

Differential effects of stress and African ancestry on preterm birth and related traits among US born and immigrant Black mothers

Hui-Ju Tsai, MPH, PhD^{a,b,c,*}, Pamela J. Surkan, ScD^{d,e}, Stella M. Yu, ScD^f, Deanna Caruso, MS^e, Xiumei Hong, PhD^e, Tami R. Bartell, BS^g, Anastacia D. Wahl, MD^h, Claire Sampankanpanich, MD^e, Anne Reily, PhD^e, Barry S. Zuckerman, MD^h, Xiaobin Wang, MD, ScD^{e,i}

Abstract

Preterm birth (PTB, <37 weeks of gestation) is influenced by a wide range of environmental, genetic and psychosocial factors, and their interactions. However, the individual and joint effects of genetic factors and psychosocial stress on PTB have remained largely unexplored among U.S. born versus immigrant mothers.

We studied 1121 African American women from the Boston Birth Cohort enrolled from 1998 to 2008. Regression-based analyses were performed to examine the individual and joint effects of genetic ancestry and stress (including lifetime stress [LS] and stress during pregnancy [PS]) on PTB and related traits among U.S. born and immigrant mothers.

Significant associations between LS and PTB and related traits were found in the total study population and in immigrant mothers, including gestational age, birthweight, PTB, and spontaneous PTB; but no association was found in U.S. born mothers. Furthermore, significant joint associations of LS (or PS) and African ancestral proportion (AAP) on PTB were found in immigrant mothers, but not in U.S. born mothers.

Although, overall, immigrant women had lower rates of PTB compared to U.S. born women, our study is one of the first to identify a subset of immigrant women could be at significantly increased risk of PTB and related outcomes if they have high AAP and are under high LS or PS. In light of the growing number of immigrant mothers in the U.S., our findings may have important clinical and public health implications.

Abbreviations: AAP = African ancestral proportion, AIM = ancestry informative marker, BMI = body mass index, LBW = low birthweight, LS = lifetime stress, PS = stress during pregnancy, PTB = preterm birth, SES = socioeconomics.

Keywords: genetic ancestry, preterm birth, stress

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^a Division of Biostatistics and Bioinformatics, Institute of Population Health Sciences, National Health Research Institutes, Zhunan, ^b Department of Public Health, China Medical University, Taichung, Taiwan., ^c Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, ^d Department of International Health, Bloomberg School of Public Health, ^e Center on the Early Life Origins of Disease, Department of Population, Family and Reproductive Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, ^f Global Health and Education Projects, Inc., Riverdale, MD, ^g Ann & Robert H. Lurie Children's Hospital of Chicago, Stanley Manne Children's Research Institute, Chicago, IL, ^h Department of Pediatrics, Boston University School of Medicine and Boston Medical Center, Boston, MA, ⁱ Division of General Pediatrics and Adolescent Medicine, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

* Correspondence: Hui-Ju Tsai, Division of Biostatistics and Bioinformatics, Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan (e-mail: tsaihj@nhri.org.tw; h-tsai@northwestern.edu).

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1. Introduction

Preterm birth (PTB) is commonly defined as a baby born before 37 weeks of gestation.^[1] In spite of unprecedented advancements in biomedical research, the rate of PTB remains high in the U.S. at about 12.5%.^[2] PTB threatens our children across racial groups, particularly African Americans (17.8% compared to 11.5% in non-Hispanic Whites). PTB is the major cause of neonatal mortality and postnatal morbidity, with an annual societal economic burden in the U.S. estimated to be at least \$26.2 billion in 2005.^[2]

As underscored by the Institute of Medicine report in 2006 and demonstrated by ours and other groups,^[3,4] PTB is the final outcome of multiple pathogenic pathways, including intrauterine infection/inflammation, uteroplacental thrombosis and intrauterine vascular lesions associated with fetal stress or decidual hemorrhage, uterine over-distension, and cervical insufficiency. These potential pathogenic pathways may individually and/or jointly affect PTB.

There is also compelling evidence that PTB is influenced by a wide range of environmental, genetic and social factors, and their interactions.^[1,5-7] For many years, research on the causative factors of PTB has primarily focused on demographic, social-behavioral, and environmental risk factors.^[2] Among those, stress is one of the known environmental risk factors associated with PTB. For example, previous results from animal studies have demonstrated that chronic stress in pregnant rats can lead to precursors of PTB such as weight loss and increased blood pressure, etc.^[8] Furthermore, observational studies have suggested that depression, anxiety, and other psychopathologies during pregnancy are positively associated with an increased risk of PTB.^[9,10]

In addition to stress, numerous studies, including our work and the work of other groups, have documented that genetics play a role in influencing the development of PTB.^[7,11,12] For example, Tsai et al^[6] found that a higher proportion of African ancestry is associated with an elevated risk of PTB and related adverse pregnancy outcomes in African American mothers. In addition, Manuck et al^[13] applied an admixture mapping approach and identified a susceptibility locus residing on chromosome 7 among African American mothers with spontaneous PTB. However, the effects of genetic ancestry, stress, and their interaction on PTB have remained largely unexplored. Furthermore, limited research has focused on determining the interplay of ancestry and stress on PTB and adverse pregnancy outcomes among U.S. born and immigrant Black women, separately.

In the present study, we analyzed 1121 African American women (628 U.S. born and 493 immigrant Black women), a subset of the Boston Birth Cohort with available data on African ancestry proportion. We aimed to examine the individual effect of genetic ancestry and stress and their joint effect on PTB and related adverse outcomes on U.S. born and immigrant Black women.

