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Associations Between Maternal Obesity, Gestational Cytokine Levels, and Child Obesity in the NEST Cohort

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Abstract

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Data Accessibility Statement: Study data is available from the corresponding author (CH) upon reasonable request.

CONFLICTS OF INTEREST STATEMENT

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Background: Although maternal systemic inflammation is hypothesized to link maternal pre-pregnancy obesity to offspring metabolic dysfunction, patient empirical data are limited.

Objectives: In this study, we hypothesized that pre-pregnancy obesity alters systemic chemo/cytokines concentrations in pregnancy, and this alteration contributes to obesity in children.

Methods: In a multi-ethnic cohort of 361 mother-child pairs, we measured prenatal concentrations of plasma TNF-α, IL-6, IL-8, IL-1β, IL-4, IFN-γ, IL-12 p70 subunit, and IL-17A using a multiplex ELISA and examined associations of pre-pregnancy obesity on maternal chemo/cytokine levels, and associations of these cytokine levels with offspring body mass index z score (BMI-z) at age 2–6 years using linear regression.

Results: After adjusting for maternal smoking, ethnicity, age, and education, pre-pregnancy obesity was associated with increased concentrations of TNF-α (p=0.026) and IFN-γ (p=0.06). While we found no evidence for associations between TNF-α concentrations and offspring BMI-z, increased IFN-γ concentrations were associated with decreased BMI-z (p=0.0002), primarily in whites (p=0.0011). Additionally, increased maternal IL-17A concentrations were associated with increased BMI-z in offspring (p=0.0005) with stronger associations in African Americans (p=0.0042) than Whites (p=0.24).

Conclusions: Data from this study is consistent with maternal obesity-related inflammation during pregnancy increasing risk of childhood obesity in an ethnic-specific manner.

Keywords

cytokines; maternal obesity; childhood obesity

INTRODUCTION

Approximately one-third of women of childbearing age in the United States have a body mass index (BMI) ≥ 30 kg/m^2 and one-fifth of conceptions occur in women with obesity.[1, 2] Pre-pregnancy obesity is an established risk factor for offspring obesity and other subclinical indicators of vascular and metabolic dysfunction in children, which can lead to systemic pathologies in early life.[3, 4] In siblings born after surgical obesity intervention compared to siblings born before, surgically-induced weight loss before pregnancy has been associated with a lower risk of offspring obesity and other metabolic risk markers.[5] Pre-pregnancy obesity is characterized by adipocyte hypertrophy, chronic release of fatty acids into circulation leading to systemic inflammation and placental infiltration by maternal macrophages, which have been hypothesized to link gestational obesity and offspring health outcomes.[6, 7] However, empirical data linking maternal obesity and inflammation are limited and conflicting.[8–10]

In humans and animal model systems, maternal circulating levels of frequently studied cytokines including interleukin (IL) 6, interferon-gamma (IFN-γ), TNF-α, IL-4, IL-13, and IL-1β have been linked to offspring obesity, however few studies examine data in an ethnic specific manner.[8–12] Yet the prevalence of both maternal and childhood obesity are higher in African Americans.[14, 15] Further, circulating chemo/cytokines are known to vary sizably by age and race/ethnicity.[11–13, 16] In addition, most of these studies focus on pro-inflammatory

cytokines such as TNF-α, IL-6 and IL-1β levels, and the outcomes examined are limited to those measurable at birth, including pre-eclampsia, low birth weight and preterm birth.[17–25] Therefore, data demonstrating which chemo/cytokines associate with pre-pregnancy obesity that increase the risk of metabolic dysfunction in at older ages, may present new avenues for prevention. In this study, we tested the hypothesis that pre-pregnancy obesity alters systemic chemo/cytokines concentrations in early pregnancy, and this alteration contributes to high obesity risk apparent in children aged 2–6 years.

METHODS

Study participants

Study participants included mother and infant dyads enrolled in the prospective Newborn Epigenetics STudy (NEST) as previously described.[26, 27] Briefly, between 2005 and 2011, more than 2,000 pregnant women visiting prenatal clinics at Duke or Durham Regional Hospitals were enrolled. Maternal blood in which cytokines were measured was collected at enrollment. The median gestational age at enrollment was 11.6 weeks, IQR=9.3–18.7. The present analyses are limited to 361 of 2,681 enrolled participants in whom chemo/cytokines were measured and pre-pregnancy obesity and childhood anthropometric measurements were available. The 361 participants included are comparable to the overall cohort with respect to maternal age at delivery (p=0.65), maternal BMI (p=0.23), and child BMI-z score at age four, five and six (p>0.50). However, the 361 mother-infant dyads had offspring with higher birthweight, were more likely to be African American and with higher education (p<0.05). We examined these factors as potential confounders. The enrollment protocols were approved by the Duke University Institutional Review Board and all participants provided written informed consent and received incentives for their participation.

Data collection

Pre-pregnancy BMI.—Pre-pregnancy weight and height were self-reported, and BMI was computed as kilograms per square meter (kg/m^2). Women were dichotomized according to World Health Organization definitions (< $30kg/m^2$ and >= $30kg/m^2$). To determine the validity of self-reported pre-pregnancy weight and height, these were compared to values abstracted from clinic measurements up to six months prior to the last menstrual period. High concordance (rho=0.98, p<0.0001) was found between questionnaire- and medical records-based weight and height when the reference period was within three months. This concordance, which varies little especially among women with obesity, was reduced somewhat (rho=0.95, p<0.0001) with increasing time in which participants were requested to recall (i.e., six months).

Indicators of childhood obesity.—Measures of child weight and height were abstracted from medical records or obtained at study visits from which BMI-z scores were computed using the Center for Disease Control and Prevention SAS macros.[28] Offspring data was compiled annually through age six years.

