Growth and risk of adverse neuro-developmental outcome in infants with congenital heart disease: A systematic review

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Abstract

Aim: Congenital heart disease (CHD) is one of the most common birth defects affecting around 1:100 infants. In this systematic review, we aimed to determine impact of growth on neurodevelopmental outcomes of infants with CHD.

Methods: Studies that reported association of growth with developmental outcomes in infants with CHD who had surgery, were included. The search strategy was prospectively registered. Relevant studies were identified by electronic searches. The Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE were searched from their earliest date to February 2022.

Results: Twenty studies met inclusion criteria. Choice of growth measures, developmental assessment tools and timing of assessment varied widely precluding conduct of a meta-analysis. Seventeen studies reported on infants who had cardio-pulmonary bypass. Birth weight was reported in thirteen studies and was associated with adverse outcome in nine. Head circumference at birth and later predicted developmental outcomes in five. Impaired postnatal growth was associated with adverse developmental outcome in seven studies.

Conclusion: Growth in infants with congenital heart disease, specifically single ventricle physiology can predict adverse neurodevelopmental outcome. Included studies showed significant clinical heterogeneity. Uniformity should be agreed by various data registries with routine prospective collection of growth and developmental data.

Keywords: congenital heart disease, growth, neurodevelopmental outcome, nutrition
1  |  INTRODUCTION

Congenital anomalies are an important cause of infant and childhood deaths, chronic illness and disability.\(^1\) In the neonatal population, CHD is one of the most common birth defects. Globally, around nine in every 1000 infants are affected by CHD. There is a global decrease in mortality from CHD, regardless of sex, age and region with the most pronounced decline in developed countries.\(^2\) Advancing expertise in surgical procedures have transformed short-term outcomes but long-term challenges persist.

The occurrence and severity of a developmental disability or delay increases with the complexity of the heart defect.\(^3\) More than 80% of infants with a mild CHD have no developmental disability compared with more than half of those with a more critical type of CHD having some form of disability or impairment.\(^4\) Derridj et al. reported that children with symptomatic CHD at birth are at greater risk of adverse neurodevelopmental outcomes at eight years of age, with the greatest risk for those who were born with both cyanosis and heart failure.\(^5\)

Many infants experience growth failure during the first few months of life secondary to increased energy expenditure often coupled with poor feeding, fluid restriction or the use of diuretics.\(^6\) There is no consensus on standardised management of feeding and nutrition for patients with CHD.\(^7\) Adding to this complexity infants with CHD have the variable foetal growth patterns across pathologies, and impaired placental structure and function.\(^7,8\)

With studies suggesting growth failure and risk of adverse neurodevelopmental outcome in infants with CHD, it is important to critically review the available evidence for this association and help guide future research.

The objective of this review is to critically appraise the literature on the effect of growth on neurodevelopmental outcomes of infants with CHD who had surgery performed in infancy, when compared to the normative or healthy control data.

2  |  METHODS

Protocol for this review was registered on PROSPERO (CRD42021224248, registration date 16/01/2021).

2.1  |  Patient population

Infants born with an antenatal or postnatal diagnosis of CHD that required surgery were eligible for inclusion except for isolated diagnosis of patent ductus arteriosus. No restriction was placed on type or timing of surgical procedure and gestational age at birth.

2.2  |  Measures of growth

Growth was measured by weight, length and head circumference at birth or at any time in postnatal period, measured once or serially.

Key Notes

- This systematic review was conducted to assess association of growth with neurodevelopmental outcomes in infants with congenital heart disease.
- Both in- and ex-utero growth in this population is reported to be associated with adverse neurodevelopmental outcome however, significant heterogeneity in studies precludes application of these results to improve clinical outcomes.
- Routine and uniform collection of growth and developmental data in this population is required.

Growth patterns as measured by body composition were eligible for inclusion.

2.3  |  Outcome measures

The outcome measure was development assessed by any standard validated method that was a norm-referenced comparison of an individual child’s performance to that of same-age children.\(^9\) No restriction was placed on timeframe of the assessment.

2.4  |  Types of studies included

We aimed to include both randomised and observational studies. Prospective or retrospective cohorts (either population or hospital based) or case-control studies were eligible. Case-reports, case-series and reports in a language other than English were excluded.

