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Maternal allostatic load in pregnancy is prospectively associated with child adiposity and metabolic function across infancy and early childhood

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Abstract

Background: Empirical evidence suggests that the origins of obesity and metabolic dysfunction can be traced to stress-related exposures in prenatal life. The aim of the present study was to examine the prospective association of a composite, multi-system measure of maternal biological stress in pregnancy -- allostatic load (AL) -- with offspring adiposity and insulin resistance across infancy and early childhood.

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Declarations of interest: none

Methods: In N= 55 mother-child dyads, maternal allostatic load was operationalized as a latent variable representing the following components: pre-pregnancy BMI, cortisol, interleukin-6, C-reactive protein, homeostasis model assessment of insulin resistance (HOMA-IR), free fatty acids, and systolic/diastolic blood pressure. Offspring percent total (%FM) and abdominal (%AbFM) fat were quantified with dual-energy X-ray absorptiometry (DXA) at birth (newborn), 6-mo, and ~5 yrs age, and HOMA-IR was quantified at ~5 yrs age. Generalized estimating equation modeling was used to estimate effects of maternal AL on serial (repeated) measures of child adiposity, and linear regression was used to estimate effects on child HOMA-IR. *A priori* model covariates included maternal race and ethnicity, socioeconomic status, infant feeding practices, child age, and sex.

Results: Maternal AL was positively associated with child %FM and %AbFM before as well as after adjustment for key maternal and offspring covariates (%FM: adjusted β=0.38, p=0.0074; %AbFM: adjusted β=0.37, p=0.0013). Maternal AL also was positively associated with child insulin resistance (adjusted β= 0.011, p=0.0324).

Conclusion: Our findings suggest that exposure to a higher biological stress milieu during prenatal development predisposes towards elevated early life adiposity and insulin resistance in early childhood, a proximate cause of type 2 diabetes and cardiometabolic disease. Collectively, these results provide evidence that a multi-systems approach to quantify early life exposures is useful in prospectively predicting variation in childhood adiposity and metabolic function.

Keywords

Stress; allostatic load; childhood obesity; adipose; insulin resistance; fetal programming

1. Introduction:

Childhood obesity continues to represent one of the most significant public health challenge in the U.S. given its high population prevalence and severe pathophysiological consequences.[1,2] Moreover, once established, obesity is extremely difficult to reverse,[3] underscoring the critical importance of *primary prevention*[4] and emphasizing the elucidation of its early-life determinants.

Growing evidence suggests the origins of obesity and metabolic dysfunction may trace back to the prenatal period of development. Various intrauterine conditions and exposures may program the structure and function of cells, tissues and organ systems to influence the propensity towards lipid accrual in adipose and other metabolic tissues, and the development of insulin resistance in these tissues (reviewed here[5,6]). These prenatal exposures include a diverse range of suboptimal maternal sociodemographic, psychosocial, behavioral, biophysical and clinical factors.[7–15] The effects of these factors on the developing fetus are ultimately mediated *via* various biological pathways (there are no direct vascular or neural connections between the maternal and fetal compartments). These biological pathways prominently feature stress-related endocrine, immune/inflammatory, oxidative and metabolic processes in gestation,[5,16] and previous studies have implicated maternal cortisol, inflammatory cytokines, maternal fuels (i.e., glucose, free fatty acids, or triglycerides) and insulin during pregnancy in the fetal programming phenomenon.[11–15,17–20]

We note, first, that previous studies have used biomarkers of only some but not all of these physiological systems, and second, have examined their separate, but not combined, effects.[11–15,17,18,20] It is evident that many of these physiological systems are highly inter-related, in that they extensively regulate and counter-regulate one another. Thus, in contrast to the typical approach of examining separate biomarkers, we suggest they should be examined concurrently in order to better characterize the *cumulative* impact across the major biological systems[21] that mediate the effects of stress-related gestational physiology. We suggest that the allostatic load framework may provide the requisite integrative approach. Allostatic load represents a biological indicator of chronic, cumulative stress exposure. The neuroendocrine, immune, metabolic, and cardiovascular systems that constitute allostatic load regulate biological and behavioral adaptation to psychological and environmental stress. Prolonged or persistent activation of these systems through chronic stress exposure leads to their dysregulation, contributing to 'allostatic load' that represents the cumulative 'wear and tear' experienced over time.[22] The allostatic load index has been shown to predict morbidity and mortality-related outcomes,[23,24] and in the context of pregnancy, to predict adverse gestational and birth outcomes,[25–27] and offspring mitochondrial activity.[28] However, allostatic load measures have not yet been used in the context of fetal programming of child adiposity and metabolic function. Our study focuses on maternal allostatic load indexed by *neuroendocrine* (cortisol), *immune* (interleukin-6 [IL-6] and C-reactive protein [CRP]), *metabolic* (homeostasis model assessment of insulin resistance [HOMA-IR], free-fatty acids [FFA]), *cardiovascular* (aggregate systolic and diastolic blood pressure), and *anthropometric* (pre-pregnancy BMI) biomarkers, because these factors *a*) are known to play obligatory roles in the initiation, maintenance and progression of gestation, fetal development, and birth;[29–31] and *b)* they drive the effects of various gestational perturbations including stress on fetal physiology,[32] by either crossing the placenta,[33–35] or by triggering placental production of stress-related ligands that are released into the fetal compartment.[36] Thus, a key goal of the present study is to characterize the role of maternal allostatic load in the context of fetal programming of childhood adiposity and metabolic function.

