)	<.001[B]
Weight-for-Length Centile	65.2	(34.6)	65.0	(33.9)	65.7	(33.3)	.984
OFC Centile	23.8	(20.8)	32.2	(24.6)	33.6	(22.6)	<.001[A,B]
OFC ≤ 3rd Centile (%)	16.3		10.9		3.2		.003
OFC ≤ 10th Centile (%)	33.3		23.4		16.7		.009
ICD Centile	39.1	(21.8)	43.0	(20.4)	47.0	(19.9)	.012[B]
IPD Centile	31.0	(25.9)	31.3	(26.6)	33.0	(27.4)	.809
PFL Centile	65.6	(31.2)	61.7	(31.1)	68.1	(32.3)	.265
# of minor anomalies	5.2	(3.0)	4.9	(2.7)	4.2	(2.6)	.019[B]
Total Dysmorphology Score	6.9	(4.5)	6.1	(4.4)	5.2	(4.0)	.008[B]
9 months	(n=117)		(n=121)		(n=125)		
Age (in days)	277.4	(8.2)	275.9	(8.0)	277.2	(9.6)	.361
Length Centile	24.5	(28.4)	33.8	(29.6)	36.5	(28.7)	.004[A,B]
<3rd Centile (%)	27.4		17.5		9.6		.002
Weight Centile	17.7	(23.0)	32.4	(30.4)	40.7	(31.5)	<.001[A,B]
<3rd Centile (%)	34.2		15.8		12.0		<.001
Weight-for-Length	113.2	(14.4)	120.8	(16.8)	123.7	(15.2)	<.001[A,B]
Weight-for-Length Centile	43.7	(32.9)	56.7	(32.5)	63.4	(31.4)	<.001[A,B]
OFC Centile	32.3	(30.2)	41.6	(33.0)	45.8	(31.7)	.004[B]
OFC ≤ 3rd Centile (%)	24.8		20.7		13.6		.084
OFC ≤ 10th Centile (%)	35.0		29.8		20.0		.030
ICD Centile	38.8	(29.4)	46.5	(27.9)	46.9	(25.1)	.040
IPD Centile	17.5	(18.6)	28.3	(25.0)	26.7	(22.8)	<.001[A,B]
PFL Centile	49.5	(33.6)	51.2	(30.7)	55.5	(30.0)	.307
# of minor anomalies	7.0	(2.8)	6.0	(2.7)	5.8	(2.6)	.001[A,B]
Total Dysmorphology Score	9.2	(4.8)	7.6	(4.7)	7.2	(4.5)	.002[A,B]

OFC: Occipital frontal (head) circumference; ICD: Inner canthal distance;
IPD: Inner pupillary distance; PFL: Palpebral fissure length
Post-hoc Dunnet C comparisons significant difference between: A. Tertile 1 & Tertile 2; B. Tertile 1 & Tertile 3; C. Tertile 2 & Tertile 3.

differences in the rate of change (slope of growth trajectory) associated with DDD or maternal weight across time (birth to 9 months).

Discussion

This paper sought to examine whether postpartum maternal weight and prenatal alcohol exposure were associated with infant physical and neurodevelopmental outcomes. This study demonstrated: 1) children in this particular population were at higher risk for growth faltering and poorer neurodevelopmental outcomes; 2) higher postpartum maternal weight may be protective in terms of overall growth and development in this population where undernutrition is common; and 3) regardless of postpartum maternal weight, prenatal alcohol exposure remains a powerful teratogen that can adversely impact infant physical and cognitive/behavioral development at birth and through 9 months of infancy.

Overall population growth parameters and neurodevelopment abilities

On average, infants in this cohort were born and remained smaller than average, compared to World Health Organization growth standards, on length, weight, and OFC through 9 months of age. Stunting and wasting, markers of an underlying inadequate fetal and early life environment (Leroy and Frongillo, 2019), were present at birth and remained present for nearly a quarter of the infants at 9 months. Similarly, ten percent of infants had microcephaly at 6 weeks, and the greater percentage with microcephaly at 9 months suggests that some infants experienced growth faltering.