Measurement of cytokines and chemokines.—Procedures for specimen collection and handling have been previously described.[26, 27] Briefly, at enrollment 10ml of peripheral

blood was drawn into EDTA vacutainer tubes and processed within four hours to obtain plasma from which cytokines were measured. Plasma was stored in 200μl aliquots to limit subsequent freeze-thaw cycles and prevent degradation. Plasma from n=80 study participants was quantified using the 30-Plex Human Cytokine Panel (ThermoFisher) on the Luminex Platform at the Medical University of South Carolina ProteoGenomics core facility to prioritize cytokines and chemokines for further analyses. This panel included IFN-γ, IFN-α, TNF-α, IL-1RA, IL-1β, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-15, IL-17, MCP-1, FGF-β, MIP-1α, MIP-1β, MIG, GM-CSF, IP-10, RANTES, G-CSF, Eotaxin, EGF, FGF-basic, VEGF, and HGF. Based on the magnitude of associations with perinatal outcomes, and augmented by a literature search, eight cytokines were prioritized for further analyses: IFN-γ, TNF-α, IL-1β, IL-6, IL-12 p70, IL-4, IL-8 and IL-17A. These eight chemo/cytokines were measured with a custom high sensitivity human cytokine 8-plex MAP kit from EMD Millipore. Plasma samples (25μl) from n=361 pregnant women were analyzed in duplicate according to the manufacturer's recommendations. Plates were read on a Luminex platform by the Duke University Human Vaccine Institute Core Facility. Data were analyzed using Milliplex Analyst version 5.1. Limits of detection for each cytokine were as follows (pg/ml): IFN-γ:0.87; IL-1b: 0.40; IL-12p70: 0.30; IL-17A: 0.56; IL-4: 0.94; TNF-α: 0.43; IL-8: 0.34; IL-6: 0.24. The intra-assay coefficient of variation (CV) for all analytes was 3.71%, and the inter-assay CV was 14.89%.

Covariate data.—Social and demographic factors previously associated with maternal obesity and cytokine concentrations and/or childhood obesity were examined for potential confounding. These factors included maternal age at delivery as continuous, ethnicity as categorical (African American, Hispanic, White, or Other), cigarette smoking during gestation (yes/no), education as an indicator of socioeconomic status (categorized as less than high school, high school graduate/GED, college graduate, or some college), infant sex (male/female), depression (continuous Center for Epidemiologic Studies scale and self-reported yes/no), preeclampsia (yes/no), maternal infection at delivery (yes/no), total non-sedentary time (in quartiles), and gestational age at blood draw as continuous as well as maternal conditions co-morbid with obesity; diabetes and asthma. In childhood obesity models we also assessed for confounding, birthweight (as continuous), birthweight-for-gestational-age to estimate intrauterine growth restriction as categorical (small, larger or appropriate for gestational age), and breast-feeding for at least three months (yes/no).

Statistical analysis

Cytokine levels were zero-protected and log transformed. Linear regression models were used to evaluate the relationships between maternal pre-pregnancy obesity and each log-transformed maternal cytokine concentration, adjusting for potential confounders, and then further stratified and re-analyzed for Whites and Blacks. Reported p-values are for each assessed multivariate regression. In addition, associations between maternal chemo/cytokine levels and offspring BMI-z outcomes were evaluated using linear regression models. Finally, these eight chemo/cytokines were examined concurrently in a multivariable model for their associations with childhood obesity. As inflammatory markers have been shown to vary by race/ethnicity, these analyses were repeated in African Americans and Whites and back transformed for interpretation according to standardized procedure.[29] Possible collinearity

between the chemo/cytokine biomarkers was examined prior to analysis. Even though some of these cytokines are all moderately positively correlated with each other, their associations with pre-pregnancy BMI remain quite different. For example, the highest correlated pair is for IL-17A and IFN-γ (rho = 0.74). Yet IFN-γ is associated with maternal BMI (p= 0.06) and the association for IL-17A is completely null. All analyses were conducted in R version 3.6.1 and SAS version 9.4. Calculated post hoc power on maternal models with all races for IFN-γ, TNF-α, and IL-6 were 72%, 91%, and 95%, respectively and 99% for the child model.[30]

RESULTS

Study participants.

Maternal and infant characteristics of women with and without obesity are summarized in Table 1. The mean pre-pregnancy BMI was 28.6 kg/m^2 (sd = 8.7) and a mean gestational weight gain of 14.2kg (sd = 8.1). Overall, 10% of women were of advanced maternal age (>35 years) and this was comparable in women with and without obesity. Approximately 65% of women had a college or higher education regardless of maternal obesity status (p>0.05). Similarly, gestational age and birthweight were not substantively different between women with and without obesity. However, when compared to Hispanics and Whites, African American women were more likely to be obese and less likely to breastfeed (p<0.05). Most infants (92%) were born at term (≥ 37 weeks) and 90% weighed ≥ 2500 grams. Males comprised 52% of the offspring population. Breastfeeding for three or more months was reported by 54% of women overall, and women with obesity were less likely to breastfeed for three months or more. These differences were accounted for in statistical analyses.

Maternal obesity before pregnancy and circulating chemo/cytokine concentrations in first trimester

Median concentrations and interquartile ranges of the eight cytokines are summarized in the left-hand column of Table 2 and are within ranges previously reported in pregnant women during the first trimester.[31] After adjusting for maternal age, ethnicity, cigarette smoking, and education, maternal obesity before pregnancy was associated with higher first trimester concentrations of TNF-α (β= 0.01, SE= 0.00, p=0.03), and was marginally associated with increased levels of IFN-γ (p=0.06) and IL-6 (p = 0.10). This translates to a one unit increase in pre-pregnancy BMI being associated with a 0.57% increase in prenatal TNF-α, and a 0.89% increase in IFN-γ concentrations. Models specific to African American and White mothers suggest that these associations may be limited to African American women although these ethnic differences were not significant (TNF-α p = 0.07, IFN-γ p = 0.10, and IL-6 p = 0.14). Heterogeneity tests confirm a difference by ethnicity for IL-6 (p = 0.0176) but not for TNF-α (p = 0.5233) or IFN-γ (p = 0.1771). Because cytokine concentrations have been shown to increase with increasing gestation,[31, 32] and 41% of women delayed blood draw until the second trimester, we further restricted these analyses to women with blood drawn at or after 18 weeks of gestation (data not shown). The patterns of association remained, suggesting that our findings are unlikely to be unduly influenced by gestational

age at blood draw. These patterns of associations also remained unaltered when further adjusting for pre-eclampsia, physical activity, maternal infection, or depression.

