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DISSERTATION

Development of Children with Congenital Heart Disease

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von

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Inhaltsverzeichnis

1. Zusammenfassung der Publikationspromotion (in englischer Sprache)

1.1. Abstract in English

Congenital heart disease (CHD) is defined as a structural anomaly of the heart present at birth. Due to advances in the field of paediatric cardiology and cardiac surgery in the past decennia, most of the affected children now survive to adulthood. A growing amount of literature points to persistent developmental delays in this special population. However, only little is known about the mechanisms leading to these delays and predicting developmental outcome has shown to be a challenge in research so far.

In this dissertation, three studies are presented. In the first study, we analysed survey data on educational levels and professional status in grown-ups with congenital heart disease (GUCHD), to see if there are systematic differences according to CHD severity. Results show that 59.4 % of respondents had high educational levels and 51.1 % were currently employed. Adults with simple CHD had higher educational levels and were employed more often than patients with complex CHD. Future studies should investigate if these differences can be explained by cognitive deficits or by other factors, such as ongoing medical issues and associated physical limitations. In the second study, we investigate the cognitive, motor, and language development of infants with tetralogy of Fallot, ventricular septal defect, or transposition of the great arteries longitudinally, during the first three years of life. Here, the detailed study protocol is presented, as data collection is ongoing. The third study is a cross-sectional pilot study, in which we evaluated feasibility of the most frequently used instrument for the assessment of infant development, the Bayley Scales of Infant and Toddler Development- 3rd Edition (BSID-III) for use with the population of infants after cardiopulmonary resuscitation. Results show that the BSID-III was a suitable instrument for the majority of infants, but 30 % of the study population had visual/hearing and/or motor impairments impeding standardized assessment. Of the eight infants with quantifiable results, four showed substantial delays in cognitive, motor, and language development, highlighting the need for further research in this population. To conclude, studying development in children with CHD is a complex endeavour that needs to acknowledge inter-individual differences and is best approached from an interdisciplinary perspective, with the goal of working toward an evidence-based model of developmental delays in children with CHD.

1.2. Abstract in German

Ein angeborener Herzfehler (AHF) ist eine strukturelle Anomalie des Herzens bei der Geburt. Durch Fortschritt in der Kinderkardiologie und Kardiochirurgie in den letzten Jahrzehnten überleben inzwischen die meisten der betroffenen Patienten bis in das Erwachsenenalter. Studien weisen jedoch auf persistierende Entwicklungsverzögerungen in dieser Population hin. Bisher ist wenig über die Mechanismen bekannt, die zu diesen Entwicklungsverzögerungen führen und deren Vorhersage stellt in der bisherigen Forschung eine Herausforderung dar.

In der vorliegenden Dissertation werden drei Studien präsentiert. In der ersten Studie haben wir Daten zum Bildungs- und Berufsstatus von Erwachsenen mit einem AHF aus einer Umfrage ausgewertet. Die Ergebnisse zeigen, dass 59.4 % der Teilnehmer einen hohen Bildungsstand haben, 51.1 % waren zum Zeitpunkt der Befragung in einem Anstellungsverhältnis. Erwachsene mit einem einfachen AHF hatten einen höheren Bildungsstand und waren häufiger angestellt als Erwachsene mit einem komplexen AHF. Zukünftige Studien sollten untersuchen, ob diese Unterschiede durch kognitive Faktoren oder andere Faktoren bedingt sind, wie beispielsweise anhaltende medizinische Probleme und damit assoziierte körperliche Einschränkungen. In der zweiten Studie untersuchen wir die kognitive, motorische und sprachliche Entwicklung von Kindern mit der Diagnose eines Ventrikelseptumdefektes, einer Fallot'schen Tetralogie oder einer Transposition der großen Arterien longitudinal, in den ersten drei Lebensjahren. Hier wird das ausführliche Studienprotokoll präsentiert, die Datenerhebung läuft. Die dritte Studie ist eine Pilotstudie, in der wir die Machbarkeit des Bayley-III Entwicklungstests für Kleinkinder nach kardiopulmonaler Reanimation im Querschnitt untersucht haben. Die Ergebnisse zeigen dass der Bayley-III Entwicklungstest für die Mehrheit der Patienten ein geeignetes Messinstrument war, jedoch 30 % der Studienpopulation eine Seh-/Hör und/oder motorische Einschränkung hatten, wodurch keine standardisierte Durchführung des Tests möglich war. Von den acht Kindern mit quantifizierbaren Ergebnissen hatten vier substantielle Einschränkungen in den Bereichen Kognition, Motorik und Sprache, weshalb weitere Studien in dieser Population wichtig sind. Das Erforschen der Entwicklung von Kindern mit einem angeborenen Herzfehler ist ein komplexes Unterfangen, bei dem inter-individuelle Unterschiede berücksichtigt werden müssen und das von einer

interdisziplinären Herangehensweise profitiert. Ziel sollte ein evidenzbasiertes Modell von Entwicklungsdefiziten bei Kindern mit einem AHF sein.