For neurodevelopment, on average, infants were performing within the normal range through 9 months, but the downward trajectory observed for the motor and social/emotional domains may indicate the possibility of additional children falling within the at-risk performance categories. Others have noted that among South African children, Bayley domain scores decrease with advancing age. The percent of children who may be at risk for experiencing developmental delay may be underestimated in this study because children were assessed for development only to nine months of age (Kalberg et al., 2019; Rademeyer and Jacklin, 2013). A 5-year longitudinal study completed in these communities found that children with FASD and children with typical development generally followed a downward developmental trajectory for the duration of the study (Kalberg et al., 2019). As children age, more advanced assessments may better differentiate children than was observed in this study.

Table 3
Child neurocognitive abilities measured by the Bayley Scales of Infant Development at 6 weeks and 9 months by maternal weight tertile

	Tertile 1 (≤53.0 kg) Mean	(SD)	Tertile 2 (53.1–64.0 kg) Mean	(SD)	Tertile 3 (≥64.1 kg) Mean	(SD)	p
Birth	(n=135)		(n=136)		(n=135)		
Sex (% Male)	51.1		52.2		48.1		.788
Gestational Age	39.2	(1.1)	39.1	(1.1)	39.3	(1.0)	.354
APGAR – 1 minute	9.1	(1.4)	8.9	(1.1)	9.0	(1.1)	.466
APGAR – 5 minutes	9.7	(0.9)	9.7	(0.6)	9.7	(0.5)	.886
6 weeks	(n=123)		(n=126)		(n=126)		
Age (in days)	44.3	(5.0)	43.5	(4.4)	44.6	(5.4)	.184
Cognitive Percentile	63.7	(27.4)	70.7	(23.2)	67.0	(25.3)	.094
Composite Score	106.7	(13.8)	109.8	(12.5)	108.1	(13.3)	.162
Language Percentile	37.8	(23.2)	41.5	(22.6)	40.3	(22.7)	.427
Composite Score	93.9	(11.7)	95.5	(11.3)	94.9	(11.6)	.508
Motor Percentile	67.0	(20.9)	70.5	(21.5)	68.5	(23.4)	.455
Composite Score	107.9	(9.9)	109.2	(10.2)	108.8	(11.5)	.569
Social-Emotional Percentile	60.7	(22.2)	65.1	(22.4)	63.3	(24.0)	.303
Composite Score	104.6	(10.9)	107.0	(11.1)	106.2	(12.0)	.569
9 months	(n=117)		(n=121)		(n=125)		
Age (in days)	277.4	(8.2)	275.9	(8.0)	277.2	(9.6)	.361
Cognitive Percentile	70.3	(28.4)	69.6	(26.2)	75.3	(23.9)	.186
Composite Score	110.4	(16.5)	109.5	(14.4)	113.2	(13.3)	.120
Language Percentile	35.1	(22.6)	35.3	(22.0)	41.2	(23.9)	.060
Composite Score	92.6	(12.1)	92.7	(11.9)	95.7	(12.1)	.060
Motor Percentile	34.3	(26.4)	40.8	(25.8)	40.5	(25.6)	.099
Composite Score	90.7	(15.5)	95.5	(12.8)	95.3	(12.6)	.011[A,B]
Social-Emotional Percentile	48.9	(31.6)	60.0	(30.0)	53.5	(31.2)	.022[A]
Composite Score	99.3	(16.3)	105.0	(15.3)	101.2	(16.1)	.019[A]

Post-hoc Dunnet C comparisons significant difference between: A. Tertile 1 & Tertile 2; B. Tertile 1 & Tertile 3; C. Tertile 2 & Tertile 3.

Higher postpartum maternal weight may be protective in this population

In this sample, infants born to heavier mothers were better developed in terms of size, were less dysmorphic, and performed better on the neurodevelopmental assessments than infants born to mothers with lower weight. With the exception of infant weight-for-length, there were no significant interactions between postpartum maternal weight and time for any of the outcomes assessed. This indicates that there was no difference in the developmental growth (slope of the trajectory) among infants in the first 9 months of life, regardless of postpartum maternal weight. Any benefit derived from higher postpartum maternal weight was observable at birth and/or 6 weeks, and the slope of the developmental trajectory among infants was similar across maternal weight. Any benefit to the infant derived from increased postpartum maternal weight was observed at first infant assessment.

