

## Original Article

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# Human milk, breastfeeding, and early neurodevelopmental outcomes for infants with critical CHD

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## Abstract

Human milk improves neurodevelopment for preterm infants, but relationships between human milk and neurodevelopment for infants with critical CHD are unknown. We aimed to (1) explore associations between human milk/direct breastfeeding and neurodevelopment at 1-year and 2-year follow-up and (2) describe patterns of human milk (maternal, donor) and commercial formula during hospitalisation in the first year of life.

This retrospective cohort study included infants who underwent surgery for CHD < 6 months old. The primary outcome was neurodevelopment via Bayley Scales of Infant Development-IV. Analysis included adjusted linear regression for associations between exclusive human milk while inpatient during the first 6 months or any direct breastfeeding while inpatient during the first year of life and 1-year Bayley-IV scores. Models were adjusted for race, insurance type, genetic diagnosis, and length of stay.

Of 98 eligible infants, 40% followed up at 1 year; 27% at 2 years. There were differences in follow-up related to demographics (race, ethnicity) and social determinants of health (insurance type, distance from clinic). In adjusted models, infants who directly breastfed had 13.18 points higher cognition (95% CI: 0.84–25.53,  $p = 0.037$ ); 14.04 points higher language (2.55–25.53,  $p = 0.018$ ); and 15.80 points higher motor scores (3.27–28.34,  $p = 0.015$ ) at 1-year follow-up. Infants fed exclusive human milk had 12.64 points higher cognition scores (−0.53–25.82,  $p = 0.059$ ).

Future investigation into nutrition and neurodevelopment in the context of critical CHD is warranted. As neurodevelopmental follow-up becomes standard of care in this population, efforts are needed to mitigate disparities in access to this care.

Up to 50% of children with critical CHD experience some form of neurodevelopmental delay,<sup>1</sup> with persistent sequelae through childhood, adolescence, and adulthood often resulting in reductions in quality of life. Both the Cardiac Neurodevelopmental Outcome Collaborative<sup>2</sup> and a 2023 American Heart Association Science Advisory<sup>3</sup> have recommended investigation into early, modifiable factors that can optimise neurodevelopment for these vulnerable infants. Nutrition is a clinically modifiable factor with major influence on early brain development for hospitalised infants.<sup>4,5</sup> Specifically, the benefits of human milk for preterm brain structure<sup>6</sup> and function<sup>7,8</sup> have been documented for more than 20 years.<sup>9</sup>

There is limited evidence about human milk and breastfeeding in the context of critical CHD,<sup>10</sup> and relationships between human milk and neurodevelopment for these infants are currently unknown. A recent study<sup>11</sup> of 2491 infants with single ventricle CHD demonstrated that human milk feeding and direct breastfeeding substantially reduced inflammatory diseases known to impact neurodevelopment (e.g., 72% lower necrotising enterocolitis; 93% lower sepsis). To our knowledge, however, no previous study has investigated relationships between human milk/breastfeeding and neurodevelopment for infants with critical CHD.

The aim of this study was to address the gap in knowledge about nutrition and neurodevelopment for infants with critical CHD by exploring associations between human milk feeding or direct breastfeeding and neurodevelopmental outcomes at 1-year and 2-year follow-up. Secondly, we sought to describe patterns of maternal human milk, donor human milk, and commercial formula intake during hospitalisation in the first year of life.

## Materials and methods

This retrospective cohort study was approved by the University of Minnesota Institutional Review Board and deemed exempt with a waiver of consent approved. We included infants born after August 1, 2018, who had surgery for CHD at our institution within the first 6 months of life.

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Infants 9–18 months old were eligible for inclusion at the 1-year neurodevelopmental assessment time point, and children 1.5–2.5 years old were eligible for the 2-year time point. Infants were excluded if they had < 7 days of inpatient enteral feeding data recorded, if they were < 32 weeks gestational age at birth, or if they died before assessment could occur (see flow diagram in Supplementary Figure S1).

### Setting

Neurodevelopmental assessments occurred at the University of Minnesota's Cardiovascular Neurodevelopmental Clinic, which is part of the Masonic Institute for the Developing Brain. The Clinic follows infants with CHD over the first years of life to provide in-depth neurodevelopmental assessment and recommendations. Children are referred by the cardiovascular surgery team or paediatric cardiologists, with the goal of seeing all children who undergo cardiac surgery in the first 6 months of life. Infants are assessed at 4 months of age by an occupational therapist, then yearly beginning at 12 months of age for standardised neurodevelopmental testing by a neuropsychologist. At each visit, children are seen by a nurse practitioner and neonatologist to assess growth, nutrition, and general well-being and to partner with the occupational therapist and neuropsychologist in making referrals for therapy or subspecialty evaluation.

### Data collection

Demographic, surgical, clinical, and neurodevelopmental data were collected in REDCap as part of a larger database of CHD neurodevelopmental outcomes. These data were primarily collected from the electronic health record by a data analyst from the University of Minnesota's Clinical and Translational Science Institute Best Practices Integrated Informatics Core. Enteral nutrition data from infants were collected and joined with the REDCap data.

### Definitions

The primary outcome was neurodevelopment at 1-year and 2-year follow-up, measured by the Bayley Scales of Infant Development, 4th Edition,<sup>12</sup> (Bayley-IV). The Bayley-IV is a validated screening tool for developmental delay in cognitive, language, and motor domains. Nutritional exposures of interest included the base diet mLs of maternal human milk, donor human milk (i.e., pooled, pasteurised milk provided via a milk bank), and commercial formula while inpatient. We examined an exclusive human milk group in which an infant received only maternal or donor human milk as the base diet while inpatient during the first 6 months of life, which is consistent with American Academy of Pediatrics recommendations for exclusive human milk through age 6 months.<sup>13</sup> We also examined a direct breastfeeding group, in which infants directly breastfed while inpatient at any point during the first year of life. This study included only data available through electronic health record chart review; therefore, nutrition data post-discharge were not collected. Covariates for model adjustment were based on previous literature,<sup>14–16</sup> and included prematurity, race, major genetic diagnosis, cardiac diagnosis, number of surgeries, and hospital length of stay. Additional covariate details can be found in Supplementary Table S1.

### Analysis

We used descriptive statistics (e.g., *n*, %) and data visualisation to explore enteral nutrition volumes and trajectories during infant hospitalisation, and quantified differences between variables by calculating standardised mean differences (SMDs). Absolute SMDs >0.10 were considered indicative of potential imbalance between groups. We used Chi-square tests to conduct post hoc analysis of differences in human milk/breastfeeding rates between infants that did and did not follow up.

