HHS Public Access

Author manuscript

J Pediatr. Author manuscript; available in PMC 2020 April 01.

Published in final edited form as:

J Pediatr. 2019 April ; 207: 130–135.e2. doi:10.1016/j.jpeds.2018.11.025.

Black Race is Associated with a Lower Risk of Bronchopulmonary Dysplasia

Rita M. Ryan, MD[1], **Rui Feng, PhD**[2], **Catalina Bazacliu, MD**[3], **Thomas W. Ferkol, MD**[4], **Clement L. Ren, MD, MBA**[5], **Thomas J Mariani, PhD**[6], **Brenda B. Poindexter, MD, MS**[7], **Fan Wang, PhD**[8], and **Paul E. Moore, MD**[9] **PROP Investigators***

[1]Pediatrics, Medical University of South Carolina, Charleston, SC, United States

[2]Biostatistics, University of Pennsylvania, Philadelphia, PA, United States

[3]Pediatrics, University of Florida, Gainesville, Florida, United States

[4]Pediatrics, Washington University, St. Louis, MO, United States

[5]Pediatrics/Pulmonology, Indiana University, Indianapolis, IN, United States

[6]Pediatrics, University of Rochester, Rochester, NY, United States

[7]Perinatal Institute, Cincinnati Children's, Cincinnati, OH, United States

[8]Molecular Cardiology/Lerner Research Institute, The Cleveland Clinic, Cleveland, OH, United States;

[9]Pediatrics, Vanderbilt University, Nashville, TN, United States

Abstract

Corresponding author: Rita M. Ryan, MD, Professor of Pediatrics, 165 Ashley Avenue, MSC 917, Charleston, SC 29425, ryanr@musc.edu, (843) 876-1684, (843) 792-2112.

*List of additional members of the PROP Investigators is available at www.jpeds.com (Appendix).

List of additional members of the PROP Investigators

Cincinnati Children's Hospital Medical Center site: Claire Chougnet, PhD, James M. Greenberg, MD, William Hardie, MD, Alan H. Jobe, MD, PhD, Karen McDowell, MD; **Washington University School of Medicine site:** Aaron Hamvas, MD1, Mark R. Holland, PhD, James Kemp, MD, Philip T. Levy, MD, Christopher McPherson, PharmD, Phillip Tarr, MD, Gautam K. Singh, MD, Barbara Warner, MD, [1]Northwestern University Feinberg School of Medicine); **University of California-San Francisco** site: Philip L. Ballard, MD, PhD, Roberta A. Ballard, MD, David J. Durand, MD[a], Eric C. Eichenwald, MD[d], Amir M. Khan, MD4, Leslie Lusk, MD, Jeffrey D. Merrill, MD[b], Dennis W. Nielson, MD, PhD, Elizabeth E. Rogers, MD ([a]Children's Hospital and Research Center Oakland, Oakland, CA, [b]Alta Bates Summit Medical Center, Berkeley, CA, [d]University of Texas Health Science Center- Houston, Houston, TX); **Vanderbilt University site:** Judy Aschner, MD[e], Candice Fike, MD[f], Scott Guthrie, MD[g], Tina Hartert, MD, Nathalie Maitre, MD, Marshall Summar, MD[h] ([e]Albert Einstein College of Medicine, Bronx, NY, [f]University of Utah, [g]Jackson-Madison County General Hospital, Jackson, TN, [h]Children's National Health System, Washington, DC); **University of Rochester/University at Buffalo site:** Carl T. D'Angio, MD, Vasanth Kumar, MD, Gloria Pryhuber, MD, Anne Marie Reynolds, MD, MPH, Kristin Scheible, MD, Timothy Stevens, MD, MPH ([i]Indiana University, [j]Medical University of South Carolina); **Duke University:** C. Michael Cotten, MD, Kim Fisher, PhD, Jack Sharp, MD[k], Judith A. Voynow, MD[l] ([k]Texas Children's Hospital, [l]Virginia Commonwealth University); **Indiana University site:** Stephanie Davis, MD; **University of Pennsylvania, DCC site:** Scarlett A. Bellamy, ScD[m], Jonas Ellenberg, PhD, Melissa Fernando, MPH, Howard Panitch, MD, Pamela A. Shaw, PhD, Barbara Schmidt, MD, MSc ([m]Drexel University); Steering Committee Chair: Lynn M. Taussig, MD, University of Denver; NHLBI Program Officer: Carol J. Blaisdell, MD.

A.J. serves as an editorial board member for *The Journal of Pediatrics*.

Portions of this study were presented at the Pediatric Academic Societies annual meeting, May 6-9, 2017, San Francisco, California.

Objective: To use a large current prospective cohort of infants <29 weeks to compare bronchopulmonary dysplasia (BPD) rates in black and white infants.

Study design: The Prematurity and Respiratory Outcome Program (PROP) enrolled 835 infants born in 2011-2013 at <29w; 728 black or white infants survived to 36w postmenstrual age (PMA). Logistic regression was used to compare BPD outcomes (defined as supplemental oxygen requirement at 36w PMA) between races, adjusted for GA, antenatal steroid use, intubation at birth, and surfactant use at birth.

Results: Of 707 Black or White infants with available BPD outcomes, BPD was lower in Black infants (38% vs. 45%), despite Black infants being of significantly lower GA. At every gestational age, BPD was more common in White infants. The adjusted odds ratio for BPD was 0.60 (95% confidence interval 0.42-0.85, p=0.004) for Black infants compared with White infants after adjusting for gestational age. Despite the lower rate of BPD, Black infants had more first year post-prematurity respiratory disease (79% Black, and 63% White).

Conclusion(s): In this large cohort of recently born premature infants <29w GA, Black infants had a lower risk of BPD than White infants but had an increased risk of persistent respiratory morbidity.