Unlike all other outcomes assessed, postpartum maternal weight was significantly and positively associated with infant weight-for-length at birth and across time. Mothers who were lighter had infants who were, on average, born with a lower body weight and gained less weight relative to their length. This resulted in a more slender infant compared to peers. Child weight-for-length may need to be monitored to ensure that children born to mothers with lower weight are not at risk for growth faltering, and that children born to mothers with higher weight are not at risk for developing obesity.

It has been asserted there may be a U-shaped relationship between maternal weight and child outcomes (Huang et al., 2014; Hinkle et al., 2012). The women in this sample may not have had a sufficiently wide distribution to fully capture the protective and/or at-risk ranges of maternal weight (Holland et al., 2013; Deputy et al., 2018). Therefore, while higher maternal weight was beneficial in these communities where undernutrition is common (May et al., 2014; May et al., 2016), there may be an upper range where maternal weight is no longer protective and possibly harmful to the infant (Deierlein et al., 2011; Adair, 2014). Future studies might explore this possibility. Nevertheless, high postpartum maternal weight appears to be protective in this population.

An adverse effect of prenatal alcohol exposure on total dysmorphology score

Our findings are consistent with previous work that indicates that alcohol consumption was associated with worse infant outcomes, especially physical outcomes in early life. Higher DDD resulted in progressively higher total dysmorphology scores over time. Because the total dysmorphology score is a summary measure where cardinal features of FASD are weighted more heavily than other more frequently occurring minor anomalies, the significant DDD by time interaction term suggests that minor anomalies associated with prenatal alcohol exposure may be less evident in very early life. While the total dysmorphology score is not intended to be a single indicator for diagnosis, the total dysmorphology score has been shown to be highly correlated with prenatal alcohol exposure and with an FASD diagnosis. Children with fetal alcohol syndrome (FAS), on average, have higher total dysmorphology scores (May et al., 2007; May et al., 2013; May et al., 2016; May et al., 2016; May et al., 2017) and the total dysmorphology score at 9 months has been a significant predictor of an FASD diagnosis at 5 years of age (Kalberg et al., 2019).

An adverse effect of prenatal alcohol exposure on neurodevelopment

In this sample, prenatal alcohol exposure was associated with poorer social/emotional performance. Given that there is no one, specific neurocognitive and behavioral phenotype of children with FASD (Mattson et al., 2011; Coles et al., 2020), the differences between affected infants may be subtle within the first year of life. Furthermore, assessment tools may be insensitive to very minor differences in early life.

The lack of an association between DDD and select infant outcomes in this sample may be, in part, due to the singular assessment of alcohol consumption in the previous 30 days. Other researchers have found an association with alcohol consumption and poorer performance on the Bayley within the first year of life, but the alcohol consumption information covered the entire pregnancy (Hendricks et al., 2019). Previous studies have shown that the quantity and timing of exposure predicts the

Table 4
Percent of infants 2 and 1.5 standard deviations (SD) below the mean on the Bayley Scales of Infant Development at 6 weeks and 9 months by maternal weight tertile.

