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Maternal Traditional dietary pattern and antiretroviral treatment exposure are associated with neonatal size and adiposity in urban, black South Africans

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Abstract

This study examines the associations between maternal Traditional dietary pattern adherence and HIV/treatment with neonatal size and adiposity in urban, black South Africans, as well as how specific maternal factors - i.e. BMI and GWG - may influence these associations. Multiple linear regression models were used to examine associations between maternal Traditional diet pattern adherence (pattern score), HIV/treatment status [three groups: HIV negative, HIV positive (antenatal antiretroviral treatment (ART) initiation), HIV positive (pre-pregnancy ART initiation)], BMI and GWG (kg/week) and: newborn (1) weight-to-length ratio (WLR, kg/m) in 393 mother-neonate pairs; (2) Peapod estimated fat mass index (FMI, kg/m3) in a 171-pair subsample. In fully adjusted models, maternal obesity and GWG were associated with 0.25 kg/m (P=0.008) and 0.48 kg/m (P=0.002) higher newborn WLR, while Traditional diet pattern score was associated with lower newborn WLR (-0.04 kg/m per +1 SD; P=0.033). Additionally, Traditional diet pattern score was associated with 0.13 kg/m3 (P=0.027) and 0.32 kg/m3 (P=0.005) lower FMI in the total sample and in newborns of normal weight women, respectively. HIV positive (pre-pregnancy ART) vs. HIV negative (ref) status was associated with 1.11 kg/m3 (P=0.002) higher newborn FMI. Promotion of a Traditional dietary pattern, alongside a healthy maternal pre-conception weight, in South African women may reduce newborn adiposity and metabolic risk profiles. In HIV-positive women, targeted monitoring and management strategies are necessary to limit treatment-associated effects on in utero fat deposition.

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Conflict of Interest
None

Authorship
SVW, KKO and SAN contributed to conceptualisation and design of the work towards this paper; SVW, PTP and SAN facilitated data acquisition; SVW analysed the data and drafted the manuscript; all authors contributed to interpretation of results and/or revision of the manuscript; all authors gave their approval of the final version for submission

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Key words/phrases

Pregnancy; Traditional dietary pattern; antiretroviral treatment; neonatal adiposity; South Africa

Introduction

Maternal pre-pregnancy body mass index (BMI) and gestational weight gain (GWG) are established predictors of fetal growth and birth outcomes; with both obesity and excessive weight gain being associated with high birth weight and large-for-gestational age (LGA) deliveries, as well as with obesity and cardiometabolic disease risk in later life (1–5). Although the effects of anthropometrically defined maternal nutritional status on birth weight have been well documented, the influence of dietary patterns on birth size – particularly in increasingly urbanised low-and-middle income countries (LMICs) such as South Africa – is not known. In addition, the predominant use of birth weight as a proxy for fetal growth fails to elucidate the effects of diet on adiposity (i.e. fat vs. fat-free mass) and therefore provides only a weak indication of newborn metabolic risk (6,7). Studies have shown that adiposity in early infancy tends to track through childhood and is associated with long term risk of central adiposity, as well as of elevated triglyceride levels and insulin resistance (8,9). Finally, the extent to which high HIV and antiretroviral treatment (ART) exposure in this setting prior to, and during, pregnancy may impact these associations is yet to be explored.

During a previous study in urban, black South Africans, we used principal component analysis (PCA) to identify three distinct dietary patterns in pregnant women; namely Western, Traditional and Mixed (10). These patterns were consistent with those expected for a transitioning African population experiencing a shift towards increasingly westernised diets high in saturated fat, sugar, salt, processed/convenience foods and edible oils and low in essential micronutrients (11,12). We further showed that adherence to the Traditional dietary pattern – characterised by high intakes of vegetables, beans and legumes, traditional meats and whole grains - was associated with lower rate of gestational weight gain (GWG) and reduced odds of excessive weight gain. These associations remained evident in women of normal weight after stratification, but not in overweight or obese subgroups. This suggests that the relationship between diet and maternal adiposity may be modified by baseline BMI. However, whether Traditional pattern intake is similarly associated with beneficial reductions in neonatal adiposity – either independently or via interactions with maternal nutritional status - is not known.

The maternal high risk profile in this setting – where 66% of women are overweight or obese and 55% experience excessive gestational weight gain - is further complicated by a 33% prevalence of HIV (10). While ART initiation is mandatory in South Africa for all HIV positive pregnant women not yet receiving treatment, and this has had undeniable benefits in the prevention of vertical transmission, the metabolic consequences for both mother and infant are not clear. Both HIV infection and ART exposure have been positively associated with weight and fat distribution changes and altered glucose and lipid metabolism in both adults and children, as well as with adverse birth outcomes (13–17). However, little is

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known about the possible effects of HIV/treatment on fetal growth and adiposity, as well the risk of non-communicable disease in the long term.

The aim of this study was therefore to examine the associations between maternal Traditional dietary pattern adherence and HIV/treatment with neonatal size and adiposity in urban, black South Africans, as well as how specific maternal factors - i.e. BMI and GWG - may influence these associations.

