

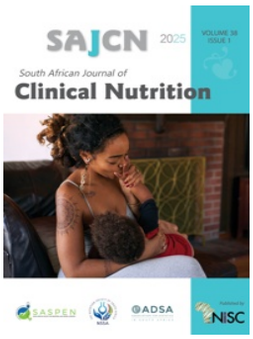
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RESEARCH ARTICLE

The triple burden of obesity, HIV, and anaemia during pregnancy and associations with delivery outcomes in urban South Africans

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Objectives: First, to explore the independent associations between obesity, HIV (with ARV treatment), and anaemia and delivery outcomes in urban South African women and, second, to identify any potential interactions between these co-morbidities.
Design: Longitudinal observational cohort study.
Setting: Soweto, South Africa.
Subjects: Mother–infant pairs (789) were recruited when mothers were < 20 weeks pregnant.
Outcome measures: Infant gestational age at delivery was calculated, and infant birth weight and length were measured by trained research nurses. Head circumference was measured using a metal head circumference tape measure. Multivariable linear regression and logistic regression models were used to test the associations between obesity, HIV-positive status, and anaemia and delivery outcomes, as well as the potential interactions between the triple burden exposures.
Results: At baseline, 14%, 11%, and 22% of women were diagnosed with only obesity, HIV, or anaemia respectively, while 42% had two conditions and 5% were exposed to the triple burden. Maternal obese vs. non-obese status was associated with a 0.32 higher weight-to-length *z*-score at birth ($p < 0.01$) and a 2.93 times higher risk of a large-for-gestational age delivery ($p < 0.01$). There were no interactions between the triple burden exposures on delivery outcomes.
Conclusions: This study presents evidence for the importance of prioritising obesity prevention prior to conception in urban African settings such as South Africa. In addition, our findings highlight the need for more research into the complex relationships between maternal co-morbidities, as well as their potential influence (alone and in combination) on maternal and offspring health in the short and longer term.

Keywords: co-morbidities, health burden, neonate size, pregnancy health

Introduction

As a result of the lifestyle changes associated with urbanisation, and the growing obesity epidemic in low- and middle-income countries, non-communicable diseases (NCDs) have rapidly become the leading causes of morbidity and mortality.[1] In South Africa in particular, a third of women are obese when they become pregnant; putting themselves and their foetus at risk of complications in the short and longer term.[2] Specifically, pre-pregnancy obesity and excessive gestational weight gain (GWG) are established predictors of adverse delivery outcomes such as preterm delivery and delivery of a large-for-gestational age (LGA) and/or macrosomic (≥4 kg) infant.[3–6] In addition, maternal overnutrition has long-term implications for the offspring's susceptibility to developing obesity and cardiometabolic diseases in later life.[5–7]

Proposed mechanisms for the relationship between obesity and adverse pregnancy outcomes such as preterm delivery and foetal growth restriction are predominantly via inflammatory pathways.[8,9] These pathways act independently of the direct effects of obesity on maternal insulin resistance and excess circulating glucose, which is associated with higher risk of macrosomia or an LGA delivery.[10] Pregnancy is known to induce a state of low-grade systemic inflammation.[11] Similarly, adipose tissue releases pro-inflammatory cytokines and hormones that are associated with chronic inflammatory states.[8,11] An interaction between these pathways may therefore be responsible for elevating maternal inflammation beyond levels compatible with normal physiological function.[8,12] Specifically, obese women exhibit comparatively higher levels of placental inflammation, which may lead to altered structure and function with a range of adverse consequences for the foetus.[8,9]

While obesity is a major public health concern, it is only one of the multiple health challenges that women in South Africa face during pregnancy. Urbanisation and a transition to energy-dense, processed, and micronutrient poor diets have not only contributed to the rapid rise in obesity, but to persisting

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micronutrient deficiencies.[13] Specifically, between 23% and 33% of South African women are anaemic at conception, with iron deficiency being proposed to cause approximately half of these cases.[14] This contributes to the triple burden of disease, which has become characteristic of emerging African settings where obesity and NCDs exist alongside micronutrient deficiencies and a high prevalence of HIV/AIDS.[13]

