The role of neighborhood deprivation in the cervicovaginal microbiota

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BACKGROUND: *Lactobacillus*-deficient cervicovaginal microbiota is associated with spontaneous preterm birth and is more common among Black individuals. Persistent racial segregation in the United States has led to differential neighborhood exposures by race that can affect pregnancy outcomes. The extent to which neighborhood exposures may explain racial differences in the cervicovaginal microbiota is unknown.

OBJECTIVE: This study aimed to determine whether neighborhood deprivation, defined as material community deprivation, is associated with a *Lactobacillus*-deficient cervicovaginal microbiota in a prospective cohort of pregnant individuals. Our hypothesis was that racial differences in neighborhood deprivation may explain the higher prevalence of *Lactobacillus*-deficient cervicovaginal microbiota in Black birthing people.

STUDY DESIGN: This study analyzed data from Motherhood and Microbiome, a prospective pregnancy cohort enrolled from prenatal clinics in a single hospital system 2013–2016 in which a *Lactobacillus*-deficient cervicovaginal microbiota was previously shown to be associated with spontaneous preterm birth. This study geocoded addresses to obtain census tract neighborhood deprivation data from the Brokamp Nationwide Community Deprivation Index that uses weighted proportions of poverty, income, public assistance, lack of health insurance, and vacant housing. Generalized linear mixed models quantified associations of deprivation with the cervicovaginal microbiota accounting for geographic clustering by census tract and potential confounders. Because of different distributions of neighborhood deprivation and the cervicovaginal microbiota, race-stratified models were used. Mediation analyses quantified the extent to which deprivation may contribute to racial differences in the cervicovaginal microbiota.

RESULTS: Higher neighborhood deprivation was associated with a *Lactobacillus*-deficient cervicovaginal microbiota. Per standard deviation increment of deprivation, participants had 28% higher adjusted odds (adjusted odds ratio, 1.28; 95% confidence interval, 1.04–1.58) of a *Lactobacillus*-deficient microbiota. Black participants had higher odds of a *Lactobacillus*-deficient microbiota than White participants (adjusted odds ratio, 4.00; 95% confidence interval, 2.05–8.26), and mediation analysis revealed that deprivation accounted for 22% (P=.046) of that disparity.

CONCLUSION: Neighborhood deprivation was associated with *Lactobacillus-deficient* cervicovaginal microbiota and may partially explain Black-White disparities in the cervicovaginal microbiota. Mechanistic studies to explore how environmental exposures modify the cervicovaginal microbiota are warranted to identify novel opportunities for future interventional strategies to prevent preterm birth. As the findings demonstrate a potential biological effect from neighborhood conditions, policies that drive urban planning should be explored to improve pregnancy outcomes.

Key words: cervicovaginal microbiota, mediation analysis, neighborhood deprivation, pregnancy, preterm birth, racial disparities, vaginal microbiome

Introduction

Preterm birth (PTB) disproportionately affects non-Hispanic Black families in the United States with Black infants born before term 50% more often than White infants.[1] Race is a social construct that serves as a proxy for several exposures in life that differ by race because of racism.[2,3] Although Black populations in the United States have higher rates of PTB, recent research has demonstrated that racial disparity in PTB is largely environmental, as opposed to genetic, in origin.[4–6] Racial segregation has led to differential environmental stressors by race.[7] However, how environmental stressors, such as neighborhood deprivation, which differ by race, lead to racial differences in PTB risk remains unknown.

Neighborhood deprivation indices are summary measures of multiple area-level factors that indicate resources in a neighborhood and often include poverty rates, educational attainment, and other factors, such as housing and employment.[8] Adverse neighborhood exposures, which can track with deprivation, including violent crime, have been shown to be associated with PTB and low birthweight risk in previous studies.[9–13] However, these studies do not measure molecular biomarkers or mechanisms by which neighborhoods may contribute to PTB risk.

