Pediatric RESEARCH

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CLINICAL RESEARCH ARTICLE

Racial/ethnic disparities and human milk use in necrotizing enterocolitis

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BACKGROUND: The impact of human milk use on racial/ethnic disparities in necrotizing enterocolitis (NEC) incidence is unknown.
METHODS: Trends in NEC incidence and human milk use at discharge were evaluated by race/ethnicity among 47,112 very low birth weight infants born in California from 2008 to 2017. We interrogated the association between race/ethnicity and NEC using multilevel regression analysis, and evaluated the effect of human milk use at discharge on the relationship between race/ethnicity and NEC using mediation analysis.
RESULTS: Annual NEC incidence declined across all racial/ethnic groups from an aggregate average of 4.8% in 2008 to 2.6% in 2017. Human milk use at discharge increased over the time period across all racial groups, and non-Hispanic (NH) black infants received the least human milk each year. In multivariable analyses, Hispanic ethnicity (odds ratio (OR) 1.27, 95% confidence interval (CI) 1.02–1.57) and Asian or Pacific Islander race (OR 1.35, 95% CI 1.01–1.80) were each associated with higher odds of NEC, while the association of NH black race with NEC was attenuated after adding human milk use at discharge to the model. Mediation analysis revealed that human milk use at discharge accounted for 22% of the total risk of NEC in non-white vs. white infants, and 44% in black vs. white infants.
CONCLUSIONS: Although NEC incidence has declined substantially over the past decade, a sizable racial/ethnic disparity persists. Quality improvement initiatives augmenting human milk use may further reduce the incidence of NEC in vulnerable populations.

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INTRODUCTION

Preterm birth and prematurity-related morbidities are associated with racial/ethnic disparities.[1,2] Preterm non-Hispanic (NH) black and Hispanic infants have higher rates of mortality, bronchopulmonary dysplasia, intraventricular hemorrhage, retinopathy of prematurity, and necrotizing enterocolitis (NEC) than preterm NH white infants.[1–4] NEC is a particularly devastating complication of prematurity, historically affecting 5–10% of very low birth weight (VLBW) infants, with a mortality of 20–30%, and often leading to life-long disability.[5,6] Promisingly, NEC incidence declined from about 7% in 2005 to 5% in 2014, among VLBW (<1500 g) infants across the United States.[5] Initiatives promoting human milk and standardized feeding protocols have increased over the past two decades and have likely contributed to the decrease in NEC incidence.[7–12] Whether vulnerable racial/ethnic groups have benefited equally from the recent decline in NEC incidence is unclear.

Racial/ethnic disparities in NEC persist despite controlling for key confounding factors, such as early gestational age (GA) and type of enteral feeding.[1–3] Janevic et al.[1] demonstrated that black and Hispanic infants compared with white infants have an increased risk of NEC, after adjusting for GA and socioeconomic factors. Jammeh et al.[3] showed that black and Hispanic infants have higher odds of NEC and NEC-related mortality, after adjusting for GA and type of enteral feeding. Furthermore, Anderson et al.[2] found that black infants have a higher risk of NEC than white infants across all GA categories. Despite these racial/ethnic disparities in NEC risk being repeatedly demonstrated, research into factors explaining the disparities has been understudied. Human milk use is a modifiable protective factor for NEC, and preterm NH black and Hispanic infants have been consistently shown to receive less human milk than NH white infants.[13–19] Our objective was to evaluate NEC incidence by racial/ethnic group over time in California and evaluate the mediating effect of human milk use between race/ethnicity and NEC.