Preterm birth affects more than 500,000 babies born in the United States each year, and 15 million children are born prematurely worldwide[1]. Despite improvements in care, preterm birth is a leading cause of death in young children[2]. Bronchopulmonary dysplasia (BPD), the most common chronic lung disease in infancy[3], results from disruption of normal lung development. National Institutes of Health consensus criteria have defined BPD as the persistence of a supplemental oxygen requirement at 36w post-menstrual age (PMA) among infants born before 32w gestation[8]. BPD is caused by premature birth, oxygen toxicity, mechanical trauma related to positive pressure ventilation, infection, genetic predispositions, and other prenatal and postnatal factors, leading to alveolar simplification, altered pulmonary microvascular growth, and lung inflammation and injury. Despite advances in neonatal care and improved survival, the incidence of BPD remains virtually unchanged or increased in extremely low gestational age newborns[4], occurring in 40-45% of infants born before 29 weeks' (w) gestation[5–7].

Previous studies demonstrated racial differences in the outcomes of prematurity, with Caucasian infants having increased likelihood of morbidities[9] with higher rates of respiratory distress syndrome (RDS)[10, 11] and retinopathy of prematurity[12]. However, the clinical results are often contradictory, some finding African American race protective[6, 13], and others found no apparent effect[14, 15]. Greater use of medications in African American infants who were bom premature and have BPD confounds the issue even further[16].

The National Heart, Lung, and Blood Institute (NHLBI) Prematurity and Respiratory Outcome Program (PROP) is a large multicenter prospective cohort of infants born less than 29w gestation, developed to identify clinical and biological markers predictive of respiratory outcomes during the first year of life[17, 18]. We hypothesized that African-American infants would have less BPD when compared with Caucasian infants, and tested this hypothesis by comparing rates of BPD in self-reported African-American vs. Caucasian infants enrolled in the PROP cohort.

METHODS

PROP is a prospective observational cohort study performed by a consortium of 6 clinical centers with 11 clinical sites and a data-coordinating center (ClinicalTrials.gov NCT01435187). A key scientific aim of PROP is to identify early clinical, physiologic, and biochemical biomarkers during the initial NICU hospitalization that can predict respiratory morbidity through 1 year of age. Individual centers enrolled between 105 and 184 participants in the cohort for a total of 835 subjects. PROP study design and the status of the 765 infants surviving at 36w PMA have been previously published[17, 19]. We chose to use the terms “Black” and “White” in discussing our findings genetically, but because infant race was reported by parents using the terms “African-American” and “Caucasian” at study enrollment, we use those terms in initial introduction of terms. Infants with multiple reported races were not included in the analysis.

Infants between $23^{0/7}$ and $28^{6/7}$ weeks gestation were eligible for enrollment within the first week of life. We excluded infants who were not considered viable, those with congenital heart disease or structural abnormalities of the upper airway, lungs, or chest wall or other congenital malformations that adversely affect cardiopulmonary development, or those whose families would be likely to be unavailable for long-term follow up. The study was approved at each clinical site by the local institutional review board and by the data-coordinating center at the University of Pennsylvania. Written informed consent from a parent or guardian was obtained for each baby enrolled.

Trained research personnel collected detailed anthropometric, medication and respiratory stats data on a daily basis until discharge home, transfer, or 40 weeks PMA. Follow-up data was collected from parents at 3, 6, 9, and 12 months corrected age (± 1 month) through a focused questionnaire adminstered via telephone or at an in-person clinic visit. At the time of each questionnaire, respiratory symtpoms and health care utilization information was obtained for the previous 3 months as reported by parents and was immediately recorded on the clinical research form by research staff.

The diagnosis of BPD was assigned by the need for supplemental oxygen at exactly $36^{0/7}$ weeks PMA. Using this strict definition described by Shennan, those on respiratory support with FiO2 21% at 36 weeks PMA are assigned “no BPD” status, regardless of type or level of respiratory support[20]. This definition was modified by assigning the outcome of “no BPD” to infants who were discharged home off respiratory support prior to 36 weeks’ PMA (“modified Shennan” definition)[4, 20]. The choice of the modified Shennan definition was adopted by the PROP group to improve the ability to classify as many infants as possible and its easier clinical applicability (for example, not having to count 28 days of oxygen exposure as for the NIH Workshop definiton[21]) and is discussed in detail by Poindexter et al.[19] In addition, we measured severe BPD using the NIH Workshop definition[21].

Post-prematurity respiratory disease (PRD) was defined as having a positive response for at least 1 domain in ≥2 separate quarterly interviews/surveys or death from cardiorespiratory failure after 36 weeks’ PMA[22]. The four domains/elements represented in the quarterly followup surveys administered through 12 months corrected gestational age (CGA) were 1.

Respiratory medications (i.e., inhaled bronchodilators or steroids, systemic steroids, methylxanthines, diuretics, pulmonary vasodilators, leukotriene receptor antagonist); 2. Hospitalization for cardiopulmonary cause; 3. Any wheeze or cough without a cold ≥l× per week; 4. Home technology dependence, e.g. use of oxygen, ventilator, CPAP/BiPAP, or tracheostomy in place.

Statistical Analyses

Among 36 week survivors, proportions, means and medians between the two races were compared using Pearson chi-square test, Fisher exact test, 2 group t-test, and Wilcoxon rank-sum test, respectively. The association between race and BPD/PRD was assessed by mixed-effect logistic regression models, adjusted by gestation weeks at birth, intubation at birth, antenatal steroid use, and sibling correlations. For the modified Workshop BPD definition, severe and moderate groups were compared with no/minimal group in two separate models. Deaths before 36 weeks PMA were compared using a logistic regression model, adjusted by gestation age at birth. The race effect on PRD was estimated using mixed-effect regression models and the details were previously presented in Table 7 of Keller et al[22].

To examine the contribution of clinical site to the effect of race, the raw odds ratios (ORs) of BPD for Black vs White were also summarized by 11 clinical centers (Cincinnati, Washington University, University of California at San Francisco, Alta Bates Summit Medical Center, University of Texas at Houston, Monroe Carell Jr. Children's Hospital at Vanderbilt, Jackson-Madison Country General Hospital, University of Rochester, University at Buffalo, Duke University, University of Indiana).