As with obesity, HIV is associated with persistently high levels of inflammation.[15,16] In turn, inflammation is known to alter iron metabolism and may increase anaemia risk.[17] This is supported by previous research demonstrating an association between HIV disease progression and severity of anaemia.[18] In addition, studies have shown that antiretroviral (ARV) treatment is associated with immune reconstitution and a reduction in circulating pro-inflammatory cytokines, as well as with improvements in anaemia.[15,17] Both HIV (with and without treatment) and anaemia are associated with adverse delivery outcomes including preterm birth and low birthweight, with proposed mechanisms via the placenta.[19,20] Additionally, anaemic HIV-positive women may be at an even greater risk of complications.[20] Although the risks associated with being exposed to these conditions during pregnancy have, to an extent, been investigated in isolation, the coexistence of multiple morbidities, and any potential interactions between these conditions during pregnancy, has received little attention.

This study aims to (i) explore the independent associations between obesity, HIV (with ARV treatment), and anaemia and delivery outcomes in urban South African women, and (ii) identify any potential interactions between these co-morbidities.

Methods

Study setting and participants

The Soweto First 1000-Days Study (S1000) was a longitudinal pregnancy cohort study conducted at the South African Medical Research Council (SAMRC)/Wits Developmental Pathways for Health Research Unit (DPHRU) at the Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto, Johannesburg, South Africa between 2013 and 2016. The description of the study setting and the methods for S1000 are published elsewhere[21] but, briefly, recruitment took place at the Antenatal Clinic and Fetal Medicine Unit at CHBAH. Eligibility criteria for inclusion in the study were as follows: black South African (self-reported ethnicity) women, 18 years or older and residents of the Soweto, or the greater Soweto area, preferably < 14 weeks (but no more than 20 weeks) pregnant with a singleton and naturally conceived foetus, and no diagnosis of epilepsy or diabetes at the time of recruitment. Data collection for S1000 took place at six time points during pregnancy (< 14 weeks; 14–18 weeks; 19–23 weeks; 24–28 weeks; 29–33 weeks; and 34–38 weeks) and at the time of delivery. Written informed consent was provided by all women prior to their inclusion in the study and ethical approval was obtained from the University of the Witwatersrand's Research Ethics Committee (Medical) with ethical clearance number M120524. In all, 1 017 women were recruited into the S1000 study.

Data collection

Demographic, health, and socioeconomic variables

Interviewer-administered questionnaires were used to collect maternal demographic, pregnancy-related and socioeconomic variables by trained members of research staff at the baseline visit (< 14 weeks gestational age). Haemoglobin levels (g/dl) were assessed using a HemoCue finger prick test (https://hemocue.com/en/) at each visit, and were then adjusted for smoking (by subtracting 0.3 g/dl if participants reported smoking)[22] and for altitude (1 632 m in Soweto) by subtracting the adjustment factor from the participant's haemoglobin level using the formula: Hb adjustment (g/dl) = ((0.0056384 × elevation) + (0.0000003 × elevation^2)/10).[22]

Anaemia was classified as an adjusted baseline haemoglobin level of < 11.0 g/dl.[22] In cases where haemoglobin levels were not assessed during the first visit, the haemoglobin level at visit 2 (14–18 weeks gestational age) was used to classify anaemia status. Women self-reported their HIV status at each pregnancy visit and this was confirmed using the participant's antenatal clinic card. As South Africa's national Prevention of Mother-to-Child Transmission (PMTCT) guidelines[23] prescribe routine HIV counselling and testing during pregnancy, as well as antiretroviral treatment (ART) initiation for any HIV-positive woman not already receiving treatment, all HIV-positive participants in this study were receiving ART. An asset index was used to assess household socioeconomic status (SES) and this scored each participant according to the number of assets that they possessed out of a possible 11 (electricity, radio, television, refrigerator, mobile phone, personal computer, bicycle, motorcycle/scooter, car, agricultural land, farm animals). This index was based on standard measures used in the Demographic and Health Surveys household questionnaire (available at: www.measuredhs.com) and has been extensively utilised in this setting.[24,25]

Maternal anthropometry

All anthropometric measurements were taken by trained research staff. Height was measured at the baseline visit using a wall-mounted Stadiometer (Holtain, Crosswell, Crymych, UK) and weight was measured at each pregnancy visit using a digital scale. Baseline weight (< 14 weeks gestational age) was used as a proxy for pre-pregnancy weight and, together with height, was used to calculate BMI (weight (kg)/height (m^2)). Women were classified as obese (≥ 30.0 kg/m^2) or not obese (< 30.0 kg/m^2).