Composite Score	All infants %	Tertile 1 (≤53.0 kg) %	Tertile 2 (53.1–64.0 kg) %	Tertile 3 (≥64.1 kg) %	P[1]
6 weeks		(n=123)	(n=128)	(n=125)	
Cognitive <70	0.8	0.8	0.8	0.8	.999
Cognitive ≤78	1.6	1.6	1.6	1.6	.999
Language <70	2.9	2.4	3.9	2.4	.716
Language ≤78	9.3	8.9	9.4	9.5	.987
Motor <70	0.3	0.0	0.0	0.8	.368
Motor ≤78	0.5	0.0	0.8	0.8	.615
Social/ Emotional <70	0.0	0.0	0.0	0.0	–
Social/ Emotional ≤78	1.6	2.4	0.8	1.6	.577
Any domain <70	3.2	3.3	3.9	2.4	.792
Any domain ≤78	10.9	12.2	9.4	11.2	.767
9 months		(n=117)	(n=120)	(n=125)	
Cognitive <70	1.4	2.6	1.7	0.0	.220
Cognitive ≤78	2.5	3.4	2.5	1.6	.662
Language <70	3.9	4.3	5.0	2.4	.552
Language ≤78	9.9	11.1	10.8	8.0	.667
Motor <70	3.3	7.7	1.7	0.8	.005[A, B]
Motor ≤78	11.6	17.9	6.7	10.4	.022[B]
Social/ Emotional <70	0.6	0.9	0.0	0.8	.604
Social/ Emotional ≤78	7.5	9.5	4.2	8.9	.233
Any domain <70	6.7	8.6	7.5	4.0	.328
Any domain ≤78	25.6	30.4	21.7	25.0	.300

Note: a composite score ≤70 is 2 standard deviations below the mean. A composite score of ≤78 is 1.5 standard deviations below the mean. Per Hoyme et al., 2016 diagnostic guidelines for FASD (Hoyme et al., 2016) a neurocognitive score 1.5 SD below the mean meets criteria for evidence of developmental delay. 1. Chi-square with the 'all infants' column excluded from the analysis. Post-hoc z-test of proportions significant difference between: [A]Tertile 1 & Tertile 2; [B]Tertile 1 & Teritle 3.

Table 5
Summary of linear mixed modeling with various child outcomes when significantly predicted by drinks per drinking day (DDD) and maternal weight[1].

Child outcome	Maternal Characteristic	
At Birth	DDD – previous 30 days	Maternal Weight
Length Centile	Inversely	Positively
Weight Centile	Inversely	Positively
Weight-for-Length	Inversely	Positively
OFC Centile	–	Positively
At 6 weeks		
Number of Minor Anomalies[2]	Positively	Inversely
Total Dysmorphology Score[2]	Positively	Inversely
Bayley Cognitive Percentile Rank	–	Positively
Bayley Language Percentile Rank	–	–
Bayley Motor Percentile Rank	–	Positively
Bayley Social/Emotional Percentile Rank	Inversely	–
Overtime		
Total Dysmorphology Score[2]	Positively	–
Weight-for-Length	–	Positively

1. Additional covariates included: trimester interviewed, gestational age at birth, infant sex, maternal tobacco use, gravidity, maternal age, postpartum day weight was measured, and time. See the Appendix for full models for each outcome.
2. Higher scores indicate worse outcome

2. Higher scores indicate worse outcome

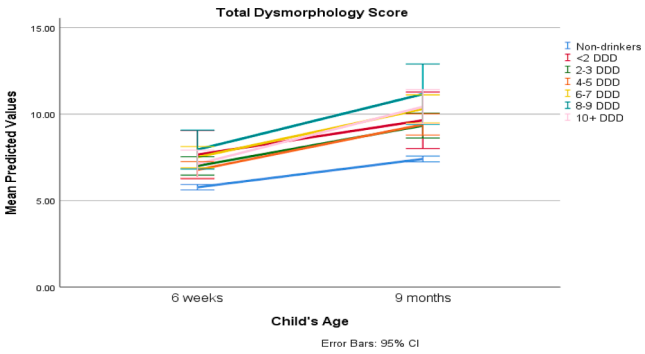

Fig. 1. Drinks per Drinking Day (DDD) differentiate Total Dysmorphology Score at 6 weeks and there was significant difference in the rate of change (slope) across time by DDD (B = 0.19, p = 0.026).