1.3. Introduction

Congenital heart disease (CHD) is defined as a structural anomaly of the heart or intrathoracic vessels present at birth[1]. In a systematic meta-analysis of 114 studies and 24,091,867 live births by van der Linde and colleagues, incidence of CHD is reported at 9.1 per 1000 live births worldwide, at 6.9 per 1000 live births in North America and at 8.2 per 1000 live births in Europe. Ventricular septal defect (VSD) represents the most common acyanotic defect, while tetralogy of Fallot (TOF) and transposition of the great arteries (TGA) represent the most common cyanotic defects[2].

Advances in cardiovascular medicine and surgery have led to drastically improved survival rates of individuals with CHD in the past decennia[3]. Cardiac arrest after cardiac surgery with subsequent cardiopulmonary resuscitation (CPR) still occurs in about 2-5 % of affected children[4-6], with reported mortality rates in children undergoing in-hospital CPR varying between 35 % and 65 %[5,7-9]. Even though most of the children with CHD now reach adulthood[3], long-term cardiac complications, for instance heart failure or arrhythmia are common[10-13] and the long-term mortality is still higher than in the general population even for mild defects[14]. Above that, developmental delays are frequently observed in children with CHD. Specifically, a growing amount of studies shows that the cognitive, motor, and language development is impaired[15], while there is considerable inter-individual variance, as deficits are often mild to moderate and typically observed in 25-50 % of the patients[15-17]. In children who survive cardiac arrest and subsequent CPR, which is especially threatening to the developing brain, an unfavourable neurological outcome at discharge from hospital is observed in approximately 11-42 %[5,8,9,18]. However, there is a scarcity of studies investigating the long-term development in this particular group.

So far, there is a limited amount of knowledge about the aetiology of developmental delays in children with CHD. Concerning the peri-operative management of these children, important diagnostic and intervention strategies have been developed in the last two decades to improve neuroprotection, e.g., near-infrared spectroscopy (NIRS)[19], antegrade or retrograde cerebral perfusion (ACP/RCP)[20], and different perfusion strategies during cardiopulmonary bypass[21]. However, large-scale randomized controlled trials investigating the optimal combination of different strategies are still needed, as research is often observational and limited to small patient cohorts[22].

In order to investigate predictors of developmental outcome, the International Cardiac Collaborative on Neurodevelopment (ICCON) analysed individual participant data from multiple studies in an integrative effort. Based on the data of 1770 children with CHD, the research group found that variables related to perioperative management and clinical course (i.e., total support duration, duration of hospital stay, implantation of extracorporeal membrane oxygenation or ventricular assist device) accounted for only about 5 % of explained variance[23]. By contrast, approximately 30 % of the variance was explained by person-related predictors, including gender, lower birth weight, presence of genetic or phenotypical anomalies, educational status of the mother, or ethnicity[24]. The authors also investigated temporal trends, showing that between 1996 and 2009, developmental outcomes improved modestly when adjusting for medical and demographic characteristics. This finding probably can be attributed to the improved medical management over the time span. Still, mean developmental scores remained well below average. As possible explanation, the authors point towards specific neurological vulnerabilities in children with CHD already forming during the prenatal phase. There is now increasing empirical support for these neurological vulnerabilities and recently, researchers have even gone so far as to speak of an "encephalopathy of congenital heart disease"[25], with important similarities to the neurological characteristics of preterm babies[26]. In particular, MRI studies of children with CHD show white matter immaturity and injury and associated destructive lesions in nuclear structures, as well as decreased cortical surface area and smaller brain volumes that are already present before surgical interventions[27,28]. These observations may be attributed to hypoxia-ischemia in the last trimester of gestation[16], and relative contributions of abnormal perfusion and oxygenation likely differ for different types of CHD[29]. Therefore, the neurological vulnerability potentially predisposes children with CHD for developmental delays[30].