2.5  |  Search methods and identification of studies

Two review authors conducted electronic searches. The Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE from their earliest dates to 01 February 2022 were searched. The MeSH terms infant, newborn OR infant, premature OR infant, low birth weight OR infant, very low birth weight OR infant, extremely low birth weight OR infant, premature diseases OR infant, newborn diseases AND heart defects, congenital AND (Growth OR growth and development OR growth disorders OR body composition) were used. Searches were limited to English language articles.

All results from searches were entered into EndNote.\(^10\) The results were then imported into Covidence Systematic Review Software\(^11\) and duplicate records were removed. Using Covidence, titles and/or abstracts of studies were screened independently by two review authors. The full texts of potentially eligible studies were then retrieved and independently assessed for eligibility by two review authors. An arbiter was assigned but, however, was not required.
2.6 | Data extraction

An electronic data collection form was designed, and the following details were collected:

- Source—name of the study, author, year of publication
- Eligibility—confirmation of eligibility or reason for exclusion
- Study design
- Summary of the participants and setting
- Summary of outcomes, including unit of measurement (if relevant)
- Results—number of participants, attrition rate, summary data
- Quality

Disagreements were managed through discussion.

2.7 | Data synthesis

Two authors assessed clinical heterogeneity and decided about pooling in meta-analysis.

2.8 | Assessment of quality

Two authors independently analysed each included study with the Newcastle-Ottawa Scale for assessing quality of non-randomised studies.

3 | RESULTS

Following the literature search and removal of duplications, 10,384 studies were screened. 10,333 studies were not relevant. Full text of 51 studies was sought and 20 were included in the final review. PRISMA diagram (Figure 1).

3.1 | Characteristics of included studies (Tables 1 and 2)

Setting: All included studies came from high-income countries. Fourteen were from single centre and six across multiple sites. Except for one, all studies included patient population from single country. Most (n = 10) studies came from the USA. Infants in the included studies were recruited from 1987 to 2016, with the earliest publication in year 2006.

Type of studies: All studies were observational. Five were retrospective cohorts and the remainder prospective. Reports form Goldberg, Newberger, and Miller were prospective reports of neurodevelopmental outcomes from a single trial as were Fuller & Gaynor and Ravishankar & Miller.

Participants: The participants, pathologies and interventions varied. Except for three, all studies included infants that required a CPB. In studies reporting participants who had CPB, eight studies reported outcomes in infants with SV physiology. No study exclusively reported association of growth and developmental outcome in infants who did not have CPB. Six studies reported exclusion of infants with genetic disorder or recognisable syndrome.

Growth variables: Seven studies reported single independent growth variable and the remainder reported multiple. The independent growth variables reported in association with neurodevelopmental outcomes were measures of both, in and ex utero growth. Seven studies reported variables that measured in utero growth, four reported ex utero measures exclusively and the remainder a combination of the two. Thirteen studies reported association of BW with developmental outcomes. Head circumference and length at birth are reported in seven and five studies respectively and growth restriction at birth in four studies. Cross-sectional Wt measurement at the time of surgical procedure was the most reported ex utero predictor of growth prior to the surgery in ten studies. The other measures of ex utero growth in association with neurodevelopmental outcomes included Ht at surgery, Wt at developmental assessment in five studies each; Ht and HC at developmental assessment in four each; HC at surgery in six studies. One study looked at trajectory of postnatal growth in association with neurodevelopmental outcomes.