We fitted unadjusted and adjusted linear regression models to explore associations at 1-year follow-up between exclusive human milk while inpatient during the first 6 months of life and Bayley-IV domain scores, and between any direct breastfeeding while inpatient during the first year of life and Bayley-IV scores. Models were adjusted for race, insurance type, major genetic diagnosis, and initial surgical hospitalisation length of stay. We considered additional variables (i.e., prematurity, higher-risk cardiac diagnosis, number of surgeries), but most models were not improved by including these additional covariates. To assess for multicollinearity, we calculated the variance inflation factor for each covariate. Significance was set at  $p < 0.05$ , and analyses were conducted using R (version 4.2.3).

### Result

Of 119 infants included in the cardiac neurodevelopmental follow-up database, 98 were eligible for the current study. These infants were 43% female, 78% white, and 42% with public insurance. A total of 20% were born preterm and 21% had a major genetic diagnosis. Most infants had multiple concurrent cardiac diagnoses that created a single ventricle or biventricular physiology with or without arch obstruction. Additional sample characteristics can be found in Supplementary Table S1.

At the 1-year time point, 37 (40%) infants had completed neurodevelopmental assessment, with 56 (60%) infants lost to follow-up and 5 still in process. The mean (standard deviation) scores for each Bayley-IV domain were 90.81 (18.88) for cognition, 80.46 (16.84) for language, and 83.49 (19.20) for motor function. At the 2-year time point, 21 (27%) infants completed neurodevelopmental assessment, with 56 (73%) lost to follow-up and 21 still in process. The mean (standard deviation) scores for each Bayley-IV domain were 85.10 (19.21) for cognition, 79.10 (21.61) for language, and 82.14 (18.70) for motor function. Most infants who completed year 2 follow-up were also in the 1-year follow-up cohort ( $n = 18$ , 86%). Differences between infants who completed assessment and those who were lost to follow-up can be found in Table 1.

### Nutrition and neurodevelopment

Bayley-IV cognition, language, and motor domain scores compared by exclusive human milk or direct breastfeeding status are visualised in Figure 1. Average scores tended to be higher in the exclusive human milk and direct breastfeeding groups at both time points, with greater magnitude of difference for exclusive human milk at the 2-year time point. A subgroup examination of higher-risk cardiac diagnoses revealed similar patterns (Supplementary Figure S2). Infants with higher-risk cardiac diagnoses did not have lower average Bayley-IV scores in this sample.

Estimation of associations between an exclusive human milk diet while inpatient during the first 6 months of life or direct breastfeeding during the first year of life and Bayley-IV scores

**Table 1.** Characteristics of infants with and without neurodevelopment assessment at 1-year follow-up (N = 93) and 2-year follow-up (N = 77)

|  | 1-year follow-up<br>n = 37 | No 1-year follow-up<br>n = 56 |       | 2-year follow-up<br>n = 21 | No 2-year follow-up<br>n = 56 |                  |
|--|----------------------------|-------------------------------|-------|----------------------------|-------------------------------|------------------|
|  | n (%) or mean (SD)         |                               | SMD   | n (%) or mean (SD)         |                               | SMD <sup>a</sup> |
| Sex  |                            |                               | 0.01  |                            |                               | 0.17             |
| Female                                     | 15 (39.5)                  | 23 (60.5)                     |       | 10 (31.3)                  | 22 (68.8)                     |                  |
| Male                                       | 22 (40.0)                  | 33 (60.0)                     |       | 11 (24.4)                  | 34 (75.6)                     |                  |
| Race                                       |                            |                               | 0.25  |                            |                               | 0.45             |
| Asian                                      | 3 (60.0)                   | 2 (40.0)                      |       | 1 (33.3)                   | 2 (66.7)                      |                  |
| Black or African American                  | 3 (30.0)                   | 7 (70.0)                      |       | 1 (12.5)                   | 7 (87.5)                      |                  |
| More than one race                         | 2 (50.0)                   | 2 (50.0)                      |       | 0 (0.0)                    | 3 (100.0)                     |                  |
| White                                      | 28 (38.9)                  | 44 (61.1)                     |       | 18 (29.0)                  | 44 (71.0)                     |                  |
| Hispanic ethnicity                         |                            |                               | 0.32  |                            |                               | 0.17             |
| Yes  | 1 (14.3)                   | 6 (85.7)                      |       | 1 (16.7)                   | 5 (83.3)                      |                  |
| No   | 36 (41.9)                  | 50 (58.1)                     |       | 20 (28.2)                  | 51 (71.8)                     |                  |
| Insurance type                             |                            |                               | 0.25  |                            |                               | 0.22             |
| Private                                    | 23 (44.2)                  | 29 (55.8)                     |       | 13 (32.5)                  | 27 (67.5)                     |                  |
| Public                                     | 12 (32.4)                  | 25 (67.6)                     |       | 8 (23.5)                   | 26 (76.5)                     |                  |
| Home zip code >50 miles from clinic        |                            |                               | 0.61  |                            |                               | 0.42             |
| Yes  | 5 (18.5)                   | 22 (81.5)                     |       | 4 (16.0)                   | 21 (84.0)                     |                  |
| No   | 32 (48.5)                  | 34 (51.5)                     |       | 17 (32.7)                  | 35 (67.3)                     |                  |
| Prenatal diagnosis                         |                            |                               | 0.46  |                            |                               | 0.42             |
| Yes  | 31 (46.3)                  | 36 (53.7)                     |       | 17 (32.7)                  | 35 (67.3)                     |                  |
| No   | 6 (23.1)                   | 20 (76.9)                     |       | 4 (16.0)                   | 21 (84.0)                     |                  |
| Preterm (32–37 weeks)                      |                            |                               | 0.33  |                            |                               | 0.35             |
| Yes  | 11 (55.0)                  | 9 (45.0)                      |       | 6 (42.9)                   | 8 (57.1)                      |                  |
| No   | 26 (35.6)                  | 47 (64.4)                     |       | 15 (23.8)                  | 48 (76.2)                     |                  |
| Gestational age                            | 37.43 (2.06)               | 38.05 (1.80)                  | −0.32 | 37.43 (1.99)               | 38.18 (1.85)                  | −0.40            |
| Major genetic diagnosis <sup>b</sup>       |                            |                               | 0.00  |                            |                               | 0.41             |
| Yes  | 8 (40.0)                   | 12 (60.0)                     |       | 7 (43.8)                   | 9 (56.3)                      |                  |
| No   | 29 (39.7)                  | 44 (60.3)                     |       | 14 (23.0)                  | 47 (77.0)                     |                  |
| Birthweight z-score                        | −0.32 (1.03)               | −0.07 (1.11)                  | −0.24 | −0.32 (1.08)               | 0.01 (1.01)                   | −0.33            |
| Birth height z-score                       | −0.06 (1.34)               | 0.02 (1.62)                   | −0.05 | −0.19 (1.74)               | 0.15 (1.52)                   | −0.22            |
| Birth OFC z-score                          | −0.42 (1.35)               | −0.15 (1.24)                  | −0.21 | −0.28 (1.43)               | −0.10 (1.26)                  | −0.14            |
| Cardiac diagnosis                          |                            |                               | 0.24  |                            |                               | 0.24             |
| SV with arch obstruction                   | 1 (25.0)                   | 3 (75.0)                      |       | 1 (25.0)                   | 3 (75.0)                      |                  |
| SV without arch obstruction                | 3 (50.0)                   | 3 (50.0)                      |       | 2 (50.0)                   | 2 (50.0)                      |                  |
| BiV with arch obstruction                  | 10 (35.7)                  | 18 (64.3)                     |       | 7 (28.0)                   | 18 (72.0)                     |                  |
| BiV without arch obstruction               | 23 (44.2)                  | 29 (55.8)                     |       | 11 (26.8)                  | 30 (73.2)                     |                  |
| Higher-risk cardiac diagnosis <sup>c</sup> |                            |                               | 0.01  |                            |                               | 0.16             |
| Yes  | 13 (39.4)                  | 20 (60.6)                     |       | 8 (32.0)                   | 17 (68.0)                     |                  |
| No   | 24 (40.0)                  | 36 (60.0)                     |       | 13 (25.0)                  | 39 (75.0)                     |                  |
| PGE-dependent                              |                            |                               | 0.12  |                            |                               | 0.06             |
| Yes  | 20 (37.7)                  | 33 (62.3)                     |       | 12 (26.7)                  | 33 (73.3)                     |                  |
| No   | 17 (43.6)                  | 22 (56.4)                     |       | 9 (29.0)                   | 22 (71.0)                     |                  |