With respect to child outcomes, we note that most previous studies of the fetal origins of obesity are limited by (i) proxy measurement of adiposity, (ii) reliance on measures of only total body (but not abdominal) adiposity, and (iii) lack of concordant measures of metabolic function. While commonly-used proxy measures of adiposity such as BMI or ponderal index are useful in the context of large-scale epidemiological studies, it is well established that these measures correlate only weakly (or modestly) with direct measures of adiposity[37] that, in turn, are associated with adverse metabolic outcomes such as glucose intolerance, hypertension, fatty liver disease, and dyslipidemia.[38,39] Second, even among studies have used direct measures of adiposity, very few have quantified abdominal adiposity,[40,41] which represents a better marker of type-2 diabetes and cardiometabolic disease risk.[42–45] Last, because insulin resistance is the key process implicated in the pathophysiological of obesity, it may be important to assess child IR in conjunction with fat mass.

Based on these considerations, the aim of the present study was to examine the prospective association of a composite multi-system measure of stress-related biology (maternal allostatic load in pregnancy) with offspring adiposity (total and abdominal) in infancy and

early childhood, and with offspring insulin resistance in early childhood. We quantified total and abdominal fat mass serially in 55 offspring from birth till early childhood (3.5–6 yrs of age) using precision adiposity measures (dual-energy X-ray absorptiometry [DXA]). We also quantified offspring insulin sensitivity using the HOMA-IR in early childhood, which is the earliest age at which time this measure predicts future risk of diabetes.[46,47] In order to isolate the effects of maternal stress during pregnancy and to improve model precision estimates, we controlled (by study design or statistically) for the effects of other key prenatal, birth and postnatal factors on child adiposity and HOMA-IR, including maternal socio-economic status (SES), maternal race and ethnicity, infant sex, and postnatal breastfeeding exposure.

2. Materials and Methods:

2.1. Participants

The study population was comprised of an ethnically-diverse population of mother–child dyads from a prospective cohort study conducted at the University of California, Irvine, Development, Health, and Disease Research Program. The study population was comprised of healthy adult women with a singleton, intrauterine pregnancy. Maternal exclusion criteria included uterine anomalies, major medical comorbidities (hypertension, infection, or diabetes), antenatal systemic corticosteroid administration, maternal use of psychotropic medications, or illicit drug use. Newborn exclusion criteria included congenital malformations, chromosomal abnormalities, major neonatal complications, or preterm birth <34 weeks. Once enrolled, women attended three prenatal study visits in early, mid and late pregnancy (at approximately 13.1±1.8 (mean ± standard deviation (SD)), 20.5±1.4, and 30.5±1.4 weeks gestation, respectively). Children attended three study visits from birth through early childhood (newborn: 24.2±10.5 days (mean± SD); six-month 192.0±9.1 days; early childhood: 4.8±0.8 yrs), at which DXA scans were conducted. A blood draw was performed at the early childhood visit. DXA scans were successfully completed in 55 children at each of the three study time pints, and the blood sample was obtained in 41 of these 55 children (we note the subset of 41 mother-child dyads did not significantly differ from the larger group in terms of any of the sociodemographic characteristics). The University of California, Irvine, Institutional Review Board approved the protocol, and written, informed consent was obtained from all mothers.

2.2. Maternal allostatic load

Maternal allostatic load was calculated as previously described.[28] In brief, at each of the 3 pregnancy visits (in early, mid and late gestation), fasting maternal antecubital venous blood samples were collected (between 7:30 am and 9:00 am), and maternal height and blood pressure were measured in duplicate. Plasma and serum aliquots were stored at −80°C and assayed for interluekin-6 (IL-6), c-reactive protein (CRP), insulin, glucose, and free-fatty acids (FFA). The homeostatic model of insulin resistance ($HOMA\text{-}IR_{log10}$) was computed using the formula: $\log_{10}$[(glucose in mg/dL × insulin in μU/mL)/405].[48] Maternal pre-pregnancy body mass index (BMI; kg/m^2) was computed based on pre-pregnancy weight abstracted from the medical record, and maternal height measured at the research laboratory visit. Immediately following each of the 3 pregnancy visits, subjects self-collected saliva

samples at home for 4 consecutive days using a Salivette sampling device (Salimetrics, Carlsbad, CA) immediately at and 30 minutes post awakening, and at 1200 hours, 1600 hours, and 2000 hours, following a protocol that has previously been described.[13] Diurnal saliva samples were assayed to determine cortisol concentrations, and for each sampling day, total cortisol output was estimated using the area under the curve (AUC) with respect to ground and was adjusted by residualization for awakening time, and then averaged across the 4 days. This approach allows for a longer-term integrated measure of hypothalamic–pituitary–adrenal axis activity, as recommended in the allostatic load framework.[49]

Based on published guidelines,[23] maternal allostatic load was indexed using *neuroendocrine* (cortisol), *immune* (IL-6 and CRP), *metabolic* (HOMA-IR, FFA), *cardiovascular* (aggregate systolic and diastolic blood pressure) systems, and *anthropometric* (pre-pregnancy BMI) biomarkers. Before computation of the allostatic load, values for each biomarker were standardized to each stage of gestation (*i.e.*, z-score created at each gestational stage). Each component z-score was then averaged across pregnancy (except the time-invariant pre-pregnancy BMI value), and an allostatic load index for each woman was computed as the sum of z-scores.[25] We note that although many of these biomarkers change (increase) across pregnancy, since the stage of gestation is accounted for within each component (*i.e.*, standardization via the z-score), women exhibited high within-individual stability of the allostatic load score (intra-class correlation (ICC)= 0.85),[28] supporting our use of the mean z-scored pregnancy allostatic load score for the proposed analyses.