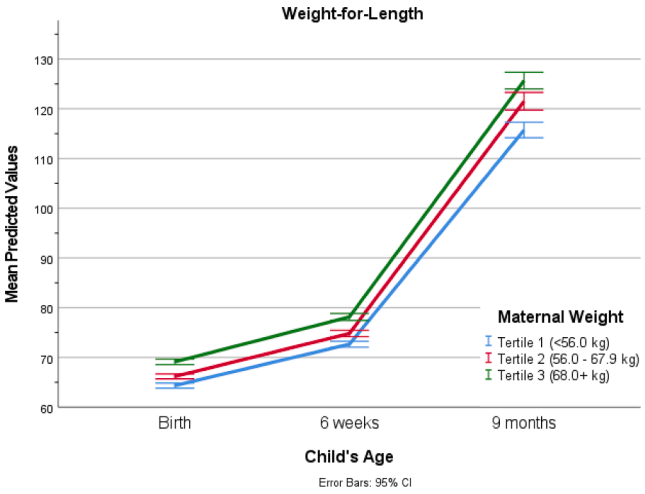

Fig. 2. Maternal weight differentiates weight-for-length at 6 weeks and there was significant difference in the rate of change (slope) across time by maternal weight (B = 0.02, p = 0.030).

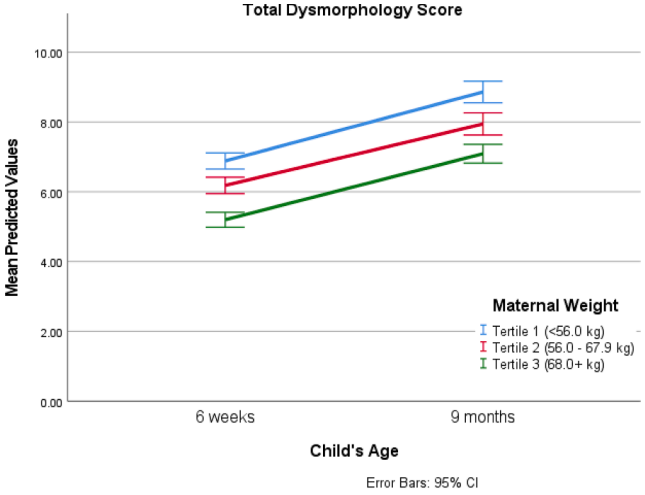

Fig. 3. Maternal weight differentiated total dysmorphology score at 6 weeks and there was no significant difference in the rate of change (slope) across time by maternal weight (p = 0.951).

development of cardinal FASD facial features and the severity of diagnosis within the FASD continuum (May et al., 2013; Lipinski et al., 2012). Women in this sample may have stopped drinking upon

pregnancy recognition which may have occurred prior to seeking prenatal care. Evidence suggests that the earlier in pregnancy when alcohol cessation occurs, the better potential outcome for the child (May et al., 2013). An alcohol measure which captures the entire pregnancy may better predict infant outcomes.

Maternal weight and alcohol exposure were independently associated with child outcomes

There was no statistical evidence for an interaction between maternal weight and DDD in the previous 30 days of pregnancy. Higher postpartum weight was associated with better child outcomes and alcohol exposure was associated with adverse child outcomes. The lack of an interaction may be due, in part, to blood alcohol concentration (BAC). BAC is influenced by alcohol quantity, frequency, and duration of drinking, age, sex, total body weight, and body composition (Jones, 2019; Cowan et al., 1996; Reiter et al., 2020). Consuming alcohol in a binge fashion, which results in a higher BAC, may have a greater risk for adverse child outcomes compared to average absolute daily intake quantities (Khaole et al., 2004). All else being equal (e.g., alcohol consumption/duration, sex, age), total weight can be identical for two individuals, but they may have different body composition distributions (adipose to lean body mass ratios). Alcohol is distributed to the total body water compartment (primarily within the lean body mass) (Jones, 2019). Among individuals of the same weight, the individual with the higher adipose to lean body mass ratio will have higher BAC than the individual with the lower adipose to lean body mass ratio. However, others have suggested that estimating BAC is not necessary if alcohol consumption exceeded a binge of 4+ drinks per occasion (NIAAA, 2004; Fillmore and Jude, 2011). In this sample, women reported, on average, 5 or more drinks per occasion. Because the duration of the drinking episode was not assessed in this study, estimating BAC could not be undertaken. Yet alcohol was clearly shown in this study to have an adverse effect on child outcomes and remains teratogenic regardless of postpartum maternal weight.