First trimester chemo/cytokine concentrations and children's BMI-z

We next examined associations of first trimester maternal cytokine concentrations and child BMI-z at age 2–6 years with a single linear regression of covariates and all eight cytokines. For these analyses, we adjusted for maternal age, maternal pre-pregnancy BMI, gestational weight gain, smoking, ethnicity, education, child sex, child age at follow-up, birth weight, and gestational age at birth. Maternal IFN-γ concentrations were associated with decreased BMI-z in children aged 2–6 years (β = −0.62, p= 0.0002; Table 3), suggesting that a 10 percent increase in maternal circulating levels of IFN-γ during the first trimester is associated with a decrease in offspring BMI-z of 6.2%. These inverse associations between prenatal concentrations of IFN-γ and children's BMI-z were stronger in offspring born to Whites (β = −0.82, p= 0.001) when compared to African Americans (β = −0.29, p= 0.19). We also found an association between increased prenatal levels of IL-17A and BMI-z in children (β = 0.58, p= 0.0005; Table 3), interpreted as a 10 percent increase in maternal IL-17A levels during the early prenatal period is associated with an increase in child BMI-z of 5.8 percentage points. In contrast to IFN-γ, these associations were only observed in African Americans (β = 0.63, p= 0.004) and not Whites (β = 0.34, p= 0.24). Heterogeneity tests did not confirm a difference by ethnicity for IFN-γ (p = 0.6005) or IL-17A (p = 0.3517). These patterns of associations also remained unaltered when further adjusting for pre-eclampsia, physical activity, maternal infection, or depression.

DISCUSSION

One-fifth of conceptions occur in women with obesity and maternal obesity is an established risk factor for childhood obesity. Accumulating evidence supports that chronic inflammation in adipose tissue that eventually promotes systemic inflammation and impaired insulin response may link maternal obesity to childhood obesity,[33–35] yet, inflammatory markers that link maternal obesity to childhood obesity remain understudied. In a pre-birth cohort in whom offspring were followed for weight and height measurements at age 2–6 years, we multiplex-measured eight chemo/cytokines to examine associations between pre-pregnancy obesity and maternal cytokine levels followed by testing the hypotheses that these circulating cytokines during pregnancy are associated with offspring obesity. We found that maternal obesity before pregnancy was associated with concentrations of circulating TNF-α, and these associations were stronger in African American women, although these concentrations were not associated with obesity in offspring aged 2–6 years. We also found that pre-pregnancy obesity was marginally associated with first trimester concentrations of IFN-γ, and elevated IFN-γ in the first trimester was inversely associated with BMI-z in offspring in Whites. Prenatal levels of IL-17A were associated with BMI-z in children and these associations were found only in African Americans. While reasons for ethnic differences in the effects of circulating cytokine levels on obesity are still unclear, it has been suggested that these effects may be exacerbated by differences in physiological factors including genetic variation, nutrient deficiency (e.g., vitamin D), sleep quality[36–38] or

psychosocial factors such as depressive mood or stress,[39, 40] which disproportionately affect African American women.

Although we were unable to directly link cytokines measured to maternal obesity and offspring obesity, we do provide evidence that maternal levels of IFN-γ are inversely associated with offspring BMI-z scores in Whites, while IL-17A levels are positively associated with BMI-z scores in African Americans. Our findings that pre-pregnancy obesity was associated with higher concentrations of circulating TNF-α in the first trimester are consistent with previous reports,[41, 42] and support the hypothesis that immune cells infiltrate adipose tissue, increasing levels of free fatty acids, and that this chronic low-grade activation of the innate immune system contributes to systemic inflammation.[43] These findings are also consistent with the now established relationship between this cytokine and obesity observed in murine and *in vitro* models, specifically that TNF-α correlated highly with BMI and are over-expressed in adipose tissue.[33, 44] Although reasons for stronger associations in some ethnic groups remain unclear, they are consistent with previous reports where stronger associations were found between pre-pregnancy obesity and TNF-α in African American women when compared to Whites.[12, 16, 36, 37, 45] While our associations between pre-pregnancy obesity and other circulating maternal levels of chemo/cytokines, such as the most studied pro-inflammatory IL-6 were marginal (p=0.10), the association was directionally consistent with previous reports.[9, 11, 39, 40, 45]

We observed a positive association between maternal obesity pre-pregnancy and IFN-γ in the first trimester, yet surprisingly, concentrations of this cytokine were inversely related to childhood obesity in Whites. However, this is consistent with epidemiologic observations recently reported by Englich et al where an odds ratio of 0.76, 95% confidence interval 0.60, 0.95 was reported.[10] IFN-γ is a Th1 cytokine that has been reported to increase in white adipose tissue of murine models with high fat diet-induced obesity, consistent with the idea that obesity among these pregnant women may have primed T cells from adipose tissue towards Th1 polarization.[46] When stimulated by IFN-γ, 3T3-L1 cells secrete numerous inflammatory mediators and may contribute to regulation of body weight, adipocyte hypertrophy, insulin resistance and glucose tolerance highlighting the role of the adaptive immune response both in the development of obesity and obesity-associated metabolic abnormalities.[47, 48] Although reasons for ethnic-specificity of these associations are still unclear, the inverse associations between prenatal concentrations of IFN-γ and obesity specific to White women may reflect the much lower frequency of obesity in White women in our cohort and the plasticity of the innate immune response.