RESULTS

Of the 835 subjects enrolled in PROP, 765 survived to 36 weeks PMA and were classified as BPD, yes or no. A total of 728 infants (447 White infants and 281 Black infants) were available for these analyses (Table 1). BPD outcome data were available for 707 of these infants, and 21 babies did not have modified Shennan status available (due to transfer before 36 weeks (n=13), discharge home on oxygen before 36 weeks (n=6), or missing data (n=1) Figure 2; available at www.jpeds.com). Of the 707 infants with outcome data, Black infants (105/274, 38%) were significantly less likely to develop BPD compared with White infants (193/433, 45%) (Table II). The adjusted odds ratio of having BPD for Black vs. White infants was estimated to be 0.60 (95% C.I. 0.42-0.85, $P = .004$), after adjusting for gestational age, antenatal steriods (ANS), and intubation at birth (Table 2). Compared with the racial percentage in no/mild BPD, Black infants also had less severe BPD than White infants, defined using the NIH workshop 1991 consensus criteria (Table 2).

Because lower gestational age (GA) is highly correlated with a greater risk for BPD, we examined the gestational age distribution in White and Black infants (Table 1). Black infants were significantly more likely to be born at earlier gestation compared with White infants (P=0.005, by Chi-square test). The rate of BPD was lower for Black babies at each week of GA at birth (Figure 1). The race effects across clinical sites were homogenous (P = 0.91, Breslow-Day Test of homogeneity); thus site was not a confounder for the effect of race on BPD.

To assess the possibility that lower survival to 36 weeks PMA in Black infants compared with White infants was responsible for their lower rate of BPD, we analyzed surivival data in our cohort. There was no difference in survival between Black and White infants even after adjusting for GA (Table 1), suggesting that differences in mortality rates did account for the difference in BPD prevalence between Black and White infants.

There have been previous studies suggesting that Black infants have more “mature” lungs at birth[11, 23–26], higher scoring on Ballard examinations,[27] lower birth weight[28] and shorter natural duration of pregnancy[29, 30]. We examined the rate of early surfactant use by race as a surrogate marker for lung maturity/respiratory distress syndrome. Despite a lower mean birth GA, Black infants were less likely (Table 1) to be exposed to ANS compared with White infants (83% vs. 88%, P=0.035, by Chi-square test). In addition, Black infants (Table 1) weighed 64.4 grams less on average (P=0.0003, by t-test) and were intubated more often (84% vs. 75%, P=0.005). Due to these differences at baseline, we included them in the assessment of race effect on BPD (Table 2) and also looked at their own independent contribution to BPD (Table 3). Exposure to ANS and higher GA were protective against BPD and intubation at birth was associated with a higher risk of BPD. However for Black infants, despite lower ANS exposure and lower GA, and higher intubation at birth, Black infants were still less likely to have BPD at 36 weeks even adjusting for these factors.

The first year respiratory outcomes for the full PROP cohort have been previously published[22]. In that paper, Black race remained independently associated with an increase in first year post-discharge respiratory morbidity (PRD), even after adjusting for GA and other confounders in the regressional analysis[22]; this is despite a lower rate of BPD. This was true when the modified Shennan definition or the NIH Workshop definition was used. However, the detailed outcome of PRD was not reported by race, and we now provide that information. Of 261 Black infants who had assessable PRD, 79% had PRD while 63% of White infants (n = 428) had PRD.

DISCUSSION

In this large contemporary PROP cohort of 728 Black or White ELGANs enrolled across 11 clinical sites, Black infants had a lower prevalence of BPD than White infants. Infants from other races were not included in analyses due to their low number. This difference was not due to Black infants being born at a later GA, as Black infants were more likely to be born at an earlier GA, and this advantage for Black race persisted across all gestational ages. The lower rate of BPD in Black infants was also not related to lower survival. When adjusted for GA, there remained no significant difference in survival based on logistic regression analysis for race (p=0.282). As one might expect, each week of gestational age remained a powerful predictor for survival (OR=0.65, 95% C.I.=0.57-0.75), $P<10^{-10}$).

As reported previously by PROP investigators[22], Black infants have more respiratory morbidity in the first 12 months corrected gestational age vs. White infants; this is despite having a lower rate of BPD at 36 weeks PMA. Of the 261 Black infants with assessable PRD, 79% had PRD while 63% of the 428 White infants had PRD.

A reduced rate of RDS in Black infants compared with White infants has been recognized for many years[9–11], and some studies have suggested this could be due to more rapid maturation of pulmonary surfactant[25, 31, 32]. Some prenatal environmental exposures, including tobacco smoke and particulate matter, are differentially elevated among Blacks compared with Whites and may contribute to increased surfactant production[33]. The reduced use of surfactant in the first 72 hours in Black infants compared with White infants in the current study of ELGANs suggests that reduced RDS in Black infants occurs even in the most premature infants.

In the baseline demographic data we noted that Black infants received less ANS compared with White infants. We did not have the appropriate data collected to explain why a baby was/was not given ANS and thus are unable to offer an evidenced-based discussion related to health care access, length of time in hospital prior to delivery, or other possible factors. However we did examine the contribution of these discrepant confounders specifically (Table 3), and, despite lower ANS and lower GA, and higher intubation at birth, Black infants were still less likely to have BPD at 36 weeks even adjusting for these factors.