Methods

Study Setting and Participants

This study was nested within a large pregnancy cohort study (Soweto First 1000-Day Study; S 1000), based at the Chris Hani Baragwanath Hospital in Soweto, Johannesburg, South Africa between 2013 and 2016. Overall, S 1000 aimed to understand the complex associations between multiple maternal factors and fetal and infant outcomes in an urban-poor African context, and to identify the levers that could optimise maternal and child health within the first 1000 days. Inclusion criteria for S 1000 were as follows: resident of Soweto, or the Greater Soweto area, <20 weeks gestational age at recruitment, non-epileptic, non-diabetic, 18 years or older and pregnant with a singleton, naturally conceived pregnancy. Data collection for S 1000 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 eight time points after delivery (<14 days; 6 weeks; 2 months; 3 months; 6 months; 12 months; 18 months and 24 months). All women provided written informed consent prior to their inclusion in the pregnancy component of the study (Soweto Fetal Growth Study), as well as prior to the inclusion of themselves and their infants in the post-delivery follow-up (Soweto Baby Growth Study). Ethical approval was obtained from the University of the Witwatersrand's Research Ethics Committee (Medical) for both components of S 1000 (M120524 and M130905). 559 women were recruited into this sub-study and had dietary intake assessed at 14-18 weeks.

Maternal Variables

Demographic, Health and Socio-Economic Variables—Maternal demographic and socio-economic variables were collected by trained members of research staff using interviewer-administered questionnaires at the first pregnancy visit (<14 weeks gestational age). Parity was defined as the number of previous births at a gestational age of 24 weeks or more - regardless of whether the infant was born alive or was stillborn. Smoking and/or chewing tobacco was reported at baseline. HIV-status was self-reported at each pregnancy visit and confirmed using the results recorded in the participant's antenatal clinic card. According to South Africa's national Prevention of Mother-to-Child Transmission (PMTCT) guidelines, routine HIV counselling and testing is required during pregnancy; for any HIV-positive woman who is not already receiving treatment, ART is initiated. All HIV-positive participants in this study were therefore receiving ART and were stratified according to whether they had been initiated on ART prior to pregnancy (pre-pregnancy ART) or during the current pregnancy (antenatal ART). Household socio-economic status (SES) was assessed using an asset index which scored each participant according to the number of

assets that they possessed out of a possible 9 (electricity, radio, television, refrigerator, mobile phone, personal computer, bicycle, motorcycle/scooter, car). This 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 (18,19). Asset index scores were subsequently grouped into low (<5), medium (5-7) and high (>7) SES categories. Maternal education was defined according to the highest level of completed (primary, secondary or tertiary).

Anthropometry—A wall-mounted Stadiometer (Holtain, UK) was used to measure maternal height to the nearest 1 mm at baseline. Maternal weight was measured to the nearest 0.1 kg at each visit during pregnancy using a digital scale. Weight at recruitment (<14 weeks) was used as a proxy for pre-pregnancy weight and, together with height, was used to calculate maternal BMI (weight (kg)/height (m2)). There were no underweight women in this sample and therefore BMI was classified according to the following categories: normal weight (18.5–24.9 kg/m2), overweight (25–29.9 kg/m2) or obese (≥30.0 kg/m2). GWG (kg/week) was calculated as: [(weight at final pregnancy visit − weight at recruitment)/duration of follow-up]. GWG was classified as inadequate, adequate or excessive according to the BMI-specific Institute of Medicine recommended weight gain ranges (20).

Dietary Intake—Habitual dietary intake was assessed at the second pregnancy visit (14-18 weeks) using an interviewer-administered quantitative food-frequency questionnaire (QFFQ). This nationally utilised QFFQ was developed by the South African Medical Research Council (SAMRC) based on analyses of 11 dietary surveys conducted in rural and urban South Africa and includes all foods consumed by at least 3% of the population (21). Retrospective data was collected on the frequency and quantity of food and beverage intake during the previous week using food flash cards (high quality photographs of food items) and a combination of household measures, two-dimensional life-size drawings of foods and utensils, and three-dimensional food models as described and validated by Steyn et al (22). According to the criteria developed by Dennis et al, this QFFQ is a very high quality tool – scoring a total of 13 points (high quality classified as a score of seven or higher) (23). This QFFQ has been extensively piloted and utilised in this setting and results are published elsewhere (10,24,25). QFFQ data was captured electronically using REDCap electronic data capture tools hosted at The University of the Witwatersrand (26).

Neonatal variables—Neonates were included in this study if they were born at term (≥37 weeks) and had complete delivery outcome data. Additionally, body composition was analysed for a sub-sample who had assessments via either air displacement plethysmography (ADP) using the Peapod (Cosmed, USA) or dual-energy x-ray absorptiometry (DXA; (Hologic DiscoveryA S/N 86254, APEX software version 4.0.2, Hologic Inc., USA) within the first two weeks of life.

Birth outcomes—Gestational age at delivery (weeks) was calculated as: [duration of pregnancy follow-up (date of delivery – date of baseline ultrasound dating scan) + gestational age at baseline (crown-to-rump length measured by ultrasound; days)]. Birth

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weight and length were measured by trained research nurses within 24 hours of delivery for 82% of neonates. Where assessment within this window was not possible – for example due to the infant being admitted to the hospital for observation – measurements were taken within 48 hours. Weight to length ratio (WLR; kg/m) was calculated to represent the best anthropometric predictor of neonatal body composition (fat-free mass and fat mass) as described by Villar et al (27).