Developmental assessment: Tools used for the assessment differed. BSID-II was the most reported method (nine studies) followed by BSID-III in four studies. Six studies reported use of multiple assessment tools. Developmental assessment was performed at ages that varied from six months to 18 years of age. Twelve studies...
| Reference | Participants | Setting | Details of study | Test | Age at assessment |
|-----------|--------------|---------|------------------|------|-------------------|
| Alton\(^{15}\) | TAPVC | Single centre, Canada | Yes | Repair | BSID-II | 18–24 months |
| Atallah\(^{13}\) | HLHS | Single Centre, Canada | Yes | Three stage palliation | WPPSI, Beery VMI ABAS | Between 48 and 72 months |
| Campbell\(^{24}\) | CHD chromosomal abnormalities included | Single centre, Australia | Yes | Open heart surgery before 4 months of age | ASQ | Preoperative, predischarge and 6 months |
| Cheung\(^{22}\) | Preterm infants | Single Centre, Canada | No | CPB at 6 weeks of CA or less | ABAS GAC (main outcome measure) | Two years of CA |
| Chock\(^{23}\) | CHD | Single centre, USA | No | As per pathology | DDST type II or CAT/CLAMS | Multiple end points between 4–30 months |
| Fuller\(^{16}\) | CHD | Single centre, USA | Yes | CPB < 6 months of age | BSID-II | 12 months |
| Gaynor\(^{21}\) | Age <6 months with CHD | Single centre, USA | Yes | CPB | BSID-II | One year |
| Gaynor\(^{12}\) | CHD | Six countries | No | CPB at age ≤9 months | BSID-II | 6–30 months |
| Goldberg\(^{17}\) | HLHS or related SV abnormality | Multiple Centres in USA | Yes | Three stage palliation | ASQ | Three years |
| Heye\(^{19}\) | CHD | Single centre, Switzerland | Yes | CPB | WPPSI, Snijders Oomen Nonverbal Test of Intelligence | 6 years |
| Hiraiwa\(^{14}\) | SV | Single centre, Japan | Yes | Three stage palliation | BSID-II | 3 and 8 years |
| Knirsch\(^{25}\) | CHD | Single Centre, Switzerland | Yes | Open heart surgery at <1 year of age | BSID II | One year |
| Majnemer\(^{31}\) | CHD | Single centre, Canada | Yes | Open heart surgery | Peabody Developmental Motor Scale (version I) | Before surgery, discharge and at 12–18 months |
| Matos\(^{27}\) | CHD | Single centre, Portugal | No | As per pathology | Multiple tests | 13–18 years |
TRIVEDI et al. reported outcomes at or prior to two years of age. Four studies reported outcomes at multiple timepoints.

Statistical analysis: Seventeen studies used regression analysis to predict neurodevelopmental outcome. Of these, 14 studies reported statistical significance of univariate independent growth variable to enter MVA. The statistical significance for univariate variables was mentioned as \( p \)-value and it varied from \(<0.05\) to \(<0.25\). Tests of correlation were reported in three. Ten studies reported population mean of 100 and SD of one as effect size and two reported it to be below two SD. Anticipated effect size was unclear or another measure in the rest of studies.

3.2 | Outcomes

BW: Birth weight, the most reported variable, predicted neurodevelopmental outcome the most. Nine studies showed association of BW with neurodevelopmental outcomes. BW predicted MDI in four studies and PDI in two, where all infants had CPB. In infants with a variety of CHD, BW correlated with visuo-construction ability and a measure of cognition at 13–18 years of age. In infants with SV repair, BW predicted MDI and FSIQ, BSID summary scores and daily living, communication and motor skills. In infants who required CPB, being SGA was a risk factor for low IQ and communication.

Wt at surgery: Predicted low GAC score and MDI in infants with SV physiology and variability of PDI in infants with total anomalous pulmonary venous connection (TAPVC).

HC: HC at birth showed correlation and predictive ability for scores of neurocognitive assessments performed at older age. Other studies reported association of HC later in life with PDI, motor delay and fine-motor skills.

Height: In infants with SV physiology, height at 14 months predicted PDI and communication and height z-score trajectory predicted with PDI.

Body composition: No studies that reported association of body composition with neurodevelopment were identified.

Quality: Most studies as per the Newcastle-Ottawa scale were in fair category with one being poor and one being good (Table 3).

Meta-analysis: The studies varied in their participant type, choice of independent growth variables, assessment tools and timing of assessment to such an extent that pooling of the data was considered inappropriate.

Characteristics of excluded studies: Among studies that got excluded after a full-text review, wrong or no comparator was the most common reason, suggesting that a variety of other clinical parameters were assessed to predict neurodevelopmental outcome or simply developmental data were reported.

4 | DISCUSSION

With declining mortality in infants with CHD, longer term outcomes of growth and its association with neurodevelopment, have gained...
## Table 2: Summary of outcome data from included studies