(Continued)

Table 1. (Continued)

|   | 1-year follow-up<br>n = 37 | No 1-year follow-up<br>n = 56 |       | 2-year follow-up<br>n = 21 | No 2-year follow-up<br>n = 56 |                  |
|---|----------------------------|-------------------------------|-------|----------------------------|-------------------------------|------------------|
|   | n (%) or mean (SD)         |                               | SMD   | n (%) or mean (SD)         |                               | SMD <sup>a</sup> |
| Number of surgeries   | 2.89 (2.16)                | 2.46 (2.09)                   | 0.20  | 2.67 (2.08)                | 2.52 (2.11)                   | 0.07             |
| Age at first surgery/intervention (days)                              | 40 (52)                    | 51 (71)                       | −0.18 | 49 (63)                    | 48 (69)                       | 0.02             |
| CPB time (min)  | 93 (61)                    | 101 (63)                      | −0.13 | 75 (68)                    | 102 (60)                      | −0.43            |
| Cross-clamp time (min)  | 51 (40)                    | 59 (41)                       | −0.20 | 47 (42)                    | 56 (41)                       | −0.23            |
| Delayed sternal wound closure   |                            |                               | 0.13  |                            |                               | 0.19             |
| Yes   | 21 (37.5)                  | 35 (62.5)                     |       | 11 (23.9)                  | 35 (76.1)                     |                  |
| No  | 11 (44.0)                  | 14 (56.0)                     |       | 7 (31.8)                   | 15 (68.2)                     |                  |
| ECMO use  |                            |                               | 0.09  |                            |                               | 0.24             |
| Yes   | 2 (50.0)                   | 2 (50.0)                      |       | 2 (50.0)                   | 2 (50.0)                      |                  |
| No  | 35 (39.8)                  | 53 (60.2)                     |       | 19 (26.4)                  | 53 (73.6)                     |                  |
| Mechanical ventilation postop (days)                                  | 3.73 (3.80)                | 3.18 (6.11)                   | 0.11  | 4.33 (4.50)                | 3.13 (6.06)                   | 0.23             |
| Initial surgical hospital length of stay (days)                       | 47 (65)                    | 41 (59)                       | 0.10  | 53 (83)                    | 42 (59)                       | 0.17             |
| Weight z-score at discharge   | −1.33 (1.06)               | −0.93 (1.24)                  | −0.35 | −1.42 (1.07)               | −0.83 (1.17)                  | −0.53            |
| Height z-score at discharge   | −0.85 (1.08)               | −0.46 (1.84)                  | −0.26 | −0.87 (1.20)               | −0.33 (1.71)                  | −0.37            |
| OFC z-score at discharge  | −1.23 (1.29)               | −0.75 (1.35)                  | −0.37 | −1.17 (1.19)               | −0.69 (1.34)                  | −0.38            |
| Exclusive human milk feeding while inpatient (first 6 months of life) |                            |                               | 0.18  |                            |                               | 0.27             |
| Yes   | 10 (47.6)                  | 11 (52.4)                     |       | 7 (36.8)                   | 12 (63.2)                     |                  |
| No  | 27 (37.5)                  | 45 (62.5)                     |       | 14 (24.1)                  | 44 (75.9)                     |                  |
| Any direct breastfeeding while inpatient                              |                            |                               | 0.20  |                            |                               | 0.20             |
| Yes   | 14 (46.7)                  | 16 (53.3)                     |       | 8 (33.3)                   | 16 (66.7)                     |                  |
| No  | 23 (36.5)                  | 40 (63.5)                     |       | 13 (24.5)                  | 40 (75.5)                     |                  |

BIV = biventricular; CPB = cardiopulmonary bypass; ECMO = extracorporeal membrane oxygenation; OFC = occipital frontal circumference; PGE = prostaglandin E1; SMD = standardised mean difference; SV = single ventricle.

<sup>a</sup>Absolute standardised mean difference >0.10 is considered indicative of potential differences between groups.

<sup>b</sup>Major genetic syndromes with the potential to impact neurodevelopment included Trisomy 21, 22q11.2 deletion syndrome, Turner syndrome, 15q13.3 microdeletion syndrome, Alagille Syndrome, VACTERL association, or PRR12-related malformation syndrome.