2.3. Child DXA imaging

Whole-body DXA scans were obtained using a Hologic Discovery Scanner (A, QDR 4500 series; Hologic, Bedford, MA) in infant (at the newborn and 6-month visit) and pediatric scan mode (at the early childhood visit). Calibration using Hologic's anthropomorphic Spine QC Phantom was performed before each scan. During the newborn and 6-month scans, infants lay supine while sleeping, wearing only a disposable diaper and swaddled in a light cotton blanket. If the infant moved during the scan, a single repeat scan was performed. At the time of the newborn DXA assessment, children were, on average, 24.9 days old [mean (±10.5 SD) days]. This age was selected to allow for stabilization of fluid shifts in the newborn that occur in the first 2 to 3 weeks following birth.[50] During the early childhood scan, children lay supine while awake, wearing a standardized light cotton short and shirt set. If the child moved during the scan, a single repeat scan was performed. For each scan, total body fat % (%FM) was defined as 100 times the ratio of global fat mass to the sum of global fat mass and global fat-free mass. Abdominal % fat (%AbFM) was quantified in the sub-region from the top of the ileac crest to the top of 2nd lumbar vertebrae. This sub-region was traced by the same technician across all scans. To account for effects of age at assessment and child sex, %FM and %AbFM were residualized for postnatal age at scan and child sex, and additionally for gestational age at birth for the newborn and 6-month scans.

2.4 Child insulin and glucose assays

Following an overnight fast, child antecubital venous blood samples were collected between 7:30 am and 9:00 am in plasma tubes (EDTA BD Vacutainer) by a trained pediatric

phlebotomist. The tubes were centrifuged for 15 min at 1200 g, and plasma aliquots stored at −80°C until analysis.

Plasma glucose was quantitatively determined enzymatically in duplicate using reagents from Randox (Kearneysville, WV). Plasma insulin was measured in duplicate using a radioimmune assay developed by EMD Millipore (Billerica, MA). Intra-assay CVs were 2.1, and 6.1%, respectively. HOMA-IR was computed using the formula: (glucose in mg/dL × insulin in μU/mL)/405.[48] HOMA-IR was base 10 logarithm transformed to normalize the skewed distribution, which provides a stronger linear correlation with gold-standard clamp-derived values of insulin resistance and glucose disposal.[51]

2.5 Sociodemographic characteristics

At the first pregnancy study visit, standardized structured interviews were administered for ascertainment of maternal sociodemographic characteristics (maternal age, education, race and ethnicity). Maternal race and ethnicity were assessed by self-report and collapsed into two major categories, Hispanic and non-Hispanic ethnicity. An index of maternal SES was defined as a combination of maternal educational level (originally assessed in categories from less than high school to advanced degree (master/doctorate) and household income (in categories from ≤ $15,000 to ≥ $100,000). The SES index was computed as a mean of the maternal education (scored 1–5) and household income (scored 1–5). Infant sex was abstracted from delivery medical records.

2.6 Infant feeding practices

Infant feeding method (breast or formula) was assessed *via* monthly maternal interviews conducted between the newborn and 6-month child assessments. A composite variable was computed indexing whether the mother primarily breastfed, formula fed, or provided mix feeding for her child from birth until 6 months of age. Feeding status was coded as follows: “primarily breastfed,” offspring with greater than 75% of the first six months of life spent exclusively breastfeeding; “primarily formula fed,” offspring with greater than 75% of the first six months of life spent exclusively formula fed; “mixed feeding practices,” offspring with intermediate values.

2.6 Statistical Methods

Descriptive statistics were used to describe baseline maternal sociodemographic characteristics. The association between maternal allostatic load and the serial measures of child adiposity (from birth till early childhood) was modeled using population-averaged generalized estimating equation (GEE). The outcome variables were child %FM and %AbFM, and GEE modeling was utilized to account for the intra-individual correlation between these measures. Additionally, in each model we examined whether the association between maternal allostatic load and child adiposity varied as a function of time (child age) by including the interaction between the child age and maternal allostatic load. In a *post-hoc* analysis, we additionally examined the association of the individual allostatic load components with child %FM and %AbFM in separate models and in a combined multivariate model (including all components in a single model).

The association between maternal allostatic load and child metabolic parameters was modeled using linear regression. The outcome variables were fasting glucose, insulin, and $\log_{10}$HOMA-IR (which, as previously described, were quantified at only a single time point in early childhood). In addition, we examined whether the association between maternal allostatic load and child metabolic data was independent of the child's current %FM. The robust variance estimates of the regression coefficient estimates were obtained. In a *post-hoc* analysis, we examined the association of the individual allostatic load components with child $\log_{10}$HOMA-IR.