The PROP Cohort allows for the examination of the association of race with not only with BPD but also with PRD. Although BPD is a reasonable predictor of post-discharge respiratory morbidity, we found higher rates of PRD, the one-year outcome for the PROP cohort, in Black compared with White infants despite the reduced BPD rate in Blacks[22]. This finding suggests that although BPD remains an important predictor of early childhood respiratory disease, there appear to be other yet unidentified race-related factors contributing to early childhood respiratory disease in Black infants after NICU discharge. Such factors may include reduced breast milk consumption and increased environmental tobacco smoke exposure in Black vs. White infants [34]. In addition, Black infants have been reported to have greater disease severity with respiratory viral illness, including bronchiolitis, compared with White infants[35, 36]. Severe bronchiolitis has been associated with recurrent wheezing, so perhaps increased PRD in Blacks reflects an increase in the number or severity of respiratory viral infections[37]. As dietary and environmental exposures also influence bronchiolitis severity[38], it is not clear whether these exposures have direct effects on PRD or are mediated through viral illnesses.

Concerning proposed biologic mechanisms, rates of PRD may also be higher in Blacks in part due to racial differences in the individual components defining PRD. Compared with White infants, Black infants are more likely to be hospitalized after a viral respiratory illness and are more likely to be prescribed respiratory medications in the first year of life[16]. Of course, bronchiolitis severity may increase likelihood of hospitalization or medication use, but other complex socioeconomic factors may also influence a provider's decision to admit or prescribe medications. Thus, higher rates of PRD in Blacks may also reflect increased healthcare utilization this population.

Finally, the lower BPD rates in Black infants may provide false reassurance about respiratory morbidity in Black infants. The preterm birth rate is nearly 50% higher for Black vs. White infants and Black infants experience nearly 4-fold as many deaths related to

shorter gestation and low birthweight, making prematurity the leading cause of infant death among Black infants[39].

Longitudinal follow up of the infants enrolled in PROP may provide additional clues about racial influences on rates of BPD, as well as short-term and long-term respiratory morbidities. Although reduced BPD rates in Blacks may be protective against the development of reduced surface area for gas exchange, the increase in PRD in Blacks may represent the development of an obstructive airway defect. The increased respiratory morbidity during the first year could reflect that asthma is more common in Black children, irrespective of the child's socioeconomic status. The difference in asthma rates between Black and White children has risen during the previous decade[40]. In addition, these results might aid in the design, conduct, and interpretation of future clinical studies and trials for BPD therapies.

Our findings have been corroborated in another recent cohort of premature infants. Infants enrolled in the Trial of Late Surfactant study (TOLSURF) have been analyzed for the contribution of race to BPD and later respiratory morbidity. Torgerson et al showed that Black race was associated with an improved survival without BPD[41]; Wai et al showed that Black race was associated with more wheezing at 18-24 months of age[42].

Limitations of our study include that infant race was self-reported by the mothers in this study. However, DNA ancestry markers of the infant correlated with the maternal self-reporting of race in our preliminary examination (See Supplemental Data [Appendix 2; available at www.jpeds.com]: among a subset of 148 PROP subjects, 147 had DNA-determined race consistent with maternal reported race [Appendix 2, Figure; available at www.jpeds.com]). The first-year respiratory morbidity data was based primarily on parental recall, which is inexact as discussed in detail in a previous publication[22]. The primary question for this study, the BPD outcome, has rigorous data collection methods, but we acknowledge that BPD can be defined in various ways[19]. We were not able to address the difference in ANS use in Black mothers vs. White mothers and suggest this could be a focus for future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to acknowledge all research staff by site:

Cincinnati Children's Hospital Medical Center site: Barbara Alexander, RN, Tari Gratton, PA, Cathy Grigsby, BSN, CCRC, Beth Koch, BHS, RRT, RPFT, Kelly Thornton BS;

Washington University School of Medicine site: Pamela Bates, CRT, RPFT, RPSGT, Claudia Cleveland, RRT, Julie Hoffmann, RN, Laura Linneman, RN, Jayne Sicard-Su, RN, Gina Simpson, RRT, CPFT;

University of California San Francisco site: Jeanette M. AsselinMS RRT-NPS[1], Samantha Balan, Katrina Bur son RN, BSN[4], Cheryl Chapin, Erna Josiah-Davis RN, NR[2], Carmen Garcia RN, CCRP[4], Hart Horneman, Rick Hinojosa BSRT, RRT, CPFT-NPS[3], Christopher Johnson MBA, RRT[3], Susan Kelley RRT, Karin L. Knowles, M. Layne Lillie, RN, BSN[3], Karen Martin RN[3], Sarah Martin RN, BSN; Julie Arldt-McAlister RN, BSN[3], Georgia E. McDavid RN[3], Lori Pacello RCP1, Shawna Rodgers RN, BSN[3], Daniel K Sperry RN[3]

[1]Children's Hospital and Research Center Oakland, Oakland CA; [2]Alta Bates Summit Medical Center, Berkeley CA; [3]University of Texas Health Science Center-Houston, Houston TX;

Vanderbilt University Medical Center site: Amy B Beller BSN, Mark O. Hunt, Theresa J. Rogers, RN, Odessa L. Settles, RN, MSN, CM, Steven Steele, RN, Sharon Wadley, BSN, RN, CLS[1], [1] Jackson-Madison County General Hospital, Jackson, TN;

University of Rochester Medical Center/University at Buffalo NY site: Shannon Castiglione, RN, Aimee Horan, LPN, Deanna Maffet, RN, Jane O'Donnell, PNP, Michael Sacilowski, MAT, Tanya Scalise, RN, BSN, Elizabeth Werner, MPH, Jason Zayac, BS, Heidie Huyck, BS, Valerie Lunger, MS, Kim Bordeaux, RRT, Pam Brown, RRT, Julia Epping, AAS, RT, Lisa Flattery-Walsh, RRT, Donna Germuga, RRT, CPFT, Nancy Jenks, RN, Mary Platt, RN, Eileen Popplewell, RRT, Sandra Prentice, CRT;

Duke University site: Kim Ciccio, RN;

Indiana University site: Charles Clem, RRT, Susan Gunn, NNP, CCRC, Lauren Jewett, RN, CCRC;

University of Pennsylvania, Perelman School of Medicine, DCC site: Maria Blanco, BS, Denise Cifelli, MS, Sara DeMauro, MD, Melissa Fernando, MPH, Ann Tierney, BA, MS.