METHODS

Study population

Using a population-based retrospective cohort approach, we examined all infants in the California Perinatal Quality Care Collaborative (CPQCC) born from January 1, 2008 to December 31, 2017, and between 22 weeks and 0 days' and 29 weeks and 6 days' GA, or with birth weights between 401 and 1500 g. We excluded infants who died in the delivery room, had congenital anomalies, or had missing outcome or race/ethnicity data. The CPQCC is a quality improvement organization that collects clinical and organization data from California neonatal intensive care units (NICUs), representing >95% of VLBW infants cared for in

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California.[20] Data elements in the CPQCC are collected using a standardized form by designated data contacts at each member NICU. Data contacts are trained by the CPQCC Data Center every year using standardized data collection protocols and manuals. At the time of data entry into the online data entry system, CPQCC uses extensive logic and range checks to ensure accurate data.[21]

Main exposures

Maternal race/ethnicity was obtained from CPQCC and was classified as NH white, NH black, white/Hispanic, Asian or Pacific Islander (API), or other. We examined the role of human milk use, which in the CPQCC was recorded as feeding with any human milk at hospital discharge. We posited that the presence of human milk at discharge would be a proxy for human milk use during the infant's early hospitalization since prior research demonstrates that racial/ethnic disparities in mother's milk use in VLBW infants are present in early hospitalization and reflect the disparity at discharge.[22]

Infant, maternal, and hospital covariates

Infant and maternal clinical data were obtained from the CPQCC. Clinical data were collected prospectively, using an expanded version of standard definitions developed by the Vermont Oxford Network.[23] Infant factors included birth year, sex, GA at birth, small for GA (SGA, birth weight <10th percentile), 5-min Apgar score, required transfer, multiple birth status, patent ductus arteriosus treatment, and postnatal steroid use. Maternal factors included receipt of prenatal care, chorioamnionitis, hypertension, diabetes, preterm premature rupture of membranes, fetal presentation/breech, bleeding/abruption/previa, and fetal distress. We linked each CPQCC record to birth certificate data from California Vital Statistics, allowing for access to maternal socioeconomic data, including maternal education, primary payer source, and country of birth. Using data from the CPQCC and California birth certificates, we considered hospital characteristics including American Academy of Pediatrics (AAP) level of neonatal care,[24] California Children's Services (CCS) level of care, number of NICU beds, annual volume of infants treated, availability of a neonatologist on call, hospital ownership, urban/rural status, and teaching hospital status. Hospital characteristics were obtained from the hospital at which the diagnosis of NEC occurred. For infants without NEC, hospital characteristics were obtained from the hospital at birth.

Outcomes

NEC in the CPQCC was defined from a classification developed by the Vermont Oxford Network. "NEC was diagnosed at surgery, at postmortem examination, or clinically and radiographically. Clinical and radiographical diagnosis required at least one of the following clinical signs present: (1) bilious gastric aspirate or emesis, (2) abdominal distension, (3) occult or gross blood in stool (no fissure) AND at least one of the following radiographic findings present: (1) pneumatosis intestinalis, (2) hepato-biliary gas, (3) pneumoperitoneum."[25] This definition for NEC excluded infants with spontaneous intestinal perforation (SIP) confirmed at laparotomy or postmortem examination. We assessed all cases of NEC and NEC requiring surgery.

Statistical analysis

We calculated yearly incidence for NEC, NEC surgery, and human milk use by dividing observed cases by the total number of infants at risk in the cohort. The population at risk was defined as all VLBW infants admitted to NICUs with available data for NEC, surgery for NEC, human milk use, and race/ethnicity. The average slope per year was calculated using linear regression of NEC, surgery for NEC, and human milk use by birth year. We further examined trends in each outcome stratified by race/ethnicity, and calculated absolute and relative risk differences. To determine if changes in rates over time were significantly different across races/ethnicities, we used nonparametric bootstrapping with 10,000 iterations to estimate a standard error for changes over time. To construct an adjusted model of the association between race/ethnicity and NEC, we used a smaller subset of infants due to availability of all covariates for only the years 2013–2017, and utilized a previously developed model for NEC from the CPQCC as a baseline model.[21] The base model included maternal race/ethnicity, GA in weeks, GA in weeks-squared, SGA, multiple births, 5-min Apgar score, sex, required transfer, prenatal care, and CCS level of care. We assessed the association of each additional infant, maternal, or hospital-level factor with NEC using a multilevel logistic regression model, adjusting for all factors in the baseline model, and including NICU as a random intercept. Any covariate that remained significant at $p < 0.05$ after adjustment for all confounders in the baseline model was included in the final multilevel model. Furthermore, the final model was analyzed with and without adjustment for human milk use.

