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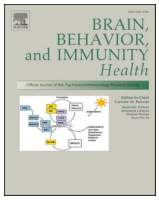

Neighborhood racial composition and experiences of racial discrimination: Associations with cytokines during pregnancy among African American women

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ABSTRACT

Background: Preterm birth rates are consistently higher in African American (AA) pregnancies compared to White pregnancies in the United States. Neighborhood racial composition, experiences of racial discrimination, and systemic inflammation are factors that have been associated with preterm birth and other adverse pregnancy outcomes that may account for these disparities. Here, we investigated whether perceived neighborhood racial composition and experiences of discrimination were predictive of cytokine levels during pregnancy among AA individuals.

Methods: 545 AA individuals completed surveys and had blood samples collected at prenatal clinics in the Midwest at three timepoints (8–18,19-29, and 30–36 weeks gestation) throughout pregnancy. Pro-inflammatory [interferon (IFN)-γ, interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α, macrophage migration inhibitory factor (MIF)] and anti-inflammatory cytokines (IL-10) were quantified. Multivariate and multilevel models were used to examine associations of perceived neighborhood racial composition and experiences of racial discrimination with cytokine levels, controlling for relevant covariates.

Results: Perceived neighborhood racial composition was significantly associated with MIF at 30–36 weeks gestation in multivariate regression ($p < 0.001$). Living in neighborhoods with more compared to fewer White people was predictive of higher levels of MIF ($b = 0.599$, $SE = 0.12$, $p < 0.001$). Experiences of discrimination were also associated with higher levels of MIF ($\beta = 0.141$, $SE = 0.07$, $p = 0.036$). Neither predictor was associated with other cytokines. Follow-up analyses revealed that neighborhood racial composition was also predictive of higher MIF levels at 8–18 weeks gestation ($p = 0.02$) and at 19–29 weeks gestation ($p = 0.04$).

Conclusions: Living in neighborhoods with more White individuals and having more lifetime experiences of racial discrimination were positively related to levels of the pro-inflammatory cytokine, MIF, among pregnant AA individuals. MIF's known positive relationships with chronic stress and preterm birth suggest that these elevations in MIF may have negative health consequences. Future studies should explore whether MIF serves as a pathway between neighborhood racial composition or experiences of racial discrimination and preterm birth risk among AA individuals.

1. Introduction

Preterm birth remains a persistent public health issue in the United States (U.S.), with the prevalence rate being significantly higher compared to other developed countries (Frey and Klebanoff, 2016). This increased prevalence has been partially attributed to racial disparities in rates of preterm birth (Frey and Klebanoff, 2016). Among African American (AA) individuals, preterm birth occurs at a rate that is 1.5–2

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times higher than the rate for White/European Americans (Christian, 2020; Osterman et al., 2023). These disparities are not fully accounted for by established risk factors including socio-economic status (SES), smoking, educational attainment, and health behaviors (Christian, 2020). As such, research in recent years has turned to examining biological mechanisms and psychosocial factors that may further account for these disparities in adverse pregnancy outcomes (Christian, 2012; Giurgescu et al., 2013; Misra et al., 2017).

Elevated systemic inflammation is one such biological mechanism that confers greater risk for preterm birth and has garnered increasing attention for its role in stress-induced alterations in immune functioning during pregnancy. Upregulation of the pro-inflammatory nuclear factor-kappa B (NF-ƙB) transcription factor and increasing levels of pro-inflammatory cytokines in late pregnancy lead to prostaglandin synthesis, degradation of connective tissues, and induction of uterine contractions preceding labor (Giurgescu et al., 2013; Golightly et al., 2011). Concordantly, in comparison to full term birth, preterm birth has been associated with increased production of the pro-inflammatory cytokines interleukin (IL)-1β, tumor necrosis factor-alpha (TNF-α), IL-6, IL-8, and macrophage migration inhibitory factor (MIF), and reduced levels of the anti-inflammatory cytokine IL-10 (Lyon et al., 2010; Pearce et al., 2008; Von Minckwitz et al., 2000). Importantly, compared to pregnant White persons, pregnant AAs have been found to have elevated levels of C-reactive protein (CRP) (Borders et al., 2015), higher stress-induced increases in IL-6 (Christian et al., 2013), and a reduced ability of glucocorticoids to suppress IL-6 production (Gyllenhammer et al., 2021). Given that glucocorticoids (GC's) downregulate pro-inflammatory cytokine production, and that prolonged stress exposure can reduce the sensitivity of immune cells to glucocorticoid's anti-inflammatory effects (Cole, 2008; Miller et al., 2002; Raison and Miller, 2003), such findings have important implications for the role of inflammation in pregnancy outcomes.

Chronic stressors, such as depression and adverse life events, are known to have an inherent connection with systemic inflammation in both pregnant and non-pregnant individuals (Lahti-Pulkkinen et al., 2020; McCormack et al., 2021; Raison et al., 2006). Studies have thus begun to elucidate psychosocial and social-environmental factors associated with chronic stress that may lead to heightened inflammation and the subsequent elevated risk of preterm birth among AAs. As explicated by social safety theory (Slavich, 2020), perceiving one's environment as safe or hostile (i.e., excessive social and/or physical threats) has implications for immune system functioning. Social threats, including factors such as social exclusion or discrimination, are particularly potent inducers of pro-inflammatory cytokines (Dickerson et al., 2009; Kemeny, 2009; Simons et al., 2021). Racial discrimination is both a distinctive social threat and source of chronic stress that is frequently experienced by AA individuals (Lee et al., 2019; Perry et al., 2013). As such, it may help account for the racial disparities observed in pregnancy outcomes via higher levels of inflammation. In support of this prediction, some studies have shown that higher reported discriminatory experiences are associated with higher levels of IL-6 and reduced glucocorticoid sensitivity of immune cells during pregnancy (Gillespie and Anderson, 2018; Giurgescu et al., 2016). Racial discrimination has also been associated with increased risks of preterm birth and lower gestational weight at birth (Alhusen et al., 2016; Giurgescu et al., 2011; Misra et al., 2010, 2017; Slaughter-Acey et al., 2016). Similarly, worry about racial discrimination has been linked with higher preterm birth risk and may explain some of the disparities observed in pregnancy outcomes between AA and White individuals (Braveman et al., 2017). Despite the reported links between racial discrimination and preterm birth, there have been relatively few studies examining the association of experiences of racial discrimination and systemic inflammation during pregnancy.

