BMJ Open

Long-term early development research in congenital heart disease (LEADER-CHD): a study protocol for a prospective cohort observational study investigating the development of children after surgical correction for congenital heart defects during the first 3 years of life

Hannah Ferentzi,[1,2] Constanze Pfitzer,[1,3,4] Lisa-Maria Rosenthal,[1,3] Felix Berger,[1,4,5] Katharina R L Schmitt[1,5]

To cite: Ferentzi H, Pfitzer C, Rosenthal L-M, *et al*. Long-term early development research in congenital heart disease (LEADER-CHD): a study protocol for a prospective cohort observational study investigating the development of children after surgical correction for congenital heart defects during the first 3 years of life. *BMJ Open* 2017;**7**:e018966. doi:10.1136/bmjopen-2017-018966

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-018966).

HF and CP contributed equally.

Received 2 August 2017
Revised 8 November 2017
Accepted 6 December 2017

For numbered affiliations see end of article.

Correspondence to
Hannah Ferentzi;
ferentzi@dhzb.de

ABSTRACT

Introduction Congenital heart disease (CHD) is the most common birth defect. Studies on the development of children with CHD point towards deficits in motoric, cognitive and language development. However, most studies are cross-sectional and there is a gap in the knowledge concerning developmental trajectories, risk and protective factors and a lack of research concerning environmental predictors. Specifically, no studies have so far considered the importance of early caregiving experiences and child temperament for the development of children with CHD.

Methods In a single-centre prospective cohort study, cognitive, motoric and language development of 180 children after corrective surgery for a simple transposition of the great arteries (TGA), tetralogy of Fallot (TOF) or ventricular septal defect (VSD) will be assessed at ages 12, 24 and 36 months with the Bayley Scales of Infant Development 3rd Edition (BSID-III). At age 12 months, a free-play video observation will be conducted to investigate the relationship between primary caregiver and child, and child temperament will be assessed with the Infant Behavior Questionnaire—Revised Short Version. Medical information will be obtained from patient records and demographic information via questionnaires.

Analysis Frequency and severity of developmental delays will be reported descriptively. Differences between groups (TGA, TOF, VSD) will be subjected to repeated-measures analysis across time points. Multiple regressions will be applied for the analysis of predictors at each time point. For the analysis of differential developmental trajectories, mixed-model analysis will be applied.

Ethics and dissemination The study has been approved by the local medical ethics committee. Written informed consent will be obtained from all participants. Parents have the option to be debriefed about BSID-III results after each assessment and about the study results after project completion. Results will be disseminated in peer-reviewed journals and presented at conferences.

Strengths and limitations of this study

- No brain MRI will be conducted at any time point; postnatal MRI of the brain might provide valuable insights into the relationship between alterations of the central nervous system, perioperative complications and developmental delays, but is beyond the scope of this study.
- The longitudinal study design allows the investigation of developmental trajectories across different time points and of specific predictors for differential trajectories.
- By investigating three congenital heart disease groups (transposition of the great arteries, tetralogy of Fallot, ventricular septal defect), valuable information can be derived for distinctive patterns of development dependent on diagnosis.
- To our knowledge, this interdisciplinary study is the first to investigate the role of quality of caregiver–child interaction for development in this patient group, which has important theoretical implications and is highly relevant for the development of secondary prevention programmes.

Trial registration number DRKS00011006; Pre-results.

INTRODUCTION

Background and rationale

Congenital heart disease (CHD) is the most common birth defect and the incidence ranges from 19 to 75 per 1000 live births worldwide.[1] During the past years, medical care for children with CHD has significantly improved due to scientific progress leading to advancement of early diagnostics[2–5] and technical possibilities.[6 7] This has led to increased

survival rates.[8 9] In Germany, more than 6500 children are born with a CHD each year, which is approximately every hundredth child, and more than 90% reach adulthood, while mortality has fallen by 60% since 1990.[10] There is now a growing research interest in morbidity and quality of life of these patients.[11 12] Studies on the development of children with CHD generally point towards deficits in motoric, cognitive and language development,[13–18] which are mostly weak to moderate and often combined.[19] Even though developmental delays tend to decline with time,[13] they are still observed many years after successful surgery and potentially manifest themselves in learning or behavioural difficulties,[20 21] which implies that they are not transient in nature. Children with cyanotic heart defects, such as transposition of the great arteries (TGA) or tetralogy of Fallot (TOF) have been found to have worse developmental outcomes than children with acyanotic heart defects, such as ventricular septal defects (VSD), in several studies,[22–26] while other studies did not find systematic differences between TGA, TOF or VSD, for instance after taking demographic, preoperative and operative variables into account.[15] These contrasting results point towards a complex relationship between physiological characteristics of the heart defect, neurological sequelae, therapeutic necessities and patient-related factors when it comes to future development.[27 28]