2. Materials and Methods

2.1. Study population and data collection

We included 1121 African American mothers (628 U.S. born mothers and 493 immigrant Black mothers) who were part of the Boston Birth Cohort enrolled from October 1998 to February 2008.^[11] PTB case mothers were defined as those who delivered singleton, live births occurring at less than 37 weeks of gestation; and term controls were defined as mothers delivering at greater than or equal to 37 weeks of gestation with birthweight

appropriate for gestational age as defined by the National Center for Health Statistics/CDC guidelines (birthweight between 2500 and 4000g).^[14] Of note, PTB case mothers and controls were matched by maternal age (± 5 years). In this study, there were 72 term babies whose birthweights were less than 2500g and 49 term babies whose birthweights were more than 4000g. We did not exclude them from subsequent analyses. Pregnancies resulting in multiple births and newborns with major birth defects were excluded. Epidemiologic data and clinical data were collected using a standardized questionnaire. In detail, epidemiologic data were collected based on a standardized questionnaire, including various aspects, for example, demographic information and socioeconomic status; information about this index pregnancy; and information about the allergic history of the baby's father and mother, reproductive history, daily physical activity, lifetime stress (LS) and stress during pregnancy (PS), home environment, smoking, alcohol drinking and drug use, dietary history, and history of medication use. We also collected venous blood samples among study participants. A detailed description of the study population and previous findings in publications derived from the same study population are described elsewhere.^[6,7,11,15] The Institutional Review Boards of Boston Medical Center, the Massachusetts Department of Public Health, Ann & Robert H. Lurie Children's Hospital of Chicago, and the Johns Hopkins Bloomberg School of Public Health approved the study protocol, and all participants gave written informed consent.

2.2. Definition of preterm birth and other key related subgroups

PTB: PTB was evaluated as a binary outcome (<37 weeks of gestation vs ≥ 37 weeks of gestation). In particular, gestational age was assessed using an algorithm based on last menstrual period and the result of an early ultrasound (<20 weeks of gestation). The last menstrual period estimate was used only if confirmed by ultrasound within 7 days or if no ultrasound estimate was obtained; otherwise, the ultrasound estimate was used. This approach has been used in previous studies.^[11,16]

PTB-related subgroups investigated in this study were defined as follows:

- (1) By mode of delivery: we categorized PTB cases as spontaneous PTB (delivered vaginally or by Cesarean section) if they occurred secondary to documented active preterm labor (uterine contractions with cervical effacement and dilation at <37 weeks), preterm premature rupture of membranes (<37 weeks without uterine contractions), or by both uterine contractions and preterm premature rupture of membranes occurring simultaneously, or as medically induced PTB, defined as a delivery (vaginally or by Cesarean section) that was not preceded by the presence of uterine contractions and/or rupture of membranes.
- (2) By degree of prematurity: in this study, we used a cut point of <32 weeks to define very PTB and 34 0/7–36 6/7 weeks to define late PTB, which has been used by other groups.^[17,18]
- (3) By major pregnancy complications: because of sample size constraints, we focused on 2 relatively common pregnancy complications: PTB with intrauterine infection/inflammation using placental histologic chorioamnionitis as a proxy—detailed description of placental collection, pathological methods, definition of maternal and fetal inflammatory responses, and quality control has been published previously;^[19] and PTB complicated by maternal hypertensive disorders—this group

consisted of PTB cases with an accompanying diagnosis of maternal preeclampsia, eclampsia, gestational hypertension, or HELLP syndrome as defined in our previous publication,^[20] with or without a history of chronic hypertension.

Of note, all of the above PTB-related key subgroups were defined by physician diagnosis and confirmed by a review of prenatal care records in accordance with published clinical studies.^[21] In addition, low birthweight (LBW) was defined as infant birthweight less than 2500 g.

2.3. Lifetime stress and stress during pregnancy

The examined stress related variables included: LS and PS, respectively. Information about LS and PS was collected using a standardized questionnaire. In detail, LS and PS were defined according to the following 2 questions: “How would you characterize the amount of stress in your life in general?” and “How would you characterize the amount of stress in your life during pregnancy?” Three response options to these 2 questions were provided to participating mothers: “Not stressful,” “Average stressful,” and “Very stressful.” We coded “Not stressful” and “Average stressful” as low stress, and “Very stressful” as high stress in the subsequent analyses.

2.4. Genotyping

We applied the Illumina (San Diego, CA) African American Panel (http://support.illumina.com/array/array_kits/african_american_admixture_panel.htm), which consists of 1509 ancestry informative markers (AIMs) identified as highly informative between West African and European ancestry,^[22,23] as the genotyping platform for 1130 African American mothers (460 PTB cases and 670 controls). For quality control, 4 duplicate DNA samples were randomly selected and placed on each 96-well plate. The concordance rate of these duplicate samples was >99.5%. In addition, 48 AIMs with low call rates were excluded from the subsequent ancestral estimation. Furthermore, we examined whether the 1509 AIMs were under Hardy–Weinberg equilibrium; 20 AIMs that were out of Hardy–Weinberg equilibrium ($P < 0.01$) were excluded. As a result, a total of 1441 AIMs were used for ancestral estimation.

2.5. Statistical analysis

We computed and compared the distributions of the demographic and clinical characteristics of our study participants, stratified by U.S. born and immigrant mothers, respectively. Specifically, the examined demographic and clinical characteristics were listed as follows: age, prepregnancy body mass index (BMI), gestational age, infants’ birthweight, educational levels (primary school, middle school, high school, some college and college degree, or above), marital status (married, unmarried, and other), parity (0 and ≥ 1), maternal smoking status (yes/no), maternal illicit drug use (yes/no), and maternal alcohol use (yes/no), separately. Of note, maternal smoking status, maternal illicit drug use, and maternal alcohol use were defined as binary variables and adjusted in the subsequent analyses.