Neighborhood racial composition, a multidimensional construct with vastly diverse conceptualizations, has also been examined in relation to preterm birth but not in relation to systemic inflammation in pregnancy. There are discrepant findings in the literature for the effect of neighborhood racial composition (i.e., measures of segregation) on pregnancy and health outcomes, depending on the operationalization. A large body of work has examined racial composition using *objective* measures from Census-tract data linked to individual's residential addresses. Some such studies that have used isolation, operationalized as the probability of minority members coming into contact with members of the same minority group (Massey and Denton, 1988), reported increased odds of preterm birth with higher exposure to members primarily of the same minority group (Bell et al., 2006; Mehra et al., 2017). Studies utilizing related indicators that capture the negative dimensions of this construct, such as structural racism and income inequality, have also observed a heightened risk of preterm birth and maternal mortality (Chambers et al., 2019; Dyer et al., 2022). These studies used indices of concentration, or the degree to which minority members account for a small proportion of the total population of a region relative to majority members (Massey and Denton, 1988; Mehra et al., 2017). However, another recent study using these very same concentration indices found both increased and reduced risk of maternal morbidity after stratifying by geographical location (Mari et al., 2023). Other studies using neighborhood racial composition, defined as the proportion of minority individuals living in the same area or neighborhood (White and Borrell, 2011), have found a reduced risk of negative health outcomes (Hutchinson et al., 2009). Studies using clustering, or the degree to which minority neighborhoods lie adjacent to one another versus spread out, have also found a reduced risk of adverse pregnancy outcomes with higher degrees of clustering (Bell et al., 2006; Mehra et al., 2017). Thus, there may be both negative and protective aspects of living in a community with members of the same minority group (Bell et al., 2006; Mehra et al., 2017). However, there is a paucity of studies utilizing subjective measures of this construct, nor any studies that have examined the relationship between objective or perceived measures of neighborhood racial composition and systemic inflammation during pregnancy.

In addition to the individual influences of neighborhood racial composition and experiences of racial discrimination on health and birth outcomes, the two constructs are intricately intertwined. For instance, discrimination, particularly in housing or employment domains, is one integral pathway by which structural racism and residential racial segregation is perpetrated (Braveman et al., 2022; Williams et al., 2019; Williams and Mohammed, 2013). Neighborhood racial composition may also serve as a moderator between experiences of racial discrimination and health outcomes. In support of these potential relationships are some studies finding a positive relationship between living in neighborhoods with a higher proportion of White residents and experiences of racial discrimination among AA neighborhood residents (Borrell et al., 2013; English et al., 2014; Hunt et al., 2007). Still other studies have found 1) no relationship between the two constructs after adjustment for individual level socioeconomic position (Dailey et al., 2010), 2) no interaction between the two constructs in the prediction of health outcomes (Forde et al., 2021), or 3) a positive association between experiences of discrimination and a measure of structural racism (Chambers et al., 2020). Such variation in findings highlights the complexity of the relationship between racial discrimination and neighborhood racial composition. Importantly, there is limited research examining the distinct contribution of either neighborhood racial composition or experiences of racial discrimination with systemic inflammation during pregnancy. The current study attempts to first address this gap in knowledge.

This study aimed to examine the associations of experiences of racial discrimination and perceived neighborhood racial composition with systemic inflammation during pregnancy among a cohort of pregnant AA individuals. It was hypothesized that higher reported experiences of racial discrimination would be associated with higher levels of systemic inflammation based on previous research. Due to the lack of studies assessing the relationship between neighborhood racial composition and

inflammation during pregnancy, no specific hypotheses were formulated for this construct.

2. Method

2.1. Design and sample

Five hundred and forty-five pregnant AA individuals were recruited at their first prenatal visit from clinics in Columbus, OH and Detroit, MI metropolitan areas for the Biosocial Impact on Black Births (BIBB) Study. Data were collected between December of 2017 through the beginning of March of 2020 at three timepoints throughout pregnancy: 8–18 weeks, 19–29 weeks, and 30–36 weeks gestation. Participants were eligible for the study if they self-identified as Black or African American, had a singleton pregnancy, were 18–45 years of age, and spoke and read the English language. Subjects were excluded if they had a multiple gestation pregnancy (e.g., twins). The third timepoint (30–36 weeks gestation) was utilized for initial analyses given that social threats during pregnancy were expected to be most salient closer to term, the association between psychosocial stress with both inflammation and preterm birth risk has been found to be weaker or not evident at mid-pregnancy (Cole-Lewis et al., 2014; Coussons-Read et al., 2007), mid-pregnancy is proposed to be an anti-inflammatory state (Chatterjee et al., 2014; Sykes et al., 2012), and 201 of the participants were enrolled between 19 and 29 weeks gestation (i.e., after timepoint 1). Three hundred thirty-five individuals had complete inflammation data for the third timepoint. Of these, 16 were missing survey data, 9 were missing gestational age at data collection, and 29 participants did not have BMI data available.

2.2. Procedure

Participants were approached by the research staff at their regularly scheduled prenatal visits, where informed consent was obtained. As part of the BIBB study, participants completed surveys on a tablet about lifetime experiences of discrimination (EOD), perceived racial segregation, depressive symptoms, and self-reported demographic characteristics at three time points throughout pregnancy. Participants whole blood was drawn via antecubital venipuncture by a registered nurse or certified phlebotomist at the prenatal clinics at each study visit into ethylenediaminetetraacetic acid (EDTA)-coated tubes, placed on ice, and transported to the laboratory for processing. Samples were centrifuged (1600 g × 15 min at 4 °C) within 2 h of the blood draw. Plasma aliquots were collected from supernatant and stored at −20 °C at the prenatal clinic. At the end of each day, samples were transferred to −80 °C alarm temperature monitored freezers for longer term storage. Samples were periodically shipped on dry ice, overnight via courier, to one of the author's (CGE) lab for analysis of inflammatory markers. Participants were reimbursed $30 per visit for their participation. All study procedures were approved by Institutional Review Boards at the participating universities and prenatal clinics.