Delivery outcomes

Details on methodology for collecting delivery outcomes are described in detail elsewhere.[21] Gestational age at delivery (weeks) was calculated and birthweight, length, and head circumference were measured. The International Newborn Size at Birth Standards Application tool was used to calculate birth weight centiles, as well as weight-to-length z-scores, according to newborn sex and gestational age at delivery (total days).[26] The following criteria were used to classify newborns according to their birthweight: small-for-gestational age, < 10th centile; appropriate-for-gestational age, 10th–90th centile; large-for-gestational age, > 90th centile.[27] Low birthweight was defined as a birthweight < 2.5 kg and macrosomia was defined as a birthweight ≥ 4.0 kg.[28,29]

Statistical analysis

Data were analysed for 789 mother–newborn pairs using StataSE version 16.0 (StataCorp, College Station, TX, USA). The flow of participants through the study to reach the final sample size is depicted in Supplementary Figure 1. Continuous variables were described as median (interquartile range [IQR]) and categorical variables were described as frequencies and percentages (%). The differences in delivery outcomes according to baseline maternal morbidity status were assessed using

Table 1: Characteristics of study participants ($n = 789$)

Item	Median (IQR) or *n* (%)
Maternal characteristics	
Demographic and health characteristics	
Maternal age, years	29 (25; 34)
Parity	
Para 0	217 (28)
Para 1	318 (40)
Para ≥ 2	254 (32)
HIV status	
HIV-negative	531 (67)
HIV-positive	258 (33)
Baseline haemoglobin, g/dl	12.3 (11.0; 13.3)
Anaemic at baseline ($n = 764$)	
No	408 (51)
Yes	394 (49)
Smokes/chews tobacco	
No	704 (89)
Yes	84 (11)
Socioeconomic characteristics	
Maternal education	
Primary	17 (2)
Secondary	578 (73)
Tertiary	194 (25)
Marital status	
Single	494 (63)
Married/cohabiting	295 (37)
Household SES	
Low	96 (12)
Medium	654 (83)
High	39 (5)
Anthropometry	
Weight, kg	69.2 (59.8; 80.6)
Height, cm	158.7 (154.8; 162.7)
BMI at recruitment, kg/m^2 (< 14 weeks)	27.6 (23.8; 31.4)
Not obese (BMI < 30 kg/m^2)	521 (66)
Obese (≥ 30 kg/m^2)	268 (34)
Gestational weight gain, kg/week	0.35 (0.23; 0.47)
Inadequate	228 (29)
Adequate	202 (26)
Excessive	359 (45)
Delivery outcomes	
Neonate sex	
Male	403 (51)
Female	368 (49)
Gestational age at delivery, weeks	39 (37; 40)
Preterm delivery	117 (15)
Mode of delivery	
Vaginal	325 (41)
Caesarean section	464 (59)
Anthropometry	
Birthweight, g	3030 (2675; 3300)
Birthweight category[a]	
Small for gestational age	136 (17)
Appropriate for gestational age	598 (76)
Large for gestational age	55 (7)
Low birthweight	136 (17)
Macrosomia	18 (2)
Birth length, cm	48.5 (46.7; 50.2)
Birthweight-for-length *z*-score[a]	−0.35 (−1.01; 0.31)
Head circumference, cm	34.0 (31.1; 35.0)

IoM GWG ranges (kg/week): inadequate, normal weight < 0.35, overweight < 0.23, obese < 0.17; adequate, normal weight 0.35–0.50, overweight 0.23–0.33, obese 0.17–0.27; excessive, normal weight > 0.50, overweight > 0.33, obese > 0.27; anaemic, adjusted Hb < 11.0 g/dl; preterm delivery, < 37 weeks gestational age; small for gestational age, birthweight < 10th centile; appropriate for gestational age, birthweight 10th–90th centile; large for gestational age, birthweight > 90th centile; low birthweight, birthweight < 2 500 g; macrosomia, birthweight ≥ 4 000 g. [a]Calculated using the International Newborn Size at Birth Standards Application tool.[26]

linear regression (continuous variables) or logistic regression (categorical variables) analyses, which tested differences between each morbidity category and no morbidity (reference category). Delivery outcomes were compared according to maternal morbidity groups as follows: (i) no morbidity; (ii) obese; (iii) HIV-positive; (iv) anaemic; (v) obese + HIV-positive; (vi) obese + anaemic; (vii) HIV-positive + anaemic; (viii) obese + HIV-positive + anaemic.