Next, we estimated African ancestral proportion (AAP) for each subject using genotyping data from AIMs and the Structure program,^[24,25] and examined the distribution’s equivalence of AAP between U.S. born and immigrant mothers using the Kolmogorov–Smirnov statistic, a nonparametric method for testing the equality of underlying probability distributions in 1 sample or between 2 samples.^[26] We applied linear and logistic

regression models, separately, to test the association of AAP, LS, and PS, individually, on PTB and related traits, stratified by U.S. born and immigrant mothers and with and without covariate adjustment. Due to the highly skewed distribution of AAP, we recoded AAP into quartiles and treated AAP as an ordinal variable in the model. To examine the joint effect between LS and AAP, we first included a product term of LS and AAP into the regression models. Next, an ordinal variable for joint association between LS and AAP was coded: low versus low, low versus high, or high versus low, and high versus high. We then performed regression models to test joint association between LS and AAP on PTB and related traits, stratified by U.S. born and immigrant mothers, with and without covariate adjustment. Of note, the group of “low versus low” was treated as the reference group in the model. Similarly, we repeated the analyses for assessing the joint association between PS and AAP. The list of adjusted covariates included maternal age, baby’s sex, parity, educational levels, marital status, smoking status, maternal illicit drug use, maternal alcohol use, and prepregnancy BMI, respectively.

All data analyses were conducted with R project software, version 3.1.1 (<http://www.r-project.org/>) and STATA 11.0 software (StataCorp, College Station, TX). P values less than 0.05 were declared to be statistically significant.

3. Results

3.1. Demographic and clinical characteristics and African ancestral proportion of study participants

A total of 1121 African American mothers (628 U.S. born mothers and 493 immigrant Black mothers) were included in this study. Table 1 presents the demographic and clinical data examined in this study, stratified by U.S. born and immigrant mothers. Of note, the rates of unmarried status, maternal smoking, maternal illicit drug use, maternal alcohol use, PTB, and LBW in U.S. born mothers were higher than those in immigrant mothers (Table 1). In addition, Fig. 1 shows that the distribution of AAP in U.S. born mothers was significantly different to the distribution in immigrant mothers ($P < 10^{-3}$).

3.2. Association of stress and African ancestral proportion with PTB and related traits

We investigated the associations of LS, PS, and AAP, respectively, with PTB and related traits across the total study population of U.S. born and immigrant mothers (Table 2). The results in Table 2 show significant inverse associations between LS and PTB and related traits among all study participants, including gestational age and birthweight; and positive association between LS and PTB and related traits in PTB, spontaneous PTB, induced PTB, and very PTB. Similarly, significant inverse associations between LS and PTB and related traits in immigrant mothers, including gestational age and birthweight; and positive association between LS and PTB and related traits in PTB, spontaneous PTB, and late PTB. No associations were found in U.S. born mothers.

Similarly, when examining the association of PS with PTB and related traits, significant associations of PS with gestational age, birthweight, PTB, spontaneous PTB, induced PTB, very PTB, and late PTB were observed among the total study population. Significant associations of PS with gestational age, birthweight, PTB, induced PTB, and late PTB were also observed in immigrant mothers, but no association was found for U.S. born mothers (Table 2). Moreover, when assessing the association of AAP with PTB and related adverse pregnancy outcomes, significant

Table 1**Demographic and clinical characteristics of the study population, stratified by U.S. born versus immigrant mothers.**

| Variable | U.S. born mothers | Immigrant mothers | <i>P</i> ^a |
|---|-------------------|-------------------|-----------------------|
| N | 628 | 493 | |
| Maternal age, years (mean ± SD) | 25.81 ± 6.49 | 30.18 ± 6.33 | <0.001 |
| Prepregnancy BMI, kg/m ² (mean ± SD) | 26.70 ± 6.94 | 26.21 ± 5.53 | 0.20 |
| Gestational age, weeks (mean ± SD) | 36.46 ± 4.01 | 37.54 ± 3.73 | <0.001 |
| Birthweight, g (mean ± SD) | 2606.81 ± 840.66 | 2881.29 ± 845.20 | <0.001 |
| Highest education completed, n, % | | | <0.001 |
| Primary school | 6 (1.0) | 21 (4.3) | |
| Middle school | 194 (31.0) | 95 (19.4) | |
| High school | 255 (40.8) | 167 (34.1) | |
| Some college | 140 (22.4) | 127 (25.9) | |
| College degree or above | 30 (4.8) | 80 (16.3) | |
| Marital status, n, % | | | <0.001 |
| Married | 66 (10.6) | 223 (45.5) | |
| Unmarried | 551 (88.6) | 255 (52.0) | |
| Other | 5 (0.8) | 12 (2.5) | |
| Parity, n, % | | | 0.04 |
| 0 | 242 (38.5) | 192 (38.9) | |
| >=1 | 386 (61.5) | 301 (61.1) | |
| Maternal smoking, n, % | | | <0.001 |
| Never | 369 (58.8) | 460 (93.3) | |
| Quit | 96 (15.2) | 17 (3.5) | |
| Current | 163 (26.0) | 16 (3.2) | |
| Maternal illicit drug use, n, % | | | <0.001 |
| No | 450 (72.0) | 477 (97.0) | |
| Yes | 175 (28.0) | 15 (3.0) | |
| Maternal alcohol use, n, % | | | <0.001 |
| No | 570 (91.0) | 483 (98.0) | |
| Yes | 56 (9.0) | 10 (2.0) | |
| Preterm birth, n, % | | | <0.001 |
| No | 327 (52.2) | 336 (68.2) | |
| Yes | 300 (47.9) | 157 (31.8) | |
| Low birthweight, n, % | | | <0.001 |
| No | 365 (58.1) | 361 (73.2) | |
| Yes | 263 (41.9) | 132 (26.8) | |

BMI = body mass index, SD = standard deviation.