2.3. Measures

2.3.1. Demographic variables

Socio-demographic characteristics, including age, annual household income, education level, and employment status were self-reported by participants at the first timepoint. Annual household income was originally assessed in 7 categories. Due to uneven group numbers, annual household income was split into low (<$10,000), mid ($10,000-$29,999), and high (≥$30,000). Low served as the reference group in all analyses. Education level was originally assessed in 7 categories but was dichotomized into 0 = high school education or less and 1 = post-high school education due to uneven group numbers. Work status was coded as 0 = currently unemployed or temporarily laid off and 1 = currently employed. Gestational age at data collection was collected from medical records.

2.3.2. Body Mass Index

Body Mass Index (BMI) was abstracted from medical records from the participant's first prenatal visit. BMI obtained prior to 14 weeks gestation has been evidenced as closely approximating pre-pregnancy BMI (Zheng et al., 2019). Thus, for the 93 participants whose first prenatal visit was past 14 weeks gestation and had available self-reported pre-pregnancy weight, BMI was calculated from self-reported pre--pregnancy weight and first prenatal visit height. In this sample, self-reported BMI and first prenatal visit BMI were highly correlated (r = 0.94).

2.3.3. Experiences of racial discrimination (EOD)

The EOD is a measure of perceived experiences of lifetime racial discrimination (Krieger et al., 2005). The EOD asks whether individuals have ever experienced discrimination due to race or ethnicity in nine domains (i.e., at work, getting health care, in public) (yes = 1 vs no = 0). If participants responded yes, they were asked to indicate how many experiences they had in that domain. A frequency score was calculated (Krieger et al., 2005), with an unendorsed situation scored as 0, one endorsed situation is scored as 1, two or three endorsed situations is scored as 2.5, and four or more endorsed situations scored as 5. The frequency scores are then summed to create a total score. Higher scores signify greater experiences of discrimination across domains. EOD has been determined to have good validity in a cohort of AA adults (Krieger et al., 2005) and has been used in previous studies with pregnant AAs (Gillespie et al., 2021; Giurgescu et al., 2016). In this sample, the Cronbach's alpha was 0.82.

2.3.4. Neighborhood racial composition

The Perceived Racial Segregation Scale (Laveist, 2003) asks about perceived racial composition in five domains (at work, high school they attended, childhood neighborhood, current neighborhood, and church/place of worship). For each place, participants were asked to identify whether there were mostly White people or mostly Black people at each domain on a 1–5 Likert scale ranging from almost all Black people to almost all White people. Higher scores on the scale indicated a larger presence of White people. This scale has been used before in a sample of AAs (Laveist, 2003). Due to a low Cronbach's alpha (0.59) and for ease of interpretability, only the current *neighborhood* racial composition item was used. Because of extreme skewness and uneven group numbers, the current neighborhood racial composition item was used as a dichotomous variable (0 = almost all AA, mostly AA; 1 = some AA, mostly White, almost all White) in initial regression models. Significant associations were further examined in post hoc analysis, with Bonferroni correction, using the original 5 categories of the neighborhood racial composition item.

2.3.5. Depressive symptoms

The Center for Epidemiological Studies-Depression Scale (CES-D) is a widely used measure of depressive symptoms that demonstrates excellent construct validity (Radloff, 1977) and has been used in studies with pregnant AA individuals with good internal reliability (Giurgescu et al., 2016; Saadat et al., 2022). This measure included 20 items inquiring about depressive symptoms experienced within the past week (e.g., I felt sad, I felt that everything I did was an effort, I had crying spells) on a 4-point scale (0 = Rarely or none of the time to 3 = Most or all of the time). The total score ranges from 0 to 60. Higher scores signify a larger number of symptoms. In this sample, the Cronbach's alpha was 0.82.

2.3.6. Systemic inflammation during pregnancy

IFN-γ, IL-6, IL-8, TNF-α, and IL-10 were measured using V-plex multiplex assays (Meso Diagnostics, Rockville MD). MIF was analyzed separately using a U-plex assay (Meso Diagnostics, Rockville MD). All blood samples from the same participant were run on the same assay

plate and all samples were run in duplicate. Samples with coefficients of variation (CVs) greater than 15% were rerun. The percentage of values that were missing due to high CVs or being above curve fit range after being rerun were 0.9%, 0.3%, 0.6%, 1.7%, 2.7%, and 1.1% for IFN-γ, IL-6, IL-8, IL-10, MIF, and TNF-α, respectively. The minimum detection limit for these assays was 4.3 pg/mL for MIF and ≤0.06 pg/mL for all other cytokines. Intra-assay coefficients of variation were 5.1%, 4.4%, 3.0%, 5.2%, 5.6%, and 4.1% for IFN-γ, IL-6, IL-8, IL-10, MIF, and TNF-α, respectively. Inter-assay coefficients of variation averaged across mid and high-calibration curve values for MIF and low and mid-calibration curve values for all other cytokines were 12.1%, 8.5%, 5.8%, 7.2%,11%, and 10.2% for IFN- γ, IL-6, IL-8, IL-10, MIF, and TNF-α, respectively.

2.4. Analysis

All cytokines were log 10 (x+1) transformed to correct for positive skew. Outliers that were greater than 3 standard deviations (SDs) from the mean were winsorized (i.e., replaced with the value at 3 SDs for each cytokine). Descriptive statistics were generated for all variables and covariates and distributions were examined. Maternal age, gestational age at data collection, BMI, CES-D, and socioeconomic variables were assessed for inclusion as covariates in all models because of their known relationships with inflammation (Christian et al., 2009; Gillespie et al., 2016; Hulsegge et al., 2016; Keenan-Devlin et al., 2022; Shin et al., 2017). Covariates that were determined to change the magnitude of associations by 10 percent or more were controlled for in regression models. To assess whether neighborhood racial composition or the EOD predicted cytokine levels, multivariate multiple regression models were utilized that treated the EOD and neighborhood racial composition each as predictors and all cytokines (IFN-γ, IL-6, IL-8, IL-10, MIF, TNF-α) as dependents. Significant associations were explored at additional time-points during pregnancy to confirm these findings using both multivariate and multilevel models. For multilevel models, a subject-level random intercept was set with time (gestational age in weeks) entered uncentered at level 1. Between-person continuous variables were grand mean centered and entered alongside dichotomous variables and gestational age at study entry at level 2. Multilevel models were estimated with restricted maximum likelihood. IBM SPSS Statistics for Windows (Version 28.0. Armonk, NY: IBM Corp) and SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) were used for all analyses.