On a neurological level, the aetiology of developmental delays in children with CHD is complex, concerning the specific time point as well as the mechanism that leads to alterations.[29] Already preoperatively, certain abnormalities of the central nervous system can be observed, in particular less mature macrostructural and microstructural brain development and lower brain volume.[28] These changes can be attributed to reduced oxygenation and perfusion, while the relative contribution depends on the specific defect.[30] White matter injury is a predisposing factor for decelerated brain development, which is often present in newborns with CHD.[31] In addition, infarction, ischaemic strokes and cerebral haemorrhage can be observed after cardiac surgery.[32]

Concerning perioperative management, duration of cardiopulmonary bypass, duration of hospital stay and postoperative complications have been found to explain approximately 5% of the variance in development of neurologic deficits in earlier research.[33] Other intraoperative predictors may be aortic clamping time,[34 35] use of deep hypothermia and circulatory arrest[36–40] and use of allogeneic blood.[41 42] Other postoperative predictors may be duration of ventilation and postoperative cardiac markers such as lactate,[43] troponin,[44] creatine kinase (CK)[45] and creatine kinase myocardial band (CK-MB).[46] Furthermore, time point of surgery might be an important predictor, with more neurological anomalies observed after cardiac surgery during the neonatal period as compared with surgery later in infancy[47] and Eisenmenger pathophysiology as a complication of uncorrected VSD later in life.[48] Beside medical aspects related to the heart defect, patient-related variables such as gender, lower birth weight, presence of genetic/phenotypical anomalies, educational status of the mother and ethnicity explained as much as 30% of the variance in development of the child.[13 49]

Importantly, most studies investigating the development of children with CHD are cross-sectional and only few studies have observed the development of children longitudinally and systematically during the first years of life. In one such study, Mussatto and colleagues investigated 99 children (19 of whom had genetic syndromes) with different CHDs (34 univentricular physiology, 65 biventricular physiology) every 6 months, during the first 3 years of life.[50] In a mixed-models analysis, no significant change in cognitive and language development, as assessed with the Bayley Scales of Infant Development 3rd Edition (BSID-III),[51] was observed for participants without genetic syndromes, pointing to a developmental pace comparable to that of healthy infants, even though the majority of children had average to low scores. Motoric scores significantly improved across time, implicating that deficits could be compensated to a certain extent by the developing brain. Children with genetic syndromes showed a decline of cognitive scores, which implies delayed development, and no significant changes in language and motoric scores. This study adds crucial insights into the dynamics of early development in children with CHD, but more studies are needed that shed light on developmental trajectories, carefully discerning the multitude of potential predictors. Multilevel analysis can be seen as a particularly useful approach for the investigation of development across time, as initial levels of functioning, intraindividual change over time, and individual differences in initial functioning and rates of change can be efficiently modelled.[52]

Another gap in research is the role of environmental predictors for the development of children with CHD, for instance the relationship between primary caregiver and child. The concept of 'sensitive responsivity' introduced by Ainsworth[53] is a well-established predictor for the cognitive development of healthy children and an increasing number of studies point to the relevance of the quality of parenting for development in medically vulnerable groups. In one such study, premature infants had lower cognitive outcomes than full-term infants if parents provided low structuring, but similar outcomes when they provided high structuring,[54] which supports the diathesis–stress model.[55] Complicating the role of parenting influences on cognitive development is the fact that not all children are equally affected by their environment. According to the differential susceptibility hypothesis, susceptibility to parenting may depend on child temperament or other individual characteristics, while this susceptibility can be advantageous (in the case of a positive environment) or disadvantageous (in the case of a negative environment).[56] The study on preterm infants supported this hypothesis: babies with highly reactive temperaments had lower cognitive functioning when little structuring was provided by their mothers, but they

had higher cognitive functioning when maternal structuring was high. This association between structuring and cognitive functioning was not found in infants with average reactivity. As premature babies share crucial characteristics with children with CHD concerning their neurological fingerprint, such as brain maturation and white matter injury,[29] a similar pattern might be observed in the population of children with CHD. When it comes to temperament, studies in children with CHD are rare. One study showed that children with univentricular physiology show a more difficult temperament (negative mood, more difficult to soothe) at 3 months when compared with children with biventricular physiology or healthy controls.[57] Children with biventricular physiology were similar in temperament to healthy controls, but differences between biventricular physiologies (TGA, TOF and VSD) were not investigated.