The cervicovaginal microbiota is clustered into distinct community state types (CSTs) based on the dominating species of bacteria.[14] CST IV, which is characterized by a paucity of *Lactobacillus* species and dominance of anaerobes, such as *Gardnerella vaginalis*, is associated with spontaneous PTB (sPTB) and may be mechanistically involved in sPTB via cervical epithelial barrier disruption.[15–17] In a previously conducted, prospective, race-matched, nested, case-control study, Motherhood and Microbiome (M&M), 48% of participants with sPTB had *Lactobacillus*-deficient cervicovaginal microbiota compared with 35% of participants with term births.[18] Although environmental stressors increase the risk of PTB[19–24] and animal evidence supports the concept that environmental stressors can affect the vaginal microbiota,[25] it is unclear

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AJOG MFM at a Glance

Why was this study conducted?

Lactobacillus-deficient cervicovaginal microbiota has been previously shown to be associated with spontaneous preterm birth and to be more common among Black pregnant people. The extent to which racial differences in neighborhood conditions may contribute to the disparity in *Lactobacillus*-deficient cervicovaginal microbiota is unknown.

Key findings

In a Philadelphia-based study, census tract neighborhood deprivation was associated with a *Lactobacillus*-deficient cervicovaginal microbiota.

What does this add to what is known?

Mediation analysis revealed that neighborhood deprivation may contribute to racial disparities in the cervicovaginal microbiota.

whether or how exposures might modify the vaginal microbiota in humans. In humans, low socioeconomic position[8,26–28] and stress[29] have been shown to be associated with bacterial vaginosis, which is a clinical condition consistent with *Lactobacillus*-deficient cervicovaginal microbiota (CST IV), suggesting that environmental stressors may affect the microbiota, perhaps via inflammation and immunomodulation.[30]

This study aimed to explore the possible associations of neighborhood deprivation, defined as material community deprivation, with a *Lactobacillus*-deficient cervicovaginal microbiota (CST IV) and to explore the extent to which higher levels of neighborhood deprivation among Black individuals contribute to racial disparities in colonization with a *Lactobacillus*-deficient cervicovaginal microbiota.

Materials and Methods

Study population

We analyzed data from the prospective cohort, M&M,[18] following the Strengthening the Reporting of Observational Studies in Epidemiology statement.[31] M&M is a prospectively enrolled pregnancy cohort of singleton pregnancies with births from April 23, 2014, to March 3, 2017, during the course of prenatal care at Penn Medicine in Philadelphia; details are published elsewhere.[18,32–35] A flow diagram demonstrating the derivation of the analytical dataset is presented in Supplemental Figure. The institutional review board of the University of Pennsylvania approved the study (protocol number: 818914), and participants signed the informed consent.

Exposure—neighborhood deprivation

To obtain neighborhood deprivation levels, individual addresses were geocoded using ArcGIS (version 10.5.1; Esri, Redlands, CA) to link to a nationwide material community deprivation index that included census tract 2015 American Community Survey data.[36] The index ranges from 0 to 1 (a higher index indicates more deprivation) and includes median household income, the fraction of residents who were below the poverty line, completed high school, received public assistance income or food stamps, and the fraction of vacant housing.[37]

Outcome—*Lactobacillus*-deficient cervicovaginal microbiota

As previously reported, the composition of the cervicovaginal microbiota was characterized using 16S rRNA gene sequencing from swabs obtained at 16 to 20 weeks of gestation.[14,18,38–40] Samples from each sPTB case and 4 race-matched full-term controls were analyzed. Briefly, polymerase chain reaction amplification of the V3 to V4 regions of the 16S rRNA gene was sequenced.[41] CSTs were assigned using VALENCIA, a novel nearest centroid classification algorithm based on the classification of more than 13,000 vaginal microbiota datasets.[42] CST IV is characterized by a paucity of *Lactobacillus* and an overrepresentation of a wide array of anaerobic bacteria. Here, as the word community could be conflated with neighborhood exposures, we, henceforth, use *Lactobacillus*-deficient microbiota instead of CST terminology where appropriate.