Neonatal body composition—Weight and length were measured and fat mass and fat-free mass estimated for nude neonates within 14 days of birth. According to a previous study in which we demonstrated the level of agreement between ADP and DXA estimated body composition in this population, ADP was utilised where available (28). In cases where a neonate had only DXA measurements, fat mass and fat-free mass were converted to their ADP equivalent estimates using the following linear equations:

- Fat mass (ADP equivalent) = 139.8311 + 0.7974718 * DXA fat mass
- Fat-free mass (ADP equivalent) = 89.40371 + 0.8728309 * DXA fat-free mass

These equations were generated for the population from the regression of ADP on DXA measurements in the aforementioned ADP/DXA comparison study and provided reliable ADP equivalent estimates (28). Fat mass index (FMI; kg/m3) was calculated from these estimates to describe adiposity in neonates. As described by Villar et al, the applicability of exponents in body composition indices to address the relationship between body composition and size may vary across populations (27). We therefore regressed fat mass on length (data in natural logarithms) to confirm that this index (kg/m3) provided the best description of the relationship between weight and length in the study population. This was indeed confirmed - regression power exponent: 2.8±0.6 (SE) (29).

ADP—Peapod assessments were performed according to standard procedures as previously described (30,31). Participants were placed inside the Peapod chamber wearing only a wig cap if necessary. Body volume was estimated using pressure and volume changes (air displacement) within the chamber and body density calculated using body mass and volume measurements. Fat mass, and fat-free mass were subsequently derived using gender-specific equations developed by Fomon et al (32).

DXA—DXA scanning was performed according to standard procedures as described elsewhere (33). Typically, neonates were fed prior to DXA scanning and were sleeping during the procedure. Neonates were placed supine on the scanning bed wearing only a disposable diaper and swaddled in a cotton blanket. Scans were satisfactory for use if the subject's body lay within the scanning region and there was minimal movement during assessment. Whole body measurements of fat mass and fat-free mass were extracted for use in analyses.

Statistical Analysis

Data were analysed for 393 mother-neonate pairs with complete data using STATA 13.0 (StataCorp, College Station, TX, USA). The flow of participants through the sub-study to reach the final sample sizes for the primary and secondary outcomes (WLR and FMI

respectively) is depicted in Supplementary Figure 1. Mother-neonate pairs included in the final analyses did not differ in any baseline maternal characteristics (demographics, socio-economic status and anthropometry) from those excluded.

The dietary patterns previously identified in this population – namely Western, Traditional and Mixed – were confirmed in this sub-sample using PCA as described elsewhere (10). PCA was conducted using orthogonal (varimax) rotation on the weekly frequency of consumption of the QFFQ food items, classified as 48 food items/groups based on those described by Crozier et al (34,35). The Kaiser-Meyer-Olkin measure of sampling adequacy (0.68) and Bartlett's test of sphericity ($p<0.001$) confirmed PCA as an appropriate dimension reduction technique for use in this sample. Eigen values, as well as their visual inflections on a scree plot, and the percentage of total variance explained were used to retain patterns. As described elsewhere, foods or food groups with factor loadings ≥ 0.2 reflected strong associations with principal components and were used to name the dietary patterns (36). Dietary pattern scores for each pattern were generated by multiplying factor loadings by the standardised intake of each food/food group and then summing these. Mean factor scores for the patterns were zero; with positive and negative scores representing high and low adherence respectively of each dietary pattern (37). Due to the associations previously demonstrated between the Traditional diet pattern and GWG in this population, maternal diet was classified according to adherence to the Traditional pattern (Traditional pattern score) in all subsequent study analyses.

Maternal and neonatal characteristics of the sample are presented as median (interquartile range) and percentages (%) for continuous and categorical variables respectively. The Kruskal-Wallis test was used to compare neonatal WLR and FMI according to the following maternal and infant factors: maternal age, parity, HIV/treatment status, smoking status, education, marital status, SES, BMI at recruitment, GWG, Traditional diet pattern adherence, neonate sex and gestational age at birth.

Based on known associations between maternal factors and birth size, as well as previously described associations in this population (10), we proposed a conceptual framework for the associations between maternal Traditional pattern adherence (continuous: diet pattern score), BMI (categorical: normal weight (ref) vs. overweight and obese), GWG (continuous: kg/week), HIV/treatment status (categorical: HIV negative (ref) vs. HIV positive (antenatal ART) and HIV positive (pre-pregnancy ART) and neonatal WLR (continuous: kg/m) and FMI (continuous: kg/m3). The bivariate associations between these maternal factors and each neonatal outcome were tested using linear regression analyses.