^a *P* value <0.05 is in bold.

associations of AAP with PTB, spontaneous PTB, late PTB, and LBW, separately, were observed in immigrant mothers. A significant association was also found between AAP and LBW but only among the total study population; no association was found for U.S. born mothers (Table 2). Of note, approximately half of the significant associations became nonsignificant after

adjusting the following covariates: maternal age, prepregnancy BMI, marital status, parity, educational level, baby's sex, illicit drug use, maternal smoking, and maternal alcohol use.

3.3. Joint association of lifetime stress and African ancestral proportion with PTB and related traits

Table 3 shows the joint association of LS and AAP with PTB and related traits in U.S. born and immigrant mothers, respectively. In the group of immigrant mothers, a significant interaction of LS and AAP was found with birthweight ($P=0.02$), PTB ($P=0.004$), spontaneous PTB ($P=0.001$), late PTB ($P=0.009$), and LBW ($P=0.009$). Specifically, participants with high LS and high AAP had a significantly increased risk of developing PTB, spontaneous PTB, late PTB, and LBW, and had significantly lower birthweight compared to those with low LS and low AAP. In contrast, no significant joint associations for LS and AAP with PTB and related traits were found in U.S. born mothers (Table 3).

3.4. Joint association of stress during pregnancy and African ancestral proportion with PTB and related traits

We also investigated the joint association of PS and AAP with PTB and related traits in U.S. born and immigrant mothers. The

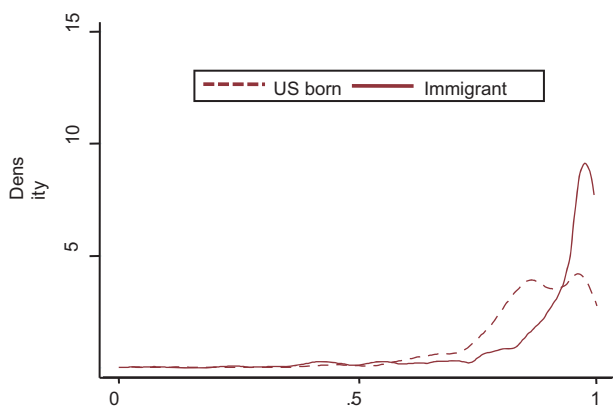


Figure 1. Distribution of African ancestral proportion in U.S. born and immigrant mothers.

Table 2 The association of LS, PS, and African ancestral proportion, individually, with preterm birth-related traits.