We assessed human milk use as a possible mediator between race/ethnicity and NEC with causal mediation analysis, using a counterfactual framework (i.e., if racism and social inequities were eliminated) and regression adjustment methods as proposed by Valeri and Vanderweele.[26–28] This method of causal mediation analysis computes a four-way decomposition of the total effect of race/ethnicity on NEC, and in doing so, the following assumptions are required: no unmeasured exposure-outcome, mediator-outcome, or exposure-mediator confounders, and no mediator-outcome confounders are affected by the exposure. We used subsets of each racial/ethnic group to assess race/ethnicity as a binary exposure, and also limited analyses to infants who survived, to eliminate bias from infants who died and may not have a chance to have human milk use coded. The total effect of race/ethnicity on NEC was estimated, with adjustment for potential confounder variables. The natural *direct* effect was the effect of race/ethnicity on NEC not mediated through human milk use. The natural *indirect* effect was the effect of race/ethnicity on NEC mediated through human milk use. As the interaction between race/ethnicity and human milk use was significant, we included an interaction term in the mediation modeling. Percentage mediated was the percentage of the total effect that was attributed to mediation through human milk use. Analyses were performed with SAS 9.4 (SAS Institute, Cary, NC) and GraphPad Prism version 8.0 (GraphPad Software, La Jolla, CA).

RESULTS

Between 2008 and 2017, 53,489 infants met birth weight and GA inclusion criteria, of which 50,255 infants survived to NICU admission. After excluding infants with congenital anomalies (2,854), those with missing primary exposure (224), and outcome data (65), 47,112 infants remained available for analyses of trends in NEC incidence. For regression analyses, this cohort narrowed to 23,011 infants born from 2013 to 2017 due to availability of covariates, of which 679 (3.0%) infants were diagnosed with NEC and 233 (1.0%) with NEC requiring surgery. The mortality rate among infants with NEC was 28.4% (193/679).

The annual incidence of NEC decreased from 4.8% in 2008 to 2.6% in 2017, a relative reduction of 47% (Fig. 1). The annual incidence of surgical NEC decreased from 1.5% in 2008 to 0.9% in 2017, a relative reduction of 40%. Human milk use at NICU discharge increased from 51.8 to 60.8% over the same time period, a relative increase of 17%. Among race/ethnicity groups, white infants had the largest absolute and relative reduction in NEC incidence from 4.5 to 1.7% (2.8% absolute and 63% relative reduction). Incidence of NEC decreased in Hispanic infants from 5.2 to 2.7% (2.5% absolute and 47% relative reduction), in black infants from 4.9 to 2.8% (2.1% absolute and 43% relative reduction), and in API infants from 4.6 to 2.5% (2.1% absolute