In order to identify the independent associations between diet, BMI, GWG, HIV/treatment status and WLR and FMI we performed hierarchical regression analyses per outcome. Covariates included in analyses were maternal or infant variables conclusively associated with infant outcome(s) (namely parity, newborn sex and gestational age at birth). Additionally, for FMI, age at scan (days) was included to adjust for variation across the two week assessment period. Regression coefficients and R^2 values are therefore presented across three models for WLR and FMI. Variables included in the models were as follows: Model 1 (M1): neonate sex and Traditional diet pattern score; Model 2 (M2): M1 with HIV/

treatment status, BMI and GWG; Model 3 (M3): M2 with parity and gestational age at delivery (and age at scan for FMI). In order to test for an interaction between BMI and dietary pattern adherence, a fourth model per outcome was run as follows: M3 with the interaction term BMI category*Traditional pattern score (data not shown). P-values tailed at 0.05 were considered statistically significant.

Results

Maternal and infant characteristics are presented in Table 1. The median age of pregnant women was 30 years. 35% and 30% of women were overweight and obese at recruitment, respectively, while 58% gained excessive weight according to the IoM BMI-specific guidelines. 34% of women were HIV positive; with 23% in total being initiated on ART during the current pregnancy. 52% of newborns were male. Neonates had a median birth weight of 3100 g and WLR and FMI were 6.4 kg/m and 3.6 kg/m3 respectively.

As previously described, for the purpose of this study maternal diet was classified according to Traditional diet pattern adherence (i.e. Traditional diet pattern score). This dietary pattern was characterised by high factor loadings for vegetables, beans and legumes, traditional meats and porridge/pap (Supplementary Table 1).

Of the maternal variables described as potential covariates in this population, only parity was consistently associated with neonatal outcomes; with higher WLR and FMI seen in infants born to mothers who had experienced at least one previous birth (Supplementary Table 2). Female neonates had significantly higher FMI than males and WLR increased with gestational age.

Conceptual models for the bivariate associations between maternal Traditional diet pattern, BMI, GWG and HIV/treatment status and outcomes of interest are presented in Figures 1 (WLR) and 2 (FMI). Compared to those of normal weight at recruitment, overweight and obese women exhibited significantly lower GWG. GWG was also lower in HIV positive (antenatal ART initiation) vs. HIV negative women. Additionally, in HIV positive women, pre-pregnancy ART initiation was associated with higher adherence to the Traditional diet pattern. Maternal obese vs. normal weight BMI was positively associated with WLR during bivariate analyses, while HIV positive (pre-pregnancy ART) status was positively associated with FMI when compared to HIV negative status.

Table 2 presents the results of hierarchical regression analyses of maternal variables on newborn WLR. In fully adjusted models (M3: adjusted for neonate sex, Traditional diet pattern score, HIV/treatment status, BMI, GWG, parity and gestational age at delivery) a 1 SD increase in Traditional diet pattern score was inversely associated with newborn WLR (-0.04 kg/m; P=0.033). In addition, compared to a normal weight BMI at recruitment, maternal obesity was positively associated with WLR (M3: 0.25 kg/m; P=0.008) and a 1 kg/week increase in GWG was associated with a 0.48 kg/m increase in newborn WLR (M3: P=0.002). M3 explained approximately 14% of the variation in newborn WLR.

The results of hierarchical regression analyses of maternal variables on newborn FMI are presented in Table 3. Traditional diet pattern adherence was associated with lower FMI

(-0.13 kg/m3 per +1 SD; P=0.027) after full adjustment for covariates (M3: adjusted for neonate sex, Traditional diet pattern score, HIV/treatment status, BMI, GWG, parity, gestational age at delivery and age at scan). HIV positive (pre-pregnancy ART) vs. HIV negative status was associated with 1.18 kg/m3 (P=0.001) higher neonatal FMI in M2 (adjusted for neonate sex, Traditional diet pattern score, HIV/treatment status, BMI, GWG). This association remained significant in the fully adjusted model (M3: 1.11 kg/m3; P=0.002). Approximately 19% of the variation in newborn FMI was explained in M3.

Although BMI and GWG were not associated with newborn FMI in any of the presented regression models; we confirmed an interaction between Traditional diet pattern adherence and maternal BMI on FMI (vs. normal weight: overweight*Traditional diet pattern, P=0.203; obese*Traditional diet pattern, P=0.024). Therefore, while dietary pattern adherence was associated with a significant reduction in FMI for infants born to normal weight women (-0.32 kg/m3; P=0.005), these effects were not seen among newborns of overweight or obese women (data not shown).

Discussion

To our knowledge this is the first study to explore the relationships between maternal nutritional status, dietary patterns and HIV/treatment exposure in African women and to examine their effects on neonatal adiposity within the first two weeks of life. We found that, although maternal obesity and GWG were associated with neonatal body composition, they predicted overall birth size rather than increased fat mass in particular. In contrast, adherence to a Traditional dietary pattern during pregnancy was associated with lower WLR and FMI; suggestive of a predominant effect on fat mass in the neonate. Finally, we showed that duration of ART exposure (pre-pregnancy vs. antenatal initiation) in HIV positive women was positively associated with newborn adiposity in this setting.