Statistical analyses were performed with SAS® Software Version 9.4, and a Type 3 analysis using Wald test was performed when *a priori* covariates were included in the model. Results were considered statistically significant at the level of $p < 0.05$. To interpret the regression beta coefficients, % difference in child outcomes were calculated by log transformation in the response variable and the following formula $100(e^{\beta c} - 1)\%$.[52] We note that allostatic load was modeled continuously, but for presentation purposes, allostatic load is presented categorically (mean split of high and low maternal allostatic load) in Figures 1–2 and Supplemental Figure 1.

Covariates and Sensitivity Analyses: All models were run with and without an *a priori* selected set of covariates (maternal race and ethnicity, SES, infant feeding practices, child sex, and age at visit). As noted above, the child's %FM and %AbFM was residualized for age at scan and child sex, therefore, they are not listed as separate covariates in the adjusted models for offspring adiposity. Maternal obesity is an established clinical predictor of child adiposity[53,54] and was thoughtfully considered as a covariate. Recent evidence has shown that BMI (in addition to CRP) is the most informative and discriminatory biomarker of the allostatic load burden, is highly correlated with the allostatic load score and is strongly suggested for inclusion in the allostatic load score.[55] Thus, maternal BMI was retained in our maternal allostatic load score; due to the conceptual and empirical coupling, it does not appropriately serve as a control variable, and inclusion would likely remove meaningful variation in the allostatic load score.[56] However, to assess whether the association of maternal allostatic load with offspring outcomes was predominately explained by maternal obesity, we excluded women with obesity in exploratory sensitivity analyses.

3. Results:

The sociodemographic characteristics of the 55 mothers and their children are reported in Table 1. The socio-demographic characteristics of 41 children who consented for a blood sample did not statistically differ from the larger group (data not shown). Child whole body percent fat values at the newborn, 6-mo and early childhood visits were 14.2±4.8 % (mean±SD), 32.6±8.3 %, and 27.6±5.6 %, respectively. These values are consistent with those reported in other published studies.[57] The child fasting glucose values (of 80.8±6.2 mg/dL) also were consistent with other published studies, however, levels of fasting insulin and $\log_{10}$HOMA-IR were higher in this cohort relative to children of similar age.[58,59] As previously described,[28] the individual components of the AL score were significantly and positively related to the combined AL score and to one another, with the exception of

cortisol (see Supplemental Table 1). Consistent with a large NHANES analysis of N=3751 adults[55], CRP and BMI correlate most strongly with the allostatic load score.

3.1 Maternal allostatic load and child adiposity.

As shown in Figure 1, maternal allostatic load was significantly associated with offspring adiposity from birth through early childhood. Specifically, maternal allostatic load was positively associated with offspring total and abdominal % fat mass before (%FM: β=0.44, 95%CI=0.18–0.70, p<0.001; %AbFM: β= 0.42, 95%CI=0.20–0.63, p<0.001, respectively) and after (%FM: β=0.39, 95%CI=0.10–0.66, p=0.007; %AbFM: β=0.37, 95%CI=0.15–0.60, p=0.001), accounting for the effects of key maternal and child covariates. There was no statistically significant interaction with the child assessment window, suggesting that the strength of the association between maternal allostatic load and child body composition did not vary as a function of child age. After excluding women with pre-pregnancy obesity (14 participants), maternal allostatic load remained significantly associated with offspring %FM and %AbFM (%FM: β=0.52, 95%CI=0.01–1.0, p=0.048; %AbFM: β= 0.56, 95%CI=0.16–0.95, p=0.006, respectively; Figures 1b, 1d, Supplemental Figure 1).

Our post-hoc analysis of the association of the *individual* components of allostatic load with offspring adiposity (see S2 Table) suggests four components -- maternal pre-pregnancy BMI, HOMA-IR, blood pressure and CRP -- were significantly and positively associated with offspring %FM and %AbFM. We note that the combined blood pressure score (systolic + diastolic) was only significantly related to offspring %AbFM, indicating a depot specific effect.

3.2 Maternal allostatic load and early childhood insulin resistance and fasting insulin:

As shown in Figure 2, maternal allostatic load during pregnancy was significantly and positively associated with child insulin-resistance (*i.e.*, $_{log10}$HOMA-IR) before (β= 0.012, 95%CI=0.001–0.023, p=0.047) and after (β= 0.011, 95%CI=0.001–0.021, p=0.032; Figure 2 a–b) accounting for the effects of key maternal and child covariates. Next, we examined the associations of maternal allostatic load with the two components of HOMA-IR – fasting insulin and fasting glucose – separately. While there was a significant and positive association between maternal allostatic load and child fasting $_{log10}$insulin (β= 0.011, 95%CI=0.001–0.022, p=0.045; adjusted β= 0.010, 95%CI=0.002–0.019, p=0.030; Figure 2 c–d), there was no relationship between maternal allostatic load and child fasting glucose levels (p>0.1, Figure 2 e–f). After excluding women with pre-pregnancy obesity (14 participants), maternal allostatic load remained significantly associated with childhood HOMA-IR (β= 0.027, 95%CI=0.01–0.054, p=0.014; Figure 2 a–f).

Next, we examined the cross-sectional associations between child % fat (total and abdominal) and child metabolic variables (i.e., $_{log10}$HOMA-IR and its separate components [insulin and glucose]). These results suggest a strong cross-sectional relationship between child's adiposity and HOMA-IR and insulin (all r's>0.43, p's< 0.01); whereas there was no relationship between child adiposity and fasting glucose concentrations. Because these outcomes were associated with one another, we examined whether the association between maternal allostatic load and child metabolic function was independent of current child

adiposity. Results suggest that after accounting for child %FM and %AbFM, the association between maternal allostatic load and child insulin resistance was no longer statistically significant ($p>0.1$ for all models).