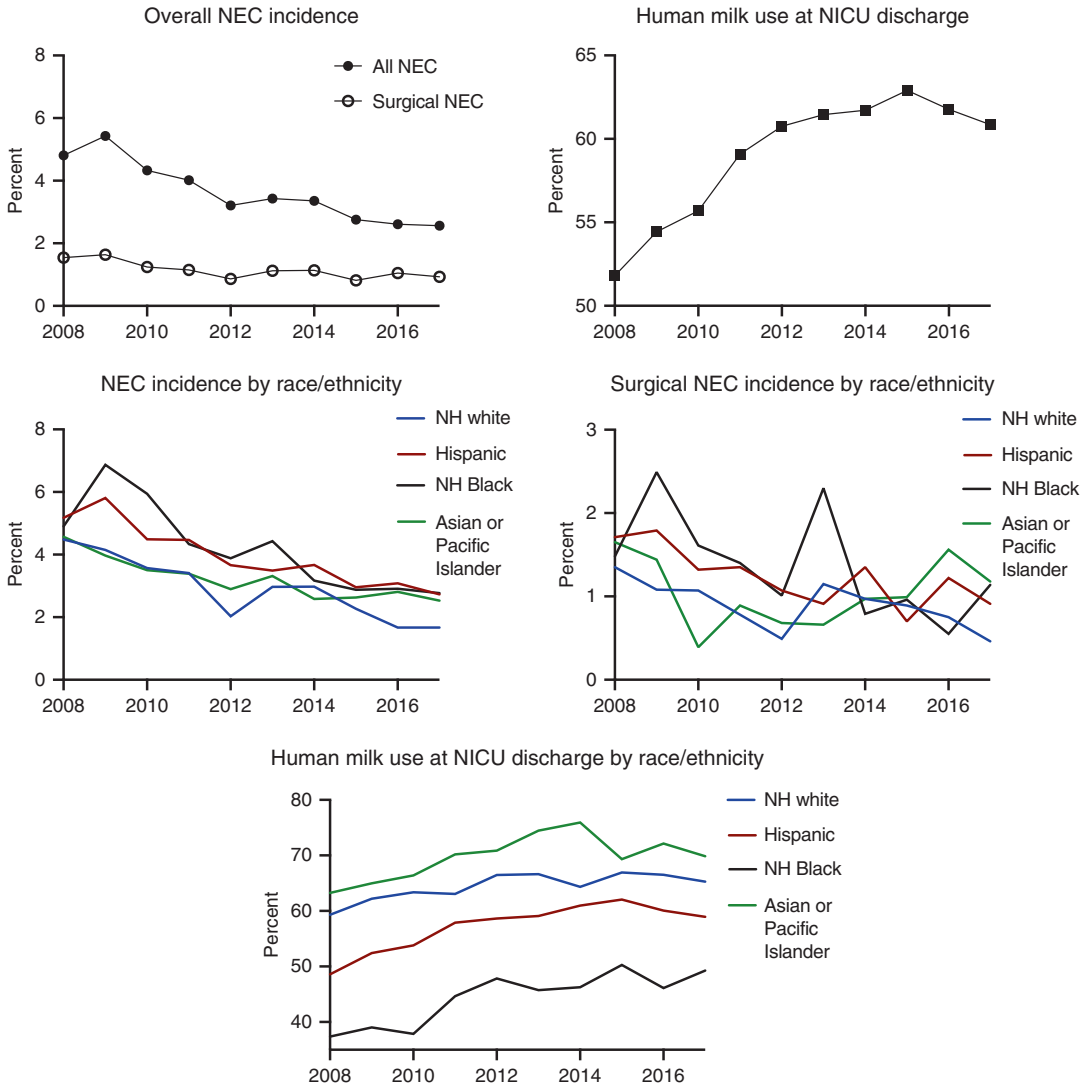

Fig. 1 Trends in NEC incidence and human milk use at NICU discharge from 2008 to 2017. Top panel illustrates overall NEC incidence and human milk use at NICU discharge by year. Middle and bottom panels illustrate NEC incidence, surgical NEC incidence and human milk use at NICU discharge by year and stratified by race/ethnicity.

and 45% relative reduction). Bootstrapping analysis of NEC incidence by year and race/ethnicity found that fitted slopes were statistically different between all pairs of races/ethnicities at $p < 0.001$. The changes per year in NEC surgery and human milk use at discharge were also significantly different across all pairs of races/ethnicities. A similar decline in surgical NEC incidence was seen among all racial/ethnic groups. Human milk use at discharge rose similarly across all racial/ethnic groups.

From 2013 to 2017, infants with and without NEC differed according to several infant-, maternal-, and hospital-level characteristics (Table 1). After adjustment for confounders, the odds of NEC were higher among Hispanic (odds ratio (OR) 1.27, 95% confidence interval (CI) 1.02–1.57) and API infants (OR 1.35, 95% CI 1.01–1.80) (Table 2). For black infants, the odds of NEC were marginally statistically significant in the adjusted model (OR 1.32, 95% CI 1.00–1.74), but no longer significant when additionally controlling for human milk use at discharge (OR 1.13, 95% CI 0.86–1.50). Compared to white infants, human milk use at discharge mediated a proportion of the relationship between race/ethnicity and NEC (Table 3 and Fig. 2), 22% for all non-white infants, 44% for black infants, and 19% for Hispanic infants).