Our findings build on data previously reported on the association between Traditional dietary pattern adherence and reduced GWG (including odds of excessive weight gain) in this population (10). Here we show that, not only is a dietary pattern high in vegetables, beans and legumes, traditional meats and whole grains associated with beneficial reductions in maternal adiposity during pregnancy, but also in fetal fat deposition. Such effects have important implications for the long term health trajectory of the infant; with previous studies showing a tendency towards tracking of adiposity through infancy, as well as of an increased risk of obesity and elevated metabolic risk profiles (including higher fasting triglyceride concentrations and insulin resistance) in later life (8,9). In addition, while Catalano et al demonstrated a significant correlation between body fat percentage at birth and at childhood follow up (mean age: 8.8 ± 1.8 years), there was no correlation in total weights at these two time points (9). This highlights the importance of neonatal adiposity as a potential predictor for longer-term obesity and metabolic disease risk.

Although the associations between a traditional diet pattern and neonatal WLR and FMI are unique to our study, they are supported by Starling et al who found that intake of a diet pattern with lower consumption of green vegetables and dairy and higher in refined grains was associated with higher birth weight, fat mass and body fat percentage in the US (38).

However, conflicting results have also been shown; with typically healthier diet patterns (Mediterranean and Traditional) being associated with higher birth weight and reduced SGA risk, while more processed or Western dietary patterns have been associated with increased risk of SGA and lower weight-for-age z-score in some high income settings (39–43).

The relationship between maternal diet and birth size and adiposity is complex and the variation in findings across populations may reflect an influence of baseline nutritional status on these associations. For example, while energy dense, processed diets have been shown to restrict fetal growth and increase SGA risk in certain populations, they may increase the risk of high birth weight and adiposity in others (42–44). As both ends of the spectrum - i.e. being born too small or too large for gestational age – are associated with long term disease risk (45–48), identifying patterns of intake which facilitate optimal fetal growth and limit excess fat deposition in increasingly urbanised African populations, is critical. Given the high level of urbanisation in Africa - and particularly South Africa - to date, as well as the representativeness of the study population to that of an urban-poor community, our findings contribute substantially to understanding these contexts. Here we confirm that, not only do the effects of maternal dietary patterns on GWG differ across BMI categories (10), but the association between Traditional diet pattern adherence and neonatal adiposity is similarly modified by maternal BMI at baseline; with the effects seen predominantly in the normal weight subgroup. This suggests that, in increasingly obesogenic populations, the beneficial effects of improved diet quality may be limited in women who exhibit excess adiposity and associated metabolic risk profiles prior to conception. Obesity induces a chronic inflammatory state that has been suggested as a key driver of insulin resistance and may intensify the naturally occurring insulin resistant profile during pregnancy (6,49,50). Reduced insulin sensitivity in the obese pregnant woman – and the subsequent increase in availability of glucose and lipids – may potentially facilitate excess substrate transfer to the fetus and, thus, fat deposition irrespective of the current dietary pattern.

While we found no differences in WLR or FMI between infants born to HIV positive women with antenatal ART initiation compared to their HIV negative counterparts, we showed a significant increase in FMI for infants whose mothers were HIV positive and initiated on ART prior to the current pregnancy. These associations were independent of baseline BMI, GWG and diet and therefore suggest a strong treatment effect in this population. ART associated metabolic complications have been widely documented in HIV positive patients, with fat redistribution (reduced subcutaneous and increased central adiposity), impaired glucose tolerance and insulin resistance, as well as dyslipidaemia being common side effects (51,52). Such changes may substantially impact the metabolic risk profile of women prior to conception; further exacerbating the pregnancy associated insulin resistant state and increasing the risk of gestational diabetes mellitus (GDM) and associated complications. These findings have important implications for HIV positive pregnancies in South Africa, during which duration of ART exposure (increasing with each subsequent pregnancy) may elevate the risk profile for both mother and infant in an already high risk population. Targeted monitoring and care strategies are therefore needed in order to minimise the adverse effects of treatment exposure on adiposity and associated metabolic

risk in the newborn; with interventions designed to optimise nutritional status and diet quality pre-conception being potentially more vital in these women.

Although we showed significant effects of maternal nutritional status, diet and HIV/treatment exposure on birth size and/or neonatal adiposity, our final models explained only 14% and 19% respectively of the variability in infant outcomes. While maternal adult size, adiposity and metabolic profile are predictive of infant outcomes, these characteristics are highly influenced by a mothers own growth and development; with studies showing strong intergenerational associations between maternal and offspring birth weight (53–56). This suggests that the gestational environment of the mother – and the resulting consequences on maternal birth size and longer term metabolic risk profile – may be an important factor in further explaining differences in neonatal size and adiposity in our study. In addition, there may be other behavioural factors which require exploration in these models, such as physical activity. Although there was no association found between physical activity and birth outcomes (including birth weight and ponderal index) in a previous study of this population (57), any potential indirect effects on birth size – for example through reductions in GWG and/or risk of GDM – as well as possible associations with fetal fat deposition and neonatal adiposity should be explored (51–53).