Multivariable linear regression models (continuous outcomes) and logistic regression models (categorical outcomes) were used to test the associations between triple burden exposures (obesity, HIV-positive status, and anaemia) and potential interactions between these exposures and delivery outcomes. Delivery outcomes included in the regression models were those gestational age- and sex-adjusted body size outcomes hypothesised to be affected by one or more of the maternal morbidities based on our review of the literature (birthweight-for-length z-score, SGA, and LGA). Regression analyses were run for each outcome across four models, namely: Model 1 (M1): neonate sex and maternal obesity status (obese vs. non-obese; ref); Model 2 (M2): neonate sex and maternal HIV status (HIV-positive vs. HIV-negative; ref); Model 3 (M3): neonate sex and anaemia status (anaemic vs. not anaemic; ref); and Model 4 (M4): neonate sex, obesity status, HIV status, and anaemia status. Additional models were run for each outcome to test potential interactions between the exposure variables, i.e. between two morbidities and each other (obese*anaemic; obese*HIV-positive; anaemic*HIV positive) and then between all three morbidities (obese*anaemic*HIV-positive). A two-tailed *p*-value of < 0.05 was considered statistically significant.

Results

Participant characteristics

Table 1 presents maternal characteristics and delivery outcomes for mother–newborn pairs. Overall, median age of pregnant women was 29 years. The prevalence of obesity was 34% at baseline, while 33% of women had HIV and 26% had anaemia. According to their starting BMI, 45% of women gained excessive weight during pregnancy. The majority of women had completed secondary-level education (73%), were single (63%), and were living in a medium SES level household (83%). Mothers delivered at a median gestational age of 39

weeks, with 15% delivering prematurely and 59% delivering via Caesarean section. Approximately half (51%) of newborns were male and the median birth weight-to-length score was −0.35. At delivery 17% of newborns were born small-for-gestational age and 17% were low birth weight, while 7% and 2% of newborns were large-for-gestational age and macrosomic respectively.

Maternal morbidity status and delivery outcomes

The distribution of delivery outcomes according to maternal morbidity status is described in Table 2. Just over a fifth of women were not diagnosed with a morbidity (i.e. obesity, HIV, and/or anaemia) at the time of the baseline visit. Nearly half (47%) of women either had only obesity (14%), only HIV (11%), or only anaemia (22%) at baseline. A large proportion (42%) had two conditions at baseline, while 5% had obesity, HIV, and anaemia. There were significant differences in the mode of delivery according to maternal baseline morbidity status, with women with obesity (77%, $P < 0.01$) and women with obesity and HIV (72%, $p < 0.05$) at baseline being more likely to deliver via Caesarean section. In addition, birthweight, birthweight-to-length z-score, low birthweight, head circumference, SGA, and LGA prevalence differed significantly by maternal morbidity status. Specifically, birthweight was higher in infants born to women with obesity ($p < 0.01$) and women with obesity and HIV ($p < 0.05$), and birthweight-to-length *z*-score was lower in those born to women with obesity ($p < 0.01$), women with obesity and HIV ($p < 0.01$), and women with obesity and anaemia ($p < 0.01$) compared with those with no morbidity at baseline. In addition, women with obesity had a significantly higher risk of delivering an LGA infant ($p < 0.01$), and were more likely to deliver an infant with a larger head circumference ($p < 0.05$) vs. those with no morbidity. Women with anaemia and women with obesity and anaemia were more likely to deliver an SGA infant ($p < 0.05$), while women with anaemia were more likely to deliver a low birthweight infant ($p < 0.05$). There were no differences in gestational age at delivery across the groups.

Associations between triple burden exposures and delivery outcomes

Results from linear regression and logistic regression models are presented in Tables 3 and 4 respectively. In all models, maternal obesity at baseline was associated with a higher birthweight-to-length *z*-score (M1: 0.32 vs. non-obese; $p < 0.001$) and with a 2.93 times higher risk of giving birth to an LGA infant ($p < 0.001$). There were no associations between maternal obesity at baseline and SGA deliveries, as well as no associations between HIV-positive status or anaemia and any delivery outcomes. There were also no interactions between the triple burden exposures on delivery outcomes (data not shown).