DISCUSSION

This study provides an analysis of racial/ethnic disparities in NEC incidence in California. Although the overall incidence of NEC among VLBW infants improved dramatically from 4.8% in 2008 to 2.6% in 2017, the racial/ethnic divide widened. A decline in NEC incidence benefited white infants more than non-white infants, with respect to both absolute and relative risk reductions. A sizable racial/ethnic disparity remains in 2017 with NEC incidence 59% higher among Hispanic infants and 65% higher among black infants than among white infants. Suggested explanations for this disparity include that NEC in non-white infants may be facilitated by increased exposure to antenatal stressors,[29] care delivery in lower quality hospitals,[30–32] and less provision of human milk.[33,34]

Our study adds to prior research into racial/ethnic disparities in NEC.[1–3] We observed higher odds of NEC in Hispanic, black, and API infants compared to white infants. When additionally controlling for human milk use in our multivariable model, the association between black race and NEC was no longer statistically significant, suggesting the importance of human milk in this relationship. Although previous studies have investigated the relationship between race/ethnicity and NEC, we report new observations on annual trends in NEC incidence among racial/

Table 1. Patient characteristics of infants with NEC, surgical NEC, and without NEC, in California, 2013–2017.

Variable	All NEC ($N = 679$), *N* (%)	NEC with surgery ($N = 233$), *N* (%)	No NEC ($N = 22{,}332$), *N* (%)
Maternal characteristics			
Prenatal care			
Yes	644 (94.9)	223 (95.7)	21,380 (95.7)
No	33 (4.9)	8 (3.4)	925 (4.1)
Race/ethnicity			
White/NH	139 (20.5)	51 (21.9)	5822 (26.1)
White/Hispanic	332 (48.9)	106 (45.5)	10,061 (45.1)
Black/NH	95 (14.0)	34 (14.6)	2830 (12.7)
Asian or Pacific Islander	85 (12.5)	33 (14.2)	2980 (13.3)
Other	28 (4.1)	9 (3.9)	639 (2.9)
Education			
Less than high school	68 (10.0)	15 (6.4)	2066 (9.3)
High school degree/GED	189 (27.8)	61 (26.2)	5559 (24.9)
Some college	182 (26.8)	67 (28.8)	6314 (28.3)
Bachelor's or graduate	180 (26.5)	71 (30.5)	6225 (27.9)
Principal source of payment			
Medi-Cal	348 (51.1)	106 (45.5)	10,463 (46.8)
Other government program	7 (1.0)	1 (0.4)	371 (1.7)
Private insurance	290 (42.7)	117 (50.2)	10,430 (46.7)
Self pay	8 (1.2)	0 (0)	496 (2.2)
Other	16 (2.4)	5 (2.2)	332 (1.5)
Chorioamnionitis			
Yes	58 (8.5)	21 (9.0)	1790 (8.0)
No	621 (91.5)	212 (91.0)	20,521 (91.9)
Infant characteristics			
Sex			
Male	393 (57.9)	133 (57.1)	11,455 (51.3)
Female	286 (41.1)	100 (42.9)	10,875 (48.7)
Gestational age (weeks)			
<27	346 (51.0)	144 (61.8)	6202 (27.8)
27–29	255 (37.6)	71 (30.5)	8351 (37.4)
≥30	78 (11.5)	18 (7.7)	7779 (34.8)
Birth weight (g)			
401–750	232 (34.2)	102 (44.2)	3698 (16.6)
751–1000	196 (28.9)	69 (29.6)	4770 (21.4)
1001–1250	150 (22.1)	42 (18.0)	5697 (25.5)
1251–1500	87 (12.8)	16 (6.9)	7512 (33.6)
>1500	10 (1.5)	1 (0.4)	582 (2.6)
Small for gestational age			
Yes	131 (19.3)	41 (17.6)	6461 (28.9)
No	548 (80.7)	192 (82.4)	15,871 (71.1)
Multiple birth			
Yes	172 (25.3)	53 (22.8)	5965 (26.7)
No	506 (74.5)	180 (77.3)	16,365 (73.3)
5-min Apgar			
<4	49 (7.2)	25 (10.7)	1218 (5.5)
4–7	315 (46.4)	110 (47.2)	7100 (31.8)
≥8	314 (46.2)	98 (42.1)	13,880 (62.2)
Postnatal steroid use			
Yes	211 (31.1)	111 (47.6)	2710 (12.1)
No	464 (68.3)	122 (52.4)	19,608 (87.8)
Treatment for patent ductus arteriosus			
Yes	106 (15.6)	63 (27.0)	1186 (5.3)
No	570 (84.0)	170 (73.0)	21,086 (94.4)
Human milk at discharge			
Yes	191 (28.1)	58 (24.9)	13,928 (62.4)
No	487 (71.7)	174 (74.7)	8258 (37.0)
Required transfer			
Yes	305 (44.9)	79 (33.9)	5898 (26.4)
No	374 (55.1)	154 (66.1)	16,434 (73.6)
NICU characteristics			
CCS level of care			
Regional	300 (44.2)	126 (54.1)	6807 (30.5)
Community	346 (51.0)	104 (44.6)	13,793 (61.8)
Intermediate	2 (0.3)	0 (0)	480 (2.2)
Non-CCS	31 (4.6)	3 (1.3)	1252 (5.6)
AAP level of care			
2	5 (0.7)	0 (0)	652 (2.9)
3	283 (41.7)	90 (38.6)	13,825 (61.9)
4	374 (55.1)	140 (60.1)	7591 (34.0)