AIMS

The aim of the current study is to investigate long-term early development of children with different congenital heart defects during the first 3 years of life. We will include children with two different cyanotic heart defects (TGA or TOF) and one acyanotic heart defect (VSD), who undergo corrective surgery before the age of 10 months. We will measure cognitive, language and motoric development at 12, 24 and 36 months. We expect clinically relevant developmental delays at ages 12, 24 and 36 months and expect that delays will be significantly higher in children with cyanotic heart defects than in children with an acyanotic heart defect. Furthermore, we hypothesise that developmental delays decline over the course of the first 3 years. We will investigate predictors for differential developmental pathways in order to add insight to the aetiology of developmental delays and potential risk and protective factors. Specifically, we will look at medical and patient-related predictors. In addition, we will investigate the quality of parenting between primary caregiver and the child as environmental predictor moderated by child temperament. We expect that these predictors will explain a clinically relevant amount of variance at each time point and development from one time point to the next.

METHODS AND ANALYSIS

This study is a single-centre prospective cohort study with three groups (TGA, TOF and VSD). Written informed consent will be obtained from all participants. The primary outcome (cognitive, motoric and language development) will be assessed at ages 12, 24 and 36 months; the secondary outcome measure death will be derived from patient files during the course of the study. The secondary outcome measure child temperament will be measured at age 12 months. For a flow chart showing the inclusion process and measurement time points, see figure 1.

Participants

The study population comprises children who undergo corrective surgery for TGA, TOF or VSD before the age of 10 months at the department of congenital heart disease/paediatric cardiology at a specialised heart centre in Germany. Participating families will be recruited during the hospital stay for corrective surgery via their attending physicians or can also be referred by resident family physicians or cardiologists. Participation is voluntary; compensation for travel costs will be provided.

Inclusion criteria

- Diagnosis of TGA, TOF or VSD
- Corrective surgery at ≤10 months
- One parent a native speaker of German

Exclusion criteria

- Genetic syndromes (except for microdeletion syndrome 22Q11) or phenotypic anomalies that might influence the cognitive/motoric development (eg, trisomy 21, 22Q deletion spectrum).
- Birth weight under 2.5 kg
- Gestational age of less than 37 weeks
- Drug/alcohol abuse/dependence in the history of the mother
- Reanimation with a duration of ≥5 min before the age of 12 months

Procedure

Assessment of eligibility, inclusion and baseline measures

Parents of children with TGA, TOF or VSD will be approached during their child's hospital stay for corrective surgery. Inclusion and exclusion criteria will be checked by the study physician. If eligible for participations, parents will receive study information (written, oral) from their attending physician. If they decide to participate, written informed consent will be obtained. Parents will then be contacted by telephone by a study nurse after release of the child from hospital in order to make the first appointment at the child's age of 12 months. If parents are interested but undecided about participation, they will be contacted by the study nurse after hospital discharge and receive additional study information. Open questions will be answered by the study nurse, physician or psychologist. If parents decide to participate, the first appointment will be scheduled at age 12 months and informed consent will be obtained at the beginning of that appointment. At baseline, the following preoperative variables will be registered: gender, birth weight, birth length, gestational age, Apgar score (0, 5, 10 min), comorbidities and time of CHD diagnosis. The following perioperative variables will be registered: age in months at surgery, duration of surgery, duration of perfusion, aortic cross clamping time, use of allogeneic blood, hypothermia, cardiac markers (lactate, troponin, CK, CK-MB) and type, dose and duration of anaesthetics, analgesics and sedatives. As indicators of the postoperative course, reoperations, secondary chest closure, ventilation time, time point of extubation, reintubation after surgery,