Developmental psychopathology as a framework for research on the developmental outcome of children with CHD

Beatrice Latal, an important researcher in this field, states, "Little is still known about the factors that lead to poor performance in one child and to good performance in another child, even if both children have the same cardiac diagnosis and hospital course"[15]. This statement highlights the difficulties we encounter when studying child development; no one child develops exactly like the other. Therefore, in order to advance our insights, it

may be helpful to consider a framework that acknowledges the complexity of developmental processes in children on the one hand, and the specific characteristics of at-risk groups on the other hand. One such framework is developmental psychopathology, which aims to understand the processes underlying continuity and change in individual patterns of maladaptation[31] and emphasizes development as an active and dynamic process from birth to old age[32]. Any developmental outcome, adaptive or maladaptive, is seen as a result of the dynamic, continuous interplay between the individual and the individual's context across time[33-35], with multiple influences at different levels at play (e.g., influences on the cultural or family level)[36]. While developmental psychopathology traditionally seeks to explain psychological disorders, it has also been applied to the neurocognitive functioning of young children[37] and to neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder (ADHD)[38], highlighting the non-deterministic quality of developmental processes.

Children with CHD- a vulnerable group?

A central idea of developmental psychopathology is that some individuals are disproportionally affected by environmental stressors because of a certain vulnerability, which puts them at risk for poor development. While these vulnerable individuals have an increased risk for negative outcome, the manifestation crucially depends on their exposure to environmental risk factors. This is the common denominator of various theoretical models within the framework, i.e., dual risk, diathesis stress, or transactional risk model[39]. If we apply this idea to children with CHD, we might argue that the neurological vulnerability puts them at risk for developmental delays, but this vulnerability manifests itself through the influence of additional risk factors. This notion is supported by a review by Marelli and colleagues, who take a life-span perspective on the development of individuals with CHD[40]. The authors state that brain dysmaturation, already forming prenatally and persisting through childhood, is the primary antecedent of developmental delays, while the contribution of various risk factors is hypothesized as "[…] multifactorial, interrelated, cumulative, and likely synergistic over time".

In order to understand the full spectrum of developmental outcomes in this population, it may be important to not only consider risk factors that increase the probability for unfavourable development, but also to consider protective factors to decrease the probability for unfavourable development[41,42]. In developmental psychopathology, understanding the push and pull of positive and negative influences leading to

differential clinical outcomes is a primary goal[43,44], as this has important implications not only for our theoretical understanding, but also for the development of therapeutic and preventive efforts. The observed variance in developmental outcome in children with CHD is likely the result of unique constellations of risk and protective factors interacting with development across time[45]. Therefore, the relation between neurological vulnerability and developmental outcome is complex, especially as during infancy and beyond, the brain is still developing and with that comes impressive neuronal plasticity[46], providing a window of opportunity for any environmental experiences to affect further development[47]. Experiences shape brain development, which in turn facilitates new experiences, which again results in neural adaption and so forth[48]. This process is best understood as dynamic and non-linearly dependent on preceding developmental states[49]. While plasticity of the brain (associated with favourable outcome) and vulnerability (associated with unfavourable outcome) seem to be contradicting positions, Anderson and colleagues propose a "recovery continuum" and suggest that the individual's position on this continuum depends on various influences, including factors related to the injury (e.g., timing or severity), individual characteristics (e.g., developmental stage or gender) and environmental factors (e.g., intervention efforts or socio-economic status)[50].

When it comes to the complex interplay between individual characteristics and environmental influences, another important concept has to be proposed, differential susceptibility. Differential susceptibility postulates that individuals differ according to their neurobiological sensitivity to the environment[39]. Highly susceptible individuals have the worst outcomes in a negative environment, but also the best outcomes in a positive environment (and are therefore referred to as "orchid-like" in the literature), whereas less susceptible individuals are relatively resilient and flourish, irrespective of environmental influences (therefore referred to as "dandelion-like")[39,51]. This neurobiological sensitivity manifests at different levels (behavioural, physiological, neurological, and genetic)[52] and has gained extensive empirical support for different risk factors (e.g., family distress), protective factors (e.g., maternal sensitivity), and outcomes in different areas of functioning (e.g., cognitive development, emotional or behaviour problems)[53]. While there are no studies investigating differential susceptibility in children with CHD so far, Gueron-Sela and colleagues tested a differential susceptibility model in a longitudinal study of 80 pre-term and 62 full-term infants by

