Maternal Black Race and Persistent Wheezing Illness in Former Extremely Low Gestational Age Newborns: Secondary Analysis of a Randomized Trial

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Objective To evaluate the relationship between maternal self-reported race/ethnicity and persistent wheezing illness in former high-risk, extremely low gestational age newborns, and to quantify the contribution of socioeconomic, environmental, and biological factors on this relationship.

Study design We assessed persistent wheezing illness determined at 18-24 months corrected (for prematurity) age in survivors of a randomized trial. Parents/caregivers were surveyed for wheeze and inhaled asthma medication use quarterly to 12 months, and at 18 and 24 months. We used multivariable analysis to evaluate the relationship of maternal race to persistent wheezing illness, and identified mediators for this relationship via formal mediation analysis.

Results Of 420 infants (25.2 ± 1.2 weeks of gestation and 714 ± 166 g at birth, 57% male, 34% maternal black race), 189 (45%) had persistent wheezing illness. After adjustment for gestational age, birth weight, and sex, infants of black mothers had increased odds of persistent wheeze compared with infants of nonblack mothers (OR = 2.9, 95% CI 1.9, 4.5). Only bronchopulmonary dysplasia, breast milk diet, and public insurance status were identified as mediators. In this model, the direct effect of race accounted for 69% of the relationship between maternal race and persistent wheeze, whereas breast milk diet, public insurance status, and bronchopulmonary dysplasia accounted for 8%, 12%, and 10%, respectively.

Conclusions Among former high-risk extremely low gestational age newborns, infants of black mothers have increased odds of developing persistent wheeze. A substantial proportion of this effect is directly accounted for by race, which may reflect unmeasured environmental influences, and acquired and innate biological differences. *(J Pediatr 2018;■■:■■-■■).*

Trial Registration ClinicalTrials.gov: NCT01022580.

Long-term respiratory morbidity is a common adverse outcome of prematurity; premature infants with and without bronchopulmonary dysplasia (BPD) remain at increased risk for respiratory disease throughout childhood.[1,2] Many of these children suffer from wheezing disorders or asthma, associated with recurrent hospitalizations and long-term medication requirements.[3,4] Children born very preterm are at highest risk, and those with early recurrent wheeze remain at increased risk for wheeze throughout early childhood.[3,5]

Racial differences in childhood asthma in the US are apparent; non-Hispanic black children are affected at higher rates than non-Hispanic white children.[6] Even after consideration of socioeconomic status (SES) and environmental risk factors, black children have increased odds of wheeze and asthma compared with white children.[7,8] However, less is known about the relationship between race and wheezing illness among preterm infants, with several studies demonstrating increased occurrence in moderately preterm black children.[9-13] Increased susceptibility to environmental pollutants and vitamin D intake may be modifying factors.[12,13]

BPD	Bronchopulmonary dysplasia
ELGAN	Extremely low gestational age newborns
ETS	Environmental tobacco smoke
iNO	Inhaled nitric oxide
RSV	Respiratory syncytial virus
SES	Socioeconomic status
TOLSURF	Trial of Late Surfactant

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*List of additional members of the TOLSURF Study Group is available at www.jpeds.com (**Appendix 1**).

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Although studies have identified environmental risk factors (eg, young siblings or exposure to environmental tobacco smoke [ETS]), few studies have quantified the effect of multiple SES and environmental factors on infant wheezing disorders, particularly among extremely preterm infants.[3,14] Beck et al found that approximately one-half of the relationship between race and asthma-related hospitalization in children could be explained by socioeconomic hardships.[15,16]

This suggests that innate and acquired biological and genetic influences explain some of the racial disparity in wheezing disorders. Whether these factors relate to differences in lung structure, function, or immunity remain undefined.

The aims of the current study were to determine the relationship between maternal black race and persistent wheezing illness among former extremely low gestational age newborns (ELGAN), and to quantify, via mediation analysis, the indirect effects of socioeconomic, environmental, and innate and acquired pulmonary biological factors on the development of wheezing disorders among infants of black mothers. We hypothesized that black maternal race would be independently associated with persistent wheezing illness among former ELGAN.