Discussion

This study characterised the triple burden of obesity, HIV, and anaemia in urban South African women during pregnancy, and explored the associations between the morbidities and delivery outcomes. We found that maternal obesity at baseline was associated with delivery of larger infants (birthweight-to-length z-score), as well as an increased risk of an LGA delivery. Maternal HIV-positive status and anaemia were not independently associated with any delivery outcomes.

The identified association between obesity and adverse delivery outcomes is well established, with pre-pregnancy obesity being shown to increase the risk of giving birth to a large infant across high, middle, and lower income settings.[3–6,30] In addition, studies show that the effects of obesity are independent of gestational diabetes mellitus (GDM) diagnosis or a diabetic metabolic state.[30] Not only do excessive foetal growth and delivery of large infants increase the risk of maternal and neonatal complications, but they have long-term implications for growth and development of the offspring, as well as susceptibility to developing obesity and NCDs via early programming pathways.[5–7] A systematic review of the available literature shows that being born to a mother with obesity increases the offspring's odds of developing obesity in childhood by almost three times.[31] Exposure to maternal overweight/obesity in utero has also been associated with type 2 diabetes mellitus at a mean age of 15 years.[32] In addition, higher infant birthweight and macrosomia have been associated with later childhood obesity.[33,34] In Soweto, we have previously demonstrated positive associations between maternal obesity at baseline (< 14 weeks gestational age) and longitudinal foetal growth assessed via ultrasound, with a particular effect on femur length and abdominal circumference.[35] Greater abdominal fat in utero has, in particular, been positively associated with childhood BMI.[36] Together, these findings support the intergenerational transfer of obesity risk and the need for preconception interventions to establish healthier trajectories of growth, development, and metabolic risk through the life course.

While our study is useful in corroborating the above findings for the urban African setting, it additionally provides novel data on the association between maternal obesity and delivery outcomes in the context of multiple maternal co-morbidities. Specifically, we highlight the relationship between obesity and foetal growth and delivery outcomes independent of other pre-existing conditions such as HIV and anaemia. In South Africa, where according to this sample over two-thirds of women have obesity or overweight at conception, targeting the obesity epidemic and establishing healthier nutritional profiles in the preconception period may therefore be a key factor in supporting healthier pregnancies, irrespective of other risk factors.[37] In addition, overnutrition often coexists with multiple micronutrient deficiencies in these settings. Interestingly, data from this study show that, even in settings with high obesity prevalence such as Soweto, anaemia is most likely to affect those on the lower end of the BMI spectrum, with an anaemia prevalence of 30% in women with a normal weight compared with prevalence rates of 19% in women with overweight or obesity (data not shown). Previous studies from LMICs have found contradictory evidence as to the direction of the association between anaemia and BMI, and researchers have indicated that it may be important to evaluate factors such as iron and Vitamin C intake to account for these discrepancies.[38] While all women in this study were receiving routine iron supplementation during pregnancy, there may be differences in iron absorption according to BMI status[39] and we were unable to account for supplement adherence. This suggests that, despite the transition towards more obesogenic nutritional profiles and the coexistence of excess adiposity with micronutrient deficiencies, undernourishment persists and cannot be overlooked in future interventions. Such high rates of anaemia across the BMI spectrum are a concern as current interventions, i.e. routine supplementation during pregnancy, may be received too late to effectively impact micronutrient profiles.[40] In addition, supplementation efficacy in South Africa is further complicated by other factors such as baseline nutritional and health status, and the suitability of a universal approach (i.e. specified nutrient(s) and specified doses) to