Steering Committee Chair: LynnM. Taussig, MD, University of Denver,

NHLBI program officer: Carol J. Blaisdell, MD

Supported by National Institutes of Health U01 HL101794 (University of Pennsylvania, B Schmidt), U01 HL101456 (Vanderbilt University, JL Aschner, U01 HL101798 (University of California San Francisco, PL Ballard, RL Keller) U01 HL101813 (University of Rochester and University at Buffalo, GS Pryhuber, R Ryan, T Mariani), U01 HL101465 (Washington University, A Hamvas, T Ferkol), U01 HL101800 (Cincinnati Children's Hospital Medical Center, AH Jobe, CA Chougnet), and 5R01HL105702 (Indiana University and Duke University, CM Cotton, SD Davis, JA Voynow). The authors declare no conflicts of interest.

Abbreviations:

BPD	bronchopulmonary dysplasia
BPCA	Best Pharmaceuticals for Children Act
ELGAN	extremely low gestational age neonate
ETS	environmental tobacco smoke exposure
GA	gestational age
GEE	generalized estimating equations
m	months
NHLBI	National Heart. Lung and Blood Institute
NICU	neonatal intensive care unit
PMA	postmenstrual age
PRD	post-prematurity respiratory disease
PROP	Prematurity and Respiratory Outcomes Program
RDS	respiratory distress syndrome
w	weeks

References

1. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379(9832):2162–2172. [PubMed: 22682464]
2. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2015;385(9966):430–440. [PubMed: 25280870]
3. Baraldi E, Filippone M. Chronic lung disease after premature birth. N Engl J Med. 2007;357(19): 1946–1955. [PubMed: 17989387]
4. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. JAMA. 2015;314(10):1039–1051. [PubMed: 26348753]
5. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics. 2010;126(3): 443–456. [PubMed: 20732945]
6. Lapcharoensap W, Gage SC, Kan P, Profit J, Shaw GM, Gould JB, et al. Hospital variation and risk factors for bronchopulmonary dysplasia in a population-based cohort. JAMA Pediatr. 2015;169(2):e143676. [PubMed: 25642906]
7. Smith VC, Zupancic JA, McCormick MC, Croen LA, Greene J, Escobar GJ, et al. Trends in severe bronchopulmonary dysplasia rates between 1994 and 2002. J Pediatr. 2005;146(4):469–473. [PubMed: 15812448]
8. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, et al. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics. 2005;116(6):1353–1360. [PubMed: 16322158]
9. Berman S, Richardson DK, Cohen AP, Pursley DM, Lieberman E. Relationship of race and severity of neonatal illness. Am J Obstet Gynecol. 2001;184(4):668–672. [PubMed: 11262470]
10. Avery ME, Tooley WH, Keller JB, Hurd SS, Bryan MH, Cotton RB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics. 1987;79(1):26–30. [PubMed: 3797169]
11. Kavvadia V, Greenough A, Dimitriou G, Hooper R. Influence of ethnic origin on respiratory distress syndrome in very premature infants. Arch Dis Child Fetal Neonatal Ed. 1998;78(1):F25–28. [PubMed: 9536836]
12. Ying GS, Quinn GE, Wade KC, Repka MX, Baumritter A, Daniel E, et al. Predictors for the development of referral-warranted retinopathy of prematurity in the telemedicine approaches to evaluating acute-phase retinopathy of prematurity (e-ROP) study. JAMA Ophthalmol. 2015;133(3):304–311. [PubMed: 25521746]
13. Laughon MM, Langer JC, Bose CL, Smith PB, Ambalavanan N, Kennedy KA, et al. Prediction of bronchopulmonary dysplasia by postnatal age in extremely premature infants. Am J Respir Crit Care Med. 2011;183(12):1715–1722. [PubMed: 21471086]
14. Petrova A, Mehta R, Anwar M, Hiatt M, Hegyi T. Impact of race and ethnicity on the outcome of preterm infants below 32 weeks gestation. J Perinatol. 2003;23(5):404–408. [PubMed: 12847537]
15. Palta M, Gabbert D, Weinstein MR, Peters ME. Multivariate assessment of traditional risk factors for chronic lung disease in very low birth weight neonates. The Newborn Lung Project. J Pediatr. 1991;119(2):285–292. [PubMed: 1861218]
16. Collaco JM, Choi SJ, Riekert KA, Eakin MN, McGrath-Morrow SA, Okelo SO. Socioeconomic factors and outcomes in chronic lung disease of prematurity. Pediatr Pulmonol. 2011;46(7):709–716. [PubMed: 21328574]
17. Pryhuber GS, Maitre NL, Ballard RA, Cifelli D, Davis SD, Ellenberg JH, et al. Prematurity and respiratory outcomes program (PROP): study protocol of a prospective multicenter study of respiratory outcomes of preterm infants in the United States. BMC Pediatr. 2015;15:37. [PubMed: 25886363]