Finally, in a post hoc analysis, we examined the association of the *individual* components of maternal allostatic load with the offspring insulin resistance (see S3 Table). Results suggest two components of maternal allostatic load -- maternal FFA, and CRP – were *individually* associated with child HOMA-IR.

4. Discussion:

The current study represents, to the best of our knowledge, the first report of the prospective association of maternal allostatic load in pregnancy with offspring adiposity and insulin resistance. Our results indicate that maternal gestational stress, indexed using a composite, multi-system allostatic load measure, was prospectively and positively associated with child total and abdominal adiposity and insulin resistance. The effects on child adiposity were evident from birth through early childhood, whereas the effect on child insulin resistance was assessed at only a single time point (in early childhood). In terms of effect size, each 1-interquartile difference in maternal allostatic load was independently associated with an 11% relative difference (95%CI 3–20%) in child total fat mass percent, and a 20% relative difference (95%CI 7–35%) in child abdominal fat mass percent from birth to early childhood. And, a 1-interquartile difference in maternal allostatic load was independently associated with a 16% relative difference (or 1.11-unit difference) in the child insulin resistance (i.e., HOMA-IR) and a 14% relative difference (or 1.10 μU/ml difference) in fasting insulin. Based on the consideration that child HOMA-IR values below 1 are considered ‘normal’ and values greater than 2 are indicative of insulin resistance,[60] we suggest that our observed effect size of a 1.1-unit difference (in child HOMA-IR) is likely to be clinically meaningful. Finally, based on the consideration that previous studies have established that elevated adiposity and insulin resistance in early childhood (4 – 5 yrs age, the same age as the children in our study cohort) predict subsequent adult risk for type 2 diabetes,[46,47,58] we suggest our study findings may have implications for future type 2 diabetes and cardiometabolic disease risk.

As reported earlier, the observed effect of maternal allostatic load in pregnancy on child HOMA-IR was driven primarily by fasting insulin rather than fasting glucose. The absence of an effect on fasting glucose in a population of young normoglycemic children (such as those in our study) is unsurprising, whereas the observation that the observed effect is driven by fasting insulin suggests that the insulin regulatory system of children exposed *in utero* to higher maternal stress already exhibits early signs (at this age) of strain relative to that of children with lower maternal stress exposure. Moreover, our finding that the observed effect of maternal allostatic load in pregnancy on child insulin resistance appeared to be secondary to but not independent of the effect on child adiposity (%FM and %abdominal fat) seems to implicate adiposity in the causal pathway.

There are several broad and potentially overlapping pathways that may underlie the observed effects of maternal allostatic load in pregnancy on child adiposity and metabolic function.

First, the allostatic load state in the maternal compartment may drive the allostatic load state in the fetal compartment to influence the fetal metabolic milieu and its proximate developmental effects on adiposity and metabolism-related systems. Consistent with this possibility, elevated maternal allostatic load in mid-pregnancy has been associated with a significant and dose-dependent increase in fetal allostatic load (assessed in fetal cord blood at birth).[27] This process may occur through a direct transfer of some of the allostatic load components (*e.g.*, glucose[61], IL-6[34,35]), or through the modification of placental structure/function to alter trans-placental transfer or placental production or through fetal production of relevant ligands (*e.g.*, fetal insulin[62]). Second, emerging evidence suggests that an unfavorable maternal and intrauterine milieu may impact programming of fetal stem/progenitor cells in a manner that promotes excess adipose tissue accrual at the expense of lean tissue (bone, muscle),[63,64] thus not only altering newborn body composition but also impacting the stem/progenitor cell pool that replenishes differentiated cells that determine body composition and adipogenic propensity across the lifespan. Third, evidence suggests that an unfavorable maternal and intra-uterine metabolic milieu may contribute to the programming of fetal/child hypothalamic–limbic–cortical brain circuitry that governs the regulation of energy homeostasis (reviewed here[65]) in a manner that impacts adipogenic propensity. Fourth, the allostatic load state in the maternal compartment may directly or indirectly program the fetal/child mitochondrial biology system in a manner that preferentially increases body fat storage. We recently demonstrated that maternal allostatic load in pregnancy is associated with offspring mitochondrial content and bioenergetic capacity.[28] Exposure to allostatic load may be energetically demanding and increase the cost of living on the developing fetus and child,[66] which may not only manifest as increased mitochondrial content, as previously shown,[28] but this increased energy forecasting may also manifest in altered body composition and preference for energy dense adipose tissue, as shown in this study. Increasing adiposity as an allostatic response would be consistent with studies of children exposed to high levels of pathogens, a type of stressor that increases the energetic cost of living, and comes – in a tradeoff manner – at the expense of growth and with increased propensity for fat deposition in order to meet subsequent immune-related energy costs (the inflammation-tradeoff hypothesis).[67] Further studies are required to replicate our findings and examine these and other potential mechanisms.