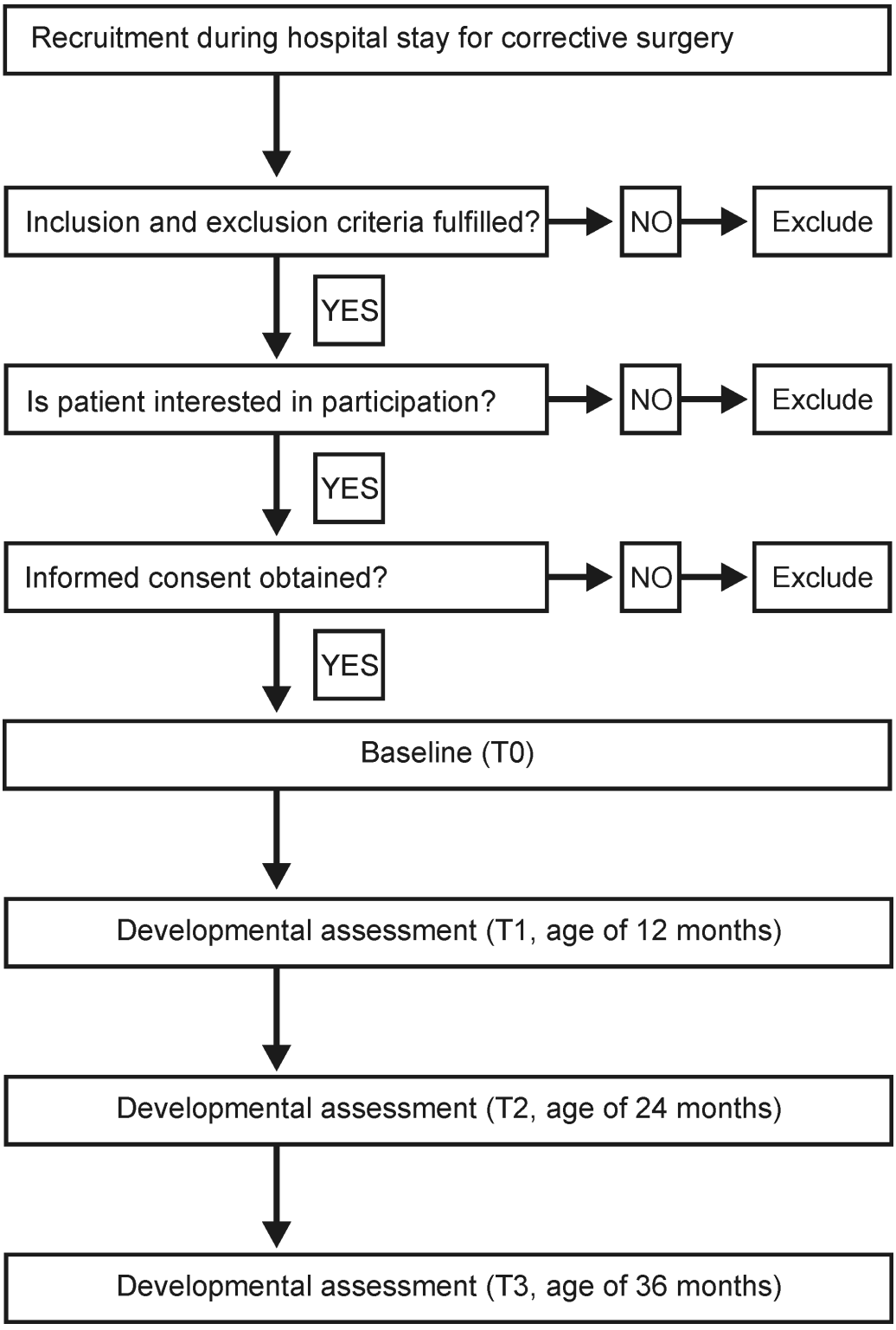

Figure 1 Flow chart of inclusion process and measurement time points.

duration of hospital stay, neurological events (including hypoxic events, ie, cerebral infarction, global cerebral ischaemia), last CO_2 level, oxygen saturation at discharge and resuscitation are registered. In the case of preoperative resuscitation, the neuronal markers NSE and S100β are registered directly after resuscitation, 24 hours, 48 hours and 72 hours after.

Measurement time points

At time 0 (T0, hospital stay for corrective surgery), medical information will be derived from patient files. At T1 (12 months), parents will fill out questionnaires on demographic variables and child temperament. After that, development of the child will be assessed and the video observation will be conducted. At ages 24 and 36

months (T2, T3), the second and third developmental assessment will be conducted, respectively. At each developmental assessment, additional medical information will be registered based on patient files and the examination records of the child's general practitioners (current weight, length, medical events and symptoms), and information about postacute rehabilitation care and use of early support services for the child will be assessed by a questionnaire developed by the research team.