Covariates

Covariates were obtained with questionnaires and medical record review. Race and ethnicity were self-reported and then combined into mutually exclusive race and ethnicitycategories. Individuals with racial and ethnic identities other than non-Hispanic Black and White were combined into a single "other" category because of small numbers.

Statistical analysis

We performed descriptive and bivariate analyses to compare the average neighborhood deprivation index among participants with and without *Lactobacillus*-deficient cervicovaginal microbiota. In other words, we compared individuals with CST IV with those with all other CSTs. In addition, we analyzed bivariate associations of each outcome with quartiles of deprivation. We performed generalized linear mixed-effects regression models to account for geographic clustering of individuals within census tracts to model associations of deprivation with the odds of *Lactobacillus*-deficient cervicovaginal microbiota compared with *Lactobacillus*-dominant microbiota, adjusting for variables, including age, parity, insurance, and race and ethnicity. These variables were chosen a priori because of their associations with sPTB. Moreover, we used race-stratified models because of large differences in both neighborhood deprivation and *Lactobacillus*-deficient cervicovaginal microbiota to determine whether associations were similar among non-Hispanic Black (Black) and non-Hispanic White (White) individuals. We tested for interaction to determine if associations by race differed statistically. Stratification and interaction testing assess differential responses to a variable that may imply differential susceptibility. In

contrast, causal mediation analysis methods can quantify the extent to which a variable may explain an association between exposures and outcomes, often from different doses of exposure.[43] Causal mediation methods address confounding between the exposures and outcomes, exposures and mediators, and mediators and outcomes.[44] We used mediation methods to quantify the extent to which neighborhood deprivation might explain racial disparities in *Lactobacillus*-deficient cervicovaginal microbiota. All analyses were performed using R (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria; 2022-10-31 ucrt).

Results

Neighborhood deprivation varied across Philadelphia (Figure 1) and was higher among Black individuals than White individuals (Figure 2). In the analytical dataset, most individuals identified as Black, and most participants were not privately insured (Table 1). We compared participants included and excluded from the current study because of either missing neighborhood deprivation (n=17) or lack of microbiota data (n=1312); only a subset of M&M participants were chosen to have microbiota analyzed for the original study.[18] Compared with excluded M&M participants, included M&M participants were more likely to have sPTB, be overweight or obese, and identify as Black (Supplemental Table).

In bivariate analysis, with each increase in the deprivation quartile, the proportion of participants with *Lactobacillus*-deficient microbiota increased (Figure 3). Moreover, the mean neighborhood deprivation levels were higher among those with *Lactobacillus*-deficient microbiota (0.53 [standard deviation (SD), 0.13]) than those with *Lactobacillus*-dominant microbiota (0.44 [SD, 0.17]) ($P<.0001$) (Table 1). Generalized linear mixed-effects models accounting for clustering by census tract revealed similar findings; per SD increment of deprivation, participants had 73% higher odds of *Lactobacillus*-deficient microbiota (unadjusted odds ratio [OR], 1.73; 95% confidence interval [CI], 1.46−2.06) (Table 2). In models adjusted for age, parity, body mass index, race, and insurance, associations attenuated but persisted; per SD increment of neighborhood deprivation, participants had 28% higher odds of *Lactobacillus*-deficient microbiota (adjusted OR [aOR], 1.28; 95% CI, 1.04−1.58) (Table 2). Point estimates were similar in race-stratified models but lacked statistical significance with CIs crossing 1 (Black participants: aOR, 1.25; 95% CI, 0.99−1.59; White participants: aOR, 1.33; 95% CI, 0.71−2.49). We did not detect an interaction