Table 2: Delivery outcomes according to baseline maternal morbidity status

	No morbidity (Reference)	Obese only	HIV-positive only	Anaemic only	Obese + HIV-positive	Obese + anaemic	HIV-positive + anaemic	Obese + HIV-positive + anaemic
N (%)	175 (22)	112 (14)	83 (11)	173 (22)	43 (5)	71 (9)	90 (11)	42 (5)
Delivery outcomes								
Gestational age at delivery, weeks	39 (37; 40)	39 (37; 40)	39 (38; 39)	39 (38; 40)	38 (38; 39)	39 (38; 40)	38 (37; 40)	39 (38; 40)
Preterm delivery, *n* (%)	27 (15)	16 (14)	13 (16)	24 (14)	5 (12)	7 (10)	18 (20)	7 (17)
Mode of delivery, *n* (%)								
Vaginal	86 (49)	35 (31)	30 (36)	83 (48)	12 (28)	27 (38)	38 (42)	14 (33)
Caesarean section	89 (51)	**77 (67)** **	53 (64)	90 (52)	**31 (72)***	44 (62)	52 (58)	28 (67)
Anthropometry								
Birthweight, g	2971 (2585; 3250)	**3108 (2782; 3505)** **	3015 (2630; 3255)	3005 (2750; 3275)	3035 (2845; 3330)	**3115 (2900; 3435)***	2900 (2570; 3255)	3028 (2595; 3300)
Birth length, cm	48.6 (46.2; 50.0)	48.9 (47.2; 51.1)	48.2 (46.4; 50.0)	48.5 (47.0; 50.4)	48.3 (46.6; 50.6)	48.5 (47.2; 50.4)	48.6 (46.0; 50.0)	49.0 (45.5; 50.2)
Birthweight-for-length *z*-score[a]	−0.60 (−1.27; 0.22)	**−0.14 (−0.81; 0.57)** **	−0.43 (−1.16; 0.23)	−0.37 (−0.98; 0.21)	**−0.15 (−0.54; 0.73)** **	**0.04 (−0.73; 0.52)** **	−0.44 (−1.28; 0.15)	−0.37 (−1.16; 0.14)
Low birthweight, % *n* (%)	37 (21)	18 (16)	16 (19)	26 (15)	4 (9)	**6 (8)***	18 (20)	9 (21)
Macrosomia, *n* (%)	5 (3)	4 (4)	2 (2)	1 (1)	1 (2)	2 (3)	2 (2)	1 (2)
Small-for-gestational age, *n* (%)[a]	39 (22)	16 (14)	15 (18)	**22 (13)***	5 (12)	**7 (10)***	23 (26)	9 (21)
Large-for-gestational age, *n* (%)[a]	9 (5)	**18 (16)** **	2 (2)	6 (3)	4 (9)	6 (8)	6 (7)	4 (10)
Head circumference, cm	34.1 (32.9; 35.0)	**34.3 (33.4; 35.5)***	34.0 (33.0; 35.0)	34.0 (33.2; 35.0)	34.3 (33.0; 35.8)	34.2 (33.4; 35.0)	34.0 (32.5; 35.0)	34.0 (33.1; 34.5)

Data presented as median (IQR) or %; delivery outcomes compared across morbidity groups via linear (continuous delivery outcomes) and logistic (categorical delivery outcomes) regression analyses; bolded values indicate significant associations: *$p < 0.05$, **$p < 0.01$ vs. no morbidity (ref). Anaemia, adjusted Hb < 11.0 g/dl; preterm delivery, < 37 weeks gestational age; small-for-gestational age, birthweight < 10th percentile; large-for-gestational age, birthweight > 90th percentile; low birthweight, birthweight < 2 500 g; macrosomia, birthweight ≥ 4 000 g. [a] Calculated using the International Newborn Size at Birth Standards Application tool.[26]

Table 3: Linear regression analyses of triple burden exposures and continuous delivery outcomes

	Birth weight-for-length z-score											
	M1 ($n = 789$)			M2 ($n = 789$)			M3 ($n = 764$)			M4 ($n = 764$)		
	β	95% CI	*p*-value	β	95% CI	*p*-value	β	95% CI	*p*-value	β	95% CI	*p*-value
Neonate sex												
Male	Ref			Ref			Ref			Ref		
Female	0.02	−0.13; 0.18	0.765	0.03	−0.12; 0.19	0.676	0.03	−0.12; 0.19	0.676	0.03	−0.13; 0.18	0.738
BMI category												
Not obese	Ref									Ref		
Obese	**0.32**	**0.16; 0.48**	**< 0.001**							**0.30**	**0.14; 0.47**	**< 0.001**
HIV status												
HIV negative				Ref						Ref		
HIV-positive				−0.04	−0.20; 0.12	0.633				−0.05	−0.22; 0.11	0.543
Anaemia status												
Not anaemic							Ref			Ref		
Anaemic							0.00	−0.16; 0.15	0.984	0.02	−0.58; 0.27	0.770

Model 1 (M1): neonate sex and obesity status (obese vs. non-obese; ref); Model 2 (M2): neonate sex and HIV status (HIV-positive vs. HIV-negative; ref); Model 3 (M3): neonate sex and anaemia status (anaemic vs. not anaemic; ref); and Model 4 (M4): neonate sex, obesity status, HIV status and anaemia status. Bolded values indicate significant associations ($p < 0.001$).