18. Maitre NL, Ballard RA, Ellenberg JH, Davis SD, Greenberg JM, Hamvas A, et al. Respiratory consequences of prematurity: evolution of a diagnosis and development of a comprehensive approach. J Perinatol. 2015;35(5):313–321. [PubMed: 25811285]
19. Poindexter BB, Feng R, Schmidt B, Aschner JL, Ballard RA, Hamvas A, et al. Comparisons and Limitations of Current Definitions of Bronchopulmonary Dysplasia for the Prematurity and Respiratory Outcomes Program. Ann Am Thorac Soc. 2015;12(12):1822–1830. [PubMed: 26397992]
20. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics. 1988;82(4):527–532. [PubMed: 3174313]
21. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163(7): 1723–1729. [PubMed: 11401896]
22. Keller RL, Feng R, DeMauro SB, Ferkol T, Hardie W, Rogers EE, et al. Bronchopulmonary Dysplasia and Perinatal Characteristics Predict 1-Year Respiratory Outcomes in Newborns Born at Extremely Low Gestational Age: A Prospective Cohort Study. J Pediatr. 2017.
23. Berman S, Tanasijevic MJ, Alvarez JG, Ludmir J, Lieberman E, Richardson DK. Racial differences in the predictive value of the TDx fetal lung maturity assay. Am J Obstet Gynecol. 1996;175(1): 73–77. [PubMed: 8694078]
24. Richardson DK, Torday JS. Racial differences in predictive value of the lecithin/sphingomyelin ratio. Am J Obstet Gynecol. 1994;170(5 Pt 1):1273–1278. [PubMed: 8178852]
25. Hulsey TC, Alexander GR, Robillard PY, Annibale DJ, Keenan A. Hyaline membrane disease: the role of ethnicity and maternal risk characteristics. Am J Obstet Gynecol. 1993;168(2):572–576. [PubMed: 8438930]
26. Robillard PY, Hulsey TC, Alexander GR, Sergent MP, de Caunes F, Papiernik E. Hyaline membrane disease in black newborns: does fetal lung maturation occur earlier? Eur J Obstet Gynecol Reprod Biol. 1994;55(3):157–161. [PubMed: 7958158]
27. Alexander GR, de Caunes F, Hulsey TC, Tompkins ME, Allen M. Ethnic variation in postnatal assessments of gestational age: a reappraisal. Paediatr Perinat Epidemiol. 1992;6(4):423–433. [PubMed: 1475217]
28. Hulsey TC, Levkoff AH, Alexander GR, Tompkins M. Differences in black and white infant birth weights: the role of maternal demographic factors and medical complications of pregnancy. South Med J. 1991;84(4):443–446. [PubMed: 2014426]
29. Papiernik E, Alexander GR, Paneth N. Racial differences in pregnancy duration and its implications for perinatal care. Med Hypotheses. 1990;33(3):181–186. [PubMed: 2292982]
30. Platt MJ. Outcomes in preterm infants. Public Health. 2014;128(5):399–403. [PubMed: 24794180]
31. Ross S, Naeye RL. Racial and environmental influences on fetal lung maturation. Pediatrics. 1981;68(6):790–795. [PubMed: 7322714]
32. Olowe SA, Akinkugbe A. Amniotic fluid lecithin/sphingomyelin ratio: comparison between an African and North American community. Pediatrics. 1978;62(1):38–41. [PubMed: 683781]
33. Rosa MJ, Pajak A, Just AC, Sheffield PE, Kloog I, Schwartz J, et al. Prenatal exposure to PM2.5 and birth weight: A pooled analysis from three North American longitudinal pregnancy cohort studies. Environ Int. 2017;107:173–180. [PubMed: 28738263]
34. Dogaru CM, Nyffenegger D, Pescatore AM, Spycher BD, Kuehni CE. Breastfeeding and childhood asthma: systematic review and meta-analysis. Am J Epidemiol. 2014;179(10):1153–1167. [PubMed: 24727807]
35. Dadlez NM, Esteban-Cruciani N, Khan A, Douglas LC, Shi Y, Southern WN. Risk Factors for Respiratory Decompensation Among Healthy Infants With Bronchiolitis. Hosp Pediatr. 2017;7(9): 530–535. [PubMed: 28830913]
36. Santiago J, Mansbach JM, Chou SC, Delgado C, Piedra PA, Sullivan AF, et al. Racial/ethnic differences in the presentation and management of severe bronchiolitis. J Hosp Med. 2014;9(9): 565–572. [PubMed: 24913444]
37. Escobar GJ, Ragins A, Li SX, Prager L, Masaquel AS, Kipnis P. Recurrent wheezing in the third year of life among children born at 32 weeks' gestation or later: relationship to laboratory-

confirmed, medically attended infection with respiratory syncytial virus during the first year of life. Arch Pediatr Adolesc Med. 2010;164(10):915–922. [PubMed: 20921348]

38. Stevenson MD, Mansbach JM, Mowad E, Dunn M, Clark S, Piedra PA, et al. Prenatal Versus Postnatal Tobacco Smoke Exposure and Intensive Care Use in Children Hospitalized With Bronchiolitis. Acad Pediatr. 2016;16(5):446–452. [PubMed: 26555856]
39. Riddell CA, Harper S, Kaufman JS. Trends in Differences in US Mortality Rates Between Black and White Infants. JAMA Pediatr. 2017;171(9):911–913. [PubMed: 28672288]
40. Akinbami LJ, Moorman JE, Simon AE, Schoendorf KC. Trends in racial disparities for asthma outcomes among children 0 to 17 years, 2001-2010. J Allergy Clin Immunol. 2014;134(3):547–553 e545. [PubMed: 25091437]
41. Torgerson DG, Ballard PL, Keller RL, Oh S, Huntsman S, Hu D, et al. Ancestry and Genetic Associations with Bronchopulmonary Dysplasia in Preterm Infants. bioRxiv. 2018.
42. Wai KC, Hibbs AM, Steurer MA, Black DM, Asselin JM, Eichenwald EC, et al. Maternal Black Race and Persistent Wheezing Illness in Former Extremely Low Gestational Age Newborns: Secondary Analysis of a Randomized Trial. J Pediatr. 2018.