| | Total study population | | | U.S. born mothers | | | Immigrant mothers | | |
|---------------------------|--------------------------------------|--------------------------------------|--------------------------------------|-----------------------|-------------------------|-----------------------|--------------------------------------|-------------------------|-----------------------|
| | Crude β [SE]/P | Adjusted β [SE]/P* | AOR [95% CI]/P | Crude β [SE]/P | Adjusted β [SE]/P | AOR [95% CI]/P | Crude β [SE]/P | Adjusted β [SE]/P | AOR [95% CI]/P |
| LS | | | | | | | | | |
| Gestational age | -0.75 (0.17)/ 10^{-3} | -0.54 (0.20)/ 10^{-3} | -131.71 (43.94)/ 10^{-3} | -0.55 (0.24)/0.02 | -0.41 (0.28)/0.14 | -95.99 (57.52)/0.10 | -0.70 (0.25)/ 6×10^{-3} | -0.62 (0.30)/0.04 | -146.90 (69.20)/0.03 |
| Birthweight | -186.34 (37.54)/ 10^{-3} | -131.71 (43.94)/ 10^{-3} | -131.71 (43.94)/ 10^{-3} | -130.85 (50.68)/0.01 | -95.99 (57.52)/0.10 | -95.99 (57.52)/0.10 | -176.96 (57.72)/ 2×10^{-3} | -146.90 (69.20)/0.03 | -146.90 (69.20)/0.03 |
| Preterm birth | | | | | | | | | |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Yes | 1.44 [1.20-1.72]/ 10^{-3} | 1.34 [1.08-1.66]/ 7×10^{-3} | 1.34 [1.08-1.66]/ 7×10^{-3} | 1.20 [0.95-1.53]/0.13 | 1.19 [0.90-1.58]/0.23 | 1.19 [0.90-1.58]/0.23 | 1.50 [1.12-2.00]/ 6×10^{-3} | 1.56 [1.10-2.20]/0.01 | 1.56 [1.10-2.20]/0.01 |
| Spontaneous preterm birth | | | | | | | | | |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Yes | 1.45 [1.19-1.78]/ 10^{-3} | 1.30 [1.02-1.66]/0.03 | 1.30 [1.02-1.66]/0.03 | 1.23 [0.94-1.61]/0.13 | 1.13 [0.82-1.55]/0.45 | 1.13 [0.82-1.55]/0.45 | 1.45 [1.03-2.03]/0.03 | 1.57 [1.05-2.36]/0.03 | 1.57 [1.05-2.36]/0.03 |
| Induced preterm birth | | | | | | | | | |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Yes | 1.42 [1.08-1.85]/0.01 | 1.42 [1.03-1.95]/0.03 | 1.42 [1.03-1.95]/0.03 | 1.17 [0.81-1.68]/0.40 | 1.34 [0.87-2.08]/0.19 | 1.34 [0.87-2.08]/0.19 | 1.60 [1.05-2.43]/0.03 | 1.62 [0.96-2.75]/0.07 | 1.62 [0.96-2.75]/0.07 |
| Very preterm birth | | | | | | | | | |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Yes | 1.64 [1.29-2.09]/ 10^{-3} | 1.46 [1.10-1.93]/ 8×10^{-3} | 1.46 [1.10-1.93]/ 8×10^{-3} | 1.46 [1.07-2.00]/0.02 | 1.38 [0.96-2.00]/0.09 | 1.38 [0.96-2.00]/0.09 | 1.59 [1.07-2.36]/0.02 | 1.56 [0.98-2.47]/0.06 | 1.56 [0.98-2.47]/0.06 |
| Late preterm birth | | | | | | | | | |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Yes | 1.31 [1.05-1.63]/0.02 | 1.23 [0.95-1.60]/0.12 | 1.23 [0.95-1.60]/0.12 | 1.05 [0.79-1.40]/0.75 | 1.02 [0.72-1.45]/0.90 | 1.02 [0.72-1.45]/0.90 | 1.44 [1.01-2.04]/0.04 | 1.67 [1.08-2.58]/0.02 | 1.67 [1.08-2.58]/0.02 |
| Preeclampsia | | | | | | | | | |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Yes | 1.35 [1.04-1.77]/0.03 | 1.30 [0.96-1.77]/0.09 | 1.30 [0.96-1.77]/0.09 | 0.98 [0.69-1.39]/0.92 | 1.10 [0.74-1.65]/0.64 | 1.10 [0.74-1.65]/0.64 | 2.01 [1.30-3.11]/ 2×10^{-3} | 1.59 [0.96-2.62]/0.07 | 1.59 [0.96-2.62]/0.07 |
| Infection | | | | | | | | | |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Yes | 1.01 [0.78-1.32]/0.92 | 0.82 [0.60-1.13]/0.22 | 0.82 [0.60-1.13]/0.22 | 0.91 [0.65-1.28]/0.61 | 0.71 [0.48-1.06]/0.10 | 0.71 [0.48-1.06]/0.10 | 0.99 [0.63-1.54]/0.95 | 0.97 [0.58-1.62]/0.90 | 0.97 [0.58-1.62]/0.90 |
| Low birthweight | | | | | | | | | |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Yes | 1.35 [1.13-1.63]/ 10^{-3} | 1.16 [0.93-1.44]/0.19 | 1.16 [0.93-1.44]/0.19 | 1.15 [0.90-1.46]/0.26 | 1.03 [0.77-1.38]/0.82 | 1.03 [0.77-1.38]/0.82 | 1.39 [1.03-1.87]/0.03 | 1.21 [0.84-1.72]/0.31 | 1.21 [0.84-1.72]/0.31 |
| PS | | | | | | | | | |
| Gestational age | -0.55 (0.16)/ 10^{-3} | -0.43 (0.19)/0.02 | -107.98 (40.66)/ 8×10^{-3} | -0.35 (0.22)/0.12 | -0.18 (0.26)/0.47 | -0.18 (0.26)/0.47 | -0.47 (0.23)/0.05 | -0.60 (0.29)/0.04 | -134.58 (65.71)/0.04 |
| Birthweight | -136.05 (34.14)/ 10^{-3} | -107.98 (40.66)/ 8×10^{-3} | -107.98 (40.66)/ 8×10^{-3} | -82.70 (46.15)/0.07 | -54.38 (52.76)/0.30 | -54.38 (52.76)/0.30 | -120.87 (52.86)/0.02 | -134.58 (65.71)/0.04 | -134.58 (65.71)/0.04 |
| Preterm birth | | | | | | | | | |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Yes | 1.41 [1.20-1.66]/ 10^{-3} | 1.38 [1.13-1.68]/ 10^{-3} | 1.38 [1.13-1.68]/ 10^{-3} | 1.28 [1.03-1.60]/0.03 | 1.24 [0.95-1.60]/0.11 | 1.24 [0.95-1.60]/0.11 | 1.32 [1.02-1.72]/0.04 | 1.51 [1.09-2.11]/0.01 | 1.51 [1.09-2.11]/0.01 |
| Spontaneous preterm birth | | | | | | | | | |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Yes | 1.38 [1.15-1.66]/ 10^{-3} | 1.32 [1.06-1.66]/0.01 | 1.32 [1.06-1.66]/0.01 | 1.29 [1.01-1.64]/0.04 | 1.20 [0.90-1.60]/0.21 | 1.20 [0.90-1.60]/0.21 | 1.18 [0.87-1.61]/0.29 | 1.40 [0.95-2.05]/0.09 | 1.40 [0.95-2.05]/0.09 |
| Induced preterm birth | | | | | | | | | |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Yes | 1.47 [1.15-1.88]/ 2×10^{-3} | 1.49 [1.11-2.01]/ 8×10^{-3} | 1.49 [1.11-2.01]/ 8×10^{-3} | 1.28 [0.92-1.78]/0.15 | 1.31 [0.88-1.95]/0.19 | 1.31 [0.88-1.95]/0.19 | 1.59 [1.09-2.32]/0.02 | 1.82 [1.10-2.99]/0.02 | 1.82 [1.10-2.99]/0.02 |
| Very preterm birth | | | | | | | | | |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Yes | 1.44 [1.16-1.79]/ 10^{-3} | 1.31 [1.01-1.70]/0.04 | 1.31 [1.01-1.70]/0.04 | 1.30 [0.97-1.75]/0.08 | 1.13 [0.81-1.60]/0.47 | 1.13 [0.81-1.60]/0.47 | 1.35 [0.94-1.94]/0.10 | 1.54 [0.99-2.38]/0.06 | 1.54 [0.99-2.38]/0.06 |