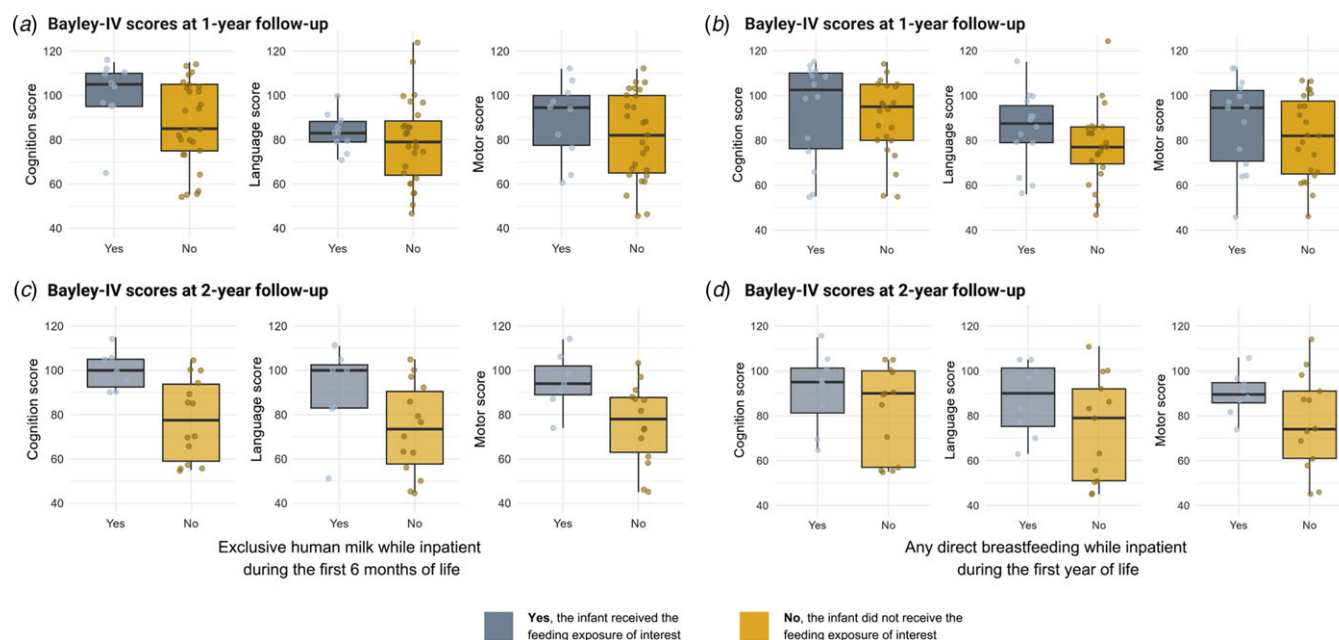
<sup>c</sup>Cardiac diagnoses with potentially higher risk for poor neurodevelopmental outcomes included single ventricle physiology, tetralogy of Fallot, and transposition of the great arteries.

at 1-year follow-up can be seen in Table 2. In adjusted linear regression analysis, all estimates were higher in the exclusive human milk group including a 12.64 points higher cognition domain score at 1-year follow-up (95% CI: −0.53–25.82,  $p = 0.059$ ). Confidence intervals for all exclusive human milk models crossed 0 and ranged widely. In adjusted models, infants who were directly breastfed had, on average, a 13.18 point higher cognition domain score at 1-year follow-up (95% CI: 0.84–25.53 points higher,  $p = 0.037$ ); a 14.04 point higher language domain score (2.55–25.53,  $p = 0.018$ ); and a 15.80 point higher motor score (3.27–28.34,  $p = 0.015$ ). Differences between feeding groups in covariates considered for adjustment can be seen in Supplementary Table S2.

### Nutrition patterns

In the full sample, 22 (22%) infants received exclusive human milk while inpatient during the first 6 months of life (i.e., exclusive human milk group). There were a median average of 26.5 days of enteral feeding while inpatient during these first 6 months (25, 75%; 14, 46.25 days; range 7–159 days). A total of 32 (33%) infants were directly breastfed at any point during the first year of

life (i.e., breastfeeding group). At the 1-year time point, 10 (27%) infants with follow-up assessment had received exclusive human milk and 14 (38%) had been breastfed. At the 2-year time point, 7 (33%) infants with follow-up assessment had received exclusive human milk, and 8 (38%) had been breastfed. Overall, infants who followed up had higher rates of exclusive human milk/breastfeeding (see Table 1). However, in post hoc analysis none of these differences reached statistical significance (e.g., 27% exclusive human milk in those with 1-year follow-up versus 20% with no follow-up,  $p = 0.405$ ; 38% breastfeeding in those with 1-year follow-up versus 29% with no follow-up,  $p = 0.349$ ). The volumes of maternal human milk, donor human milk, and commercial formula per day of life while inpatient are visualised in Figure 2. Volumes of maternal human milk were highest during the first 1–2 months of life, with commercial formula becoming the dominant source of nutrition after approximately 3 months. From birth to 6 months, maternal human milk comprised 55.3% of inpatient enteral nutrition, with 43.8% commercial formula. Donor human milk was used by 25 (26%) infants, comprising 3.1% of total inpatient feeding volume during the first 28 days of life and 0.7% of feeding volume over the first year.



**Figure 1.** Bayley Scales of infant and toddler development-IV scores at 1-year and 2-year follow-up, compared by exclusive human milk feeding while inpatient during the first 6 months of life and by any direct breastfeeding while inpatient during the first year of life.

Supplementary Figure S3 is a data visualisation of individual feeding patterns for infants who completed 1-year neurodevelopmental assessment. Most infants established maternal human milk feeding, but available nutrition data varied widely among infants and there were no clear visual patterns of association between higher Bayley-IV scores and enteral nutrition. Infants with major genetic diagnoses tended to have the lowest Bayley-IV scores.

## Discussion

### Nutrition and neurodevelopment

In this single-site retrospective cohort study, we identified differences in early neurodevelopmental outcomes related to infant feeding. In adjusted analysis, any direct breastfeeding while inpatient during the first year of life was associated with significantly higher scores in all Bayley-IV domains at 1-year follow-up. For infants who received an exclusive human milk-based diet while inpatient during the first 6 months of life, the average estimate for cognition score was 12.64 points higher, although the confidence interval ( $-0.53 - 25.82$ ) crossed zero in this small cohort. To our knowledge, this is the first report of relationships between human milk/breastfeeding and neurodevelopment for infants with critical CHD and provides support for further investigation into the relationship between nutrition and neurodevelopment in this at-risk population.

Our results align with evidence from preterm populations. In a retrospective, multisite cohort of very-low birthweight infants, Hair *et al.*<sup>8</sup> compared infants fed an exclusive human milk-based diet with those exposed to bovine-based formula/fortifier. At 18-month follow-up, cognition scores were on average 6.9 points higher in the human milk group ( $p < 0.001$ ). Patra *et al.*<sup>7</sup> reported similar results for a cohort of 251 very-low birthweight infants, with each 10 mL/kg/day increase in maternal human milk during the neonatal ICU stay associated with a 0.35 increase in cognition

score at 20-month follow-up ( $p = 0.03$ ). Additional large, multisite studies have described a dose-dependent relationship between human milk and all Bayley-IV domains at 18-month<sup>17</sup> and 30-month<sup>18</sup> follow-up. Lechner and Vohr's<sup>9</sup> 2017 review describes positive associations between human milk and neurodevelopment for preterm infants going back more than 20 years, with the strongest results in cognitive domains. While the estimate for cognition in our sample was 12.64 points higher ( $\sim 0.67$  standard deviation) for infants who received exclusive human milk, our study was powered only to detect a large effect and this result did not reach statistical significance at the  $p < 0.05$  level. Future well-powered studies are needed to clarify the relationship between human milk and cognitive development in critical CHD populations.