| Reference | Anticipated effect size | Eligible/assessed (reason for losses) | Growth variable | Results, MVA only |
|-----------|-------------------------|--------------------------------------|-----------------|------------------|
| Alton<sup>15</sup> | Developmental indices lower than 70 (2 SD below mean) | 41/34 (death) | WT at surgery | WT at surgery contributed to variability of PDI |
| Atallah<sup>13</sup> | Population norm score (SD): 100 (15) | 117/68 (death) | BW, WT at BCPA, WT at Fontan | FSIQ, PIQ, VIQ and Beery VMI showed no association Lower WT at the time of the BCPA predicted lower GAC score |
| Campbell<sup>24</sup> | Age defined cut-off | 123/60 (as per exclusion criteria) | WT at surgery | No association |
| Cheung<sup>22</sup> | Population norm score (SD): 100 (15) | 115/94 (death, 76 without chromosomal syndromal abnormalities) | Z-score for WT, L and HC | BW of 2000-2499 predicted low ABAS GAC scores |
| Chock<sup>23</sup> | ≥2-month delay at subject’s adjusted age | ~/35 | BW | Lower BW predicted developmental delay |
| Fuller<sup>16</sup> | Population norm score (SD): 100 (15) | 675 eligible, 550 enrolled | BW | Higher BW predicted higher MDI |
| Gaynor<sup>21</sup> | Population norm score (SD): 100 (15) | 675/188 (criteria of study, lack of return) | WT, L, HC at birth | BW predicted MDI and PDI |
| Gaynor<sup>12</sup> | Population norm score (SD): 100 (15) | 2501/177 (test not performed) | BW | BW predicted low MDI PDI |
| Goldberg<sup>17</sup> | Delayed scores: >2 SD below the mean | 325/203 (death, heart transplant, late consent, questionnaire not completed) | BW <2.5 kg, WT & HT pre-Norwood, 14 months, 2 years; HC-for-age z pre-Norwood, 14 months | Height at 14 months predicted communication; HC-for-age z at 14 months predicted fine motor |
| Heye<sup>19</sup> | – | 181/143 (death, refusal, could not be reached, moved) | WT, HT & HC at birth and surgery, SGA | Smaller HC at birth predicted lower IQ at 6 years With one growth variable in MVA, SGA and HT at birth predicted IQ at 6 years |
| Hiraiwa<sup>14</sup> | Low MDI and FSIQ >1 SD below the normative mean (100) | 53/35 (exclusion criteria, follow-up at another institution) | BW, HC at birth, HT and WT at stage II & III, WT at BSID & WISC | BW predicted MDI and FSIQ WT at stage II predicted MDI |
| Knirsch<sup>25</sup> | – | 107/101 (death and follow-up) | Preoperative WT | No association |
| Majnemer<sup>31</sup> | Scores <1.5 SD below normative mean (<78) | 131/94 (Death, attrition, refusal) | HC | Pre and postoperative HC predicted fine motor delay |
| Matos<sup>27</sup> | – | ~/93 | BW, HC and L at birth | HC positively correlated with WDT, RCFc and CWSi, and negatively with TMT BW correlated positively with RCFc and BKS |
focus. This was evident by the fact that all studies identified in this review were published in or after 2006. None of the included reports published in English language came from low-income countries.

This issue remains complex mainly for three reasons:

- The variety of defects that can be labelled as CHD
- Different measures of growth
- Number of tools that can be used to assess development and cognition

Many defects come under the broad umbrella of CHD. In this systematic review, except for the studies that looked specifically at TAPVC or hypoplastic left heart syndrome (HLHS), the pathologies were pooled.

Heart surgery in children can lead to brain damage, primarily through mechanisms that occur during CPB. The factors that make an impact on neurodevelopment could be patient-specific (mostly innate and not modifiable) and procedure-specific (in part modifiable). Children with SV pathologies including HLHS are at high risk for delayed intrauterine brain development as well as perioperative cerebral injuries. It was clear in this review that infants with CHD who had CPB, and SV physiology were the most studied. No study exclusively reported association of growth and developmental outcome in infants who did not have CPB.

Growth can be measured on cross-sectional or longitudinal basis and in utero or ex utero. Anthropometric measurements at birth such as BW, Length and HC help measure in utero growth. These measures remain innate to the foetus and in utero environment. The overall risks of both SGA and severe SGA were higher in isolated CHD than what would be expected in the general population with substantial differences across the subtypes of CHD. Most studies included in this review focused on measures of innate foetal growth and its association with neurodevelopment. These variables are routinely collected and easy to measure. Ex utero growth measurements although easy to collect, are prone to attrition that increases with longer follow-up. Whether growth in CHD is considered an outcome or a risk factor, anthropometry is one of the best clinical markers for teasing out the drivers of heterogeneity in outcomes, particularly those that can be modified or minimised if identified early.

BW was the growth variable that was most reported and consistently associated with mental and motor development and cognition. Ex utero growth as measured by weight at surgery was also associated with developmental outcomes such as GAC scores and MDI in infants with SV physiology. The causality of these measures remains speculative given the observational measures of the studies.