ethnic groups and on the mediating effect of human milk in this relationship. Additionally, our large sample size of high quality data from a diverse population suggests good generalizability.

Increased use of human milk among preterm infants likely has been crucial in leading to the recent decline in NEC incidence.[13] We observed an overall decline in NEC incidence and a rise in human milk use over the same time period, supporting the hypothesized link. We found that human milk use varied substantially among racial/ethnic groups, consistent with prior studies.[35] Black infants had the lowest human milk use among all racial/ethnic groups. Furthermore, we show that human milk use at discharge mediated a larger proportion of the difference in NEC incidence between black and white infants, than with other races/ethnicities compared to white infants.

Multiple barriers contribute to racial/ethnic disparities in provision of mother's milk in the NICU.[36] Studies have shown that black and Hispanic mothers have lower rates of providing human milk in the NICU than white mothers.[14,18,19,30,37,38] Parker et al.[22] found that initiation of mothers' milk was similar across racial/ethnic groups, but that infants of Hispanic mothers and black mothers stopped receiving milk earlier during the NICU hospitalization than infants of white mothers. This finding is particularly troublesome given that NEC tends to develop later during a NICU hospitalization and that provision of human milk over time likely is particularly important for NEC prevention.[39] Barriers to provision of human milk may include NICU access to donor human milk, mothers' need to return to work, transportation, sibling care, and maternal comorbidities.[19] It may be that

Table 2. Association between race/ethnicity and NEC, California, 2013–2017.

Variable	NEC ($N = 679$), *N* (%)	No NEC ($N = 22{,}332$), *N* (%)	Crude OR (95% CI)	Model 1 Adjusted OR[a,b] (95% CI)	Model 2 Adjusted OR[b,c] (95% CI)
Race/ethnicity					
White	139 (20.5)	5822 (26.1)	Reference	Reference	Reference
Hispanic	332 (48.9)	10,061 (45.1)	1.33 (1.08–1.64)	1.33 (1.07–1.65)	1.27 (1.02–1.57)
Black	95 (14.0)	2830 (12.7)	1.32 (1.00–1.74)	1.32 (1.00–1.74)	1.13 (0.86–1.50)
API	85 (12.5)	2980 (13.3)	1.29 (0.97–1.71)	1.27 (0.95–1.69)	1.35 (1.01–1.80)
Other	28 (4.1)	639 (2.9)	1.78 (1.16–2.72)	1.93 (1.25–2.97)	1.80 (1.16–2.79)