This study, along with our previous work[28], extends the utility of the allostatic load construct to the context of fetal programming and intergenerational effects. The allostatic load construct had provided a useful framework in understanding the multi-system physiological impact of sustained (chronic) stress on health and well-being,[24] including within-individual effects on adiposity and insulin resistance,[68,69] however we report here the first intergenerational (mother-to-child) relationship between these measures. While the strength of the cumulative and multi-system allostatic load index has been established,[23,24] substantial heterogeneity exists across studies as to the type and number of parameters to be considered. To enhance comparability across studies[21] and support future work interrogating allostatic load in the fetal programming context, we additionally report the relationship between the individual components of our allostatic load index and our offspring outcomes. Although no other study has examined a multisystem panel of biomarkers in pregnancy (combined into allostatic load) upon direct measures of *childhood* adiposity (*i.e.*, BOD POD

or DXA), there is increasing efforts to model multi-factorial and multi-system exposures in the context of pregnancy upon pregnancy and child health outcomes.[19,20,70–72] For example, Walsh et al. (2019)[70] utilized a data-driven approach that incorporated 27 maternal variables derived from questionnaires, ambulatory diaries, and physical assessments. We note that the traditional biophysical allostatic load components included in this study overlap with three components in the present analysis: pre-pregnancy BMI, blood pressure, and diurnal cortisol. Future studies should aim to replicate the current findings in larger mother-child cohort, while integrating data driven approaches to refine the allostatic load index, and consider such strategies like those employed by Walsh et al. (2019)[70] to bridge allostatic load and psychosocial modeling frameworks.

We note that of all the maternal allostatic load components, CRP was a consistent independent predictor of both child adiposity and insulin resistance. Consistent with our findings, Gaillard et al.[14] previously demonstrated that higher maternal CRP in pregnancy was associated with higher total and abdominal adiposity in children 7–10 yrs age.[14] In parallel, Lui et al. (2021)[55] demonstrated that CRP was one of the most informative biomarkers for allostatic load in a NHANES study of N=3,751 adults. These data support the importance of the immune/inflammatory pathways in the fetal programming of childhood metabolic health and highlight CRP as a key component to include in the allostatic load index for future studies examining the intergenerational impact of allostatic load upon offspring health outcomes.

Our study is limited by the modest sample size and the findings should be validated in larger cohorts in future research. Our findings are strengthened by the repeated measures design, and the comprehensive characterization of maternal gestational biological stress, child adiposity (DXA-based %FM and %AbFM) and insulin resistance markers. We note that that commonly-employed proxy measures such as BMI relate only moderately with measures of fat mass, %FM particularly in young pediatric populations,[37] thus, our use of DXA %FM is an important strength. Another notable strength is our characterization of child abdominal fat mass, a particularly important determinant of metabolic dysfunction.[42–45] Last, our study is strengthened by the inclusion of an ethnically-diverse population with more than 40% of Hispanic ethnicity. As rates of childhood obesity and risk for type 2 diabetes are highest in Hispanic populations,[73] our cohort supports the generalizability of our findings to populations at highest risk. However, it will be important for future studies to assess how the allostatic load indicators function for different race and ethnicity groups. Our study sample comprised a high percentage of overweight and obese mothers, and future studies are needed to confirm whether the findings also apply to a normal weight sample. Our sensitivity analyses helped to establish that the association of maternal allostatic load with offspring outcomes was not predominately explained by maternal obesity. However, the impact of maternal overweight or elevated adiposity should be carefully interrogated in future studies, potentially with latent factor approaches, with larger sample size across the BMI strata.

In conclusion, our findings extend the growing body of evidence supporting the role of maternal stress biology in the process of fetal programming of child adiposity and metabolic function. Importantly, this study includes offspring phenotypes that extend beyond

infancy into early childhood, a measurement time-point with established associations with obesity and cardiometabolic disease in adulthood; thus, substantiating the potential lifelong importance of these data. Our study also demonstrates the utility of the composite, multi-system maternal allostatic load construct in this context, and supports its possible use as a tool for early risk identification and to guide potential interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- Exposure to high intrauterine biological stress (i.e., allostatic load) associates with greater childhood adiposity, from birth into early childhood.
- Intrauterine stress associates with hyperinsulinemia and insulin resistance in early childhood.
- Demonstrates the utility of the composite, multi-system maternal allostatic load construct in the fetal programming context.