3. Results

3.1. Maternal characteristics

Three hundred and thirty-five individuals had complete data for systemic inflammation for the third timepoint (30–36 weeks gestation). Participants had a mean age of 26.7 ± 5.7 years and a mean gestational age of 32.5 ± 1.8 weeks at the time of blood draw for the third time-point. Almost half of participants (46.7%) reported an annual household income of less than $10,000. Subjects had a CES-D mean score of 16.7 ± 10.2. Participants most frequently reported experiencing racial discrimination in the domains of getting service at a store or restaurant (31%), in public settings (29%), from the police or in court (20.9%), and at work (18.5%). The majority of subjects reported living in neighborhoods composed of mostly (38.2%) or some (40.1%) AAs. Approximately half of participants were 1) employed at the time of data collection (48.2%) and 2) had graduated high school or obtained a GED (47.6%). Demographics and plasma cytokine levels are presented in Table 1.

The EOD scores were positively correlated with maternal age, education level, and CES-D scores. Participants with an annual household income between $10,000 and $29,999 tended to have lower levels of IFN-γ and MIF. Maternal age was negatively correlated with IFN-γ and positively correlated with IL-8. Education level was positively correlated with IL-6 and IL-8. Gestational age at data collection was positively correlated with IL-6 and IL-10. BMI was positively correlated with IL-6 and TNF-α, and negatively correlated with IL-10. Neighborhood racial composition was not significantly correlated with any covariates.

Table 1
Descriptive statistics (n = 335).

Variable	N	Mean (SD)
Maternal age (years)	332	26.70 (5.74)
Gestational age at data collection (weeks)	326	32.5 (1.79)
BMI (kg/m^2)	306	31.51 (9.89)
CES-D	328	16.70 (10.18)
EOD	330	3.90 (5.9)
IFN-γ (pg/mL)[a]	335	1.12 (0.59)
IL-6 (pg/mL)[a]	335	0.62 (0.28)
IL-8 (pg/mL)[a]	335	1.12 (0.38)
IL-10 (pg/mL)[a]	335	0.26 (0.16)
MIF (pg/mL)[a]	335	10.71 (0.75)
TNF-α (pg/mL)[a]	335	0.83 (0.18)
Variable		**Number (%)**
Annual household income	330	
<$10,000		154 (46.7)
$10,000–19,999		56 (17)
$20,000–29,999		56 (17)
$30,000–39,999		37 (11.2)
$40,000–59,999		16 (4.8)
>$60,000		11 (3.3)
Education	330	
Less than high school		53 (16.1)
Graduated high school or GED		157 (47.6)
Technical/vocational training		30 (9.1)
Some college		71 (21.5)
Associate degree		11 (3.3)
Bachelor's degree or higher		8 (2.4)
Neighborhood racial composition	319	
Almost all AA		34 (10.7)
Mostly AA		122 (38.2)
Some AA		128 (40.1)
Mostly White		24 (7.5)
Almost all White		11 (3.4)
Work status	330	
Employed		159 (48.2)
Temporarily laid off		10 (3)
Unemployed		161 (48.8)

AA = African American.
BMI=Body Mass Index.
CES-D = Center for Epidemiological Studies Depression Scale.
EOD = Lifetime Experiences of Discrimination Scale Frequency Score.
[a] $\log_{10}$ (x+1) transformation.

3.2. Bivariate associations among neighborhood racial composition, experiences of discrimination, and cytokine levels

Spearman rank-order associations for neighborhood racial composition (higher proportion of white neighbors), lifetime experiences of racial discrimination, and cytokines are shown in Table 2.

Neighborhood racial composition or living in neighborhoods with a higher proportion of white individuals was positively correlated with MIF ($\rho = 0.28$, $p < 0.001$) and negatively correlated with IL-6 ($\rho = -0.12$, $p = 0.02$). The EOD score was positively correlated with MIF ($\rho = 0.18$, $p < 0.001$). Neighborhood racial composition and the EOD were not correlated in this sample. Many cytokines were significantly correlated with each other (see Table 2).

3.3. EOD predicting cytokine levels

The overall multivariate test for the unadjusted model with the EOD predicting all cytokines as dependents was not significant ($F = 1.649$ (6323), $p = 0.13$). However, the univariate test for MIF was significant ($F = 5.171$ (1328), $p = 0.02$, $R^2 = 0.02$), with the frequency of lifetime experiences of discrimination ($\beta = 0.141$, $SE = 0.062$, $p = 0.02$) being a

Table 2
Associations among neighborhood racial composition (higher proportion of white neighbors), experiences of discrimination, cytokines (n = 335).

	1.	2.	3.	4.	5.	6.	7.
1. Neighborhood racial composition	1.00	–	–	–	–	–	–
2. Experiences of discrimination	−0.05	1.00	–	–	–	–	–
3. IFN-γ	−0.01	0.04	1.00	–	–	–	–
4. IL-6	**−0.12***	0.01	**0.28***	1.00	–	–	–
5. IL-8	0.04	0.06	**0.11***	**0.26***	1.00	–	–
6. IL-10	−0.09	−0.10	**0.36***	**0.23***	**0.11***	1.00	–
7. MIF	**0.28***	**0.18***	−0.02	−0.03	**0.41***	0.02	1.00
8. TNF-α	0.01	0.10	**0.16***	**0.19***	**0.26***	0.08	**0.31***

Note. Plasma cytokine levels (pg/mL) were $\log_{10}$ (x+1) transformed. *$p < 0.05$.

significant predictor of MIF levels. No other cytokines were significantly predicted by the EOD.