CI confidence interval, *OR* odds ratio, *API* Asian or Pacific Islander.
[a]Model 1 adjusted for birth year, gestational age (in weeks), gestational age (in weeks^2), small for gestational age, multiple birth, 5-min Apgar, sex, required transfer, prenatal care, and AAP level of care. Includes NICU as a random effect.
[b]NICU location included as a random effect was significantly associated with NEC ($p < 0.001$).
[c]Model 2 adjusted for any human milk use at discharge in addition to the covariates in Model 1. Includes NICU as a random effect.

Table 3. Mediation by human milk use in the relationship between race/ethnicity and NEC.

	Estimate[a] (95% CI)	*P* value
Black and white		
Total effect	0.008 (0.001–0.01)	0.02
Natural direct effect	0.004 (−0.003 to 0.01)	0.23
Natural indirect effect	0.003 (0.001–0.005)	<0.001
Percentage mediated	43.81 (−2.07 to 89.69)	0.06
Hispanic and white		
Total effect	0.006 (0.001–0.01)	0.02
Natural direct effect	0.005 (0.000–0.01)	0.06
Natural indirect effect	0.001 (0.001–0.002)	<0.001
Percentage mediated	18.75 (0.84–36.66)	0.04
API and white		
Total effect	0.002 (−0.004 to 0.008)	0.56
Natural direct effect	0.004 (−0.002 to 0.01)	0.25
Natural indirect effect	−0.001 (−0.003 to 0.001)	<0.001
Percentage mediated	N/A[b]	N/A[b]
Non-white and white		
Total effect	0.006 (0.001–0.01)	0.01
Natural direct effect	0.004 (0.000–0.009)	0.05
Natural indirect effect	0.001 (0.001–0.002)	<0.001
Percentage mediated	21.77 (3.04–40.50)	0.02

API Asian or Pacific Islander, *N/A* not available.
[a]Regression beta coefficient, adjusted for birth year, gestational age (in weeks), gestational age (in weeks^2), small for gestational age, multiple birth, 5-min Apgar, sex, required transfer, prenatal care, and AAP level of care.
[b]Sample size too small to estimate mediation.

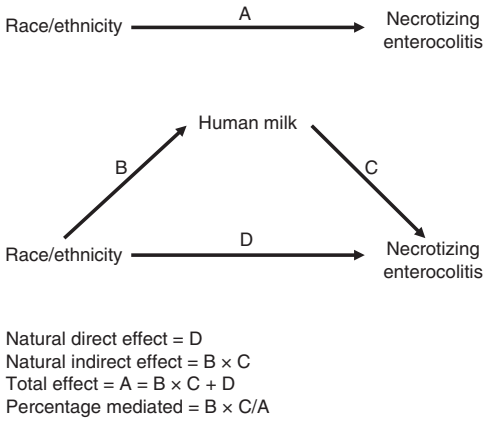

Fig. 2 Mediation analysis framework, demonstrating the total effects of race/ethnicity on risk of necrotizing enterocolitis (top panel), the natural direct and indirect effects for mediation by human milk (middle panel), and the corresponding formulas (bottom panel).

non-white mothers receive less lactation support in the NICU and/or receive care in worse overall quality NICUs.[40–42] Standardized hospital lactation support, when offered, does not necessarily alleviate observed disparities in human milk provision and breastfeeding.[22] Racial/ethnic groups have unique lactation needs and preconceptions,[43] and quality improvement efforts should be tailored to communities experiencing low rates of human milk provision.