Interestingly we also found that prenatal IL-17A levels were associated with indicators of obesity in children, but not pre-pregnancy obesity. Higher maternal obesity may activate inflammatory pathways in the placental microenvironment particularly in the decidua[49] which could directly induce epigenetic changes in the offspring leading to obesity development. IL-17A, a pro-inflammatory cytokine that has been implicated in experimental models of obesity and inflammatory diseases, is the predominant cytokine released by Th17 cells but can also be released by gamma delta cells and neutrophils.[50, 51] Specifically IL17A regulates adiopogenesis, adipocyte differentiation and glucose homestasis in experimemental animal models.[52] Obesity in children has also been independently associated with

significantly higher levels of IL-17A and increased frequency of Th17 cells in the absence of chronic inflammatory disease.[53, 54] The Th17 immune response also demonstrates significant plasticity and whether its effect on adipogenesis could be ethnicity specific remains unknown but warrants further investigation.

A strength of this study is the sample size large enough to facilitate the use of agnostic approaches to examining a moderately large panel of chemo/cytokines, enabling mutual adjustment of multiple cytokines, to identify patterns of inflammatory cytokines that can be targeted for intervention. The relatively large sample size has also facilitated evaluation of ethnic differences on associations between pre-pregnancy obesity, cytokines/chemokines during pregnancy and postnatal obesity in offspring. This longitudinal design where maternal pre-pregnancy obesity was ascertained for the period before pregnancy, markers of inflammation measured in the first trimester and obesity in children assessed at age 2–6 years at least provides some preliminary evidence that mechanisms involved in the development of childhood obesity may occur early in pregnancy. This enabled our assessment of first trimester chemo/cytokines, with a wider range of opportunities for early detection and prevention, and offspring obesity at age 2–6 years, when outcomes are likely predictive of later life obesity. There are some limitations that should be considered in interpreting the study findings. Although overall median gestation age at enrollment and blood draw used to measure cytokines was 11–12 weeks, in 5% of our participants, gestation age at blood draw was as late as 30 weeks. However, our sensitivity analysis restricted to women with age at blood draw at or after 18 weeks did not materially change our findings. Another limitation is that pre-pregnancy obesity was self-reported and obesity status may be under-reported. However, comparison of medical records-derived BMI and self-reported BMI of more than 200 women in this cohort showed a correlation >98%, consistent with previous reports.[55] It is important to acknowledge the integral role of the immune system in maintaining a successful pregnancy from implantation to delivery. However any immune imbalance and the resulting inflammatory reponse both peripherally and in the placental microenvironment can lead to pregnancy related complications. In fact elevated peripheral blood levels of IL-6, IL-1β, and IL-23 have been observed in the peripheral blood and decidua of women with preeclampsia, preterm births and unexplained recurrent pregnancy loss.[56–60] Another limitation of this study is that our model did not adjust for all of these pregnancy related complications which could also partly explain the differences in cytokine levels by ethnicity. Additionally, we did not account for multiple maternal and offspring variables such as diet, sedentary lifestyle, social stressors and neuropsychiatric disorders both in the prenatal and postnatal period which have been associated with childhood obesity.[61–65] Though we demonstrated an association between pre-pregnancy BMI and an increase in antenatal IFN-γ and TNF-α the effect sizes were modest and of uncertain clinical significance. Additionately though we can infer from the maternal cytokine profile that childhood obesity could be associated with a Th1 and Th17 immune mediated response we did not identitify the predominant existing immune cell populations to further delineate the immune-modulatory mechanisms involved. Additionally, although the sample size was adequate for the primary analyses, we may have been under-powered to examine race-specific effects, resulting in some risk estimates being unstable.

Despite these limitations, the data presented here support that pre-pregnancy obesity is associated with elevated levels of TNF-α and IFN-γ in circulation during gestation, and that maternal circulating levels of IFN-γ and IL-17A are associated with childhood obesity—and these associations may be ethnic specific. These data raise the intriguing possibility that depending on ethnicity, pre-pregnancy obesity may activate distinct immune pathways which in turn may have implications for designing intervention strategies, including refining dietary interventions, to prevent metabolic dysfunction in young children. Larger studies that include ethnic minorities are required to clarify these findings.

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Abbreviations:

BMI-z	body mass index z score
BMI	body mass index
IL	interleukin
IFN-γ	interferon-gamma
NEST	Newborn Epigenetics STudy

REFERENCES

1. Singh GK, DiBari JN. Marked Disparities in Pre-Pregnancy Obesity and Overweight Prevalence among US Women by Race/Ethnicity, Nativity/Immigrant Status, and Sociodemographic Characteristics, 2012–2014. J Obes. 2019;2019:2419263. doi:10.1155/2019/2419263 [PubMed: 30881701]
2. Villarroel M, Blackwell D, Jen A. Tables of Summary Health Statistics for U.S. Adults: 2018 National Health Interview Survey. 2019. Accessed October 31, 2019. http://www.cdc.gov/nchs/nhis/SHS/tables.htm
3. Fuemmeler BF, Wang L, Iversen ES, Maguire R, Murphy SK, Hoyo C. Association between Prepregnancy Body Mass Index and Gestational Weight Gain with Size, Tempo, and Velocity of Infant Growth: Analysis of the Newborn Epigenetic Study Cohort. Childhood obesity (Print). 6 2016;12(3):210–8. doi:10.1089/chi.2015.0253 [PubMed: 27135650]
4. Drake AJ, Reynolds RM. Focus on obesity: Impact of maternal obesity on offspring obesity and cardiometabolic disease risk. Reproduction. 2010;140:387–398. [PubMed: 20562299]

