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], for the Prematurity and Respiratory Outcome Program (PROP) Investigators*

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 <29 weeks of gestation; 728 black or white infants survived to 36 weeks postmenstrual age (PMA). Logistic regression was used to compare BPD outcomes (defined as supplemental oxygen requirement at 36 weeks PMA) between the races, adjusted for gestational age (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%), even though they were of significantly lower GA. At every GA, BPD was more common in white infants. The aOR for BPD was 0.60 (95% CI, 0.42-0.85; $P = .004$) for black infants compared with white infants after adjusting for GA. Despite the lower rate of BPD, black infants had a higher rate of first-year post-prematurity respiratory disease (black, 79%; white, 63%).

Conclusions In this large cohort of recently born preterm infants at <29 weeks GA, compared with white infants, black infants had a lower risk of BPD but an increased risk of persistent respiratory morbidity. *(J Pediatr 2018;■■:■■-■■).*

See editorial, p •••

Preterm birth affects more than 500 000 babies born in the US each year, and 15 million children are born prematurely worldwide.[1] Despite improvements in care, preterm birth remains 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 (NIH) consensus criteria have defined BPD as the persistence of a supplemental oxygen requirement at 36 weeks postmenstrual age (PMA) among infants born before 32 weeks of gestation.[4]

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 neonates (ELGANs),[5] occurring in 40%-45% of infants born before 29 weeks of gestation.[6-8]

Previous studies have demonstrated racial differences in the outcomes of prematurity, with Caucasian infants having an increased likelihood of morbidities,[9] with higher rates of respiratory distress syndrome (RDS)[10,11] and retinopathy of

ANS	Antenatal steroid
BPD	Bronchopulmonary dysplasia
ELGAN	Extremely low gestational age neonate
GA	Gestational age
NIH	National Institutes of Health
PMA	Postmenstrual age
PRD	Post-prematurity respiratory disease
PROP	Prematurity and Respiratory Outcomes Program
RDS	Respiratory distress syndrome

From the [1]Department of Pediatrics, Medical University of South Carolina, Charleston, SC; [2]Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania, Philadelphia, PA; [3]Department of Pediatrics, University of Florida, Gainesville, FL; [4]Department of Pediatrics, Washington University, St. Louis, MO; [5]Division of Pediatric Pulmonology, Allergy and Sleep Medicine, Department of Pediatrics, Indiana University, Indianapolis, IN; [6]Department of Pediatrics, University of Rochester, Rochester, NY; [7]Perinatal Institute, Cincinnati Children's Hospital Medical Center, Cincinnati; [8]Department of Molecular Cardiology, Lerner Research Institute, The Cleveland Clinic, Cleveland, OH; and [9]Department of Pediatrics, Vanderbilt University, Nashville, TN

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

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prematurity.[12] However, the clinical results are often contradictory, with some showing African American race as protective[7,13] but others showing no apparent effect.[14,15] Greater use of medications in African American infants who were born premature and have BPD confounds the issue even further.[16]

The National Heart, Lung, and Blood Institute's Prematurity and Respiratory Outcome Program (PROP) is a large multicenter prospective cohort of infants born at <29 weeks of gestation, developed to identify clinical and biological markers predictive of respiratory outcomes during the first year of life.[17,18] We hypothesized that black infants would have less BPD compared with white infants and tested this hypothesis by comparing rates of BPD in maternal 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, physiological, and biochemical biomarkers during the initial neonatal intensive care unit hospitalization that can predict respiratory morbidity through age 1 year. Individual centers enrolled between 105 and 184 participants in the cohort, for a total of 835 subjects. The PROP study design and the status of the 765 infants surviving at 36 weeks PMA have been published previously.[17-19] We chose to use the terms "black" and "white" in discussing our findings generically, 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 born between $23^{0/7}$ and $28^{6/7}$ weeks of 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; and those whose families likely would 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 infant enrolled.