Other limitations of our study include the use of baseline BMI as a proxy for pre-pregnancy BMI and the variation in timing of maternal anthropometric measurements for assessing maternal GWG as previously described (10). Although first trimester weight has been identified as an adequate proxy for pre-pregnancy weight – correctly classifying 91-95% of women according to pre-pregnancy BMI - BMI specific differences in weight gain during trimester one have been shown (61,62). While use of baseline weight may have resulted in a degree of misclassification in our study, any effects on study findings were likely to be negligible due to the low overall amount of weight gained prior to 14 weeks; particularly in black women at higher BMIs (62). In addition, although the categorisation of pregnant women into three HIV/treatment status groups (i.e. HIV negative, HIV positive (antenatal ART) and HIV positive (pre-pregnancy ART)) allowed for effective comparison of overall treatment exposure in our sample, inclusion of additional measures of duration and/or adherence to ART would allow for more robust comparison of ART exposure on a continuous scale. While we present strong evidence for an effect of ART exposure on neonatal adiposity, use of an objective measure such as viral load – an established proxy for ART adherence/effectiveness (63) - would be beneficial in further explaining the influence of treatment on fetal fat deposition and metabolic risk in future research. Given the focus of our study and the differential patterns of growth (both in fat mass and fat free mass) between pre-term and term infants, we included only term neonates in our analyses (27). While this reduced the final sample size, it allowed for better interpretation of the effects of maternal factors (principally diet and HIV/treatment status) on newborn adiposity. However, future studies should explore these associations in pre-term infants in order to further elucidate the relationships with newborn size and adiposity according to gestational age. Lastly, neonatal body composition was measured using two techniques (Peapod and DXA) within the first two weeks of life which may reduce comparability across the sample; particularly due to the reduced sample size for these objective assessments. However, the comparability between techniques previously shown in this population allowed for correction of DXA to Peapod

measurements and therefore equivalent fat mass estimates in the sub-sample (28). Although the variation in day of neonatal body composition assessment must be considered - with physiological weight loss occurring during this period – any changes in body composition are predominantly due to reductions in body water and would therefore have little effect on the comparability of fat mass estimates between subjects (64).

Conclusions

Our findings suggest that increased adherence to a Traditional diet pattern - high in whole grains, beans and legumes, vegetables and traditional meats and low in processed/ convenience foods— may reduce neonatal adiposity in urban, black South Africans. However, early intervention to ensure a healthy BMI prior to pregnancy is needed in order to optimise the beneficial effects of diet quality on adiposity and associated metabolic risk for both mother and infant. Although ART initiation and adherence is critical for both maternal and infant health, the effects of treatment exposure on maternal metabolic risk and neonatal adiposity highlights the vulnerability of HIV positive pregnant women and the importance of tailored care in this population. Targeted monitoring and management strategies are therefore necessary to limit treatment-associated effects on in utero fat deposition and to potentially reduce metabolic risk profiles and poor health trajectories of infants in both the short and longer term.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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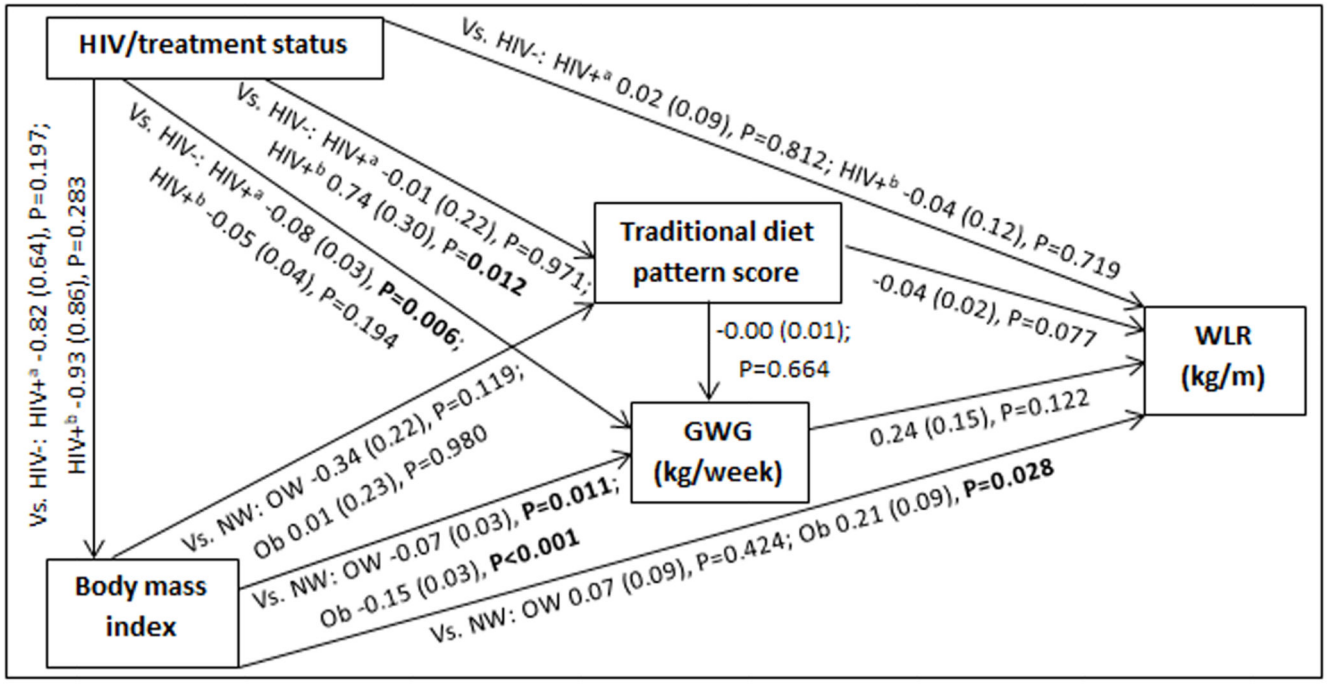

Figure 1.