Other environmental factors were associated with infant outcomes

Also consistent with previous work, other known maternal risk factors for FASD were associated with infant outcomes in this study. Tobacco use during pregnancy and higher gravidity consistently were significantly and negatively associated with infant growth in the regression analysis. Women in the higher tertiles of postpartum weight were, on average, older. Older maternal age has been previously identified as a risk factor for FASD with latter born children having an increased risk for adverse outcomes (May et al., 2005, 2016a,b, 2017, 2021; May and Gossage, 2011). A decrease in the efficiency of alcohol metabolism may partially explain the association with advanced maternal age and severity of adverse child outcomes. One could speculate that in alcohol-exposed pregnancies among women with advanced age and/or high gravidity, postpartum maternal weight may be even more important protective factor.

Longer gestational age resulted in better growth parameters. Declines of length centiles are typically seen in low- and middle- income countries within the first two years of life (Roth et al., 2017), yet the environmental conditions (socioeconomic, cultural, sanitation/housing) were very similar among all women in these communities and declines would be expected to be similar among all participants. Virtually all women in this study were: of mixed-race ancestry ('Cape Coloured'), averaged 6–8 years of formal education, and frequently worked in agricultural or agricultural support jobs. The majority (>80%) of women initiate and sustain breastfeeding through an average of 18 months (May et al., 2016). Alcohol can freely enter the breastmilk, so the possibility of continued alcohol exposure via breastmilk adversely affecting child growth and development cannot be ruled out in this study.

Clinical and public health implications

South Africa has the highest reported prevalence of FASD in the world with recent estimates ranging from 17 to 31% (May et al., 2000; Viljoen et al., 2005; May et al., 2007; May et al., 2013; May et al., 2016; May et al., 2016; May et al., 2017; May et al., 2021). Many children with FASD go undiagnosed or are misdiagnosed in populations around the world (Chasnoff et al., 2015). There is a critical need for early evaluation and diagnosis for children with suspected prenatal alcohol exposure. Because the adverse effects of prenatal alcohol exposure are sustained throughout the lifetime (Streissguth et al., 2004), it is imperative that diagnosis and developmental support begins as early as possible. While alcohol is the teratogenic agent leading to a diagnosis within the FASD continuum, other early life indicators may help to better identify children at highest risk for an FASD diagnosis (Carter et al., 2016; Hasken et al., 2021; Kalberg et al., 2019). This study in this rather unique population suggests that higher postpartum maternal weight is a positive predictor of infant outcomes within the first year of life. In this population, higher postpartum maternal weight may have a biological effect (e.g., more body mass to distribute alcohol, thus lower concentration of fetal exposure) or higher postpartum maternal weight may be an indication of more favorable postnatal environmental factors. However, there is growing evidence that higher maternal weight (obesity) can be a risk factor for adverse child outcomes (Deierlein et al., 2011; Adair, 2014). The Western Cape Province has the highest rate of maternal overweight/obesity in South Africa, which may predispose children to altered metabolic profiles and long-term consequences. Yet in alcohol-exposed pregnancies, higher maternal weight may result in better outcomes (Carter et al., 2013), with the understanding that higher maternal weight may not be consistently beneficial.

In some populations, pre-pregnancy weight and/or gestational weight gain may not be easily measured and/or known. Whether postpartum maternal weight is an appropriate proxy for pre-pregnancy weight can be debated, but this study demonstrated that postpartum maternal weight was still informative, and lower postpartum maternal weight was associated with poorer child physical and neurodevelopmental outcomes. Postpartum maternal weight is easily and routinely assessed in primary care clinics and can be used by clinicians while assessing the development of a newborn. Careful consideration of the prenatal history, including alcohol exposure, childbearing history, and maternal weight, may be important indicators to identify children at risk for a possible diagnosis within the FASD continuum or other adverse health outcomes. In this study, even without a formal diagnosis on the FASD continuum, a substantial proportion of children were stunted, underweight, and more infants fell within the at-risk, borderline neurodevelopmental range than would otherwise be expected. It may be more advantageous in this population, and others, to continue to assess physical and neurocognitive development into early childhood to track the developmental trajectory or change in trajectory across time, especially if prenatal alcohol exposure is suspected.