Trained research personnel collected detailed anthropometric, medication, and respiratory status data on a daily basis until discharge to home, transfer, or 40 weeks PMA. Follow-up data were collected from parents at 3, 6, 9, and 12 months corrected age (±1 month) through a focused questionnaire adminstered by telephone or at an in-person clinic visit. At the time of questionnaire administration, respiratory symptoms and health care utilization information for the previous 3 months was obtained from the parents and 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 a fraction of inspired oxygen of 21% at 36 weeks PMA are assigned "no BPD" status, regardless of the type or level of respiratory support.[20] This definition was modified by assigning the outcome of "no BPD" to infants who were discharged to home off respiratory support before 36 weeks PMA ("modified Shennan" definition).[5,20] The modified Shennan definition was chosen by the PROP group to improve the ability to classify as many infants as possible and its easier clinical applicability (eg, 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 assayed 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 4 domains/elements represented in the quarterly follow-up surveys administered through 12 months corrected gestational age (GA) were (1) respiratory medications (ie, inhaled bronchodilators or steroids, systemic steroids, methylxanthines, diuretics, pulmonary vasodilators, or leukotriene receptor antagonists); (2) hospitalization for cardiopulmonary cause; (3) any wheeze or cough without a cold, 1 or more times per week; and (4) home technology dependence (eg, use of oxygen, ventilator, continuous positive airway pressure/bilevel positive airway pressure, tracheostomy in place).

Statistical Analyses

Among 36 week survivors, proportions, means, and medians were compared between the 2 races using the Pearson χ^2 test, Fisher exact test, 2-group *t* test, and Wilcoxon rank-sum test, respectively. The association between race and BPD was assessed by mixed-effects logistic regression models, adjusted by GA at birth, intubation at birth, antenatal steroid (ANS) use, and sibling correlations. For the modified NIH Workshop BPD definition, the severe and moderate groups were compared with the no/minimal group in 2 separate models. The race effect on PRD was estimated using mixed-effects regression models, as described previously by Keller et al.[22]

To examine the contribution of clinical site to the effect of race, the raw ORs of BPD for black infants vs white infants 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 University, Jackson-Madison Country General Hospital, University of Rochester, University at Buffalo, Duke University, and University of Indiana.

Results

Of the 835 subjects enrolled in PROP, 765 survived to 36 weeks PMA and were classified as BPD-positive or BPD-negative. A total of 728 infants (447 white and 281 black) were available

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Table I. Characteristics of PROP white and black infants

Characteristics	White (n = 447)*	Black (n = 281)*	*P* value for comparing race†
Male sex, n (%)	243 (54)	130 (46)	.033
GA, n (%)			.005
23-24 wk	47 (11)	55 (20)	
25 wk	72 (16)	42 (15)	
26 wk	93 (21)	63 (22)	
27 wk	114 (26)	66 (23)	
27 wk	121 (27)	55 (20)	
GA, wk, mean ± SD	26.8 ± 1.4	26.5 ± 1.4	.002
Birth weight, g, median (IQR)	938.5 (240.7)	874.1 (215.6)	.0003
Any ANS use, n (%)	394 (88)	232 (83)	.035
Resuscitation at birth, n (%)	111 (25)	74 (26)	.650
Intubation at birth, n (%)	336 (75)	236 (84)	.005
Surfactant use within 72 h after birth, n (%)	365 (82)	239 (85)	.235
Comorbidities, n (%)			
Pulmonary hemorrhage	13 (3)	5 (2)	.464
Pneumothorax	17 (4)	6 (2)	.278
Patent ductus arteriosus	226 (51)	133 (47)	.396
Pulmonary hypertension	37 (8)	28 (10)	.437
Sepsis	90 (20)	55 (20)	.854
Necrotizing enterocolitis	31 (7)	29 (10)	.106
Retinopathy of prematurity	235 (53)	142 (51)	.592
Intraventricular hemorrhage	131 (29)	74 (26)	.385
Maternal education, n/N or n (%)			2.7×10^{-11}
High school diploma or less, unknown	222/444‡ (50)	179 (64)	
Some college	70/444‡ (16)	70 (25)	
College degree or beyond	152/444‡ (34)	32 (11)	
Maternal body mass index at birth, median (IQR)	30.6 (25.5-37.6)	32.5 (27.1-38.4)	.017
Smoking during pregnancy, n/N or n (%)	85/446‡ (19)	59 (21)	.523
Death before 36 wk PMA (of all enrolled), n/N or n (%)§	37/484§ (8)	22/303§ (7)	.842