All covariates apart from the CES-D and work status changed the magnitude of associations by 10 percent or more. Thus, the model was rerun adjusting for maternal age, annual household income, BMI, education level, and gestational age at data collection. The overall covariate-adjusted multivariate multiple regression, which treated the EOD as a predictor and all cytokines as dependents, was now significant (F = 2.94 (42,1728), p < 0.001). The EOD was not a significant predictor of cytokine levels (p = 0.2). The univariate test for MIF was not significant in this adjusted model (p = 0.07). However, the EOD was still significantly associated with MIF (β = 0.141, SE = 0.07, p = 0.036). For each one standard deviation increase of the EOD score, participants had 0.14 standard deviations increase in MIF levels. The EOD was not significantly associated with any cytokines apart from MIF. The univariate test for IL-6 was significant (F = 9.12 (7288), p < 0.001, R^2 = 0.18). This was largely accounted for by its association with BMI (β = 0.362, SE = 0.053, p < 0.001). The univariate test for IL-10 was also significant (F = 2.09 (7288), p = 0.044, R^2 = 0.05), but there were no predictors significantly associated with IL-10 (see Table 3).

Table 3
Multivariate regression results: Parameter estimates of lifetime experiences of discrimination (EOD) and covariates (n = 288).

Dependent Variable	Parameter	β	SE	t	p
IFN-γ	*EOD*	*.045*	*.066*	*0.675*	*.500*
	Maternal age	*−.121*	*.064*	*−1.898*	*.059*
	Gestational age at data collection	*.046*	*.061*	*0.757*	*.449*
	BMI	*−.022*	*.059*	*−0.367*	*.714*
	Education[a]	*.162*	*.143*	*1.135*	*.258*
	Annual household income mid[a]	*−.137*	*.138*	*−0.988*	*.324*
	Annual household income high[a]	*.217*	*.166*	*1.312*	*.191*
IL-6	*EOD*	*.019*	*.060*	*0.320*	*.749*
	Maternal age	*−.064*	*.058*	*−1.118*	*.264*
	Gestational age at data collection	***.159***	*.055*	*2.897*	***.004***
	BMI	***.362***	*.053*	*6.826*	***< .001***
	Education[a]	*−.039*	*.128*	*−0.303*	*.762*
	Annual household income mid[a]	*−.002*	*.124*	*−0.019*	*.985*
	Annual household income high[a]	***.356***	*.149*	*2.387*	***.018***
IL-8	*EOD*	*.032*	*.066*	*0.490*	*.625*
	Maternal age	*.064*	*.064*	*0.998*	*.319*
	Gestational age at data collection	*.116*	*.061*	*1.896*	*.059*
	BMI	*.068*	*.059*	*1.151*	*.251*
	Education[a]	*.173*	*.143*	*1.209*	*.227*
	Annual household income mid[a]	*−.073*	*.138*	*−0.532*	*.595*
	Annual household income high[a]	*.030*	*.166*	*0.181*	*.856*
IL-10	*EOD*	*−.077*	*.065*	*−1.176*	*.240*
	Maternal age	*−.113*	*.063*	*−1.782*	*.076*
	Gestational age at data collection	*.096*	*.060*	*1.601*	*.110*
	BMI	*−.105*	*.058*	*−1.806*	*.072*
	Education[a]	*.159*	*.141*	*1.129*	*.260*
	Annual household income mid[a]	*−.098*	*.137*	*−0.718*	*.473*
	Annual household income high[a]	*.123*	*.164*	*0.753*	*.452*
MIF	*EOD*	***.141***	*.067*	*2.112*	***.036***
	Maternal age	*.013*	*.065*	*0.206*	*.837*
	Gestational age at data collection	*−.016*	*.062*	*−0.254*	*.800*
	BMI	*.003*	*.060*	*0.048*	*.962*
	Education[a]	*−.120*	*.144*	*−0.830*	*.407*
	Annual household income mid[a]	*.015*	*.140*	*0.109*	*.913*
	Annual household income high[a]	***.441***	*.168*	*2.632*	***.009***
TNF-α	*EOD*	*.055*	*.067*	*0.815*	*.416*
	Maternal age	*−.063*	*.065*	*−0.963*	*.336*
	Gestational age at data collection	*.010*	*.062*	*0.157*	*.876*
	BMI	***.141***	*.060*	*2.355*	***.019***
	Education[a]	*.282*	*.145*	*1.941*	*.053*
	Annual household income mid[a]	*−.233*	*.141*	*−1.653*	*.099*
	Annual household income high[a]	*−.170*	*.169*	*−1.006*	*.315*

Note. Bold indicates p < 0.05.
EOD = Experiences of Discrimination (frequency score).
BMI=Body Mass Index.
[a] Partially standardized estimate.

3.4. Neighborhood racial composition predicting cytokine levels

The overall multivariate test for the unadjusted model with neighborhood racial composition as a predictor and all cytokines as dependents was significant (F = 6.372 (6312), p < 0.001). The univariate test for MIF was significant (F = 28.88 (1317), p < 0.001, R^2 = 0.08), with neighborhood racial composition (b = 0.588, SE = 0.109, p < 0.001) being a significant predictor of MIF levels. No other cytokines were significantly predicted by neighborhood racial composition (proportion of White people in the neighborhood).

For the adjusted model, all covariates apart from the CES-D and work status changed the magnitude of associations by 10 percent or more. Thus, the model was rerun adjusting for maternal age, annual household income, BMI, education level, and gestational age at data collection. The overall covariate-adjusted multivariate multiple regression, which treated neighborhood racial composition as a predictor and all cytokines as dependents, was significant (F = 3.39 (42,1662), p < 0.001). The proportion of White people in the neighborhood still significantly predicted cytokine levels (F = 5.423 (6272), p < 0.001). The univariate test for MIF was significant (F = 5.06 (7277), p < 0.001, R^2 = 0.11). Participants that reported living in neighborhoods with more White individuals had significantly higher levels of MIF compared to participants living in neighborhoods with more AAs (b = 0.599, SE = 0.12, p < 0.001). The univariate test for IL-6 was now significant (F = 9.09 (7277), p < 0.001, R^2 = 0.18). This was largely accounted for by its association with BMI (β = 0.366, SE = 0.055, p < 0.001). The univariate test for IL-10 was also now significant (F = 2.09 (7277), p = 0.045, R^2 = 0.05). However, no predictors were significantly associated with IL-10 (see Table 4).