5. Barisione M, Carlini F, Gradaschi R, Camerini G, Adami GF. Body weight at developmental age in siblings born to mothers before and after surgically induced weight loss. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. Jul-Aug 2012;8(4):387–91. doi:10.1016/j.soard.2011.09.016 [PubMed: 22093379]
6. Lecoutre S, Breton C. Maternal nutritional manipulations program adipose tissue dysfunction in offspring. Frontiers in physiology. 2015;6:158. doi:10.3389/fphys.2015.00158 [PubMed: 26029119]
7. O'Reilly JR, Reynolds RM. The risk of maternal obesity to the long-term health of the offspring. Clin Endocrinol (Oxf). 1 2013;78(1):9–16. doi:10.1111/cen.12055 [PubMed: 23009645]
8. Dahlgren J, Nilsson C, Jennische E, et al. Prenatal cytokine exposure results in obesity and gender-specific programming. American journal of physiology Endocrinology and metabolism. 8 2001;281(2):E326–34. [PubMed: 11440909]
9. Danielsen I, Granstrom C, Rytter D, et al. Subclinical inflammation during third trimester of pregnancy was not associated with markers of the metabolic syndrome in young adult offspring. Obesity (Silver Spring, Md). 5 2014;22(5):1351–8. doi:10.1002/oby.20650
10. Englich B, Herberth G, Rolle-Kampczyk U, et al. Maternal cytokine status may prime the metabolic profile and increase risk of obesity in children. International journal of obesity (2005). 5 10 2017;doi:10.1038/ijo.2017.113
11. Menon R, Williams SM, Fortunato SJ. Amniotic fluid interleukin-1beta and interleukin-8 concentrations: racial disparity in preterm birth. Reprod Sci. 4 2007;14(3):253–9. doi:10.1177/1933719107301336 [PubMed: 17636239]
12. Velez DR, Fortunato SJ, Morgan N, et al. Patterns of cytokine profiles differ with pregnancy outcome and ethnicity. Human reproduction (Oxford, England). 8 2008;23(8):1902–9. doi:10.1093/humrep/den170
13. Stowe RP, Peek MK, Cutchin MP, Goodwin JS. Plasma cytokine levels in a population-based study: relation to age and ethnicity. The journals of gerontology Series A, Biological sciences and medical sciences. 4 2010;65(4):429–33. doi:10.1093/gerona/glp198
14. Leonard SA, Main EK, Scott KA, Profit J, Carmichael SL. Racial and ethnic disparities in severe maternal morbidity prevalence and trends. Ann Epidemiol. 5 2019;33:30–36. doi:10.1016/j.annepidem.2019.02.007 [PubMed: 30928320]
15. Skinner AC, Ravanbakht SN, Skelton JA, Perrin EM, Armstrong SC. Prevalence of Obesity and Severe Obesity in US Children, 1999–2016. Pediatrics. 3 2018;141(3)Skinner AC, Ravanbakht SN, Skelton JA, Perrin EM, Armstrong SC. Prevalence of Obesity and Severe Obesity in US Children, 1999–2016. Pediatrics. 2018;141(3):e20173459." 2018. Pediatrics 142 (3). 10.1542/peds.2018-1916. https://www.ncbi.nlm.nih.gov/pubmed/30177517. doi:10.1542/peds.2017-3459 [PubMed: 29483202]
16. Menon R, Thorsen P, Vogel I, et al. Racial disparity in amniotic fluid concentrations of tumor necrosis factor (TNF)-alpha and soluble TNF receptors in spontaneous preterm birth. Am J Obstet Gynecol. 5 2008;198(5):533 e1–10. doi:10.1016/j.ajog.2007.11.025 [PubMed: 18279834]
17. Aggarwal R, Jain AK, Mittal P, Kohli M, Jawanjal P, Rath G. Association of pro- and anti-inflammatory cytokines in preeclampsia. J Clin Lab Anal. 5 2019;33(4):e22834. doi:10.1002/jcla.22834 [PubMed: 30666720]
18. Ferguson KK, Meeker JD, McElrath TF, Mukherjee B, Cantonwine DE. Repeated measures of inflammation and oxidative stress biomarkers in preeclamptic and normotensive pregnancies. Am J Obstet Gynecol. 5 2017;216(5):527 e1–527 e9. doi:10.1016/j.ajog.2016.12.174 [PubMed: 28043842]
19. Spradley FT. Metabolic abnormalities and obesity's impact on the risk for developing preeclampsia. Am J Physiol Regul Integr Comp Physiol. 1 1 2017;312(1):R5–R12. doi:10.1152/ajpregu.00440.2016 [PubMed: 27903516]
20. Belousova VS, Svitich OA, Timokhina EV, Strizhakov AN, Bogomazova IM. Polymorphism of the IL-1beta, TNF, IL-1RA and IL-4 Cytokine Genes Significantly Increases the Risk of Preterm Birth. Biochemistry (Mosc). 9 2019;84(9):1040–1046. doi:10.1134/S0006297919090062 [PubMed: 31693463]