Methods

This was a secondary analysis from the randomized controlled Trial of Late Surfactant (TOLSURF, ClinicalTrials.gov: NCT01022580), under Institutional Review Board approval at 25 US academic centers.[17] Infants ≤$28^{0/7}$ weeks of gestational age, who were mechanically ventilated between 7 and 14 days of life, were randomized to late surfactant and inhaled nitric oxide (iNO) vs iNO-alone. Those with major anomalies, life expectancy <7 days, or active comorbidities at time of enrollment were excluded from the trial. No difference was seen by treatment group for the primary outcome, survival without BPD at 36 weeks of postmenstrual age (by physiological testing), although infants of black mothers were less likely to have BPD after receiving iNO.[17,18]

Perinatal characteristics and sociodemographic data were collected at enrollment. To identify maternal race/ethnicity, mothers selected Hispanic/Latino vs not Hispanic/Latino and (all that apply) White/Caucasian, Black/African American, Asian, American Indian/Alaska Native, and Native Hawaiian/Other Pacific Islander. For this study, race/ethnicity was dichotomized to black (non-Hispanic) vs nonblack. Mothers who selected multiple races were included in the nonblack group.

At discharge, parents/caregivers were surveyed for factors known to modify respiratory morbidity in former ELGAN and other children.[19] Specifically, we collected data on the presence of additional children <5 years of age in the home, furry pets in the home, anticipated daycare attendance, breast milk diet, maternal educational attainment, public insurance status, and parental history of asthma (Discharge Questionnaire, **Appendix 2**; available at www.jpeds.com). Potential ETS exposure was defined by factors previously shown to be associated with elevated cotinine levels in children: (1) allowing any smoking in the home, (2) having a parent or other household member who smokes, or (3) travelling regularly in a car with someone who smokes.[20,21]

Parent/caregiver questionnaires were administered at 3, 6, 9, 12, 18, and 24 months corrected (for prematurity) age to assess events related to respiratory health including exposure to inhaled medications (bronchodilators or corticosteroids), wheeze auscultated by a medical professional, and diagnosis of respiratory syncytial virus (RSV) infection. At 18 and 24 months, we asked if the child had a physician diagnosis of asthma, eczema, or hay fever. Infants were classified with a history of atopy if caregivers reported eczema or hay fever. Data collected by questionnaire were not further verified by medical record review.

We defined persistent wheezing illness as having one of the following: physician diagnosis of asthma at 18-24 months and wheezing or medication (inhaled bronchodilator or corticosteroid) exposure at any questionnaire; or medication in the first 12 months and wheeze in the second 12 months of life; or wheeze in the first 12 months and medication in the second 12 months; or medication exposure in both the first and second 12 months; or wheeze and medication exposure in the second 12 months of life reported at separate visits (18 and 24 months). These criteria were adapted from the 3-year definition used in the Vitamin D Antenatal Asthma Reduction Trial (on average, ELGAN are 21-27 months chronological age at 18-24 months corrected age).[22]

Statistical Analyses

Our primary question was the effect of maternal race (black vs nonblack) on persistent wheezing illness. All analyses were 2-sided ($P < .05$) and used Stata v 14.0 (StataCorp, College Station, Texas). Univariate analyses were analyzed by χ^2 or t test. Because of the clinical importance of gestational age, sex, and birth weight, all multivariable models were adjusted for these characteristics. To evaluate the independent influence of maternal race on persistent wheezing illness, we considered other baseline characteristics that are published risk factors for respiratory illness in preterm infants (antenatal corticosteroids, birth weight percentile, product of multiple gestation, maternal age) as potential confounders (**Figure 1**, A), as well as TOLSURF treatment assignment (late surfactant vs control); a priori, we planned to adjust the mediation analysis for factors that changed the effect size of maternal black race by ≥20%.[3] Generalized estimating equations accounted for nonindependence between siblings (exchangeable correlation).

We proceeded step-wise with mediation analysis. We evaluated if BPD, as well as additional sociodemographic characteristics, environmental and other exposures after hospital discharge, and family or personal history of asthma/atopy satisfied the statistical conditions required to be a mediator between maternal race and persistent wheezing illness by the following steps (**Figure 1**, B)[23,24]: (1) establish that race is significantly associated with the outcome, persistent wheezing illness, (2) establish that race is significantly associated with the potential mediator of interest, and (3) establish that the potential mediator of interest is independently associated with persistent wheezing illness, after controlling for race. If all 3

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