(continued)

Table 2
(continued).

| | Total study population | | | U.S. born mothers | | | Immigrant mothers | | |
|---------------------------|--|--|------|----------------------|-------------------------|------|--|-------------------------|------------------|
| | Ref | OR [95% CI] | P | Ref | OR [95% CI] | P | Ref | OR [95% CI] | P |
| Late preterm birth | | | | | | | | | |
| No | Ref | | | Ref | | | Ref | | |
| Yes | 1.39 [1.15–1.69] $\times 10^{-3}$ | 1.41 [1.11–1.80] $\times 10^{-3}$ | 0.07 | 1.27 [0.98–1.65] | 1.30 [0.95–1.78] | 0.10 | 1.30 [0.94–1.78] | 0.11 | Ref |
| Preeclampsia | | | | | | | | | |
| No | Ref | | | Ref | | | Ref | | |
| Yes | 1.26 [0.99–1.61] | 1.17 [0.88–1.56] | 0.27 | 0.94 [0.69–1.29] | 0.93 [0.65–1.35] | 0.72 | 1.74 [1.17–2.60] $\times 10^{-3}$ | | 1.54 [0.96–2.46] |
| Infection | | | | | | | | | |
| No | Ref | | | Ref | | | Ref | | |
| Yes | 0.95 [0.75–1.21] | 0.76 [0.57–1.02] | 0.06 | 0.88 [0.64–1.20] | 0.68 [0.47–1.00] | 0.05 | 0.90 [0.59–1.37] | 0.61 | 0.90 [0.54–1.49] |
| Low birthweight | | | | | | | | | |
| No | Ref | | | Ref | | | Ref | | |
| Yes | 1.29 [1.09–1.52] $\times 10^{-3}$ | 1.21 [0.99–1.48] | 0.07 | 1.10 [0.88–1.37] | 1.03 [0.79–1.34] | 0.85 | 1.30 [0.99–1.71] | 0.06 | 1.30 [0.92–1.82] |
| AAP | | | | | | | | | |
| Gestational age | Crude β [SE]/P | Adjusted β [SE]/P | | Crude β [SE]/P | Adjusted β [SE]/P | | Crude β [SE]/P | Adjusted β [SE]/P | |
| Birthweight | 0.02 (0.10)/0.87 | -0.08 (0.13)/0.53 | | -0.06 (0.14)/0.66 | 0.02 (0.17)/0.92 | | -0.06 (0.15)/0.69 | -0.16 (0.19)/0.40 | |
| | -3.87 (22.78)/0.87 | -36.30 (27.91)/0.19 | | -38.08 (29.95)/0.20 | -13.38 (34.43)/0.70 | | -7.86 (34.39)/0.82 | -52.02 (43.22)/0.23 | |
| | COR [95% CI]/P | AOR [95% CI]/P | | COR [95% CI]/P | AOR [95% CI]/P | | COR [95% CI]/P | AOR [95% CI]/P | |
| Preterm birth | | | | | | | | | |
| No | Ref | | | Ref | | | Ref | | |
| Yes | 1.03 [0.92–1.14] | 1.05 [0.92–1.20] | 0.46 | 1.02 [0.89–1.18] | 0.95 [0.80–1.13] | 0.58 | 1.21 [1.02–1.44] $\times 10^{-3}$ | | 1.29 [1.04–1.61] |
| Spontaneous preterm birth | | | | | | | | | |
| No | Ref | | | Ref | | | Ref | | |
| Yes | 1.04 [0.92–1.17] | 1.13 [0.97–1.32] | 0.13 | 1.06 [0.91–1.23] | 1.01 [0.84–1.22] | 0.91 | 1.32 [1.08–1.62] $\times 10^{-3}$ | | 1.49 [1.15–1.93] |
| Induced preterm birth | | | | | | | | | |
| No | Ref | | | Ref | | | Ref | | |
| Yes | 1.01 [0.86–1.18] | 0.90 [0.74–1.10] | 0.32 | 0.95 [0.76–1.17] | 0.81 [0.62–1.06] | 0.12 | 1.04 [0.81–1.34] | 0.74 | 0.99 [0.72–1.36] |
| Very preterm birth | | | | | | | | | |
| No | Ref | | | Ref | | | Ref | | |
| Yes | 1.04 [0.90–1.19] | 1.06 [0.89–1.26] | 0.53 | 1.02 [0.85–1.22] | 0.92 [0.73–1.14] | 0.45 | 1.13 [0.89–1.42] | 0.33 | 1.16 [0.87–1.56] |
| Late preterm birth | | | | | | | | | |
| No | Ref | | | Ref | | | Ref | | |
| Yes | 1.02 [0.90–1.16] | 1.04 [0.88–1.22] | 0.66 | 1.03 [0.87–1.22] | 0.96 [0.78–1.17] | 0.68 | 1.28 [1.03–1.58] $\times 10^{-3}$ | | 1.39 [1.06–1.82] |
| Preeclampsia | | | | | | | | | |
| No | Ref | | | Ref | | | Ref | | |
| Yes | 1.05 [0.89–1.23] | 1.01 [0.83–1.23] | 0.93 | 1.00 [0.81–1.22] | 0.97 [0.76–1.24] | 0.81 | 0.98 [0.75–1.28] | 0.87 | 0.81 [0.59–1.11] |
| Infection | | | | | | | | | |
| No | Ref | | | Ref | | | Ref | | |
| Yes | 0.94 [0.80–1.10] | 1.00 [0.82–1.22] | 0.99 | 1.03 [0.85–1.26] | 1.03 [0.81–1.31] | 0.79 | 1.10 [0.83–1.44] | 0.52 | 1.15 [0.82–1.62] |
| Low birthweight | | | | | | | | | |
| No | Ref | | | Ref | | | Ref | | |
| Yes | 1.08 [0.97–1.21] | 1.18 [1.03–1.36] $\times 10^{-3}$ | 0.02 | 1.11 [0.96–1.27] | 1.08 [0.90–1.28] | 0.41 | 1.22 [1.02–1.47] $\times 10^{-3}$ | | 1.38 [1.09–1.73] |