MEASUREMENTS

Primary outcome measure

Cognitive, language and motoric development will be assessed with the BSID-III[51] at ages 12, 24 and 36 months. The BSID-III is an internationally recognised developmental assessment tool with a large normative sample of n=1009 for children between the ages of 16 days to 42 months and 15 days. During this test, the child has to solve different tasks with ascending difficulty in a playful manner. The BSID-III comprises five subtests: fine and gross motoric skills, receptive and expressive language, and cognition. The starting point is age dependent; the number of tasks and ending point depend on the individual performance of the child. Assessment time is approximately 60 to 90 min. The language and motoric subtests can be summarised into one score each (language and motoric skills, respectively).

Secondary outcome measures

Death

Death of participating children will be registered as secondary outcome measure throughout the study.

Child temperament

Child temperament at 12 months will be assessed with the Infant Behaviour Questionnaire-Revised, Short Version, which is a 91-item questionnaire with good psychometric properties.[58]

Video observation

At age 12 months, a free-play video observation will be conducted with the primary caregiver and the child. Toys (rubber snake, bubbles, building blocks, a cloth, stacking rings) will be placed on a blanket on the floor and the parent will be instructed to spend time with their child during the upcoming 20 min. The interaction is recorded with a digital video camera and coded by two independent raters using the 'Emotional Availability Scales',[59] which describe the quality of the interaction on several dimensions: sensitivity, structuring, intrusion and hostility of the primary caregiver, as well as child responsivity, and child inclusion of the primary caregiver.

Data handling

Study participant numbers will be used on all documentation to ensure confidentiality. All electronic study-related information will be stored on hospital servers in folders, to which only members of the research team have access. One password-protected file linking study participant number and patient identification will be stored separately. Study information on paper will be kept in locked cabinets with restricted access. Data will be archived for 15 years after completion of data collection. Data entry will be conducted in duplicate, in order to check for data entry mistakes. Principal and coinvestigators will have access to final data files. Authorship of study reports will be assigned according to contribution to design, conduction, data analysis, interpretation and reporting of the results in writing and oral presentation. Study participants and funding institutions will be informed of the results at the end of the study period.

Statistical analyses

Power analysis and sample size

An a priori sample size calculation was performed using G*Power for F-test for repeated-measures ANOVAs with between–within interaction. Effect sizes for our patient and age group could not be inferred from earlier studies or meta-analyses. Based on clinical observation, we expect small to medium effects. We therefore specified an estimated effect size of Cohen's f=0.15, which corresponds to a Cohen's d of 0.3. Alpha error probability was set to 0.0125 to correct for multiple testing (Bonferroni correction), as there are three subscales of the primary outcome measure (cognitive, language and motoric development). Accordingly, significant results with regard to one, two or three of the subscales will reflect true effects. Power was set to 0.80 to detect differences between time points (three measures, three groups, non-sphericity correction of 1). This results in an estimation of the total sample size of 123, or 41 per group. Calculating loss to follow-up of 20%, we strive to include 180 infants after corrective surgery, resulting in 40–50 completive participants in each of the 3 CHD groups.

Analyses plan

Primary analyses

Frequency and severity of developmental delays will be described by proportions of mean values. In order to investigate differences between groups (TGA, TOF, VSD) across time (12, 24, 36 months), repeated-measures analyses will be conducted with cognitive, motoric and language scores as dependent variables. Time will be entered as within-subjects factor and group as between-subjects factor. Time point of surgery will be entered as covariate. Multiple regressions will be applied for the analysis of medical, person-related and environmental predictors of cognitive, motoric and language scores at each measurement time point.

Secondary analyses

In order to investigate if the three groups (TGA, TOF, VSD) differ in temperament at T1 (12 months), exploratory analysis will be conducted by applying an analysis of covariance, with group (TGA, TOF, VSD) as factor and potentially confounding variables (time point of surgery, gender) entered as covariates.

In order to analyse differential developmental trajectories of the three groups (TGA, TOF, VSD) across time, multilevel modelling will be used with the goal to investigate differences in interindividual variability (rates of change) and potential predictors influencing individual trajectories.