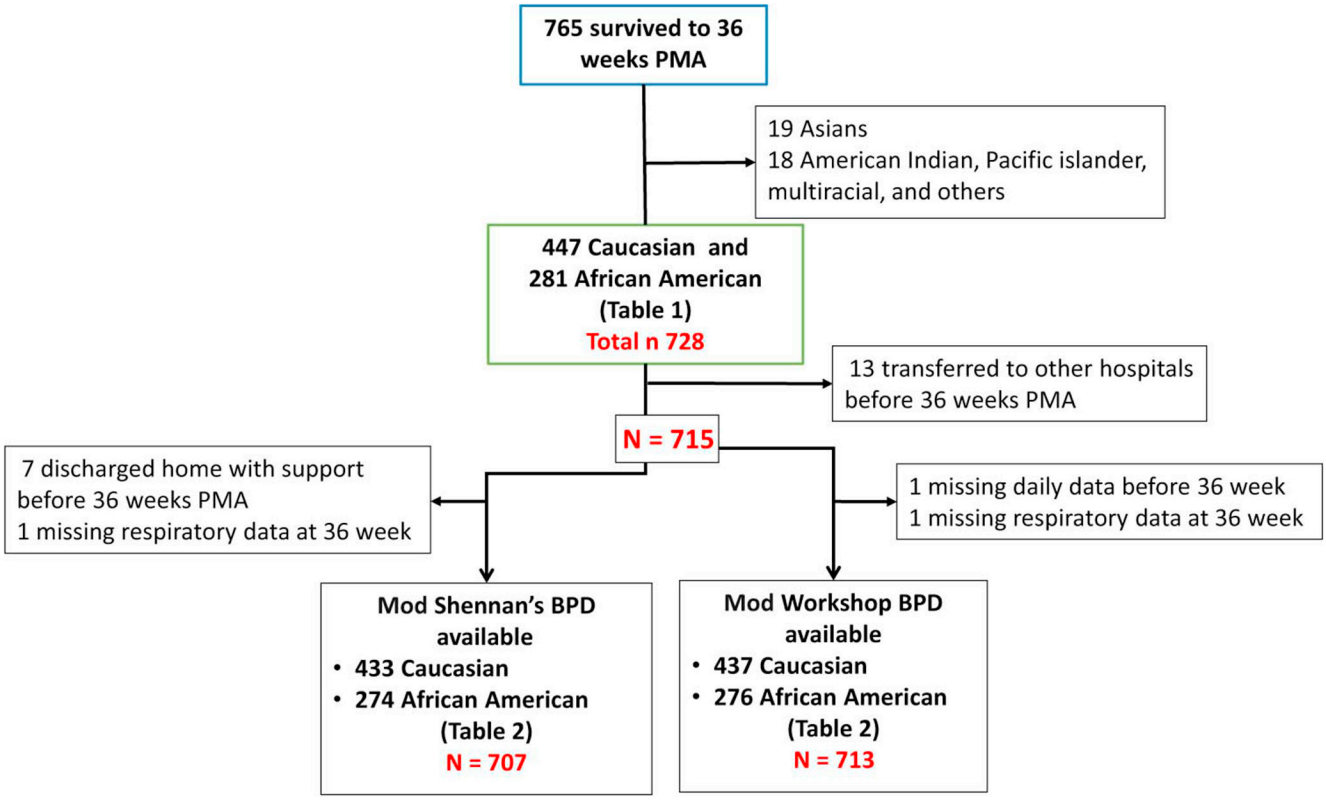

Figure 1.

Percentage of babies with bronchopulmonary dysplasia by race and gestational age in PROP cohort of babies <29 weeks gestation.

Data were collected for 707 newborn infants born at <29 weeks gestation for whom both race and BPD outcome were known. For race based on maternal self-report, and using the modified Shennan definition of BPD (supplemental oxygen at 36 weeks postmenstrual age), the rate of BPD was lower for Black babies at each week of GA at birth. The odds ratio for BPD was **0.60** (95% confidence interval 0.42-0.85, P=0.004) for Black infants compared with White infants after adjusting for gestational age, intubation at birth, antenatal steroid use, surfactant use within 72 hours after birth, and sibling correlations.