AOR=adjusted odds ratio, BMI=body mass index, COR=cross ratio, LS=lifetime stress, PS=stress during pregnancy, SE=standard error.

* P value <0.05 is in bold.

† Adjusted variables included: maternal age, pregnancy BMI, marital status, parity, educational level, baby's sex, illicit drug use, maternal smoking, and maternal alcohol use.

Table 3
Joint associations of lifetime stress and African ancestral proportion with preterm related traits among U.S. born and immigrant mothers.

| | U.S. born mothers | | | Immigrant mothers | | |
|---------------------------|---|--|--------------------------|---|--|--------------------------------------|
| | Low/high or high/low Adjusted β [SE]/ $P^{*,\dagger}$ AOR [95% CI]/ P | High/high Adjusted β [SE]/ P AOR [95% CI]/ P | $P_{\text{interaction}}$ | Low/high or high/low Adjusted β [SE]/ P AOR [95% CI]/ P | High/high Adjusted β [SE]/ P AOR [95% CI]/ P | $P_{\text{interaction}}$ |
| Birthweight | 28.58 [125.46]/0.82 | 57.81 [129.29]/0.66 | 0.66 | -100.18 [124.26]/0.42 | -387.67 [144.59]/8×10^{-3} | 0.02 |
| Preterm birth | 0.79 [0.43-1.46]/0.46 | 0.80 [0.43-1.51]/0.50 | 0.48 | 2.36 [1.14-4.86]/0.02 | 3.87 [1.74-8.58]/10^{-3} | 4×10^{-3} |
| Spontaneous preterm birth | 0.80 [0.40-1.61]/0.54 | 0.85 [0.41-1.73]/0.65 | 0.89 | 2.40 [0.98-5.89]/0.06 | 5.18 [1.99-13.48]/10^{-3} | 10^{-3} |
| Late preterm birth | 0.81 [0.39-1.70]/0.58 | 0.83 [0.39-1.78]/0.64 | 0.78 | 3.32 [1.19-9.29]/0.02 | 5.48 [1.82-16.52]/2×10^{-3} | 9×10^{-3} |
| Low birthweight | 0.82 [0.44-1.54]/0.54 | 0.75 [0.39-1.42]/0.38 | 0.84 | 1.14 [0.57-2.26]/0.71 | 2.19 [1.03-4.68]/0.04 | 9×10^{-3} |

Participants with low lifetime stress and low African ancestral proportion were used as the reference group. AOR=adjusted odds ratio, BMI=body mass index, CI=confidence interval, SE=standard error.
* P value <0.05 is in bold.

\dagger Adjusted variables included: maternal age, prepregnancy BMI, marital status, parity, educational level, baby's sex, illicit drug use, maternal smoking and maternal alcohol use.

results in Table 4 show that among immigrant mothers, a significant interaction of PS and AAP was observed with birthweight ($P=0.02$), PTB ($P=0.005$), spontaneous PTB ($P=0.003$), late PTB ($P=0.003$), and LBW ($P=0.003$). Specifically, participants with high PS and high AAP had a significantly elevated risk of developing PTB, spontaneous PTB, late PTB, and LBW; and they had significantly LBW compared to those with low PS and low AAP. Similar to the results shown in Table 3, no significant joint association of PS and AAP with PTB and related traits was found in U.S. born mothers (Table 4).

In addition, maternal controls with 72 term babies whose birthweights less than 2500g and with 49 term babies whose birthweights more than 4000g were recruited in the present study. We did not exclude them in primary analyses. Moreover, when we excluded those subjects and repeated the analyses, we found the results were comparable to the analyses without excluding the subjects.

4. Discussion

Racial disparities in PTB have long been observed in the U.S., especially among African American women who experience the highest rates of PTB (17.8%) among various ethnic groups.^[27] To our knowledge, the present study is one of the first to date to investigate the interplay of genetic ancestry and stress on PTB and related traits in a sample of 1121 Black women (628 U.S. born Black women and 493 immigrant Black women). Our sample has the strength of a uniquely large cohort of immigrant Black women. The findings from this study suggest that African ancestry and maternal stress (both LS and PS) are individually

associated with PTB and related traits in immigrant Black women. Furthermore, a joint association of African ancestry and maternal stress with PTB and related adverse pregnancy outcomes was also observed in immigrant Black women. In contrast, neither individual associations nor joint associations of African ancestry and maternal stress with PTB and related traits were found in U.S. born Black women.

Previous PTB-related studies have mainly focused on Black/White racial disparities, but have rarely investigated the influence of PTB and related traits between U.S. born and immigrant Black women.^[28-30] For example, David and Collins^[31] examined birthweights among infants from different racial backgrounds: African born Blacks, U.S. born Blacks, and U.S. born Whites, separately. Consistent with our results, they found that infants of U.S. born Black mothers tended to have LBWs than infants born to African born Black mothers. Moreover, Howard et al^[32] investigated the risk of LBW and PTB among U.S. born and immigrant Black women. They concluded that birthweight was lower, but the occurrence of PTB was higher among U.S. born Black mothers than among Black mothers born outside of the U.S., which was similar to the findings in this study.