Time point, cause and circumstances of death will be described and if necessary considered for further analyses.

Author affiliations
[1]Department of Congenital Heart Disease—Paediatric Cardiology, Deutsches Herzzentrum Berlin, Berlin, Germany
[2]Unit for Psychosomatic Medicine, Deutsches Herzzentrum Berlin, Berlin, Germany
[3]Berlin Institute of Health (BIH), Berlin, Germany
[4]Department of Paediatry, Division of Cardiology, Charité Universitätsmedizin, Berlin, Germany
[5]German Centre for Cardiovascular Disease (DZHK), Berlin, Germany

Correction notice This article has been corrected since it was first published. 'kinderherzen' and 'Germany' have been added to the Funding statement.

Acknowledgements The authors thank Anne Gale for the native speaker correction and Julia Stein for statistical advice. CP and LMR are participants in the BIH Charité Junior Clinician Scientist Program funded by the Charité—Universitätsmedizin Berlin and the Berlin Institute of Health.

Contributors HF, CP and KRLS made substantial contributions to the conception or design of the work. HF and CP contributed equally to protocol drafting and protocol editing. KRLS, LMR and FB reviewed the protocol and made amendments. All authors critically reviewed and approved the final version. All authors agree to be accountable for all aspects of the work.

Funding This work is funded by kinderherzen, Fördergemeinschaft Deutsche Kinderherzzentren e.V, Germany.

Competing interests None declared.