FIGURE 1
Neighborhood deprivation across Philadelphia, 2015

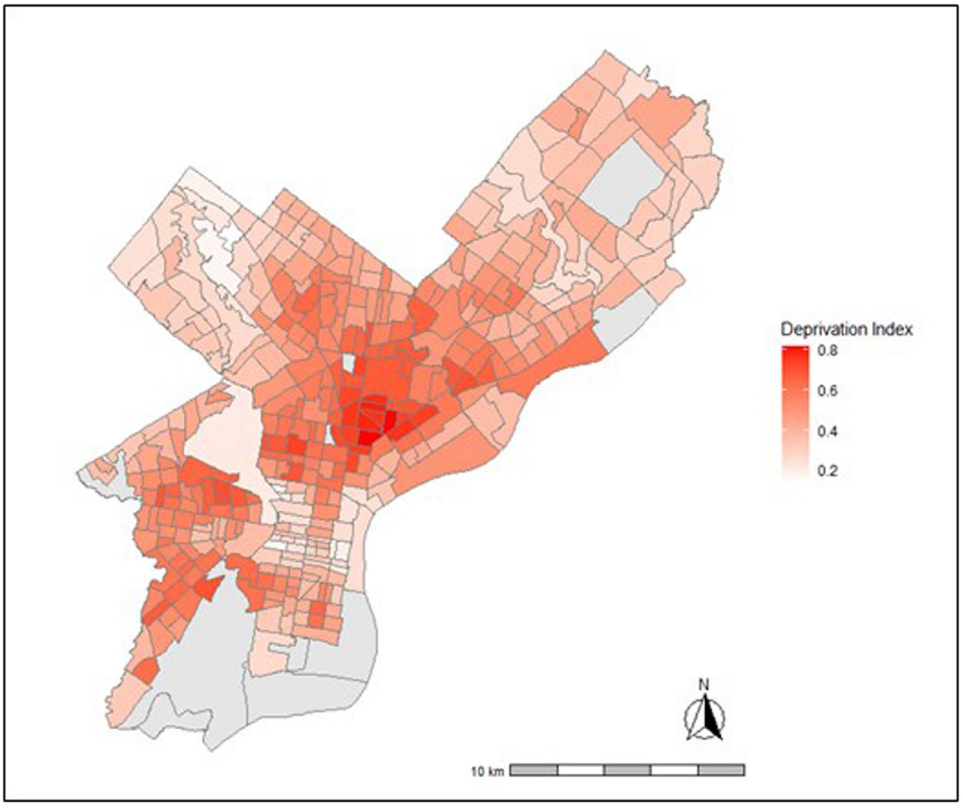

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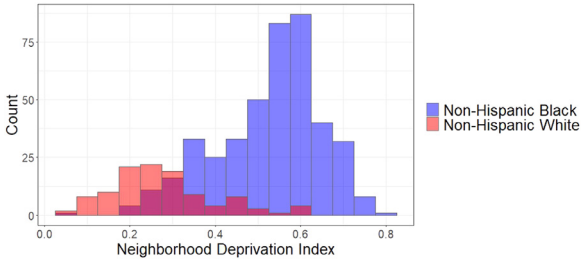
FIGURE 2
Black-White disparities in neighborhood deprivation (424 Black and 111 White participants)



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between race and deprivation on the outcome of *Lactobacillus*-deficient microbiota in unadjusted (*P*=.894) or adjusted (*P*=.996) models.

As previously published, there were racial disparities in *Lactobacillus*-deficient cervicovaginal microbiota[18]; in adjusted models, Black participants had 4-fold higher odds of *Lactobacillus*-deficient cervicovaginal microbiota than White participants (aOR, 4.00; 95% CI, 2.05–8.26). When neighborhood deprivation was introduced to the adjusted model, the association between race and *Lactobacillus*-deficient cervicovaginal microbiota was attenuated (aOR, 2.99;

TABLE 1
Characteristics of Motherhood & Microbiome pregnancy cohort, Philadelphia, Pennsylvania, 2013–2017