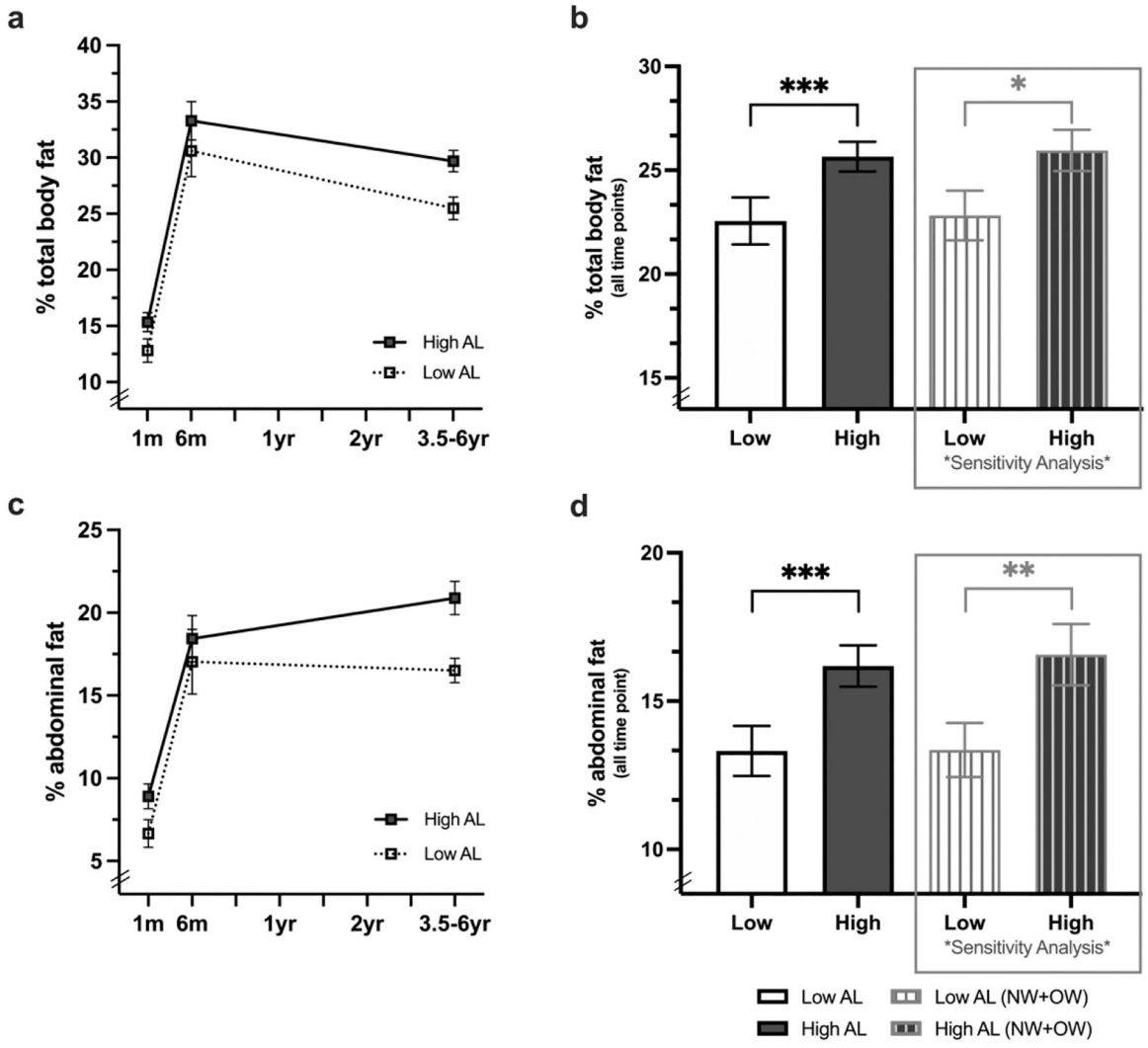

Figure 1:

Greater maternal allostatic load (AL) in pregnancy significantly associated with higher offspring (a, b) % total body fat (%FM), and (c, d) % abdominal fat from (%AbFM) birth to early childhood. There was no significant interaction with child age, so the relationship was consistent across birth to early childhood (figures a and c display %fat at each child measure, and figures b and d display the mean across all time points, which represents the final model). Figures b and d display the additional sensitivity analyses, which excluded pregnant moms with obesity from the analyses. After excluding women with pre-pregnancy obesity (n=14), maternal allostatic load remained significantly associated with offspring total and abdominal adiposity ($p<0.05$).

We note that the models were run with AL as a continuous measure, but are presented as mean split of high/low AL for visualization purposes. Data are mean ±SEM. *** $p<0.001$, **$p<0.01$, *$p<0.05$; AL=allostatic load, NW= normal weight, OW= overweight.