Ethics approval The study has been approved by the Medical Ethics Committee Charité Mitte (N. EA2/118/12) on 14 July 2016.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Mendis S, Puska P, Norrving B. *Global atlas on cardiovascular disease prevention and control*: World Health Organization, 2011.
2. Engel M, Kochilas L. Pulse oximetry screening: a review of diagnosing critical congenital heart disease in newborns. *Med Devices* 2016;9:199–203.
3. Verdurmen KM, Eijsvoogel NB, Lempersz C, *et al*. A systematic review of prenatal screening for congenital heart disease by fetal electrocardiography. *Int J Gynaecol Obstet* 2016;135:129–34.
4. Bruno CJ, Havranek T. Screening for critical congenital heart disease in newborns. *Adv Pediatr* 2015;62:211–26.
5. Olney RS, Ailes EC, Sontag MK. Detection of critical congenital heart defects: review of contributions from prenatal and newborn screening. *Semin Perinatol* 2015;39:230–7.
6. Ohye RG, Bove EL. Advances in congenital heart surgery. *Curr Opin Pediatr* 2001;13:473–81.
7. Sizarov A, Boudjemline Y. Novel materials and devices in the transcatheter management of congenital heart diseases—the future comes slowly (part 1). *Arch Cardiovasc Dis* 2016;109:278–85.
8. Holland BJ, Myers JA, Woods CR. Prenatal diagnosis of critical congenital heart disease reduces risk of death from cardiovascular compromise prior to planned neonatal cardiac surgery: a meta-analysis. *Ultrasound Obstet Gynecol* 2015;45:631–8.
9. Khairy P, Ionescu-Ittu R, Mackie AS, *et al*. Changing mortality in congenital heart disease. *J Am Coll Cardiol* 2010;56:1149–57.
10. Klawki R, Schmidt K, Heinemann M. *Deutscher Herzbericht 2016*. Frankfurt am Main: Deutsche Herzstiftung e.V, 2016.
11. Bouma BJ, Mulder BJ. Changing landscape of congenital heart disease. *Circ Res* 2017;120:908–22.
12. Ntiloudi D, Giannakoulas G, Parcharidou D, *et al*. Adult congenital heart disease: a paradigm of epidemiological change. *Int J Cardiol* 2016;218:269–74.
13. Gaynor JW, Stopp C, Wypij D, *et al*. Neurodevelopmental outcomes after cardiac surgery in infancy. *Pediatrics* 2015;135:816–25.
14. Snookes SH, Gunn JK, Eldridge BJ, *et al*. A systematic review of motor and cognitive outcomes after early surgery for congenital heart disease. *Pediatrics* 2010;125:e818–e827.
15. Gaynor JW, Gerdes M, Nord AS, *et al*. Is cardiac diagnosis a predictor of neurodevelopmental outcome after cardiac surgery in infancy? *J Thorac Cardiovasc Surg* 2010;140:1230–7.
16. Hallioglu O, Gurer G, Bozlu G, *et al*. Evaluation of neurodevelopment using Bayley-III in children with cyanotic or hemodynamically impaired congenital heart disease. *Congenit Heart Dis* 2015:10:537–41.
17. Karsdorp PA, Everaerd W, Kindt M, *et al*. Psychological and cognitive functioning in children and adolescents with congenital heart disease: a meta-analysis. *J Pediatr Psychol* 2007;32:527–41.
18. Massaro AN, El-Dib M, Glass P, *et al*. Factors associated with adverse neurodevelopmental outcomes in infants with congenital heart disease. *Brain Dev* 2008;30:437–46.
19. Latal B. Neurodevelopmental outcomes of the child with congenital heart disease. *Clin Perinatol* 2016;43:173–85.
20. Hövels-Gürich HH, Konrad K, Skorzenski D, *et al*. Long-term behavior and quality of life after corrective cardiac surgery in infancy for tetralogy of Fallot or ventricular septal defect. *Pediatr Cardiol* 2007;28:346–54.
21. Jones B, Muscara F, Lloyd O, *et al*. Neurodevelopmental outcome following open heart surgery in infancy: 6-year follow-up. *Cardiol Young* 2015;25:903–10.
22. Hövels-Gürich HH, Konrad K, Skorzenski D, *et al*. Attentional dysfunction in children after corrective cardiac surgery in infancy. *Ann Thorac Surg* 2007;83:1425–30.
23. Cassidy AR, White MT, DeMaso DR, *et al*. Executive function in children and adolescents with critical cyanotic congenital heart disease. *J Int Neuropsychol Soc* 2015;21:34–49.
24. Hövels-Gürich HH, Bauer SB, Schnitker R, *et al*. Long-term outcome of speech and language in children after corrective surgery for cyanotic or acyanotic cardiac defects in infancy. *Eur J Paediatr Neurol* 2008;12:378–86.
25. Hövels-Gürich HH, Konrad K, Skorzenski D, *et al*. Long-term neurodevelopmental outcome and exercise capacity after corrective surgery for tetralogy of Fallot or ventricular septal defect in infancy. *Ann Thorac Surg* 2006;81:958–66.
26. Miatton M, De Wolf D, François K, *et al*. Neurocognitive consequences of surgically corrected congenital heart defects: a review. *Neuropsychol Rev* 2006;16:65–85.
27. Hovels-Gurich HH. Psychomotor development of children with congenital heart defects. Causes, prevalence and prevention of developmental disorders after cardiac surgery in childhood. *Monschr Kinderheilkd* 2012;160:118–28.
28. Marelli A, Miller SP, Marino BS, *et al*. Brain in congenital heart disease across the lifespan: the cumulative burden of injury. *Circulation* 2016;133:1951–62.
29. McQuillen PS, Miller SP. Congenital heart disease and brain development. *Ann N Y Acad Sci* 2010;1184:68–86.
30. Rollins CK. A mixed bag: Differential influences of oxygenation and perfusion on brain development in congenital heart disease. *J Thorac Cardiovasc Surg* 2016;152:960–1.
31. Beca J, Gunn JK, Coleman L, *et al*. New white matter brain injury after infant heart surgery is associated with diagnostic group and the use of circulatory arrest. *Circulation* 2013;127:971–9.
32. Dimitropoulos A, McQuillen PS, Sethi V, *et al*. Brain injury and development in newborns with critical congenital heart disease. *Neurology* 2013;81:241–8.
33. International Cardiac Collaborative on Neurodevelopment (ICCON) Investigators. Impact of operative and postoperative factors on neurodevelopmental outcomes after cardiac operations. *Ann Thorac Surg* 2016;102:843–9.
34. Farouk A, Karimi M, Henderson M, *et al*. Cerebral regional oxygenation during aortic coarctation repair in pediatric population. *Eur J Cardiothorac Surg* 2008;34:26–31.