3.5. Post hoc analysis of neighborhood racial composition categories predicting MIF

To explore which group differences accounted for the significant relationship observed between living in neighborhoods with a higher proportion of White people and MIF in both adjusted and unadjusted models, a multiple linear regression was run that used the original five categories of the neighborhood racial composition item. The neighborhood categories of “almost all AA” and “mostly AA” were treated as reference groups and the same covariates were adjusted for. Post hoc

Table 4
Multivariate regression results: Parameter estimates of neighborhood racial composition and covariates (n = 277).

Dependent Variable	Parameter	β	SE	t	p
IFN-γ	*Neighborhood racial composition*[a]	−.094	.120	−0.785	.433
	Maternal age	−.112	.065	−1.717	.087
	Gestational age at data collection	.053	.062	0.848	.397
	BMI	−.010	.061	−0.163	.871
	Education[a]	.120	.145	0.826	.409
	Annual household income mid[a]	−.116	.141	−0.822	.412
	Annual household income high[a]	.238	.167	1.424	.156
IL-6	*Neighborhood racial composition*[a]	−.145	.108	−1.345	.180
	Maternal age	−.037	.059	−0.627	.531
	Gestational age at data collection	**.165**	.056	2.951	**.003**
	BMI	**.366**	.055	6.720	**< .001**
	Education[a]	−.100	.130	−0.768	.443
	Annual household income mid[a]	.021	.126	0.165	.869
	Annual household income high[a]	**.374**	.150	2.491	**.013**
IL-8	*Neighborhood racial composition*[a]	.045	.120	0.375	.708
	Maternal age	.063	.065	0.967	.334
	Gestational age at data collection	**.127**	.062	2.036	**.043**
	BMI	.087	.061	1.431	.154
	Education[a]	.180	.145	1.241	.215
	Annual household income mid[a]	−.100	.141	−0.709	.479
	Annual household income high[a]	.005	.168	0.028	.977
IL-10	*Neighborhood racial composition*[a]	−.153	.118	−1.295	.196
	Maternal age	−.112	.064	−1.735	.084
	Gestational age at data collection	.111	.061	1.809	.071
	BMI	−.089	.060	−1.480	.140
	Education[a]	.091	.142	0.640	.523
	Annual household income mid[a]	−.073	.139	−0.528	.598
	Annual household income high[a]	.155	.165	0.939	.349
MIF	*Neighborhood racial composition*[a]	**.599**	.118	5.067	**< .001**
	Maternal age	−.020	.064	−0.317	.752
	Gestational age at data collection	−.010	.061	−0.157	.875
	BMI	.004	.060	0.068	.946
	Education[a]	.073	.142	0.514	.608
	Annual household income mid[a]	−.084	.139	−0.606	.545
	Annual household income high[a]	**.380**	.165	2.308	**.022**
TNF-α	*Neighborhood racial composition*[a]	.025	.123	0.202	.840
	Maternal age	−.049	.067	−0.731	.465
	Gestational age at data collection	−.006	.064	−0.100	.921
	BMI	**.131**	.063	2.097	**.037**
	Education[a]	**.293**	.149	1.974	**.049**
	Annual household income mid[a]	−.275	.145	−1.897	.059
	Annual household income high[a]	−.189	.172	−1.102	.272

Note. Bold indicates p < 0.05.
BMI=Body Mass Index.
[a] Partially standardized estimate.

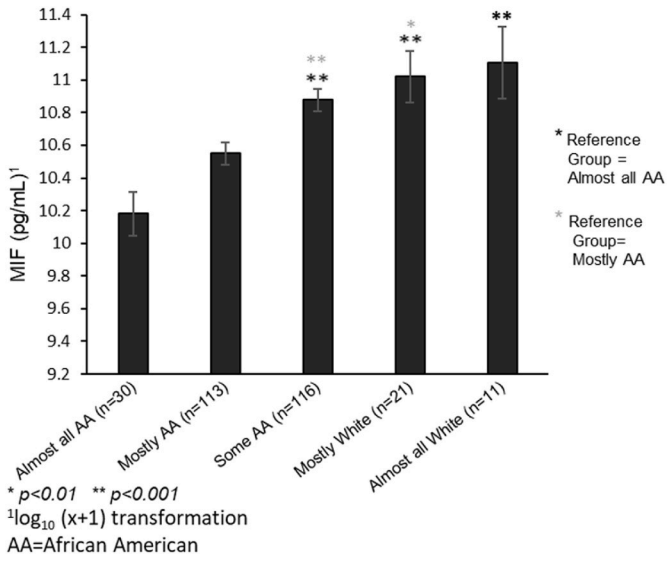

Fig. 1. MIF mean levels by neighborhood racial composition group.

comparisons revealed that participants living in neighborhoods with mostly White individuals had significantly higher levels of MIF compared to participants living in neighborhoods with almost all AAs (b = 1.132, SE = 0.28, p < 0.001) or mostly AAs (b = 0.636, SE = 0.233, p = 0.007). In addition, participants living in neighborhoods with some AAs had significantly higher levels of MIF compared to participants living in neighborhoods with almost all AAs (b = 0.937, SE = 0.21, p < 0.001) or mostly AAs (b = 0.441, SE = 0.13, p < 0.001). Finally, participants living in neighborhoods with almost all White individuals had significantly higher levels of MIF than participants living in neighborhoods with almost all AAs (b = 1.244, SE = 0.34, p < 0.001) (see Fig. 1). All differences reported withstood Bonferroni adjustment for multiple comparisons (p < 0.05).