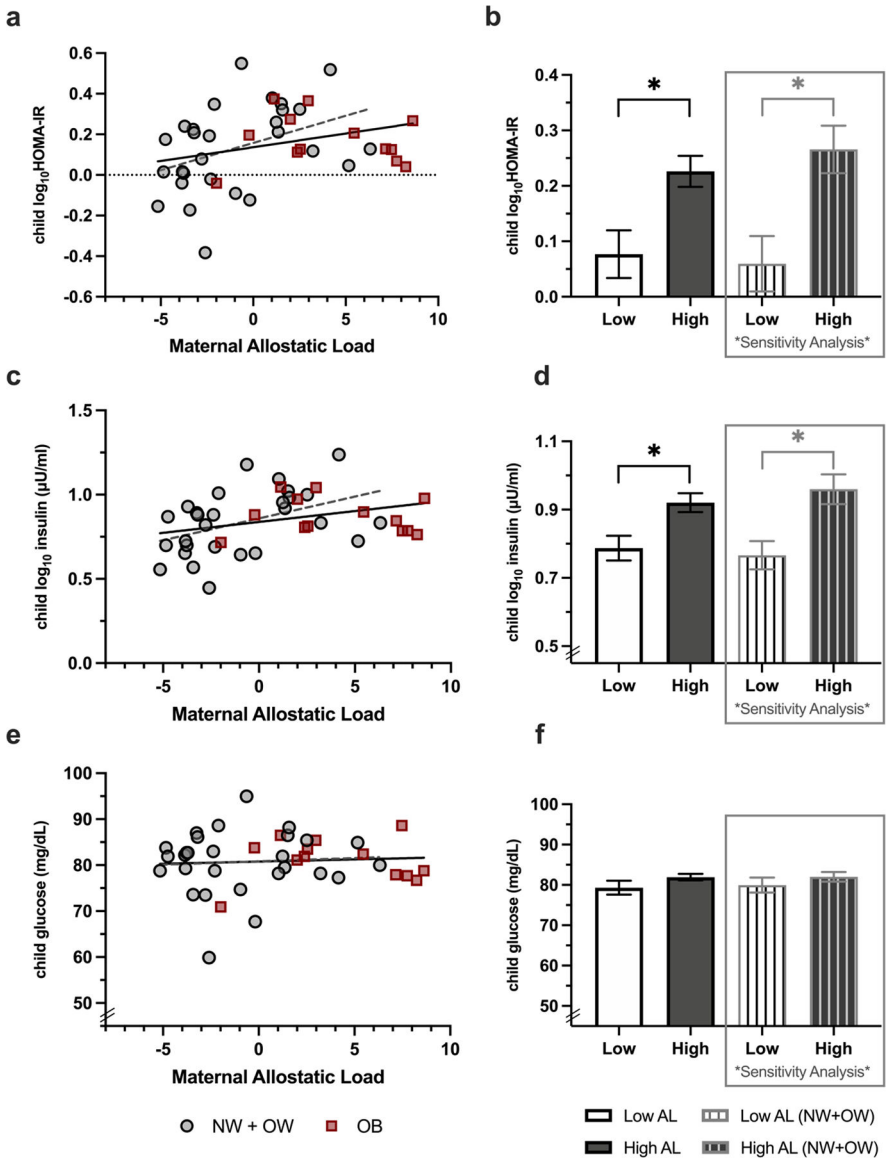

Figure 2:

Greater maternal allostatic load (AL) in pregnancy significantly associated with higher offspring (a, b) insulin resistance (log_{10}HOMA-IR), and (c, d) fasting insulin in early childhood. There was no relationship between maternal AL and child fasting glucose (e, f). In figures a, c, and e, the dotted grey line indicates the regression line for the sensitivity analyses, which excluded pregnant moms with obesity from the analyses. In figures b, d and f, the sensitivity analyses are represented by additional box plots, outlined in grey. After excluding women with pre-pregnancy obesity (n=14), maternal allostatic load remained significantly associated with childhood HOMA-IR and fasting insulin ($p<0.05$).

We note that models were run with AL as a continuous measure (figures a, c, e), but are additionally presented as mean split of high/low AL for visualization purposes (figures b, d, f). Data are mean ±SEM. *$p<0.05$; AL=allostatic load, NW= normal weight, OW= overweight, OB= obesity.

Table 1:

Maternal and Child Characteristics

	Mean		SD	IQR	Range
Maternal Variables:					
Age (yrs)	27.6	±	4.7	7.00	18 – 37
SES index	3.18	±	0.59	1.00	1.6 – 4.3
Ethnicity, (*n, %Hispanic*)	23		(42%)	-	-
Pre-pregnancy obesity, (n, %)	14		(25%)	-	-
Allostatic Load Composite Score	0.84	±	3.92	5.82	−5.15 – 9.20
Cortisol AUC (μg/dL)	3.38	±	1.30	0.87	0.99 – 8.95
log_{10}HOMA-IR	0.46	±	0.21	0.24	−0.09 – 0.96
FFA (mean18)	15.28	±	4.90	6.32	4.16 – 27.0
CRP (mg/L)	11.28	±	9.02	10.1	0.44 – 41.4
IL-6 (pg/ml)	0.98	±	0.86	0.83	0.08 – 3.44
Blood pressure (diastolic + systolic)	172.00	±	15.58	18.4	142 – 212
Pre-pregnancy BMI (kg/m^2)	27.76	±	6.25	7.50	18.4 – 45.0
Child Variables:					
Offspring Sex, (*n, %Male*)	29		(53%)	-	-
Newborn %FM	14.15	±	4.75	6.71	5.84 – 23.4
6-month %FM	32.54	±	8.31	12.69	19.3 – 48.1
Early Childhood %FM	27.62	±	5.57	7.88	16.1 – 40.0
Newborn %AbFM	7.83	±	3.99	5.22	0.16 – 17.2
6-month%AbFM	17.95	±	6.88	7.24	5.87 – 35.2
Early childhood %AbFM	18.74	±	5.21	6.75	9.77 – 31.9
Early childhood fasting insulin (μU/ml)	7.56	±	3.03	4.10	2.80 – 17.3
Early childhood fasting glucose (mg/dL)	80.84	±	6.21	6.70	59.9 – 95.0
Early childhood log_{10}HOMA-IR	0.15	±	0.19	0.25	−0.38 – 0.55
Infant feeding practices, *n(%)*					
Primarily breastfed	19		(35%)	-	-
Primarily formula fed	16		(29%)	-	-
Mixed feeding practices	20		(36%)	-	-

Data are provided as mean ± standard deviation (SD) with interquartile range (IQR) and range (minimum and maximum), or as frequency (*n*) and %, as noted. AUC= area under the curve; SES= socioeconomic status; FFA= free fatty acids, CRP= c-reactive protein; IL-6-= interleukin-6; BMI= body mass index; %FM= percent fat mass; %AbFM= percent abdominal fat mass; log_{10}HOMA-IR= logarithmic base10 homeostatic model of insulin resistance.