35. Rodriguez RA, Weerasena N, Cornel G, *et al*. Cerebral effects of aortic clamping during coarctation repair in children: a transcranial Doppler study. *Eur J Cardiothorac Surg* 1998;13:124–9.
36. Dominguez TE, Wernovsky G, Gaynor JW. Cause and prevention of central nervous system injury in neonates undergoing cardiac surgery. *Semin Thorac Cardiovasc Surg* 2007:19:269–77.
37. Brotschi B, Gunny R, Rethmann C, *et al*. Relationship between temperature variability and brain injury on magnetic resonance imaging in cooled newborn infants after perinatal asphyxia. *J Perinatol* 2017;37:1032–7.
38. Kornilov IA, Sinelnikov YS, Soinov IA, *et al*. Outcomes after aortic arch reconstruction for infants: deep hypothermic circulatory arrest versus moderate hypothermia with selective antegrade cerebral perfusion. *Eur J Cardiothorac Surg* 2015;48:e45–50.
39. Newburger JW, Jonas RA, Wernovsky G, *et al*. A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. *N Engl J Med* 1993;329:1057–64.
40. Bellinger DC, Jonas RA, Rappaport LA, *et al*. Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. *N Engl J Med* 1995;332:549–55.
41. Busch C, Pfitzer C, Raschzok S, *et al*. Clinical outcome and inflammatory response after transfusion of washed and unwashed red blood cells in children following cardiovascular surgery. *Prog Pediatr Cardiol* 2017.
42. Garraud O, Hamzeh-Cognasse H, Laradi S, *et al*. [Blood transfusion and inflammation as of yesterday, today and tomorrow]. *Transfus Clin Biol* 2015;22:168–77.
43. Mann C, Latal B, Padden B, *et al*. Acid–base parameters for predicting magnetic resonance imaging measures of neurologic outcome after perinatal hypoxia–ischemia: is the strong ion gap superior to base excess and lactate? *Am J Perinatol* 2012;29:361–8.
44. Landesberg G, Shatz V, Akopnik I, *et al*. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol* 2003;42:1547–54.
45. Markowitz SD, Ichord RN, Wernovsky G, *et al*. Surrogate markers for neurological outcome in children after deep hypothermic circulatory arrest. *Semin Cardiothorac Vasc Anesth* 2007;11:59–65.
46. Bolton CF. Neuromuscular manifestations of critical illness. *Muscle Nerve* 2005;32:140–63.
47. Galli KK, Zimmerman RA, Jarvik GP, *et al*. Periventricular leukomalacia is common after neonatal cardiac surgery. *J Thorac Cardiovasc Surg* 2004;127:692–704.
48. Penny DJ, Vick GW. Ventricular septal defect. *The Lancet* 2011;377:1103–12.
49. Gaynor JW, Wernovsky G, Jarvik GP, *et al*. Patient characteristics are important determinants of neurodevelopmental outcome at one year of age after neonatal and infant cardiac surgery. *J Thorac Cardiovasc Surg* 2007;133:1344–53.
50. Mussatto KA, Hoffmann RG, Hoffman GM, *et al*. Risk and prevalence of developmental delay in young children with congenital heart disease. *Pediatrics* 2014;133:e570–577.
51. Bayley N. In: Reuner G, Rosenkranz J, eds. *Bayley Scales of Infant and Toddler Development: Bayley-III. deutsche bearbeitung*. Frankfurt am Main: Pearson Assessment & Information GmbH, 2006.
52. Ram N, Grimm K. Using simple and complex growth models to articulate developmental change: matching theory to method. *Int J Behav Dev* 2007;31:303–16.
53. Ainsworth MD. Infant–mother attachment. *Am Psychol* 1979;34:932–7.
54. Gueron-Sela N, Atzaba-Poria N, Meiri G, *et al*. Temperamental susceptibility to parenting among preterm and full-term infants in early cognitive development. *Infancy* 2015.
55. Monroe SM, Simons AD. Diathesis–stress theories in the context of life stress research: implications for the depressive disorders. *Psychol Bull* 1991;110:406–25.
56. Belsky J, Bakermans-Kranenburg MJ, Van IJzendoorn MH. For better and for worse: differential susceptibility to environmental influences. *Curr Dir Psychol Sci* 2007;16:300–4.
57. Torowicz D, Irving SY, Hanlon AL, *et al*. Infant temperament and parental stress in 3-month-old infants after surgery for complex congenital heart disease. *J Dev Behav Pediatr* 2010;31:202–8.
58. Putnam SP, Rothbart MK. Development of short and very short forms of the Children's Behavior Questionnaire. *J Pers Assess* 2006;87:102–12.
59. Biringen Z, Derscheid D, Vliegen N, *et al*. Emotional availability (EA): theoretical background, empirical research using the EA scales, and clinical applications. *Developmental Review* 2014;34:114–67.