Characteristic	Overall (N=581) n (%)	*Lactobacillus*-deficient cervicovaginal microbiota (CST IV) (n=224) n (%)	*Lactobacillus*-dominant cervicovaginal microbiota (other CSTs) (n=357) n (%)	*P* value
Age (y)				<.001
<25	178 (30.6)	87 (38.8)	91 (25.5)	
25 to <35	302 (52.0)	113 (50.4)	189 (52.9)	
≥35	101 (17.4)	24 (10.7)	77 (21.6)	
Race and ethnicity				<.001
Non-Hispanic Black	424 (73.0)	199 (88.8)	225 (63.0)	
Non-Hispanic White	111 (19.1)	13 (5.8)	98 (27.5)	
Other[a]	46 (7.9)	12 (5.4)	34 (9.5)	
Private insurance	274 (47.2)	70 (31.3)	204 (57.1)	<.001
Body mass index (kg/m^2)				
<25	197 (33.9)	61 (27.2)	136 (38.1)	.005
25 to < 30	162 (27.9)	60 (26.8)	102 (28.6)	
≥30	222 (38.2)	103 (46.0)	119 (33.3)	
Nulliparous	245 (42.2)	87 (38.8)	158 (44.3)	.23
Smoked in pregnancy	47 (8.1)	24 (10.7)	23 (6.4)	.09
Neighborhood deprivation, mean (SD)	0.47 (0.16)	0.53 (0.13)	0.44 (0.17)	<.001
Birth outcome				.02
Term	421 (72.5)	148 (66.1)	273 (76.5)	
Spontaneous preterm	103 (17.7)	49 (21.9)	54 (15.1)	
Medically indicated preterm	57 (9.8)	27 (12.1)	30 (8.4)	

CST characterizes the vaginal microbiota.

BMI, body mass index; *CST*, community state type; SD, standard deviation.

[a] Other race and ethnicity: Hispanic (n=23), non-Hispanic Asian (n=21), and other, not specified (n=2)

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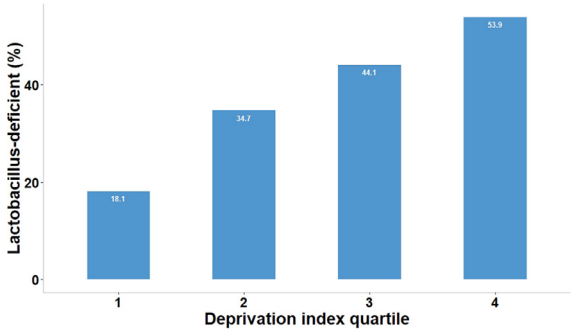
FIGURE 3
Proportion of participants (n=581) with *Lactobacillus*-deficient cervicovaginal microbiota per neighborhood deprivation quartile



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95% CI, 1.39−6.40). Subsequently, we tested for whether there was significant mediation and found that 22% of the association between non-Hispanic Black race and ethnicity and *Lactobacillus*-deficient cervicovaginal microbiota was mediated by neighborhood deprivation differences between Black and White participants (*P*=.046).

Comment

Principal findings

In a racially diverse cohort of pregnant individuals, we found that neighborhood deprivation is associated with a *Lactobacillus*-deficient cervicovaginal microbiota, known to confer increased risk of sPTB. Importantly, we found that racial differences in neighborhood deprivation may partially explain racial disparities in the presence of *Lactobacillus*-deficient cervicovaginal microbiota.

TABLE 2
Unadjusted and adjusted associations of neighborhood deprivation with *Lactobacillus*-deficient cervicovaginal microbiota (community state type IV) in the Motherhood and Microbiome

Model	OR (95% CI)
All participants (N=581)	
M1: unadjusted	1.73 (1.46−2.06)
M2: age, parity, BMI, and insurance	1.43 (1.18−1.74)
M3: M2 + race and ethnicity	1.28 (1.04−1.58)
Race-stratified models	
Non-Hispanic Black (n=424)	
M1: unadjusted	1.34 (1.07−1.67)
M2: age, parity, BMI, and insurance	1.25 (0.99−1.58)
Non-Hispanic White (n=111)[a]	
M1: unadjusted	1.28 (0.73−2.24)
M2: age, parity, BMI, and insurance	1.33 (0.71−2.49)

Estimates are per standard deviation increment of deprivation.