3.6. Exploratory analyses of neighborhood racial composition predicting MIF at other timepoints during pregnancy

To confirm whether neighborhood racial composition also predicted MIF levels at other timepoints during pregnancy, a multivariate multiple regression was first utilized with the dichotomized neighborhood racial composition item predicting MIF levels at timepoint 1 (8–18 weeks gestation), timepoint 2 (19–29 weeks gestation), and timepoint 3 (30–36 weeks gestation). Because the univariate test for MIF in the adjusted model was only significant for the model with neighborhood racial composition (tested at timepoint 3), only neighborhood racial composition was examined as a predictor of MIF levels at these additional timepoints during pregnancy. For the adjusted model, all covariates apart from education level and work status changed the magnitude of associations by 10 percent or more. Thus, the model included maternal age, annual household income, BMI, the CES-D, and gestational age at data collection as covariates. The overall multivariate test was significant (F (21,408) = 3.05, p < 0.001). In addition, all univariate tests for MIF were significant: timepoint 1 (F (7,136) = 2.61, p = 0.015, adjusted R^2 = 0.07), timepoint 2 (F (7,136) = 2.35, p = 0.03, adjusted R^2 = 0.06), timepoint 3 (F (7,136) = 9.62, p < 0.001, adjusted R^2 = 0.297). Similar to our initial analysis, neighborhood racial composition significantly predicted higher MIF levels at each timepoint: timepoint 1 (b = 0.463, SE = 0.16, p = 0.004), timepoint 2 (b = 0.620, SE = 0.19, p = 0.001), timepoint 3 (b = 1.035, SE = 0.15, p < 0.001). Hence, living in a neighborhood with more White people was associated with higher MIF levels in AA individuals; this was seen at all three timepoints of pregnancy and was most evident in late pregnancy.

To ascertain whether neighborhood composition was predictive of MIF levels in early pregnancy in the full sample that had MIF data at any timepoint (N = 466), a two-level multilevel model with a subject-level random intercept was employed. Time (gestational age in weeks) was entered uncentered at level 1 and neighborhood racial composition and prior covariates (maternal age, BMI, CES-D, household income) were entered alongside gestational age at study entry at level 2. There was a significant linear trend in MIF trajectories over time (b = 0.0051, SE = 0.0023, p = 0.025). Both neighborhood racial composition (b = 0.274, SE = 0.062, p < 0.0001) and the CES-D (b = 0.0063, SE = 0.003, p = 0.03) significantly predicted MIF levels in early pregnancy. Specifically, participants reporting living in neighborhoods composed of a higher proportion of White individuals had MIF levels that were on average 0.273 pg/mL higher in early pregnancy compared to participants reporting living in neighborhoods composed of mostly or all AAs. In addition, for every unit increase in the CES-D score from the mean score, MIF levels were 0.006 pg/mL higher in early pregnancy.

4. Discussion

Greater experiences of lifetime racial discrimination were associated with higher levels of the pro-inflammatory cytokine MIF. Our finding is consistent with prior studies finding a positive association between racial discrimination and systemic inflammation in both non-pregnant

and pregnant minority populations (Brody et al., 2015; Cunningham et al., 2012; Gillespie et al., 2021; Giurgescu et al., 2016). In addition, neighborhood racial composition was a significant predictor of MIF in both the overall adjusted and unadjusted multivariate models. Participants that reported living in neighborhoods with increasing proportions of White individuals had higher levels of MIF. These differences were significant when comparing participants living in neighborhoods with almost all AAs to participants living in neighborhoods 1) with some AAs, 2) with mostly White individuals, and 3) with almost all White individuals, and when comparing participants living in neighborhoods with mostly AAs to 1) some AAs and 2) mostly White individuals. This relationship was evident at all three timepoints during pregnancy, suggesting that these associations were not spurious. Interestingly, this relationship was much stronger later in pregnancy, with neighborhood racial composition predicting between 4–5x the amount of the variance of MIF in late pregnancy (29.7% of the variance) compared to mid-pregnancy (6% of the variance) or early pregnancy (7% of the variance).

The lack of significant associations found between either predictor with cytokines other than MIF could be due to MIF's unique properties (Calandra and Roger, 2003). MIF is a cytokine that is constitutively expressed by various types of immune cells and has the distinctive role of counter-regulating the anti-inflammatory actions of GCs (Calandra and Roger, 2003). MIF is released under conditions of stress and promotes glucocorticoid resistance in immune cells (Aeberli et al., 2006), thereby reducing the anti-inflammatory effects of GCs. Moreover, unlike other pro-inflammatory cytokines, the secretion of MIF is induced rather than suppressed by the release of GCs (Calandra et al., 1995). Notably, MIF is secreted by tissues and glands integral to the stress response (e.g., anterior pituitary gland) (Calandra and Bucala, 2017), and has been observed to be elevated in the context of either acute or chronic stress (Calandra et al., 1995; Hawkley et al., 2007). Higher MIF levels have also been observed to be associated with increased risk of preterm birth (Pearce et al., 2008). Specifically, MIF levels were significantly higher in early to mid-pregnancy for individuals that later went on to give birth preterm in this relatively large, nested case-control study (Pearce et al., 2008). Individuals with higher versus lower MIF levels, dichotomized based on a cutoff determined from receiver operating curve analysis, were also found to have over 3 times greater odds of preterm delivery (Pearce et al., 2008). Hence, apart from being a pro-inflammatory cytokine implicated in preterm birth risk, MIF levels appear tightly and positively linked to stress. Studies have reported higher post-vaccine MIF production in depressed pregnant persons and substantially higher levels of MIF being observed for depressed individuals (Christian et al., 2010; Edwards et al., 2010). This connection between elevated MIF and chronic stress or depression is concordant with the present findings of higher MIF levels being associated with 1) greater lifetime experiences of racial discrimination exposure during the third trimester of pregnancy and 2) higher levels of depressive symptoms in early pregnancy.