Understanding how care processes interact with socioeconomic determinants of health and structural racial inequality is essential to improving health outcomes and decreasing NEC incidence in NICU infants. Research suggests that non-white families and poor families are vulnerable to not receiving optimal family-centered care in the NICU[42] and that family-centered care improves breastfeeding rates.[44] Creating equity in family-centered care may be critical to improving mother's milk provision and achieving equity in NEC prevention. Partnering with former NICU parents in specific communities[43,45] and integrating families into collaborative NICU-level quality improvement efforts may increase the use of human milk. By raising awareness and sharing knowledge and personal experiences, families provide unique emotional support and mentorship to those affected by NEC.[46]

This study has to be viewed in light of its design. Interpretation of our results of race/ethnicity as a risk factor for NEC must be mindful that race/ethnicity is not a biological but a social construct and that it represents a proxy for many other factors, such as structural or interpersonal racism. In performing the causal mediation analyses, we made assumptions regarding unmeasured confounding. Although we attempted to account for measured sources of confounding in our analyses, it is likely that there is still some unmeasured confounding, particularly given the complex construct and multitude of other factors that may affect relationships between race/ethnicity, human milk use, and NEC. In addition, for our mediation analysis we stratified the sample to infants who survived to discharge, since data for type of feeding would not be available for nonsurvivors. However, this selection bias would attenuate our results towards the null (i.e., lowering the magnitude of effect), because non-white infants are more likely to

die from NEC, and thus would not impact internal validity. Another limitation is that NEC cases may inadvertently include some cases of spontaneous intestinal perforation; however, this misclassification would likely be non-differential.

We acknowledge that formally a mediator (i.e., human milk use) should temporarily occur before rather than after the outcome (i.e., NEC). However, we think that based on Parker et al.'s study, human milk use at discharge is a reasonable proxy for human milk use during early NICU hospitalization, the time period when human milk may directly affect the causal pathway between race/ethnicity and NEC. Parker et al.[22] show that maternal human milk provision among VLBW infants gradually wanes across all racial/ethnic groups throughout the NICU hospitalization, but decreases more rapidly in black and Hispanic infants. However, the degree to which this drop off of human milk use is non-differential between infants with and without NEC is unknown. We realize that our assumptions may introduce misclassification bias in cases where an infant may receive human milk during early hospitalization, develop NEC, and be ultimately discharged on formula. An alternative scenario in which an infant received formula early in their hospitalization and is discharged on human milk would be rare. On balance, we judge the potential misclassification bias to be relatively small and consider worthwhile the advantage of the mediation analysis in providing an approximate effect size of the use of human milk use at discharge on racial/ethnic differences in NEC.

In conclusion, we report that the annual incidence of NEC and surgical NEC in California from 2008 to 2017 declined substantially across all racial/ethnic groups, and most benefited white infants. A sizable racial/ethnic disparity remains, with NEC incidence higher among Hispanic and black infants than white infants. Hispanic, black, and API races/ethnicities were each associated with NEC in our multivariable model. Black race was not associated with NEC after adjusting for human milk use, suggesting the critical role of human milk in explaining some of the disparity in NEC incidence among black versus white infants. Furthermore, we show that the disparity in risk of NEC in non-white vs. white infants is mediated, in part, through human milk use. Our results suggest that there is significant capacity to reduce NEC incidence among specific racial/ethnic groups and future quality improvement initiatives should consider the potential differential effects on vulnerable populations to ensure disparities are not widened.[45]

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AUTHOR CONTRIBUTIONS

G.P.G., J.P., J.L., H.C.L., K.G.S., and G.M.S. participated in the planning and design of the study. J.P., J.L., and H.C.L. participated in acquisition of the data. J.L. and G.P.G. analyzed the data. G.P.G. and V.V.P. participated in the primary manuscript writing. All authors participated in editing the manuscript. G.P.G. and J.P. had primary responsibility for the final content. All authors read and approved the final manuscript.

ADDITIONAL INFORMATION

Competing interests: K.G.S. serves on the advisory board of Evolve, is a paid consultant of Avexegen, received lecture fees from Mednax, and receives grant support from Sera Care. H.C.L. is on the advisory board of Lansinoh Laboratories, Inc. The authors declare no further conflicts of interest.

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