*Race based on maternal report of infant as Caucasian or African-American.
†The χ^2 test, Fisher exact test, *t* test, or Wilcoxon rank-sum test.
‡Missing data; the denominator is the number of subjects with data available.
§Withdrawals before 36 weeks were excluded.

for these analyses (**Table I**). BPD outcome data were available for 707 of these infants, and 21 did not have modified Shennan status available (due to transfer before 36 weeks, n = 13; discharge to home on oxygen before 36 weeks, n = 7; or missing data, n = 1) (**Figure 1**; available at www.jpeds.com). Of the 707 infants with outcome data, black infants (105 of 274; 38%) were significantly less likely to develop BPD compared with white infants (193 of 433; 45%) (**Table II**). The estimated aOR of having BPD in black infants vs white infants was 0.60 (95% CI, 0.42-0.85; $P = .004$), after adjusting for GA, ANS use, and intubation at birth (**Table II**). Black infants also had less severe BPD compared with white infants, as defined using the NIH Workshop 1991 consensus criteria (**Table II**).

Because lower GA is highly correlated with an increased risk for BPD, we examined the GA distribution in white infants and black infants (**Table I**). Black infants were significantly more likely than white infants to be born at earlier gestation ($P = .005$, χ^2 test). The rate of BPD was lower for black infants at each week of GA at birth (**Figure 2**). The race effects across clinical sites were homogenous ($P = .91$, Breslow-Day test of homogeneity); thus, site was not a confounder for the effect of race on BPD.

To assess the possibility that the lower survival to 36 weeks PMA in black infants compared with white infants was responsible for their lower rate of BPD, we analyzed survival data in our cohort. There was no difference in survival between black

Table II. BPD by race in the PROP cohort of infants born at <29 weeks of gestation

Criteria	White, n/N (%)	Black, n/N (%)	Unadjusted OR* (95% CI)	aOR† (95% CI)	*P* value†
Modified Shennan BPD			0.77 (0.57-1.05)	0.60 (0.42-0.85)	.004
No	240/433 (55)	169/274 (62)			
Yes	193/433 (45)	105/274 (38)			
Modified Workshop BPD					
None/mild	238/437 (54)	166/276 (60)		Reference group	
Moderate	64/437 (15)	27/276 (10)	0.88 (0.63-1.24)‡	0.55 (0.33-0.90)‡	.019‡
Severe	135/437 (31)	83/276 (30)	0.60 (0.37-0.99)§	0.63 (0.42-0.94)§	.023§

*Univariate logistic regression for black compared with white: race based on maternal report of infant as Caucasian or African American.
†Mixed-effects logistic regression, adjusted by GA in weeks, intubation at birth, and any ANS use, and accounting for dependence among siblings (as a random effect).
‡Moderate BPD vs no/mild BPD.
§Severe BPD vs no/mild BPD.

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Table III. Effects of other covariates on BPD per modified Shennan definition

Covariates	Unadjusted OR* (95% CI)	aOR† (95% CI)	*P* value†
GA for each week higher	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)	.027
Any ANS use	0.52 (0.34-0.80)	0.49 (0.30-0.79)	.003

*Univariate logistic regression.
†Mixed-effects logistic regression, adjusted by GA in weeks, intubation at birth, and any ANS use, and accounting for dependence among siblings (as a random effect).

and white infants even after adjusting for GA (**Table I**), suggesting that differences in mortality rates could not account for the difference in BPD prevalence between black and white infants.

Previous studies have suggested that black infants have more "mature" lungs at birth,[11,23-26] higher scores on Ballard examination,[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/RDS. Despite a lower mean birth GA, black infants were less likely than white infants to be exposed to ANS (83% vs 88%; $P = .035$, χ^2 test) (**Table I**). In addition, black infants weighed 64.4 g less on average ($P = .0003$, t test) and were intubated more often (84% vs 75%; $P = .005$) (**Table I**). Owing to these differences at baseline, we included these variables in the assessment of race effect on BPD (**Table II**) and also examined their independent contributions to BPD (**Table III**). Exposure to ANS and higher GA were protective against BPD, and intubation at birth was associated with a higher risk of BPD.