BMI, body mass index; *CI*, confidence interval; *OR*, odds ratio.

[a] Robust standard errors instead of random effect for lack of convergence.

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Results in the context of what is known

Our study is consistent with others that have shown that neighborhood is important concerning reproductive health, specifically PTB risk.[9−13] However, to the best of our knowledge, no previous study has linked neighborhood to the cervicovaginal microbiota. Multiple reports have previously established that individuals colonized with vaginal microbiota that lack *Lactobacillus* dominance are at higher risk of PTB[15,16,18,45] and are more likely to identify as Black.[14,18,46] In a 2011 study to describe the cervicovaginal microbiota, Ravel et al[14] investigated the vaginal microbiome of 396 nonpregnant, reproductive-age women in Atlanta and Baltimore and found that *Lactobacillus* was the dominant genus for most people. They reported significant racial differences in microbial profiles; *Lactobacillus* dominance was found in 89.7% of White individuals but only 61.9% of Black individuals. These results were similar to a study by Zhou et al,[46] which demonstrated racial differences in the vaginal microbiota of 75 White and 69 African American menstruating individuals from 5 centers across North America. Specifically, anaerobic species dominated the vaginal microbiota more often among Black subjects (32%) than White subjects (8%). Environmental contributions to microbiota differences were not examined. M&M is the first pregnancy cohort large and racially diverse enough to test rigorously whether racial differences in the likelihood of colonization with a *Lactobacillus*-deficient microbiota in pregnancy may be because of environmental exposures. Adding to the evidence that environmental exposures can affect the cervicovaginal microbiota, we recently reported that air pollution was also associated with a *Lactobacillus*-deficient cervicovaginal microbiota.[47] However, overall, there is a paucity of data exploring how exposures might influence the

cervicovaginal microbiota and contribute to adverse pregnancy outcomes.

There is evidence that other aspects of the human microbiome are environmentally responsive. Rosenfeld postulated that environmental exposures could lead directly to changes in the gut microbiota or could change host immunologic and inflammatory status, making it more or less welcoming to specific bacterial species or genera.[48] Multiple animal studies demonstrate gut microbiota disruption in response to arsenic,[49−53] lead,[54−56] and particulate matters.[57,58] A study of 44 healthy adults in Chicago demonstrated that lower neighborhood socioeconomic status was associated with reduced diversity of the gut microbiota.[59] Hierarchical linear regression models revealed that as socioeconomic status of an individual's residential census tract decreased, so did the alpha diversity of the microbiota. Furthermore, neighborhood socioeconomic status explained 12% to 18% of the variability in the diversity of the gut microbiota.

Research in animal models suggests that environmental stress during pregnancy (a risk factor for human PTB[19−24]) can affect vaginal microbiota composition. In a pregnant mouse model, stressed dams (fox odor, restraint, constant light, saturated bedding, and novel object exposure) had significantly lower vaginal *Lactobacillus* abundance than control dams.[25] Providing support for this finding in humans, low socioeconomic position[26−28] and stress[29] have been shown to be associated with *Lactobacillus*-deficient cervicovaginal microbiota. Amabebe and Anumba[30] proposed that stress-induced cortisol production alters the vaginal microenvironment through changes to nuclear factor kappa B−mediated cytokine activity interrupting the balance of *Lactobacillus* and anaerobes. Area-level exposures, such as neighborhood deprivation,[60] may alter vaginal microbiota through immune modulation. In a previous analysis of M&M, we found that individuals with both high perceived stress and low β-defensin 2 levels (an innate immune marker) had increased odds of sPTB.[35] Collectively, these findings suggest that lived experiences and environmental exposures may modify the cervicovaginal microbiota. If replicated and validated, then reducing the harmful exposures and/or targeting the microbiome-host interactions may prove to be a new strategy to reduce PTB.