Our findings of associations between direct breastfeeding and higher Bayley-IV scores are unique, as we did not identify any previous studies focused specifically on breastfeeding and neurodevelopmental outcomes in hospitalised infants. However, skin-to-skin maternal contact may improve preterm neurodevelopmental outcomes,<sup>19</sup> and direct breastfeeding confers some differential benefits for hospitalised neonates (e.g., improved gut microbiome,<sup>20</sup> reduced sepsis<sup>11</sup>). It is possible that infants who did not breastfeed were more critically ill. However, this hypothesis has not been consistently validated in research and is not clearly supported by our data. For example, a previous national registry analysis used machine learning techniques to identify the strongest predictors of human milk and breastfeeding for infants with single ventricle CHD.<sup>14</sup> While clinical stability played a role, demographic/social variables and clinical site practices were more important in determining whether an infant would breastfeed. While samples across sites may vary, in the current study cohort breastfeeding rates at 1-year follow-up were often higher for infants with potential indicators of clinical complexity (e.g., prematurity, major genetic diagnosis, higher-risk cardiac diagnosis; see Supplementary Table S2), and previous national registry analysis demonstrates wide variation in direct breastfeeding prevalence, even among sites with large volumes of high-complexity single ventricle patients.<sup>21</sup>



**Table 2.** Associations between an exclusive human milk diet while inpatient during the first 6 months of life or any direct breastfeeding while inpatient during the first year of life and Bayley-IV domain scores at age 1 year, via unadjusted and adjusted<sup>a</sup> linear regression models

|                            | $\beta$ | SE   | 95% CI       | p value      |
|----------------------------|---------|------|--------------|--------------|
| <b>Cognition score</b>     |         |      |              |              |
| Exclusive HM (unadjusted)  | 13.28   | 6.72 | −0.37–26.92  | 0.057        |
| Exclusive HM (adjusted)    | 12.64   | 6.44 | −0.53–25.82  | 0.059        |
| Any direct BF (unadjusted) | 3.87    | 6.46 | −9.24–16.97  | 0.553        |
| Any direct BF (adjusted)   | 13.18   | 6.04 | 0.84–25.53   | <b>0.037</b> |
| <b>Language score</b>      |         |      |              |              |
| Exclusive HM (unadjusted)  | 4.17    | 6.28 | −8.59–16.92  | 0.512        |
| Exclusive HM (adjusted)    | 0.95    | 6.52 | −12.39–14.28 | 0.886        |
| Any direct BF (unadjusted) | 7.19    | 5.66 | −4.30–18.68  | 0.212        |
| Any direct BF (adjusted)   | 14.04   | 5.62 | 2.55–25.53   | <b>0.018</b> |
| <b>Motor score</b>         |         |      |              |              |
| Exclusive HM (unadjusted)  | 7.42    | 7.10 | −6.99–21.83  | 0.303        |
| Exclusive HM (adjusted)    | 6.57    | 7.05 | −7.84–20.99  | 0.359        |
| Any direct BF (unadjusted) | 6.57    | 6.51 | −6.64–19.78  | 0.515        |
| Any direct BF (adjusted)   | 15.80   | 6.13 | 3.27–28.34   | <b>0.015</b> |

BF = breastfeeding; CI = confidence interval; HM = human milk; SE = standard error.

<sup>a</sup>All models adjusted for race, insurance type, major genetic syndrome, and index surgical hospitalisation length of stay.

Furthermore, our models were adjusted for surrogates of illness (e.g., length of stay). An alternate hypothesis is that engagement in breastfeeding – a complex task – could stimulate the development of neural pathways and connections.

We considered covariates for model adjustment that have been linked to both neurodevelopment and human milk/breastfeeding, including indicators of clinical status and diagnostic risk (length of stay; higher-risk cardiac diagnosis, number of surgeries, prematurity, major genetic diagnosis), demographic (race), and socio-economic (insurance type) variables. The role of social determinants of health and socio-economic factors on neurodevelopmental outcomes for infants with CHD is receiving increasing attention.<sup>22–24</sup> For example, Bucholz et al.<sup>22</sup> identified associations between neighbourhood socio-economic status and neurodevelopment at age 6 years for infants with single ventricle physiology, when adjusting for multiple indicators of clinical complication. Bucholz et al.<sup>23</sup> also reported mirrored associations between neighbourhood socio-economic status or maternal education and neurodevelopmental outcome trajectories for infants with single ventricle physiology ages 3–6 years. Well-designed, rigorous studies in preterm<sup>24–26</sup> and healthy term<sup>27–28</sup> populations have identified associations between human milk/breastfeeding and improved neurodevelopment in childhood and adulthood that persist, even when accounting for covariates such as maternal education and socio-economic status. However, relationships between social factors, early nutrition, and neurodevelopment for infants with critical CHD have not been explored. Future studies with larger samples and collection of multiple individual-level covariates (eg, maternal/paternal education, household income, parent employment status) are needed to support better understanding of the relationships between early nutrition, infant and family social factors, and neurodevelopment.