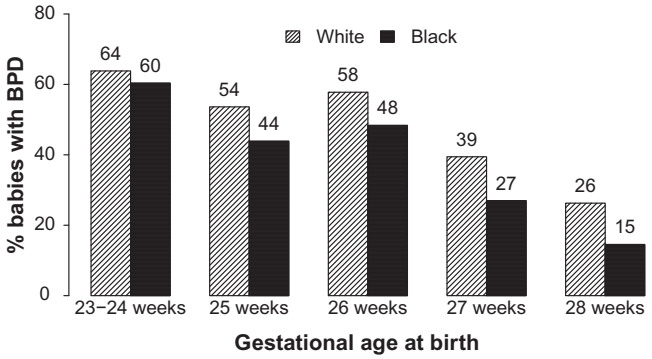

Figure 2. Percentage of infants with BPD by race and GA in the PROP cohort of infants born at <29 weeks of gestation. Data were collected for 707 newborn infants born at <29 weeks of gestation in whom both race and BPD outcome were known. For race based on maternal self-report, and using the modified 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.

However, despite their lower ANS exposure, lower GA, and higher rate of intubation at birth, black infants were still less likely to have BPD at 36 weeks even after adjusting for these factors.

The first year respiratory outcomes for the full PROP cohort have been published previously.[22] In that study, black race remained independently associated with an increase in first-year postdischarge respiratory morbidity (PRD), even after adjusting for GA and other confounders in the regressional analysis and despite a lower rate of BPD. This was true whether the modified Shennan definition or the NIH Workshop definition was used. However, the outcome of PRD was not reported by race, and here we provide that information. Among the infants assessed for PRD, PRD occurred in 79% of black infants and 63% of white infants.

Discussion

In this large contemporary PROP cohort of 728 black and white ELGANs enrolled across 11 clinical sites, the black infants had a lower prevalence of BPD compared with the white infants. Infants from other races were not included in our analyses owing to their low numbers. The lower prevalence of BPD in black infants was not related to being born at a later GA, because black infants were more likely to be born at an earlier GA, and this advantage for black race persisted across all GAs. The lower rate of BPD in black infants also was not related to lower survival. As might be expected, each week of GA remained a powerful predictor for survival (OR, 0.65; 95% CI, 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 GA compared with white infants, despite their lower rate of BPD at 36 weeks PMA. Among infants with assessable PRD, 79% of the 261 black infants had PRD, compared with 63% of the 428 white infants.

A lower rate of RDS in black infants compared with white infants has been recognized for many years,[9-11] and some studies have suggested that this might 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 between blacks and whites and may contribute to increased surfactant production.[33] The lower use of surfactant in the first 72 hours in black infants compared with white infants in our ELGANs suggests that even the most premature black infants have a lower risk of RDS.

The baseline demographic data show less ANS use in black infants compared with white infants. We did not have the appropriate data to explain why an infant was or was not given ANS, and thus are unable to offer an evidenced-based discussion related to health care access, length of hospital stay before delivery, or other possible factors. However, we did examine the contribution of these discrepant confounders specifically (**Table III**), and despite lower ANS use and lower GA and higher intubation at birth, black infants were still less likely to have BPD at 36 weeks even after adjusting for these factors.

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The PROP cohort allows for examination of the association of race not only with BPD, but also with PRD. Although BPD is a reasonable predictor of postdischarge respiratory morbidity, we found higher rates of PRD (the 1-year outcome for the PROP cohort) in black infants compared with white infants despite the lower BPD rate in blacks.[22] This finding suggests that although BPD remains an important predictor of early childhood respiratory disease,[22] there appear to be other, as-yet unidentified race-related factors contributing to early childhood respiratory disease in black infants after neonatal intensive care unit discharge. Such factors may include reduced breast milk consumption and increased environmental tobacco smoke exposure in black infants compared with 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 the higher rate of PRD in blacks reflects an increase in the number or severity of respiratory viral infections.[37] Because dietary and environmental exposures also influence bronchiolitis severity,[38] whether these exposures have direct effects on PRD or are mediated through viral illnesses is unclear.