Strengths & limitations

This paper has several strengths. The recruitment of women in antenatal clinics and providing standardized dysmorphology exams at fixed timepoints allow for the analysis of growth and physical development over time rather than limiting analysis to a single time point. Previous studies in these communities have demonstrated that women are generally accurate in recalling and reporting alcohol consumption during pregnancy (Jacobson et al., 2004; May et al., 2005, 2008, 2013; Viljoen et al., 2002). While there was some attrition during the duration of the study with 43 children not been seen at 9 months, <12% of child outcome data were missing at any timepoint. Inevitably there are missing data in longitudinal studies. However, the linear mixed model approach employed here is robust in analyzing results with missing data, for this approach utilizes any available data for each infant.

There were also limitations to this study. Because this was a prospective cohort recruited in the prenatal clinic, maternal interviews were completed at the time when a woman sought prenatal care. At the time of interview, alcohol consumption was queried for the previous 30 days. However, most women were interviewed in the 2nd and 3rd trimesters. The lack of detailed information about alcohol exposure throughout pregnancy may have attenuated or amplified some of the findings. Second, while a diagnosis within the FASD continuum can be made in infancy for severe cases (e.g., FAS) (Kalberg et al., 2019), given the age of the infants at the time these data were collected, no formal diagnoses were yet assigned to any infants. Third, maternal weight was measured postpartum at varying times, but all times were within 10 days of birth. It is possible that a few women may have returned to pre-pregnancy weight within 10 days postpartum, in part, due to parity, limited gestational weight gain, and/or breastfeeding practices. Also, maternal height was not measured; therefore, BMI could not be calculated nor was body fat distribution ascertained. Fourth, cognitive assessments in early life can be insensitive to minor differences among children. Assessments later in life may provide better differentiation between children. Fifth, this population is somewhat unique in terms of socioeconomic and nutrition environment (e.g., 22% experiencing poverty (Statistics South Africa, 2018) and 30% overweight or obese (Republic of South African, Department of Health, South African Demogrpahic and Health Survey, 2016); therefore, findings here may not be readily applicable to other populations, particularly Western societies.

Conclusion

Other studies have suggested that pre-pregnancy maternal weight may be a protective factor in alcohol-exposed pregnancies, such that higher maternal weight may result in less severe effects, or outcomes, in children with prenatal alcohol exposure (Carter et al., 2013) . Overall, our findings suggest that infant growth, dysmorphology, and neurodevelopment were influenced both by maternal weight and prenatal alcohol exposure. Women with higher postpartum maternal weight produce larger, less dysmorphic infants. Prenatal alcohol exposure results in smaller, more dysmorphic infants. Higher postpartum maternal weight also contributed to higher initial neurodevelopmental performance, but the developmental growth across time may be similar among all infants regardless of postpartum maternal weight. In alcohol exposed pregnancies, higher maternal weight may be a protective factor for the fetus, but higher weight does not erase the totality of the adverse, teratogenic effects of alcohol on the fetus and infant. Prenatal alcohol exposure during pregnancy can adversely affect fetal development regardless of postpartum maternal weight. Longitudinal studies are warranted to determine whether prenatal and/or postpartum maternal weight remain protective in alcohol-exposed pregnancies.

CRediT authorship contribution statement

Julie Hasken: Conceptualization, Formal analysis, Writing – original draft. **Linda Adair:** Writing – review & editing. **Stephanie Martin:** Writing – review & editing. **Amanda Thompson:** Writing – review & editing. **Anna-Susan Marais:** Project administration, Data curation. **Marlene de Vries:** Project administration, Data curation. **Wendy Kalberg:** Conceptualization, Project administration. **David Buckley:** Project administration. **H. Eugene Hoyme:** Conceptualization. **Soraya Seedat:** Project administration. **Charles Parry:** Project administration. **Philip May:** Conceptualization, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crtox.2022.100076.

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