## Nutrition patterns

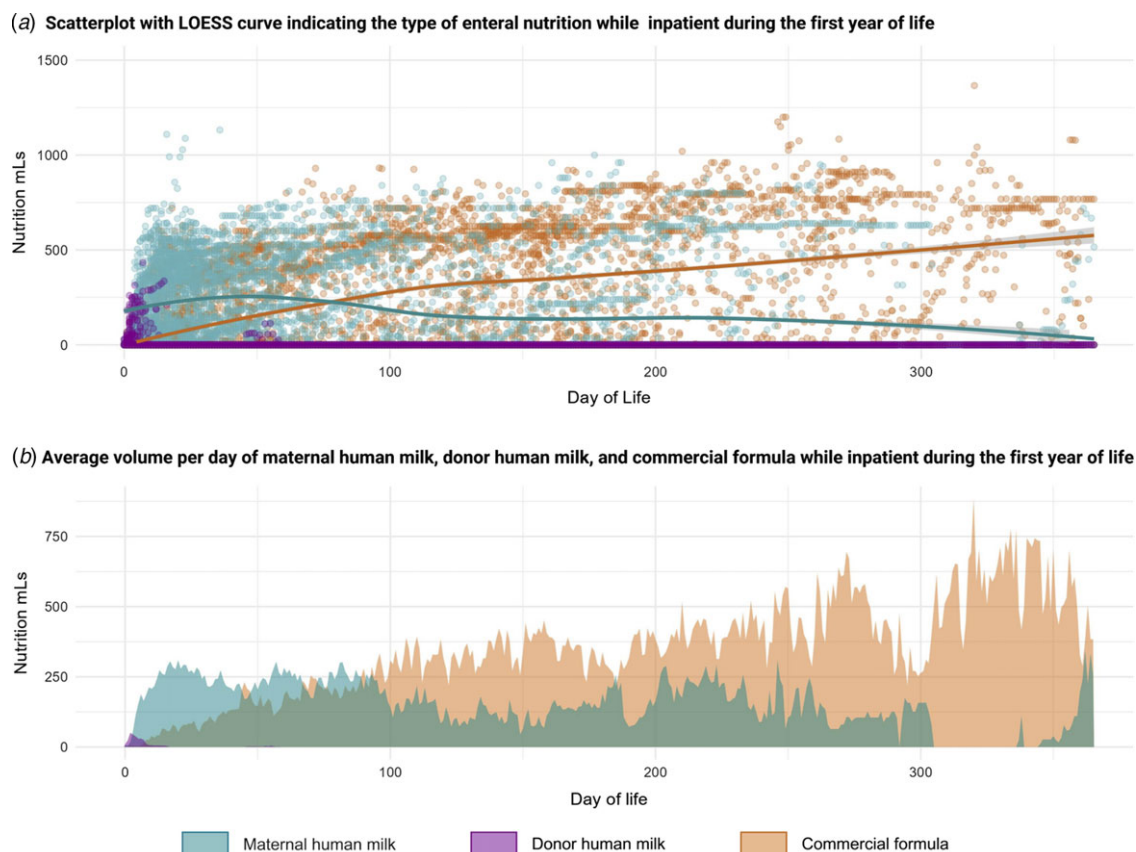
In our sample, nearly all infants received some maternal human milk, which is in line with the United States average of 83.2% breastfeeding initiation<sup>29</sup> and with 85.7% human milk feeding initiation for preoperatively-fed infants with single ventricle physiology.<sup>21</sup> Maternal human milk was the most common nutrition in early hospitalisation, with commercial formula beginning to dominate at approximately 3 months of age. While lactating parents of infants with critical CHD often initiate milk expression via pumping due to parent/infant separation after birth or infant physiologic instability, qualitative reports have underscored the burden of extended pumping.<sup>30</sup> Direct breastfeeding is associated with increased duration of human milk feeding for infants with critical CHD,<sup>14,21</sup> but support for direct breastfeeding in this population is inconsistent both between and within institutions,<sup>30</sup> and interventions to facilitate breastfeeding have not been tested in the context of critical CHD. Given that increased duration of human milk feeding has been associated with neurodevelopmental benefits throughout childhood for preterm infants, improved support for direct breastfeeding, as clinically indicated, could be an important intervention to support neurodevelopment. Additionally, our results highlight a need for lactation support beyond the neonatal period in this population, with the 2- to 3-month postnatal time frame a potentially sensitive window of opportunity for care.

Donor human milk was not widely used in our sample, comprising only 3.1% of inpatient feeding volume for infants  $\leq$  28 days old. Recent quality improvement initiatives in CHD populations have achieved substantially higher rates (e.g., 24% of neonatal feeding volume;<sup>31</sup> 81.6% of infants using some donor human milk<sup>32</sup>). For preterm infants, donor human milk does not conclusively improve neurodevelopment compared to commercial formula, but is associated with other relevant benefits (e.g., reduced necrotising enterocolitis<sup>26</sup>). To date, donor human milk has been underexamined and underutilised in critical CHD populations.<sup>33</sup>

Individual feeding intake patterns varied widely, and infants were often in and out of the hospital during the first year of life. This unpredictable clinical course highlights the difficulty in conducting retrospective nutrition research in this population. Rigorous examinations of associations between human milk/breastfeeding and neurodevelopment for infants with critical CHD will require multisite collaborations to obtain larger sample sizes; should include infants with similar critical CHD diagnoses to improve comparability; and should supplement nutrition data from the medical record with at-home feeding data.

## Neurodevelopmental follow-up

Participation in neurodevelopmental follow-up assessment was suboptimal in our sample, with only 40% of eligible infants following up at the 1-year time point, and 27% at the 2-year time point. These rates are much lower than in the affiliated neonatal intensive care unit (ICU) follow-up clinic at our site (~85% participation), but in line with reports from other CHD neurodevelopmental follow-up clinics (e.g., 17–63% participation in the first two years of life<sup>34</sup>). Infants born preterm were more likely to follow up at both time points, and infants with a major genetic diagnosis were more likely to follow up at age 2 years. These infants may have had more immediately perceived need for developmental support. Furthermore, preterm infants spending more time in the neonatal ICU versus the cardiovascular ICU may have been exposed to different clinical messaging about neurodevelopmental



**Figure 2.** Volume of maternal human milk, donor human milk, and commercial formula received while inpatient by the full cohort of infants with critical CHD (N = 98).

follow-up or to different institutional workflow practices (e.g., automatic order sets for clinic referral). We identified additional differences in follow-up related to demographics, social determinants of health, and healthcare access. Infants with public insurance were less likely to follow up at both time points, although the percentage of those with public insurance was stable over time (38% at 1-year and 2-year follow-up). Infants whose home zip code was >50 miles from the clinic and those with postnatal critical CHD diagnosis were less likely to follow up, which may reflect lack of access to prenatal care. Infants of Hispanic or Latino ethnicity were less likely to follow up at both time points, and Black or African American infants and infants of more than one race were less likely to follow up at the 2-year time point. Our findings are consistent with Locco et al.,<sup>35</sup> who found that lack of private insurance was the strongest risk factor for non-attendance at CHD neurodevelopmental follow-up, and with evidence in preterm populations linking insurance type and race to lower rates of neurodevelopmental follow-up.<sup>36</sup> Interestingly, in contrast to our results, Monteiro et al.<sup>34</sup> reported approximately 2 times higher attendance at cardiac neurodevelopmental follow-up among Hispanic infants, compared to white infants, at a large Texas centre. The authors describe substantial institutional support for Spanish-speaking families, suggesting that some sociocultural barriers to neurodevelopmental follow-up are clinically modifiable.

Social determinants of health, health inequities, structural racism, and provider bias impact outcomes,<sup>37</sup> including developmental outcomes,<sup>22,23,38</sup> for infants with CHD. Therefore, as outlined by Lopez et al. in a 2022 American Heart Association Scientific Statement,<sup>39</sup> mitigating these health disparities and

ensuring that all infants with CHD have equitable access to neurodevelopmental follow-up is of high priority. While improving health equity is a complicated endeavour, evidence-based recommendations that could facilitate neurodevelopmental follow-up include (1) routine screening for social determinants of health and subsequent referral for services (e.g., transportation assistance) when needed,<sup>37</sup> and (2) developing a network of trained parent mentors, in which parents who have a child with critical CHD act as community health workers to guide new parents through the medical system.<sup>37</sup> To our knowledge, interventions to improve equity in access to neurodevelopmental follow-up have not been tested in critical CHD populations, and research in this area is urgently needed.

### Limitations

The primary limitation of this study was the small sample size, with power only to detect large effects. As in many single-site studies, our sample included infants with heterogeneous diagnoses and timing of the index surgery, and we did not have power to conduct subgroup analyses. While we included preterm infants, we excluded those born before 32 weeks gestational age who would be at the highest risk for poor neurodevelopmental outcomes. Infants who followed up differed from those who did not, and our findings may not generalise to all infants or across sites. Our retrospective, observational approach was not intended to determine causality, and there could be unmeasured confounders; for example, maternal education. Furthermore, we only had access to inpatient feeding data and were not able to consider infants' outpatient nutrition which may not have fully reflected

nutritional status. Future studies with detailed, consistent, longitudinal nutrition measures are needed. Considering the current lack of evidence on nutrition and neurodevelopment for infants with critical CHD, this study provides initial evidence for future hypotheses.