21. Hadley EE, Sheller-Miller S, Saade G, et al. Amnion epithelial cell-derived exosomes induce inflammatory changes in uterine cells. Am J Obstet Gynecol. 11 2018;219(5):478 e1–478 e21. doi:10.1016/j.ajog.2018.08.021 [PubMed: 30138617]
22. Melekoglu R, Yilmaz E, Ciftci O, Kafadar YT, Celik E. Associations between second-trimester amniotic fluid levels of ADAMTS4, ADAMTS5, IL-6, and TNF-alpha and spontaneous preterm delivery in singleton pregnancies. J Perinat Med. 4 24 2019;47(3):304–310. doi:10.1515/jpm-2018-0297 [PubMed: 30730845]
23. Ahmed MA, Alqosaibi AI, Mohamed MA, Soliman MG. Evaluation of Some Cytokines and Gene Expressions in Pre-eclampsia. Pak J Biol Sci. 2019;22(3):148–153. doi:10.3923/pjbs.2019.148.153 [PubMed: 30972985]
24. Quan LM, Xu QL, Zhang GQ, Wu LL, Xu H. An analysis of the risk factors of preeclampsia and prediction based on combined biochemical indexes. Kaohsiung J Med Sci. 2 2018;34(2):109–112. doi:10.1016/j.kjms.2017.10.001 [PubMed: 29413226]
25. Pandey M, Chauhan M, Awasthi S. Interplay of cytokines in preterm birth. Indian J Med Res. 9 2017;146(3):316–327. doi:10.4103/ijmr.IJMR_1624_14 [PubMed: 29355137]
26. Hoyo C, Murtha AP, Schildkraut JM, et al. Methylation variation at IGF2 differentially methylated regions and maternal folic acid use before and during pregnancy. Epigenetics. 7 2011;6(7):928–36. doi:16263 [pii] [PubMed: 21636975]
27. Liu Y, Murphy SK, Murtha AP, et al. Depression in pregnancy, infant birth weight and DNA methylation of imprint regulatory elements. Research Support, N.I.H., Extramural. Epigenetics. 7 2012;7(7):735–46. doi:10.4161/epi.20734 [PubMed: 22677950]
28. CDC. A SAS Program for the 2000 CDC Growth Charts (ages 0 to <20 years). Accessed March 16, 2020, https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm
29. Ford C Interpreting Log Transformations in a Linear Model. Accessed October 31, 2019, https://data.library.virginia.edu/interpreting-log-transformations-in-a-linear-model
30. Soper D Multiple Regression Post-hoc Statistical Power Calculator. Accessed October 1, 2020, 2020. https://www.analyticscalculators.com/calculator.aspx?id=9
31. Kaplan PB, Gucer F, Sayin NC, Yuksel M, Yuce MA, Yardim T. Maternal serum cytokine levels in women with hyperemesis gravidarum in the first trimester of pregnancy. Fertil Steril. 3 2003;79(3):498–502. doi:10.1016/s0015-0282(02)04699-x [PubMed: 12620429]
32. Curry AE, Thorsen P, Drews C, et al. First-trimester maternal plasma cytokine levels, pre-pregnancy body mass index, and spontaneous preterm delivery. Acta Obstet Gynecol Scand. 2009;88(3):332–42. doi:10.1080/00016340802702219 [PubMed: 19241227]
33. Kern PA, Saghizadeh M, Ong JM, Bosch RJ, Deem R, Simsolo RB. The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase. J Clin Invest. 5 1995;95(5):2111–9. doi:10.1172/JCI117899 [PubMed: 7738178]
34. Godfrey KM, Reynolds RM, Prescott SL, et al. Influence of maternal obesity on the long-term health of offspring. Lancet Diabetes Endocrinol. 1 2017;5(1):53–64. doi:10.1016/S2213-8587(16)30107-3 [PubMed: 27743978]
35. Segovia SA, Vickers MH, Gray C, Reynolds CM. Maternal obesity, inflammation, and developmental programming. Biomed Res Int. 2014;2014:418975. doi:10.1155/2014/418975 [PubMed: 24967364]
36. Blair LM, Porter K, Leblebicioglu B, Christian LM. Poor Sleep Quality and Associated Inflammation Predict Preterm Birth: Heightened Risk among African Americans. Sleep. 8 01 2015;38(8):1259–67. doi:10.5665/sleep.4904 [PubMed: 25845693]
37. Bobbitt KR, Peters RM, Li J, Rao SD, Woodcroft KJ, Cassidy-Bushrow AE. Early pregnancy vitamin D and patterns of antenatal inflammation in African-American women. Journal of reproductive immunology. 2 2015;107:52–8. doi:10.1016/j.jri.2014.09.054 [PubMed: 25453750]
38. Yao S, Hong CC, Ruiz-Narváez EA, et al. Genetic ancestry and population differences in levels of inflammatory cytokines in women: Role for evolutionary selection and environmental factors. PLoS Genet. 6 2018;14(6):e1007368. doi:10.1371/journal.pgen.1007368 [PubMed: 29879116]
39. Blackmore ER, Groth SW, Chen DG, Gilchrist MA, O'Connor TG, Moynihan JA. Depressive symptoms and proinflammatory cytokines across the perinatal period in African American women.

J Psychosom Obstet Gynaecol. 3 2014;35(1):8–15. doi:10.3109/0167482X.2013.868879 [PubMed: 24350831]