Table 4: Logistic regression analyses of triple burden exposures and categorical delivery outcomes

	M1 ($n = 789$)			M2 ($n = 789$)			M3 ($n = 764$)			M4 ($n = 764$)		
	RR	**95% CI**	***p*-value**	**RR**	**95% CI**	***p*-value**	**RR**	**95% CI**	***p*-value**	**RR**	**95% CI**	***p*-value**
Small-for-gestational age												
Neonate sex												
Male		Ref			Ref			Ref			Ref	
Female	1.10	0.76; 1.60	0.607	1.08	0.74; 1.56	0.688	1.01	0.69; 1.48	0.952	1.01	0.69; 1.47	0.968
BMI category												
Not obese		Ref									Ref	
Obese	0.68	0.45; 1.03	0.066							0.75	0.50; 1.14	0.181
HIV status												
HIV negative					Ref						Ref	
HIV-positive				1.34	0.91; 1.96	0.136				1.40	0.94; 2.07	0.096
Anaemia status												
Not anaemic								Ref			Ref	
Anaemic							0.91	0.62; 1.33	0.632	0.88	0.60; 1.29	0.504
Large-for-gestational age												
Neonate sex												
Male		Ref			Ref			Ref			Ref	
Female	1.06	0.61; 1.84	0.838	1.10	0.63; 1.90	0.741	1.02	0.58; 1.78	0.958	0.99	0.56; 1.75	0.979
BMI category												
Not obese		Ref									Ref	
Obese	**2.93**	**1.68; 5.12**	**< 0.001**							**2.94**	**1.66; 5.20**	**< 0.001**
HIV status												
HIV negative					Ref						Ref	
HIV-positive				0.83	0.45; 1.52	0.546				0.85	0.46; 1.60	0.616
Anaemia status												
Not anaemic								Ref			Ref	
Anaemic							0.72	0.41; 1.26	0.247	0.78	0.44; 1.39	0.408

Model 1 (M1): neonate sex and obesity status (obese vs. non-obese; ref); Model 2 (M2): neonate sex and HIV status (HIV-positive vs. HIV-negative; ref); Model 3 (M3): neonate sex and anaemia status (anaemic vs. not anaemic; ref); and Model 4 (M4): neonate sex, obesity status, HIV status and anaemia status. Bolded values indicate significant associations ($p < 0.001$).

supplementation, as well as barriers to compliance such as experience of side effects, cultural norms, and poor education and support services.[40,41] Recent data from a prospective study conducted in Johannesburg showed that – even with routine iron, folic acid, and calcium supplementation during pregnancy – anaemia prevalence increased from 29% to 45% and iron deficiency from 15% to 33% between < 18 and 36 weeks' gestational age.[14]

In low-income settings such as Soweto, identifying strategies for obesity prevention and management at individual, household, and community levels is challenging due to established barriers to making healthier lifestyle choices.[42] Studies show that during the preconception period, young women from Soweto do not feel empowered to improve their diets due to the high availability and access to unhealthy, energy-dense foods, alongside low access to, and high cost of, healthy food alternatives.[42,43] In addition, poor infrastructure and facilities, as well as safety concerns, restrict opportunities for females to be physically active across age groups.[43,44] Such factors are largely out of the individual's control, and require cross-cutting solutions that promote and facilitate sustainable behaviour change.