## Conclusions

For infants with critical CHD, direct breastfeeding while inpatient during the first year of life was associated with improved neurodevelopment at 1-year follow-up, and infants fed exclusive human milk while inpatient during the first 6 months of life had higher average cognition scores. Future research with larger samples, more detailed feeding data, and multiple measures of neurodevelopment (e.g., electroencephalogram; MRI) is warranted. As neurodevelopmental follow-up becomes standard of care for infants with critical CHD, efforts are needed to ensure that disparities in health access are mitigated and that all infants have the opportunity to receive this care.

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**Competing interests.** None.

**Ethical standard.** The authors assert that all procedures contributing to this work comply with ethical standards of the United States Federal Policy for the Protection of Human Subjects and with the Helsinki Declaration of 1975, as revised in 2008 and have been approved by the University of Minnesota Institutional Review Board.

## References

- Ortinau CM, Smyser CD, Arthur L, et al. Optimizing neurodevelopmental outcomes in neonates with congenital heart disease. *Pediatrics* 2022; 150: e2022056415L. DOI: [10.1542/peds.2022-056415L](https://doi.org/10.1542/peds.2022-056415L).
- Sanz JH, Anixt J, Bear L, et al. Characterisation of neurodevelopmental and psychological outcomes in CHD: a research agenda and recommendations from the cardiac neurodevelopmental outcome collaborative. *Cardiol Young* 2021; 31: 876–887. DOI: [10.1017/S1047951121002146](https://doi.org/10.1017/S1047951121002146).
- Lisanti AJ, Uzark KC, Harrison TM, et al. Developmental care for hospitalized infants with complex congenital heart disease: a science advisory from the American heart association. *JAHA* 2023; 12: e7967. DOI: [10.1161/JAHA.122.028489](https://doi.org/10.1161/JAHA.122.028489).
- Georgieff MK, Ramel SE, Cusick SE. Nutritional influences on brain development. *Acta Paediatr* 2018; 107: 1310–1321. DOI: [10.1111/apa.14287](https://doi.org/10.1111/apa.14287).
- Ramel SE, Gray HL, Christiansen E, Boys C, Georgieff MK, Demerath EW. Greater early gains in fat-free mass, but not fat mass, are associated with improved neurodevelopment at 1 year corrected age for prematurity in very low birth weight preterm infants. *J Pediatr* 2016; 173: 108–115. DOI: [10.1016/j.jpeds.2016.03.003](https://doi.org/10.1016/j.jpeds.2016.03.003).
- Ottolini KM, Andescavage N, Kapse K, Jacobs M, Limperopoulos C. Improved brain growth and microstructural development in breast milk-fed very low birth weight premature infants. *Acta Paediatr* 2020; 109: 1580–1587. DOI: [10.1111/apa.15168](https://doi.org/10.1111/apa.15168).
- Patra K, Hamilton M, Johnson TJ, et al. NICU human milk dose and 20-month neurodevelopmental outcome in very low birth weight infants. *Neonatology* 2017; 112: 330–336. DOI: [10.1159/000475834](https://doi.org/10.1159/000475834).
- Hair AB, Patel AL, Kiechl-Kohlendorfer U, et al. Neurodevelopmental outcomes of extremely preterm infants fed an exclusive human milk-based diet versus a mixed human milk + bovine milk-based diet: a multi-center study. *J Perinatol* 2022; 42: 1485–1488. DOI: [10.1038/s41372-022-01513-3](https://doi.org/10.1038/s41372-022-01513-3).
- Lechner BE, Vohr BR. Neurodevelopmental outcomes of preterm infants fed human milk. *Clin Perinatol* 2017; 44: 69–83. DOI: [10.1016/j.clp.2016.11.004](https://doi.org/10.1016/j.clp.2016.11.004).
- Elgersma KM, McKechnie AC, Schorr EN, et al. The impact of human milk on outcomes for infants with congenital heart disease: a systematic review. *Breastfeed Med* 2022; 17: 393–411. DOI: [10.1089/bfm.2021.0334](https://doi.org/10.1089/bfm.2021.0334).
- Elgersma KM, Wolfson J, Fulkerson JA, et al. Human milk feeding and direct breastfeeding improve outcomes for infants with single ventricle congenital heart disease: propensity score matched analysis of the NPC-QIC registry. *JAHA* 2023; 12: e030756. DOI: [10.1101/2023.04.26.23289126](https://doi.org/10.1101/2023.04.26.23289126).
- Bayley N, Aylward G. Bayley Scales of Infant and Toddler Development. 4th edn. Pearson, New Jersey, 2019.
- Meek JY, Noble L, Section on Breastfeeding. Policy statement: breastfeeding and the use of human milk. *Pediatrics* 2022; 150: e2022057988. DOI: [10.1542/peds.2022-057988](https://doi.org/10.1542/peds.2022-057988).
- Elgersma KM, Wolfson J, Fulkerson JA, et al. Predictors of human milk feeding and direct breastfeeding for infants with single ventricle congenital heart disease: machine learning analysis of the national pediatric cardiology quality improvement collaborative registry. *J Pediatr* 2023; 261: 1–12. DOI: [10.1016/j.jpeds.2023.113562](https://doi.org/10.1016/j.jpeds.2023.113562).
- Rollins CK, Ortinau CM, Stopp C, et al. Regional brain growth trajectories in fetuses with congenital heart disease. *Ann Neurol* 2021; 89: 143–157. DOI: [10.1002/ana.25940](https://doi.org/10.1002/ana.25940).
- Bellinger DC, Rivkin MJ, DeMaso D, et al. Adolescents with tetralogy of Fallot: neuropsychological assessment and structural brain imaging. *Cardiol Young* 2015; 25: 338–347. DOI: [10.1017/S1047951114000031](https://doi.org/10.1017/S1047951114000031).
- Vohr BR, Poindexter BB, Dusick AM, et al. Beneficial effects of breast milk in the neonatal intensive care unit on the developmental outcome of extremely low birth weight infants at 18 months of age. *Pediatrics* 2006; 118: e115–e123. DOI: [10.1542/peds.2005-2382](https://doi.org/10.1542/peds.2005-2382).
- Vohr BR, Poindexter BB, Dusick AM, et al. Persistent beneficial effects of breast milk ingested in the neonatal intensive care unit on outcomes of extremely low birth weight infants at 30 months of age. *Pediatrics* 2007; 120: e953–e959. DOI: [10.1542/peds.2006-3227](https://doi.org/10.1542/peds.2006-3227).
- Wang Y, Zhao T, Zhang Y, Li S, Cong X. Positive effects of kangaroo mother care on long-term breastfeeding rates, growth, and neurodevelopment in preterm infants. *Breastfeed Med* 2021; 16: 282–291. DOI: [10.1089/bfm.2020.0358](https://doi.org/10.1089/bfm.2020.0358).
- Moossavi S, Sepehri S, Robertson B, et al. Composition and variation of the human milk microbiota are influenced by maternal and early-life factors. *Cell Host Microbe* 2019; 25: 324–335.e4. DOI: [10.1016/j.chom.2019.01.011](https://doi.org/10.1016/j.chom.2019.01.011).
- Elgersma K, Spatz D, Fulkerson J, et al. Patterns of breastfeeding and human milk feeding in infants with single ventricle congenital heart disease: a population study of the NPC-QIC registry. *Breastfeed Med* 2023; 18: 315–325. DOI: [10.1089/bfm.2023.0036](https://doi.org/10.1089/bfm.2023.0036).
- Bucholz EM, Sleeper LA, Goldberg CS, et al. Socioeconomic status and long-term outcomes in single ventricle heart disease. *Pediatrics* 2020; 146: e20201240. DOI: [10.1542/peds.2020-1240](https://doi.org/10.1542/peds.2020-1240).
- Bucholz EM, Sleeper LA, Newburger JW. Neighborhood socioeconomic status and outcomes following the norwood procedure: an analysis of the pediatric heart network single ventricle reconstruction trial public data set. *JAHA* 2018; 7: e007065. DOI: [10.1161/JAHA.117.007065](https://doi.org/10.1161/JAHA.117.007065).
- Jackson JL, Grant V, Barnett KS, et al. Structural racism, social determinants of health, and provider bias: impact on brain development