40. Christian LM, Kowalsky JM, Mitchell AM, Porter K. Associations of postpartum sleep, stress, and depressive symptoms with LPS-stimulated cytokine production among African American and White women. J Neuroimmunol. 3 15 2018;316:98–106. doi:10.1016/j.jneuroim.2017.12.020 [PubMed: 29406850]
41. Fujimori M, Franca EL, Morais TC, Fiorin V, de Abreu LC, Honorio-Franca AC. Cytokine and adipokine are biofactors can act in blood and colostrum of obese mothers. Biofactors. 3 2017;43(2):243–250. doi:10.1002/biof.1339 [PubMed: 28419655]
42. McArdle MA, Finucane OM, Connaughton RM, McMorrow AM, Roche HM. Mechanisms of obesity-induced inflammation and insulin resistance: insights into the emerging role of nutritional strategies. Front Endocrinol (Lausanne). 2013;4:52. doi:10.3389/fendo.2013.00052 [PubMed: 23675368]
43. Engin AB. Adipocyte-Macrophage Cross-Talk in Obesity. Advances in experimental medicine and biology. 2017;960:327–343. doi:10.1007/978-3-319-48382-5_14 [PubMed: 28585206]
44. Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. Nature. 10 9 1997;389(6651):610–4. doi:10.1038/39335 [PubMed: 9335502]
45. Gillespie SL, Porter K, Christian LM. Adaptation of the inflammatory immune response across pregnancy and postpartum in Black and White women. Journal of reproductive immunology. 4 2016;114:27–31. doi:10.1016/j.jri.2016.02.001 [PubMed: 26895093]
46. Wellen KE, Hotamisligil GS. Obesity-induced inflammatory changes in adipose tissue. J Clin Invest. 12 2003;112(12):1785–8. doi:10.1172/JCI20514 [PubMed: 14679172]
47. Rocha VZ, Folco EJ, Sukhova G, et al. Interferon-gamma, a Th1 cytokine, regulates fat inflammation: a role for adaptive immunity in obesity. Circ Res. 8 29 2008;103(5):467–76. doi:10.1161/CIRCRESAHA.108.177105 [PubMed: 18658050]
48. Winer S, Chan Y, Paltser G, et al. Normalization of obesity-associated insulin resistance through immunotherapy. Nature medicine. 8 2009;15(8):921–9. doi:10.1038/nm.2001
49. Aye IL, Lager S, Ramirez VI, et al. Increasing maternal body mass index is associated with systemic inflammation in the mother and the activation of distinct placental inflammatory pathways. Biology of reproduction. 6 2014;90(6):129. doi:10.1095/biolreprod.113.116186 [PubMed: 24759787]
50. Dragasevic S, Stankovic B, Kotur N, et al. Metabolic Syndrome in Inflammatory Bowel Disease: Association with Genetic Markers of Obesity and Inflammation. Metab Syndr Relat Disord. 2020;18(1):31–38. [PubMed: 31750766]
51. Chehimi M, Vidal H, Eljaafari A. Pathogenic Role of IL-17-Producing Immune Cells in Obesity, and Related Inflammatory Diseases. J Clin Med. 7 14 2017;6(7)doi:10.3390/jcm6070068
52. Zúñiga LA, Shen WJ, Joyce-Shaikh B, et al. IL-17 regulates adipogenesis, glucose homeostasis, and obesity. Journal of immunology (Baltimore, Md : 1950). 12 1 2010;185(11):6947–59. doi:10.4049/jimmunol.1001269
53. Susilowati R, Sulistyoningrum DC, Witari NP, Huriyati E, Luglio HF, Julia M. Sexual dimorphism in interleukin 17A and adipocytokines and their association with insulin resistance among obese adolescents in Yogyakarta, Indonesia. Asia Pacific journal of clinical nutrition. 12 2016;25(Suppl 1):S93–s101. doi:10.6133/apjcn.122016.s13 [PubMed: 28027637]
54. Schindler TI, Wagner JJ, Goedicke-Fritz S, et al. T(H)17 Cell Frequency in Peripheral Blood Is Elevated in Overweight Children without Chronic Inflammatory Diseases. Frontiers in immunology. 2017;8:1543. doi:10.3389/fimmu.2017.01543 [PubMed: 29201026]
55. Roth LW, Allshouse AA, Lesh J, Polotsky AJ, Santoro N. The correlation between self-reported and measured height, weight, and BMI in reproductive age women. Maturitas. 10 2013;76(2):185–8. doi:10.1016/j.maturitas.2013.07.010 [PubMed: 23958434]
56. Meekins JW. Interleukin-6, tumour necrosis factor and soluble tumour necrosis factor receptors in women with pre-eclampsia. British journal of obstetrics and gynaecology. 10 1995;102(10):842–3. doi:10.1111/j.1471-0528.1995.tb10859.x

57. Benyo DF, Miles TM, Conrad KP. Hypoxia stimulates cytokine production by villous explants from the human placenta. The Journal of clinical endocrinology and metabolism. 5 1997;82(5):1582–8. doi:10.1210/jcem.82.5.3916 [PubMed: 9141553]
58. Conrad KP, Miles TM, Benyo DF. Circulating levels of immunoreactive cytokines in women with preeclampsia. American journal of reproductive immunology (New York, NY : 1989). 8 1998;40(2):102–11. doi:10.1111/j.1600-0897.1998.tb00398.x
59. Wang B, Koga K, Osuga Y, et al. High mobility group box 1 (HMGB1) levels in the placenta and in serum in preeclampsia. American journal of reproductive immunology (New York, NY : 1989). 8 2011;66(2):143–8. doi:10.1111/j.1600-0897.2010.00975.x
60. Sadowsky DW, Adams KM, Gravett MG, Witkin SS, Novy MJ. Preterm labor is induced by intraamniotic infusions of interleukin-1beta and tumor necrosis factor-alpha but not by interleukin-6 or interleukin-8 in a nonhuman primate model. American journal of obstetrics and gynecology. 12 2006;195(6):1578–89. doi:10.1016/j.ajog.2006.06.072 [PubMed: 17132473]
61. Mourtakos SP, Tambalis KD, Panagiotakos DB, et al. Maternal lifestyle characteristics during pregnancy, and the risk of obesity in the offspring: a study of 5,125 children. BMC pregnancy and childbirth. 3 21 2015;15:66. doi:10.1186/s12884-015-0498-z [PubMed: 25885759]
62. Liao XP, Yu Y, Marc I, et al. Prenatal determinants of childhood obesity: a review of risk factors (1). Canadian journal of physiology and pharmacology. 3 2019;97(3):147–154. doi:10.1139/cjpp-2018-0403 [PubMed: 30661367]
63. Hemmingsson E Early Childhood Obesity Risk Factors: Socioeconomic Adversity, Family Dysfunction, Offspring Distress, and Junk Food Self-Medication. Current obesity reports. 6 2018;7(2):204–209. doi:10.1007/s13679-018-0310-2 [PubMed: 29704182]
64. Vos MB, Welsh J. Childhood obesity: update on predisposing factors and prevention strategies. Current gastroenterology reports. 8 2010;12(4):280–7. doi:10.1007/s11894-010-0116-1 [PubMed: 20563673]
65. Larqué E, Labayen I, Flodmark CE, et al. From conception to infancy - early risk factors for childhood obesity. Nature reviews Endocrinology. 8 2019;15(8):456–478. doi:10.1038/s41574-019-0219-1

Table 1.