Clinical implications

Given persistent racial disparities in many adverse pregnancy outcomes, including sPTB, it is necessary to understand how lived experiences drive biological pathways that contribute to sPTB. Clinically, Black race has been used as a risk factor for PTB.[61] However, given that socioeconomic position and race often determine where Americans live, it follows that environmental exposures differ by race.[6,7,62−66] Longstanding residential segregation has led to Black families disproportionately living in neighborhoods with higher concentrations of deprivation and is one striking example of structural racism.[67,68] Historically and continuing today, certain policies in the United States have contributed to residential segregation.[69] Practices, such as redlining, result in systematic disinvestment in predominantly Black neighborhoods. The effect of this practice on reproductive health is now evident with higher PTB rates in historically redlined neighborhoods.[70,71] Reducing racial disparity in PTB and other adverse pregnancy outcomes will require mitigating harmful exposures and supporting beneficial exposures in predominantly Black neighborhoods. Revealing how environmental stressors can affect biological pathways should serve as further impetus for policymakers to implement policies and practices to reduce disparities and adverse outcomes outside of standard medical care. Policies, such as the Earned Income Tax Credit or other efforts to relieve neighborhood deprivation, could be explored.

Research implications

Many unanswered questions remain about the link between environmental stressors from neighborhood conditions and the cervicovaginal microbiota. From a translational perspective, there are opportunities to delineate mechanistic pathways between environmental exposures and reproductive tract function. Such exploration would enable the development of therapeutics to interrupt pathophysiological processes to improve outcomes for individuals who come into pregnancy with lifetimes of environmental exposures. From a public health policy perspective, additional research studies on the effect of environmental interventions on health are needed to prioritize resource allocation to improve outcomes.

Strengths and limitations

The strengths of this study include the use of multilevel modeling to account for area-level and individual-level factors in addition to using a prospectively enrolled cohort with molecular phenotyping (microbiota). Rigorous collection of covariates allowed for confounder adjustment. The limitations of this study include threats to generalizability, given the use of a single site. Although our data link 1 composite, area-level variable—neighborhood deprivation—to the cervicovaginal microbiota, we did not examine the multitude of other environmental factors to which people are exposed before and during pregnancy. There are key assumptions inherent to mediation methods if causal inference is desired. Specifically, 1 assumption is "sequential ignorability," which means that the preexisting covariates and the treatment are independent of all potential values of the outcome and mediating variables.[72] Moreover, it requires that the observed mediator is independent of all potential outcomes given the observed treatment and pretreatment covariates. As we are not confident that the sequential ignorability assumption holds in our analysis, we do not claim that deprivation is truly on the causal pathway between self-identified race and the vaginal microbiota. We recognize that it may be a proxy for a set of variables that could be causal. Our sample size may have lacked power; statistical significance was not reached in race-stratified models, but point estimates were similar compared with the primary analysis

demonstrating significant associations of deprivation with *Lactobacillus*-deficient microbiota. Moreover, we did not detect significant interaction between race and deprivation in the microbiota. Overall, this means that, regardless of race, neighborhood deprivation is associated with the cervicovaginal microbiota.

Conclusions

Our study found that neighborhood deprivation is associated with a cervicovaginal microbiota characterized by a paucity of *Lactobacillus* species, a known risk factor for sPTB. Neighborhood deprivation may partially explain racial disparities in the cervicovaginal microbiota. More research is needed to explore causal links between neighborhood environment and biological changes that contribute to PTB risk. Such findings could have substantial urban planning policy implications for cities working toward birth outcome equity. ■

CRediT authorship contribution statement

Heather H. Burris: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Nancy Yang:** Formal analysis, Visualization, Writing – review & editing. **Valerie Riis:** Data curation, Investigation, Project administration, Validation, Writing – review & editing. **Linda Valeri:** Methodology, Supervision, Writing – review & editing. **Eugenia C. South:** Conceptualization, Funding acquisition, Writing – review & editing. **Jacques Ravel:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. **Michal A. Elovitz:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. ■

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ajogmf.2024.101291.

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