Concerning proposed biological mechanisms, the higher rate of PRD in blacks may be due in part 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 influence a provider's decision to admit or prescribe medications. Thus, higher rates of PRD in blacks also may 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 infants compared with white infants, and black infants experience nearly 4-fold more deaths related to shorter gestation and lower birth weight, 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 the lower BPD rate in blacks may be protective against the development of reduced surface area for gas exchange, the higher PRD rate in blacks may represent the development of an obstructive airway defect. The increased respiratory morbidity during the first year could reflect the higher incidence of asthma in black children, irrespective of the child's socioeconomic status. The difference in asthma rate between black and white children has widened over the past 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 (TOLSURF) study have been analyzed for the contribution of race to BPD and later respiratory morbidity. Torgerson et al reported an association between black race and improved survival without BPD,[41] and Wai et al reported an association between black race and more wheezing at 18-24 months of age.[42]

Limitations of the present study include the self-reporting of infant race by mothers. However, infants' DNA ancestry markers were correlated with the maternal self-reporting of race in our preliminary analysis (**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 were based primarily on parental recall, which is inexact, as discussed in detail previously.[22] A rigorous data collection method was applied for the study's primary outcome—BPD outcome—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 as a focus of future studies. ■

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Reprint requests: Rita M. Ryan, MD, Pediatrics, 165 Ashley Ave, MSC 917, Charleston, SC 29425. E-mail: ryanr@musc.edu

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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, MD[l], Mark R. Holland, PhD, James Kemp, MD, Philip T. Levy, MD, Christopher McPherson, PharmD, Phillip Tarr, MD, Gautam K. Singh, MD, Barbara Warner, MD, ([l]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, MD[d], 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; **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; National Heart, Lung, and Blood Institute Program Officer: Carol J. Blaisdell, MD.

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

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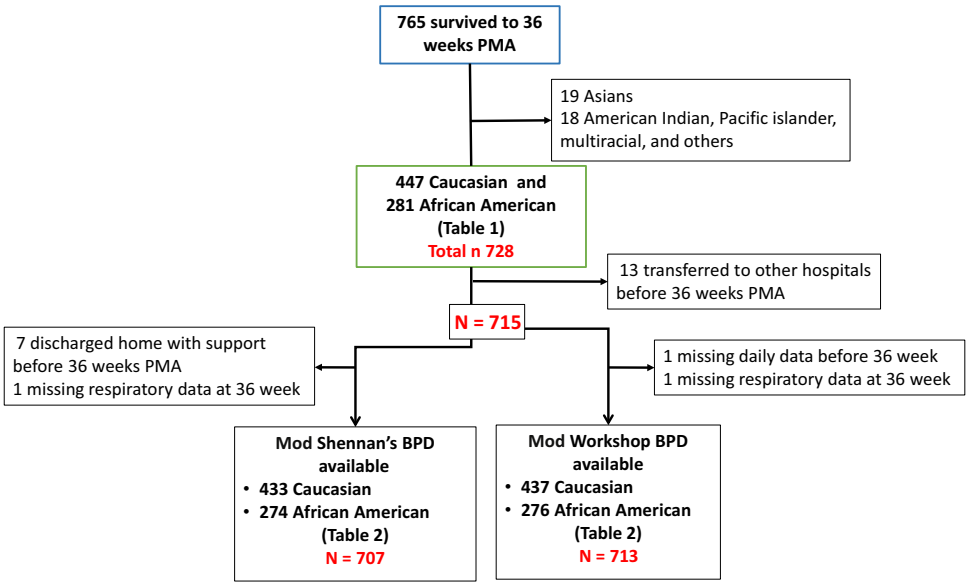

Figure 1. CONSORT diagram to describe the final populations studied. These are infants who had both race data and BPD outcome data available. *BPD*, bronchopulmonary dysplasia; *Mod*, modified Shennan and NIH Workshop definitions are described in text; *PMA*, postmenstrual age.

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