- in critical congenital heart disease. *Can J Cardiol* 2023; 39: 133–143. DOI: [10.1016/j.cjca.2022.11.001](https://doi.org/10.1016/j.cjca.2022.11.001).
25. Belfort MB, Knight E, Chandarana S, et al. Associations of maternal milk feeding with neurodevelopmental outcomes at 7 years of age in former preterm infants. *JAMA Netw Open* 2022; 5: e2221608. DOI: [10.1001/jama-networkopen.2022.21608](https://doi.org/10.1001/jama-networkopen.2022.21608).
  26. Lapidair W, Lucas A, Clayden JD, Clark C, Fewtrell MS. Human milk feeding and cognitive outcome in preterm infants: the role of infection and NEC reduction. *Pediatr Res* 2022; 91: 1207–1214. DOI: [10.1038/s41390-021-01367-z](https://doi.org/10.1038/s41390-021-01367-z).
  27. Victora CG, Horta BL, de Mola CL, et al. Association between breastfeeding and intelligence, educational attainment, and income at 30 years of age: a prospective birth cohort study from Brazil. *Lancet Glob Health* 2015; 3: e199–e205. DOI: [10.1016/S2214-109X\(15\)70002-1](https://doi.org/10.1016/S2214-109X(15)70002-1).
  28. Isaacs EB, Fischl BR, Quinn BT, Chong WK, Gadian DG, Lucas A. Impact of breast milk on intelligence quotient, brain size, and white matter development. *Pediatr Res* 2010; 67: 357–362. DOI: [10.1203/PDR.0b013e3181d026da](https://doi.org/10.1203/PDR.0b013e3181d026da).
  29. Centers for Disease Control and Prevention. Breastfeeding report card: United States 2022. Published September 29, 2022. <https://www.cdc.gov/breastfeeding/data/reportcard.htm>. Accessed September 15, 2023.
  30. Elgersma KM, McKechnie AC, Sommerness SA, Tanner LR, Swanson NM. Wayfinding through the “ocean of the great unknown”: how lactating parents establish a direct breastfeeding relationship with an infant with critical CHD. *Cardiol Young* 2022; 9: 1–12. DOI: [10.1017/S1047951122003808](https://doi.org/10.1017/S1047951122003808).
  31. Gauntt J, Tucker A, Dolan K, Gajarski R, Krawczeski CD. Increasing the percentage of neonates consuming human milk in a pediatric cardiothoracic intensive care unit: a quality improvement initiative. *J Pediatr* 2023; 258: 113441. DOI: [10.1016/j.jpeds.2023.113441](https://doi.org/10.1016/j.jpeds.2023.113441).
  32. Kataria-Hale J, Roddy DJ, Cognata A, et al. A preoperative standardized feeding protocol improves human milk use in infants with complex congenital heart disease. *J Perinatol* 2021; 41: 590–597. DOI: [10.1038/s41372-021-00928-8](https://doi.org/10.1038/s41372-021-00928-8).
  33. McCune S, Perrin MT. Donor human milk use in populations other than the preterm infant: a systematic scoping review. *Breastfeed Med* 2021; 16: 8–20. DOI: [10.1089/bfm.2020.0286](https://doi.org/10.1089/bfm.2020.0286).
  34. Monteiro S, Serrano F, Guffey D, et al. Factors affecting rates of neurodevelopmental follow-up in infants with congenital heart disease. *Int J Cardiol Congenit Heart Dis* 2022; 10: 100419. DOI: [10.1016/j.ijcchd.2022.100419](https://doi.org/10.1016/j.ijcchd.2022.100419).
  35. Locco EC, Yu S, Donohue J, et al. Prevalence and risk factors associated with non-attendance in neurodevelopmental follow-up clinic among infants with CHD. *Cardiol Young* 2018; 28: 554–560. DOI: [10.1017/S1047951117002748](https://doi.org/10.1017/S1047951117002748).
  36. Hintz SR, Gould JB, Bennett MV, et al. Factors associated with successful first high-risk infant clinic visit for very low birth weight infants in California. *J Pediatr* 2019; 210: 91–98.e1. DOI: [10.1016/j.jpeds.2019.03.007](https://doi.org/10.1016/j.jpeds.2019.03.007).
  37. Davey B, Sinha R, Lee JH, Gauthier M, Flores G. Social determinants of health and outcomes for children and adults with congenital heart disease: a systematic review. *Pediatr Res* 2021; 89: 275–294. DOI: [10.1038/s41390-020-01196-6](https://doi.org/10.1038/s41390-020-01196-6).
  38. Newburger JW, Sleeper LA, Bellinger DC, et al. Early developmental outcome in children with hypoplastic left heart syndrome and related anomalies: the single ventricle reconstruction trial. *Circulation* 2012; 125: 2081–2091. DOI: [10.1161/CIRCULATIONAHA.111.064113](https://doi.org/10.1161/CIRCULATIONAHA.111.064113).
  39. Lopez KN, Baker-Smith C, Flores G, et al. Addressing social determinants of health and mitigating health disparities across the lifespan in congenital heart disease: a scientific statement from the American heart association. *JAHA* 2022; 11: e025358. DOI: [10.1161/JAHA.122.025358](https://doi.org/10.1161/JAHA.122.025358).