Description of study participants

Maternal/infant characteristic	Number (%) BMI < 30kg/m^2 N = 237	Number (%) BMI >= 30kg/m^2 N = 124	Number (%) All Participants N = 361
Maternal age			
18–25 years	80 (34.0)	42 (33.9)	122 (34.0)
26–35 years	132 (56.0)	69 (55.6)	201 (56.0)
36+ years	23 (10.0)	13 (10.5)	36 (10.0)
Maternal ethnicity			
African American	108 (45.6)	86 (69.3)	194 (53.7)
European American	112 (47.3)	29 (23.4)	141 (39.1)
Hispanic	8 (3.4)	4 (3.2)	12 (3.3)
Other	9 (3.8)	5 (4.0)	14 (3.9)
Maternal education			
No College	73 (31.3)	46 (38.3)	119 (33.7)
Some college	160 (68.7)	74 (61.7)	234 (66.3)
Gestational cigarette smoking			
Yes	37 (15.8)	25 (21.0)	62 (17.6)
No	197 (84.1)	94 (79.0)	291 (82.4)
Infant sex			
Male	118 (50.2)	67 (54.0)	185 (51.5)
Female	117 (49.8)	57 (46.0)	174 (48.5)
Gestational age at birth			
< 37 weeks	17 (7.3)	11 (8.9)	28 (7.9)
≥ 37 weeks	215 (90.7)	113 (91.1)	328 (92.1)
Birth weight			
< 2500 grams	16 (7.0)	8 (6.5)	24 (6.8)
≥ 2500 grams	213 (93.0)	114 (93.5)	327 (93.2)
Breast feeding: 3+ Months			
Yes	121 (59.9)	40 (41.6)	161 (54.0)
No	81 (40.1)	56 (58.4)	137 (46.0)

Table 2.

Regression coefficients and 95% confidence intervals (CIs) for associations between pre-pregnancy BMI and cytokine/chemokine concentrations.

	*Plasma Concentration	All N = 348			Whites N = 141			African Americans N = 182		
Cytokine	**Median (IQR)**	**β ** (95% CI)**	**T- β**	**p value**	**β ** (95% CI)**	**T- β**	**p value**	**β ** (95% CI)**	**T- β**	**p value**
TNFα	**4.7 (3.5–6.2)**	**0.01 (0.00,0.01)**	**0.57**	**0.03**	0.00 (−0.01,0.01)	0.50	0.29	**0.01 (−0.00,0.01)**	**0.58**	**0.07**
IL8	4.0 (2.9–5.9)	−0.00 (−0.01,0.01)	−0.06	0.85	0.01 (−0.00,0.02)	0.68	0.16	−0.00 (−0.01,0.00)	−0.35	0.41
IL1β	4.4 (2.6–6.8)	−0.00 (−0.01,0.00)	−0.34	0.33	−0.00 (−0.01,0.01)	−0.19	0.75	−0.00 (−0.01,0.01)	−0.32	0.48
IL-17A	5.3 (2.8–10.7)	−0.00 (−0.01,0.01)	−0.03	0.95	−0.01 (−0.02,0.01)	−0.57	0.50	0.00 (−0.01,0.01)	0.13	0.85
IL4	4.1 (2.4–7.6)	−0.01 (−0.02,0.00)	−0.68	0.16	−0.01 (−0.03,0.00)	−1.03	0.18	0.00 (−0.01,0.01)	−0.18	0.79
IFN-γ	**17.2 (10.5–27.3)**	**0.01 (−0.00,0.01)**	**0.89**	**0.06**	0.0 (−0.01,0.02)	0.31	0.70	**0.01 (−0.00,0.02)**	**1.06**	**0.10**
IL6	**2.8 (1.7–4.2)**	**0.01 (−0.00,0.01)**	**0.59**	**0.10**	0.01 (−0.00,0.02)	0.61	0.25	0.01 (−0.00,0.02)	0.72	0.14
IL12	4.7 (2.5–7.7)	−0.00 (−0.01,0.01)	−0.28	0.55	−0.00 (−0.02,0.01)	−0.18	0.79	−0.00 (−0.01,0.01)	−0.16	0.77

Models were adjusted for maternal smoking, age, education and race (All). Whites and African Americans were run separately with non-race covariates.

* In picograms/ml.

** Cytokine data were zero-protected and log-transformed for regression models. **T** - Beta (T- β) estimates were back-transformed after regression. **Example**: For *TNFα*, each one unit increase in maternal BMI is associated with 0.57% increase in maternal plasma levels of TNFα.

** For all, depending on cytokine, N ranged from 342–348 – N reflects Analyzed complete cases for those 3 covariates

*** For White 137–141

**** For Black 180–182

Table 3.

Single multivariate regression coefficients for associations of all 8 cytokines on child BMIz scores at 2–6 years of age.

	All (N = 318)			Whites (N = 123)			Blacks (N = 171)		
Cytokine	**β**	**SE**	**p**	**β**	**SE**	**p**	**β**	**SE**	**p**
IFN-γ	**−0.62**	**0.16**	**0.0002**	**−0.82**	**0.24**	**0.0011**	−0.29	0.23	0.1949
IL1β	−0.03	0.20	0.8943	0.37	0.29	0.2165	−0.32	0.27	0.2384
IL12	−0.03	0.19	0.8635	0.44	0.34	0.1929	−0.28	0.25	0.2662
IL-17A	**0.58**	**0.16**	**0.0005**	0.34	0.28	0.2376	**0.63**	**0.22**	**0.0042**
IL4	0.08	0.14	0.5808	0.25	0.24	0.2992	−0.03	0.17	0.8451
TNFα	−0.37	0.26	0.1483	−0.34	0.42	0.4219	−0.21	0.35	0.5530
IL8	0.34	0.21	0.1018	0.31	0.38	0.4141	0.19	0.26	0.4578
IL6	0.12	0.19	0.5374	−0.07	0.41	0.8733	0.10	0.23	0.6612

All cytokines (zero-protected and log transformed) and covariates were modeled concurrently for all individuals in a multivariate linear regression and then stratified for Whites and Blacks. Models adjusted for maternal age, smoking, educational attainment, race (when not stratified), pre-pregnancy BMI, gestational weight gain, and child characteristics - sex, birth weight, child age at follow-up, and gestational age at birth. For cytokines, the estimates can be interpreted as follows: *IL-17A*- for every 10% increase in *IL-17A* levels, child BMI-Z increases by β/10 = 0.058 units or 5.8%.