Our findings of increased MIF levels in pregnant AA participants living in neighborhoods with a higher proportion of White people suggest that there may be some aspect of living with more White people that is eliciting stress for these individuals. Although experiences of racial discrimination and neighborhood racial composition were not correlated in this sample, this could be partly due to the racial discrimination measure utilized in this study measuring across multiple domains and being a broad lifetime measure versus a specific assessment of racial discrimination at the time of survey completion. Future studies are needed to gather more specific information on racial discrimination and stress at a neighborhood level to elucidate this point. Other potential explanations for the association found between MIF and neighborhood racial composition could be that the subjective neighborhood racial composition measure used in the present study is capturing aspects of related constructs known to be sources of chronic stress for AA individuals, such as worry about racial discrimination. For instance, AA women have been found to be more likely to report anticipated and vicarious racial discrimination when it is directed against close others (family members, members of their social network) than against themselves (Nuru-Jeter et al., 2009; Woods-Giscombé et al., 2015). This suggests that this extension of worry may be a more prevalent stressor compared to personally experienced racial discrimination, as the EOD was measuring in the present study. Given that worry about racial discrimination has been associated with preterm birth (Braveman et al., 2017), it would be important for future studies across pregnancy to examine the relevancy of this construct to our observed findings.

Alternatively, there may be stress-buffering effects of living in proximity with individuals of the same minority racial group. As opposed to objective measures of neighborhood context that may capture negative aspects of this construct (e.g., concentrated poverty, structural racism, poorer neighborhood quality, reduced access to socioeconomic resources), the subjective measure used in this study may reflect protective facets, such as social capital and neighborhood social cohesion. In support of this possibility, both social capital and social cohesion have been found to differ by measures of neighborhood racial composition (Collins et al., 2017; Hutchinson et al., 2009; Neal and Neal, 2014). Social capital – i.e., the aspects of societal structures (interpersonal trust, norms of reciprocity, social networks) that serve as resources for personal and collective benefit (Carpiano, 2006; Putnam, 1993) – has been found to interact with neighborhood racial composition in the prediction of health outcomes (Hutchinson et al., 2009).

Neighborhood social cohesion – i.e., "the degree of connectedness and solidarity in a community" (Kawachi and Berkman, 2000) – has been found to be higher among neighborhoods with a higher proportion of AAs among a sample of multiethnic neighborhoods when controlling for concentrated disadvantage (Walker and Brisson, 2017). Such cohesion has also been found to mitigate the harmful consequences of stress associated with living in disadvantaged neighborhoods (Henderson et al., 2016). Important to our present finding, neighborhood social cohesion has also been found to be negatively associated with inflammation among AA women (Neergheen et al., 2019). This agrees with a sizable body of evidence supporting a stress-buffering effect of social integration on inflammation, and the theory that social safety attenuates pro-inflammatory processes (Slavich, 2020; Uchino et al., 2018). Living in a neighborhood that is perceived as more cohesive or supportive would be expected to have more prominent stress-buffering effects at the end of pregnancy when such social resources would be more proximal and likely to be drawn upon. However, future investigation of whether perceived neighborhood racial composition relates to MIF levels via these distinct but related constructs across pregnancy among AA individuals is needed to address such possibilities.

4.1. Limitations and future directions

There are several limitations of this study worth noting. First, the annual household income of the population used in this study was strongly skewed, with over 60% of participants having an income of $19,999 or less. This limits the generalizability of these findings. Second, a small portion of participants did not have BMI data available. However, due to the lack of association between MIF and BMI in this sample and that the results of the unadjusted model were largely unchanged with the addition of BMI as a covariate, it is unlikely the addition of these individuals would have altered the present findings. Last, using a *current* neighborhood racial composition item alongside a *lifetime* experiences of discrimination scale might have hindered our ability to find an association between the two constructs due to differing timelines of assessment.

To the authors' awareness, this study is the first to look at the relationship between any measure of neighborhood racial composition and inflammatory cytokines among pregnant AA individuals. Given that elevations of pro-inflammatory cytokines and MIF have been observed in cases of preterm birth (Lyon et al., 2010; Pearce et al., 2008; Von Minckwitz et al., 2000), the higher levels of MIF seen here for

participants in neighborhoods with more White individuals and for participants reporting more lifetime experiences of racial discrimination may have negative implications for pregnancy outcomes that should be examined in future studies. Although no associations were observed here between the EOD or CES-D scores with neighborhood racial composition, it is possible that these variables may interact in the prediction of MIF concentrations. For instance, the relationships found between either experiences of racial discrimination or depressive symptoms with MIF could be stronger for individuals living in neighborhoods with more White individuals. This would be in accordance with the possibility that the measure used in the present study captures protective or stress-buffering aspects of this construct, such as neighborhood social cohesion. This possibility needs to be assessed in future analyses. Considering MIF's counter regulation of GC's and cortisol's potential role in birth timing (Calandra and Roger, 2003; McLean et al., 1995), it would also be important to examine whether elevations in MIF reflect alterations in overall or diurnal cortisol production and how this might relate to preterm birth risk. Finally, investigation of the distinct dimensions of neighborhood composition, along with intermediary variables such as social cohesion and worry about racial discrimination, is needed to clarify what is driving the relationship observed between neighborhood racial composition and MIF.

5. Conclusion

This study evaluated the relationships between pertinent psychosocial variables and cytokines among pregnant AA individuals and found an association between levels of the pro-inflammatory cytokine MIF with 1) living in neighborhoods composed of more White individuals, 2) higher reported lifetime experiences of racial discrimination, and 3) higher levels of depressive symptoms at the beginning of pregnancy. This relationship between living in neighborhoods with a larger proportion of White people and MIF was consistently observed at additional timepoints during pregnancy and was notably stronger in late pregnancy. Given MIF's role as a pro-inflammatory cytokine and its known association with negative birth outcomes, these findings bring attention to the importance of considering neighborhood context alongside distinctive stressors frequently experienced by AA individuals for identifying factors that influence biological indicators of preterm birth risk. Future studies are needed to discern which specific aspects of the neighborhood racial composition construct utilized in this study account for this finding and whether its relationship with MIF across pregnancy informs pregnancy outcomes.

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CRediT authorship contribution statement

Molly A. Wright: Conceptualization, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Carmen Giurgescu:** Data curation, Funding acquisition, Investigation, Project administration, Resources, Supervision, Visualization, Writing – review & editing. **Dawn P. Misra:** Data curation, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. **Jaime C. Slaughter-Acey:** Methodology, Supervision, Writing – review & editing. **Christopher G. Engeland:** Data curation, Resources, Supervision, Visualization, Writing – review & editing.

Declaration of competing interest

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

Data availability

Data collection recently completed and dataset is not able to be made available at this time.

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