Conceptual model with bivariate associations between maternal factors and neonatal weight-to-length ratio (kg/m) in urban, black South Africans Values are regression coefficients with standard errors [β(SE)] from linear regression analyses; significant results presented in bold (P<0.05) Abbreviations: GWG, gestational weight gain; HIV-, HIV negative; HIV+a, HIV positive (antenatal ART); HIV+b, HIV positive (pre-pregnancy ART); NW, normal weight; OW, overweight; Ob, obese; Vs, versus (i.e. compared to the following reference category); WLR, newborn weight-to-length ratio

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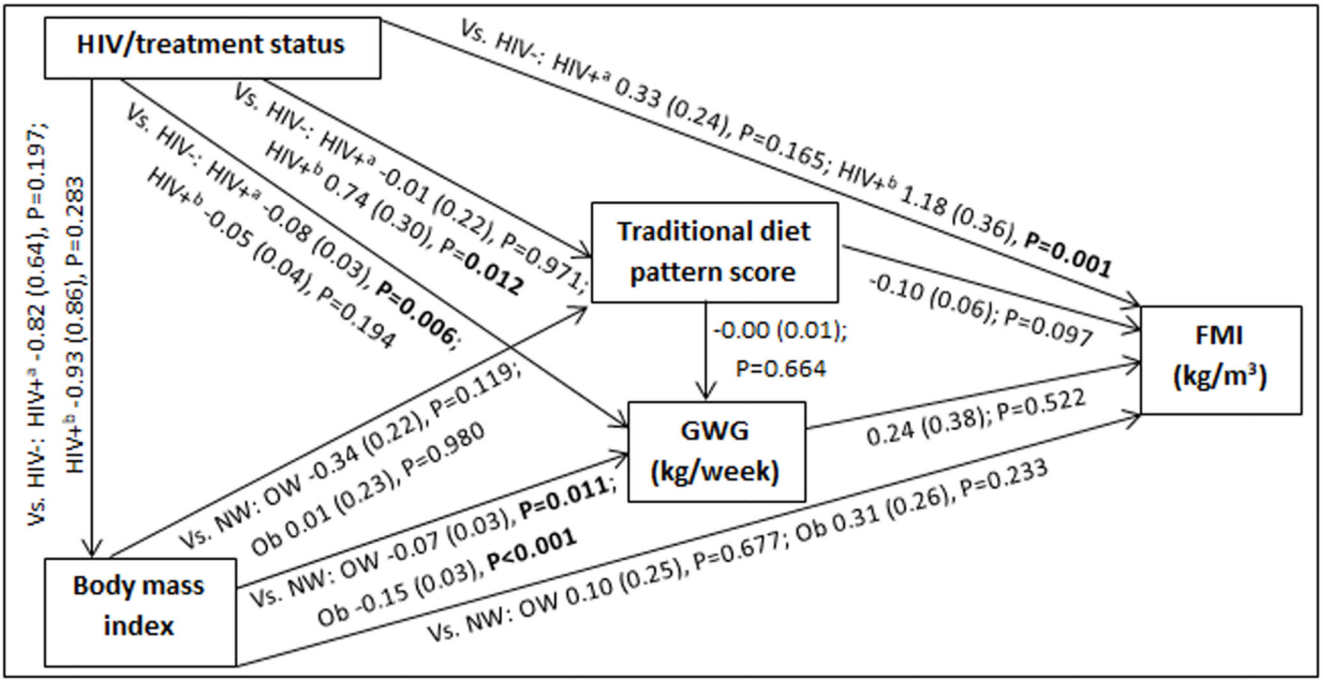

Figure 2.

Conceptual model with bivariate associations between maternal factors and neonatal fat mass index (kg/m3) in urban, black South Africans Values are regression coefficients with standard errors [β(SE)] from linear regression analyses; significant results presented in bold (P<0.05) Abbreviations: FMI, neonatal fat mass index; GWG, gestational weight gain; HIV-, HIV negative; HIV+a, HIV positive (antenatal ART); HIV+b, HIV positive (pre-pregnancy ART); NW, normal weight; OW, overweight; Ob, obese; Vs, versus (i.e. compared to the following reference category)

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Table 1
Maternal and neonatal characteristics of urban, black South Africans (n=393)

	Median (IQR) or %
Maternal variables	
Demographic and health characteristics	
Maternal age, y	30 (25-35)
Parity	
Para 0	25
Para 1	45
Para ≥2	30
HIV status	
HIV-negative	66
HIV-positive (antenatal ART)	23
HIV-positive (pre-pregnancy ART)	11
Smokes/chews tobacco	
No	87
Yes	13
Socioeconomic characteristics	
Maternal education	
Primary	2
Secondary	70
Tertiary	28
Marital status [n=387]	
Single	61
Married/cohabiting	39
Household SES	
Low	13
Medium	80
High	7
Anthropometry	
BMI at recruitment, kg/m^2 (<14 weeks)	27.2 (23.8-30.9)
Normal weight (18.5-24.9)	35
Overweight (25-29.9)	35
Obese (≥30)	30
GWG, kg/week	0.41 (0.28-0.56)
Inadequate	22
Adequate	20
Excessive	58
Neonatal variables	
Sex	
Male	52
Female	48