Several possible explanations might help to elucidate the observed differential effect of stress and African ancestry on PTB and related outcomes. First, previous studies have documented that maternal age is one of the predicting factors for LBW, but an association between age and PTB has been found to be more profound among Black women than White women.^[33,34] Consistently, we found that immigrant Black women gave birth at older ages than U.S. born Black women in the present study. Second, although not explored in this study, poor social support

Table 4
Joint associations of stress during pregnancy and African ancestral proportion with preterm related traits among U.S. born and immigrant mothers.

| | U.S. born mothers | | | Immigrant mothers | | |
|---------------------------|---|--|--------------------------|---|--|--------------------------------------|
| | Low/high or high/low Adjusted β [SE]/ $P^{*,\dagger}$ AOR [95% CI]/ P | High/high Adjusted β [SE]/ P AOR [95% CI]/ P | $P_{\text{interaction}}$ | Low/high or high/low Adjusted β [SE]/ P AOR [95% CI]/ P | High/high Adjusted β [SE]/ P AOR [95% CI]/ P | $P_{\text{interaction}}$ |
| Birthweight | -47.59 [126.27]/0.71 | 4.27 [131.18]/0.97 | 0.77 | -171.21 [118.83]/0.15 | -389.93 [136.42]/5×10^{-3} | 0.02 |
| Preterm birth | 1.20 [0.65-2.23]/0.56 | 1.03 [0.54-1.97]/0.92 | 0.58 | 2.78 [1.39-5.55]/4×10^{-3} | 3.71 [1.74-7.92]/10^{-3} | 5×10^{-3} |
| Spontaneous preterm birth | 1.17 [0.58-2.35]/0.67 | 1.07 [0.52-2.21]/0.86 | 0.99 | 2.94 [1.25-6.94]/0.01 | 4.55 [1.82-11.35]/10^{-3} | 3×10^{-3} |
| Late preterm birth | 1.35 [0.63-2.89]/0.44 | 1.20 [0.54-2.67]/0.65 | 0.98 | 3.61 [1.38-9.44]/9×10^{-3} | 4.89 [1.75-13.68]/2×10^{-3} | 0.01 |
| Low birthweight | 1.07 [0.57-2.03]/0.83 | 0.94 [0.48-1.81]/0.85 | 0.60 | 1.44 [0.73-2.85]/0.29 | 2.80 [1.34-5.85]/6×10^{-3} | 3×10^{-3} |

Participants with low lifetime stress and low African ancestral proportion were used as the reference group. AOR=adjusted odds ratio, BMI=body mass index, CI=confidence interval, SE=standard error.
* P value <0.05 is in bold.

\dagger Adjusted variables included: maternal age, prepregnancy BMI, marital status, parity, educational level, baby's sex, illicit drug use, maternal smoking, and maternal alcohol use.

among immigrant Black women might be one of the elements leading to the observed differential effect of stress on PTB and related adverse pregnancy outcomes. Previous reports have provided strong evidence for the role of social relationships in buffering potentially deleterious health effects such as psychosocial stress, or moderating health outcomes such as complications of pregnancy and LBW.^[35–37] In addition, results from Almeida et al.^[38] suggest that the association between social support and depression might differ between foreign-born and U.S. born individuals. Third, numerous studies have documented that genetics play a role in the development of PTB.^[12,13,15] Given the significant difference in African ancestry between U.S. born and immigrant Black women, susceptible genetic background might partially explain the observed differential genetic effect on PTB and related outcomes in the present study.

Several limitations of this study should be noted. First, our stress indicator might be subject to recall bias since LS and PS were recalled by participating mothers. Second, LS and PS were classified based on data collected in response to 2 individual items on the questionnaire; these data might only partially reflect a woman's stress level, as compared to other more comprehensive indicators or biological indicators such as allostatic load. However, the questions used in this study have been employed in other studies that have shown that exposure to stress was associated with an increased risk of several diseases, for example, cancer, dementia, and hypertension.^[39–41] Third, although we adjusted for several PTB-related risk factors such as parity, maternal smoking, and maternal alcohol use in the models, there remains the possibility of residual confounding by unmeasured factors, for example, history of previous PTB. In addition, the mean age of the study population was 27.7 years, and the majority of maternal participants did not have a history of diabetes or hypertension. Thus, we did not adjust for diabetes and hypertension in the models. Fourth, we did not evaluate the potential influence of socioeconomic and overall psychological status on PTB and related outcomes between U.S. born and immigrant Black women. Further investigation would be warranted to assess the impact of socioeconomic and overall psychological status. As such, the results should be interpreted with caution.

Taken together, the findings from the present study provide suggestive evidence of the differential individual and/or joint effects of stress and genetic ancestry on PTB and related outcomes between U.S. born and immigrant Black women. Currently, early screening cervical length and/or progesterone treatment during pregnancy have remained controversial and inconclusive in clinical practice. It is of importance to identify women at high risk of PTB. Further research is needed to better understand the underlying mechanisms that are causing the observed differential effects on PTB; a better understanding potentially could have a major impact on decreasing the burden of PTB, particularly in high-risk Black women. Given the findings, public health and clinical interventions to address the impact of individual and joint effects of stress and genetic ancestry on PTB might be beneficial among immigrant Black women, especially in areas with high population concentrations.

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