Developmental and cognitive outcomes can be measured by a variety of tools and the period of follow-up is dictated by the researcher. This reflected in our systematic review with such outcomes reported from early infancy to teenage years. These outcomes can be measured as cross-sectional at one timepoint or longitudinally. In this review BSID-II was the most common tool followed by BSID-III. BSID is a widely used developmental assessment tool that is often considered gold standard in assessment of early childhood development. BSID-II was criticised for its lack of subscale-standardised scores for assessing cognitive and language development and
| Study          | Selection Representativeness of exposed cohort | Selection of nonexposed cohort | Ascertainment of exposure | Outcome not present at start of study | Comparability | Outcome Assessment of outcome | Length of follow-up | Adequacy of follow-up of cohorts |
|---------------|-----------------------------------------------|-------------------------------|----------------------------|---------------------------------------|---------------|-------------------------------|---------------------|----------------------------------|
| Atallah\(^{13}\)         | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |
| Alton\(^{15}\)                   | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |
| Campbell\(^{24}\)                 | *                                              |                               | *                           |                                      | *             |                               | *                   | *                                |
| Cheung\(^{22}\)                  | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |
| Chock\(^{23}\)                   | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |
| Fuller\(^{16}\)                  | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |
| Gaynor\(^{21}\)                  | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |
| Gaynor\(^{12}\)                  | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |
| Goldberg\(^{17}\)                | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |
| Hiraïwa\(^{18}\)                 | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |
| Heye\(^{19}\)                    | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |
| Knirsch\(^{25}\)                 | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |
| Majnemer\(^{31}\)               | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |
| Matos\(^{27}\)                   | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |
| Miller\(^{29}\)                  | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |
| Miller\(^{26}\)                  | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |
| Newburger                        | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |
| Ravishanar\(^{30}\)              | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |
| Soto\(^{20}\)                    | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |
| Tseng\(^{28}\)                   | *                                              |                               | *                           |                                      | *             |                               |                     |                                  |

**Note:** Overall score: 0–3 points = "poor quality"; 4–6 points = "fair quality"; 7–9 points = "good quality". Each * gives one point to the overall score.
BSID-III for overestimation of children's neurodevelopment. This raises some questions regarding validity of the tools. In included studies, not only the cut off population means of developmental scores were different but the significance of univariate p-values that reported the association of growth with development also varied. It is possible that the outcome of statistical analysis could have been different if uniform statistical measures were used. Assessment of General Movements is a well-recognised tool to detect cerebral palsy. Recently, studies have reported use of this tool in infants with CHD however association of outcomes of this assessment with growth, has not be reported.

Only six studies explicitly stated exclusion of infants with genetic disorders or recognisable syndromes. Potential inclusion of such infants in other studies may have contributed to adverse growth and developmental outcomes.

Such a complex interplay makes pooling of the data difficult. Though most studies came across as “fair” on the chosen quality assessment tool, the design of trials makes it difficult to prognosticate the impact of growth. It appears that linking growth with developmental outcomes in this population is gaining momentum, however, we did not identify any study that looked at impact of nutritional interventions on growth and development.

5 | STRENGTHS AND LIMITATIONS

The strengths of this systematic review were that the objective was clear with explicit inclusion and exclusion criteria. This systematic review included infants who had operative surgery at any timepoint. This, however, was a deviation from protocol where infants who had surgery in the neonatal period only were eligible for inclusion. The included studies were observational in nature and no causality of growth with adverse neurodevelopmental outcomes can be established. Another limitation of this review is identification of studies exclusively from high-income countries, mostly from single centre, potentially limiting wider generalisability. Further improvement in precision could not be achieved by pooling of data for meta-analysis.

6 | CONCLUSION

In conclusion, this systematic review suggests that infants with CHD, specifically SV physiology in- and ex utero growth could potentially predict risk of adverse neurodevelopmental outcomes. The measurement of growth and development is variable and dictated by the researcher.

7 | RECOMMENDATION FOR FUTURE

We recommend that within and across established registries for CHD, consensus should be achieved on measurement of growth and methodology of collection of neurodevelopmental data. Foetal growth monitoring protocols addressing management of modifiable factors should be established in this population. Postnatal and post-discharge nutritional assessment and management of infants who had cardiopulmonary bypass, especially with SV physiology should be carefully addressed and researched. Use of a short-term developmental assessment tool such as the assessment of general movements can address the issue of long-term attrition. Growth and developmental outcomes of infants where CPB was not required should be reported as a separate group.

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CONFLICT OF INTEREST

None of the authors have any competing interest

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