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	Median (IQR) or %
Gestational age at delivery, weeks	39 (38-40)
Anthropometry	
Birth weight, g	3100 (2850-3365)
Birth length, cm	48.9 (47.3-50.3)
Weight to length ratio (kg/m)	6.4 (5.9-6.8)
Body composition [n=171][a]	
Age at scanning, d	8 (4)
Fat mass, g	435 (331-548)
Fat-free mass, g	2774 (2530-2929)
Fat mass index, kg/m^3	3.6 (2.9-4.6)

Abbreviations: BMI, body mass index; GWG, gestational weight gain; ART, antiretroviral treatment 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

[a]Measured by air displacement plethysmography (ADP; Peapod) or dual-energy x-ray absorptiometry (DXA) corrected for the measurement differences between techniques

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Table 2

Hierarchical regression for the associations between maternal factors and neonatal weight to length ratio (n=393)

	WEIGHT TO LENGTH RATIO (kg/m)								
Independent Variables	**Model 1**			**Model 2**			**Model 3**		
	B	**95% CI**	**P-value[b]**	**β**	**95% CI**	**P-value[b]**	**β**	**95% CI**	**P-value[b]**
Neonate sex									
Male		Ref			Ref			Ref	
Female	-0.02	-0.17; 0.13	0.769	-0.05	-0.19; 0.10	0.533	-0.06	-0.20; 0.08	0.396
Maternal dietary pattern									
Traditional pattern score	-0.04	-0.08; 0.00	0.078	-0.04	-0.08; 0.00	0.081	-0.04	-0.08; -0.00	**0.033**
HIV/treatment status									
HIV negative					Ref			Ref	
HIV-positive (antenatal ART)				0.07	-0.11; 0.25	0.422	0.07	-0.10; 0.24	0.436
HIV-positive (pre-pregnancy ART)				0.01	-0.23; 0.26	0.906	-0.02	-0.26; 0.21	0.833
BMI category									
Normal weight					Ref			Ref	
Overweight				0.09	-0.09; 0.26	0.343	0.09	-0.08; 0.26	0.301
Obese				0.27	0.08; 0.46	**0.005**	0.25	0.07; 0.43	**0.008**
Gestational weight gain									
Rate, kg/week				0.36	0.05; 0.67	**0.024**	0.48	0.18; 0.78	**0.002**
Parity									
Para 0								Ref	
Para 1							0.33	0.15; 0.50	**<0.001**
Para ≥2							0.32	0.13; 0.52	**0.001**
Gestational age									
Gestational age at birth, weeks							0.18	0.12; 0.24	**<0.001**
R2 per model		*0.008*			*0.035*			*0.137*	

Values are regression coefficients with 95% confidence intervals

[a]Multiple linear regression analyses; significant results are presented in bold (p<0.05)

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Table 3

Hierarchical regression for the associations between maternal factors and neonatal fat mass index (n=171)

	FAT MASS INDEX (kg/m^3)								
Independent Variables	**Model 1**			**Model 2**			**Model 3**		
	β	**95% CI**	**P-value[b]**	**β**	**95% CI**	**P-value[b]**	**β**	**95% CI**	**P-value[b]**
Neonate sex									
Male		Ref			Ref			Ref	
Female	0.44	0.04; 0.84	**0.033**	0.40	0.00; 0.79	**0.049**	0.39	0.01; 0.78	**0.044**
Maternal dietary pattern									
Traditional pattern score	-0.09	-0.22; 0.03	0.130	-0.10	-0.22; 0.02	0.086	-0.13	-0.25; -0.02	**0.027**
HIV/treatment status									
HIV negative					Ref			Ref	
HIV-positive (antenatal ART)				0.37	-0.10; 0.84	0.123	0.29	-0.17; 0.75	0.218
HIV-positive (pre-pregnancy ART)				1.18	0.48; 1.87	**0.001**	1.11	0.42; 1.81	**0.002**
Gestational weight gain									
Rate, kg/week				0.44	-0.29; 1.18	0.238	0.46	-0.26; 1.18	0.213
BMI category									
Normal weight					Ref			Ref	
Overweight				0.17	-0.30; 0.65	0.469	0.20	-0.26; 0.66	0.390
Obese				0.37	-0.13; 0.87	0.147	0.24	-0.25; 0.74	0.335
Parity									
Para 0								Ref	
Para 1							0.76	0.27; 1.25	**0.002**
Para ≥2							0.64	0.11; 1.17	**0.018**
Neonate age									
Gestational age at birth, weeks							0.09	-0.08; 0.26	0.286
Age at examination, days							0.05	0.00; 0.10	**0.035**
R2 per model		*0.043*			*0.121*			*0.194*	

Values are regression coefficients with 95% confidence intervals

[a]Multiple linear regression analyses; significant results are presented in bold (p<0.05)