Although it is clear that targeting the obesity epidemic in the preconception period is fundamental to have an impact in the longer term, given the substantial number of overweight and obese pregnant women in South Africa, management of these women during pregnancy is also critical. While most women will have their BMI calculated during their first antenatal visit and a pregnancy in a women with obesity may be flagged as 'high risk', there is currently no established guideline for monitoring of these women, unless they are subsequently diagnosed with GDM. In addition, current nutrition guidelines and recommendations for pregnant women are largely based on those with normal weight, as well as on universal supplementation strategies; with a substantial gap in our understanding of appropriate monitoring and care of women with overweight and obesity. In a sub-study of S1000, we previously showed that higher adherence to a 'traditional' dietary pattern – high in whole grains, vegetables, legumes, and traditional meats and low in processed foods – and lower adherence to 'Western' and 'mixed, high sugar' dietary patterns – high in fat, processed and convenience foods and added sugar – were associated with lower GWG, as well as with lower foetal growth, birth size, and neonatal adiposity.[35,45,46] This suggests that, even in populations with a high prevalence of obesity, nutritional management strategies that promote and empower women to make beneficial dietary changes during pregnancy may be an important component of optimising pregnancy outcomes.

Although the lack of associations identified between either HIV or anaemia and delivery outcomes may be surprising, existing literature shows mixed results. Systematic reviews show strong evidence for associations between HIV and adverse delivery outcomes, but this has predominantly been in women not receiving ART.[47] Findings from studies conducted in those receiving treatment vary, with longer treatment duration also potentially being linked to adverse outcomes.[48,49] While our study collected data on treatment initiation (i.e. whether ART was initiated prior to or during the current pregnancy), the sample size – and specifically the numbers within the treatment groups – restricted our ability to further stratify and test these differences. Similarly, while maternal anaemia is an established predictor of poor delivery outcomes, some studies suggest that the timing of anaemia during the antenatal period may be an important predictor of poor outcomes such as preterm birth and SGA deliveries.[50–52] In addition, supplementation with iron/folic acid during pregnancy has been shown to reduce iron deficiency and iron deficiency anaemia in pregnant women, with some benefit for birth outcomes such as low birthweight, and multi-micronutrient supplements are now recommended during pregnancy.[53] While all women in our study were receiving ART and iron/folic acid supplementation during their pregnancy, the duration of ART differed substantially between participants and the compliance with supplementation – as well as its effects on anaemia status – was not known. Given the complexity of the relationships between HIV and treatment, as well as anaemia (and potentially supplementation), and pregnancy outcomes – alongside potential interactions between these and other factors – larger studies that are able to distinguish between such complexities are needed.

Strengths and limitations

This longitudinal study provided a good platform for investigating the associations between multiple maternal morbidities during pregnancy and delivery outcomes in a sample of urban South African women. Given the influence of urbanisation – and its associated lifestyle changes – on health and morbidity profiles in low- and middle-income settings, our findings contribute to a greater understanding of where to focus interventions for improvements in maternal and child health outcomes. However, our study is not without limitations. We used baseline BMI as a proxy for pre-pregnancy BMI, which may potentially have misclassified women who gained or lost weight between conception and recruitment as obese or non-obese. However, as an established proxy for pre-pregnancy weight, first trimester weight has been shown to accurately classify 91–95% of women and therefore is unlikely to have influenced study findings.[54] In addition, while our sample size allowed us to adequately stratify by distinct morbidity categories (i.e. obese vs. HIV-positive vs. anaemic), the numbers within multiple morbidity groups – and in those having all three conditions – restricted the power of these analyses. This limitation, as well as potential complex interactions between the conditions and factors such as treatment and/or supplementation, require further investigation. Lastly, it has been proposed that obesity, HIV, and anaemia all influence health outcomes – at least to an extent – through inflammatory pathways.[8,9,16,17,20] Future studies should therefore incorporate exploration into the inflammatory effects of these triple burden exposures, as well as how these pathways may influence delivery outcomes – both independently and in combination.

Conclusion

This study presents evidence for the importance of prioritising obesity prevention in the pre-conception period in urban African settings such as South Africa. Specifically, while South African women may experience multiple morbidities during pregnancy, we show that establishing a healthy bodyweight prior to conception may reduce the risk of adverse delivery outcomes, irrespective of other pre-existing conditions. Interventions aimed at reducing the obesity burden in adolescent girls and young women – alongside appropriate nutritional management of obese pregnant women – are therefore critical to shifting the transgenerational epidemic of obesity and NCDs. In addition, our findings highlight the need for more research into the complex relationships between maternal co-morbidities, as well as their potential influence (alone and in

combination) on maternal and offspring health in the short and longer term.

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