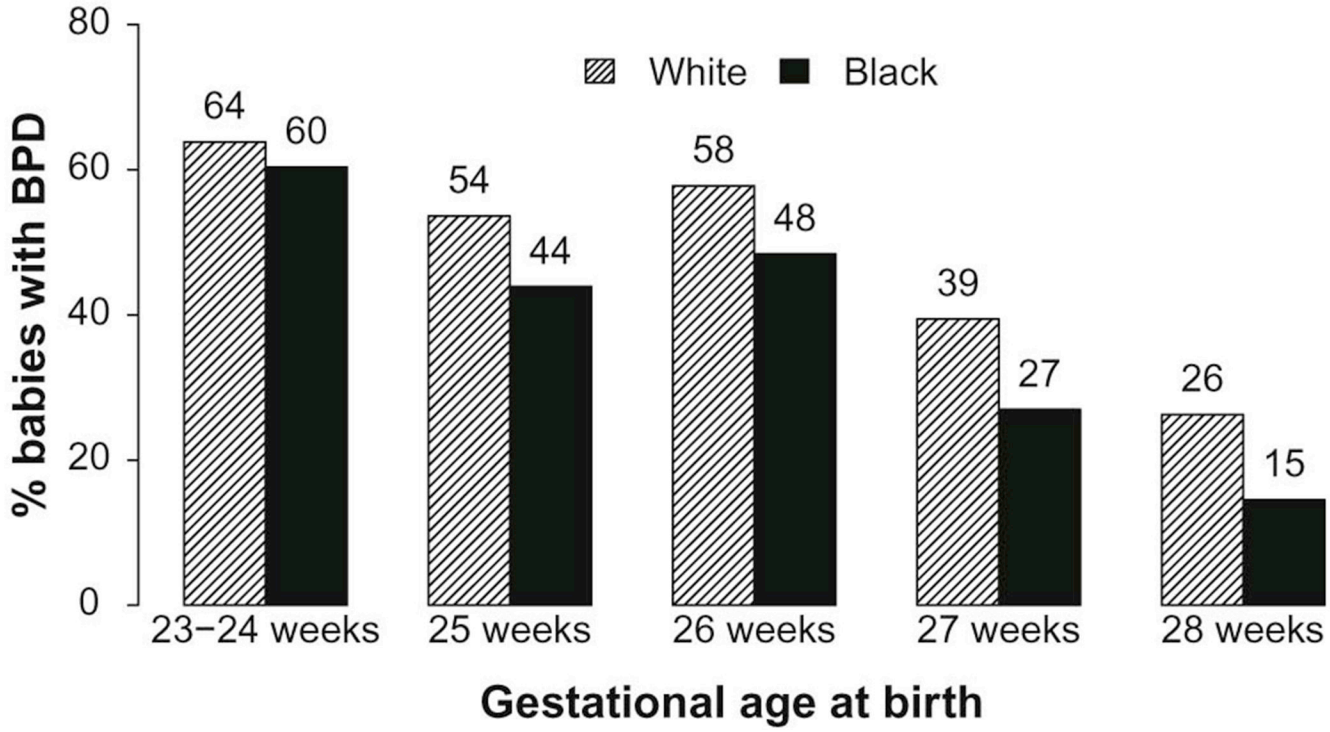

Figure 2.

Percentage of infants with BPD by race and GA in the PROP cohort of infants born at <29 weeks of gestation. Data were collected for 707 newborn infants born at <29 weeks of gestation in whom both race and BPD outcome were known. For race based on maternal self-report, and using the modified Shennan definition of BPD (ie, supplemental oxygen at 36 weeks postmenstrual age), the rate of BPD was lower for black infants at each week of GA at birth. The OR for BPD was 0.60 (95% CI, 0.42-0.85; P = .004) for black infants compared with white infants after adjusting for GA, intubation at birth, ANS use, surfactant use within 72 hours after birth, and sibling correlations.

Table 1.

Characteristics of PROP White and Black Babies

	White[a] (N=447) n (%) or mean ± SD or median (IQR)	Black[a] (N=281) n (%) or mean ± SD or median (IQR)	p-value for comparing race[b]
Male	243 (54%)	130 (46%)	0.033
Gestational age			0.005
23-24w	47 (11%)	55 (20%)	
25w	72 (16%)	42 (15%)	
26w	93 (21%)	63 (22%)	
27w	114 (26%)	66 (23%)	
27w	121 (27%)	55 (20%)	
Gestational age, wks	26.8 ± 1.4	26.5 ± 1.4	0.002
Birth weight, g	938.5 (240.7)	874.1 (215.6)	0.0003
Any antenatal steroids	394 (88%)	232 (83%)	0.035
Resuscitation at birth	111 (25%)	74 (26%)	0.650
Intubation at birth	336 (75%)	236 (84%)	0.005
Surfactant use within 72 hours after birth	365 (82%)	239 (85%)	0.235
Comorbidities			
Pulmonary Hemorrhage	13 (3%)	5 (2%)	0.464
Pneumothorax	17 (4%)	6 (2%)	0.278
PDA	226 (51%)	133 (47%)	0.396
Pulmonary Hypertension	37 (8%)	28 (10%)	0.437
Sepsis	90 (20%)	55 (20%)	0.854
NEC	31 (7%)	29 (10%)	0.106
ROP	235 (53%)	142 (51%)	0.592
IVH	131 (29%)	74 (26%)	0.385
Maternal education			2.7×10^{-11}
HS or less, unknown	222/444[c] (50%)	179 (64%)	
Partial college	70/444[c] (16%)	70 (25%)	
College grad or beyond	152/444[c] (34%)	32 (11%)	
Maternal BMI at birth	30.6 (25.5-37.6)	32.5 (27.1-38.4)	0.017
Smoking during pregnancy	85/446[c] (19%)	59 (21%)	0.523
Death before 36 week PMA (out of all enrolled)[d]	37/484[d] (8%)	22/303[d] (7%)	0.842

[a]Race based on maternal report of infant as Caucasian or African-American

[b]Chi-square test of Fisher's exact test or t-test or Wilcox on test

[c]Missing data, denominator is the number of subjects with data available SD, standard deviation, IQR, interquartile range, PDA, patent ductus arteriosus, NEC, necrotizing enterocolitis, ROP, retinopathy of prematurity, IVH, intraventricular hemorrhage, HS, high school, BMI, body-mass index, PMA, postmenstrual age, w, weeks

[db]Withdrawals before 36 weeks were excluded

Table 2.

BPD by Race in PROP cohort of babies <29 weeks gestation

	White	Black	Unadjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)	p-value[b]
Modified Shennan's BPD			0.77 (0.57-1.05)	0.60 (0.42-0.85)	0.004
No	240/433 (55%)	169/274 (62%)			
Yes	193/433 (45%)	105/274 (38%)			
Modified Workshop BPD					
No/Mild	238/437 (54%)	166/276 (60%)		- reference group -	
Moderate	64/437 (15%)	27/276 (10%)	0.88 (0.63-1.24)[c]	0.55 (0.33-0.90)[c]	0.019[c]
Severe	135/437 (31%)	83/276 (30%)	0.60 (0.37-0.99)[d]	0.63 (0.42-0.94)[d]	0.023[d]

[a] Univariate logistic regression, for African American compared with Caucasian, race based on maternal report of infant as Caucasian or African-American

[b] Mixed-effect logistic regression, adjusted by gestational age in weeks, intubation at birth, and any antenatal steroids, and accounted for dependence among siblings (as random effect)

[c] moderate BPD vs. no/mild BPD

[d] severe BPD vs. no/mild BPD

Table 3.

Effects of other covariates on BPD per modified Shennan's definition

	Unadjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)	p-value[b]
Gestational age in weeks	0.66 (0.58-0.73)	0.65 (0.57-0.75)	2.8×10^{-10}
Intubation at birth	2.31 (1.56-3.48)	1.64 (1.06-2.54)	0.027
Any antenatal steroids	0.52 (0.34-0.80)	0.49 (0.30-0.79)	0.003

[a] Univariate logistic regression

[b] Mixed-effect logistic regression, adjusted by race, gestational age in weeks, intubation at birth, and any antenatal steroids, and accounted for dependence among siblings (as random effect).