investigating differential effects of parental caregiving on cognitive outcomes[54]. The authors found partial support for a dual risk process of cognitive development and partial support for differential susceptibility. In line with dual risk models, prematurity acted as a vulnerability factor and low-quality caregiving as environmental risk factor: pre-term infants had worse cognitive outcomes than full-term babies at the age of 12 months, but only if the quality of caregiving was low. This result did not support differential susceptibility, because when they were exposed to high-quality caregiving, the cognitive capacities of pre-term infants did not exceed the ones of full-term babies. However, infant temperament acted as differential susceptibility factor; when quality of caregiving was low, the cognitive outcome of highly reactive infants was worse than that of infants with average reactivity. When the quality of caregiving was high, the cognitive outcome of highly reactive infants was higher than of infants with average reactivity. By contrast, when the infants carried both susceptibility factors (prematurity *and* highly reactive temperament), neither positive nor negative effects of caregiving on outcome were found. Another study of 106 pre-term infants found opposite results. In this study, parenting was related to cognitive skills at age 36 months, but only for infants with highly reactive temperament, in that they showed more optimal cognition when the quality of parenting was more optimal. In pre-term infants with average reactivity, parenting was not related to cognitive skills[55]. While these diverging results might be attributed to differences in study design and different aspects of caregiving and/or cognitive development measured, they nicely illustrate that in medical at-risk groups, individual characteristics, risk and protective factors may interact in unique ways to explain the outcome of interest. Even though premature infants and infants with CHD share important neurological characteristics, research is needed to investigate if these populations also share similar pathways of risk and resilience for developmental outcome.

To sum up, the neurological vulnerability may predispose children for developmental delays. However, outcomes may not only be crucially dependent on the exact timing and nature of neurological vulnerabilities and related to that, the type of CHD, but also on a complex interplay between risk and protective factors interacting with development over time. Above that, children differ in their susceptibility to the environment, which complicates the picture even further.

Person-related predictors for developmental delays in children with CHD

As mentioned above, person-related factors such as genetic comorbidities, gender, maternal education, or ethnicity account for a relatively large proportion of variance in developmental outcome in children with CHD. Genetic comorbidities (e.g., trisomy 21) are independently associated with specific neurodevelopmental sequelae[56]. Therefore, individuals with both a CHD and a specific genetic comorbidity have to be considered as a separate population with unique developmental dynamics. The observed effect of gender might be attributed to neurodevelopmental differences[57] or gender-specific environmental influences[58]. Variables including ethnicity and maternal education are often subsumed under the term "person-related", but they might, in fact, constitute distal factors for more proximal environmental risks. Put differently, the relationship between a person-related variable and the outcome might be mediated by an environmental factor. A Canadian research group recently explored one possible mediating pathway between these person-related variables and developmental outcome. In a longitudinal study of 501 healthy new-borns, Wade and colleagues examined parental competence as potential pathway by which cumulative psychosocial adversity (comprising risk factors such as single parenthood, low education or low income) may affect cognitive outcomes[59]. Cumulative psychosocial adversity was associated with poor parenting competencies, which was in turn associated with lower cognitive abilities of the child, thereby supporting the mediation model. This result has yet to be replicated in the population of children with CHD, but it points towards the possibility that some non-modifiable risk factors (e.g., low income or maternal education) are mediated by a modifiable risk factor (the quality of parenting). Accordingly, it is of vital importance to study the association between the quality of parenting and developmental outcome in children with CHD, as this bares great potential for secondary preventive efforts and therefore has high clinical and societal relevance.

Methodological implications - the value of longitudinal research

As illustrated above, developmental outcome can be seen as a result of the complex interplay between individual characteristics, risk, and protective factors across time. Complicating this matter is the fact that child development is marked by the consecutive emergence of function at a higher level (for instance from an immobile infant to a crawling, then walking child). Consequently, the concepts we study change in a systematic, yet dynamic way, across time[60]. The term "developmental cascades" is often

used to describe the dynamic nature of development from basic to more advanced levels of functioning, by taking into account prior levels of adaption, and/or individual characteristics[61]. Inherent to the concept of developmental cascades is the idea that across time, different forces are at play, interacting with the evolving system and leading to a certain outcome[62].

In order to investigate this dynamic interplay between risk and protective factors for explaining individual differences in emergent skills across time, longitudinal studies are needed[44]. Previous research addressing the development of children with CHD has predominantly used cross-sectional methods, with only a few exceptions[63,64]. Cross-sectional methods provide insight into the scope of developmental delays and variables associated with those impairments at a given moment, by taking a snap-shot of the outcome variable. By contrast, longitudinal designs allow us to investigate discontinuity (the mean level of a trait in the group with increases or decreases over time) and instability (the relative order of individuals within a group with changes over time) on a group level[65], as well as meaningful variation from one time point to the next on an individual level (intra-individual variance). In child development, deficits might emerge, decrease, stabilize, or remain absent, and, as described in the sections above, not necessarily in the same way for all children. In support of this, a recently published article showed considerable variance in developmental scores from age two to four in children with CHD; a higher rate of delays was observed at age four, pointing towards emerging deficits in some children[63]. The authors conclude that more longitudinal studies in this field are needed. They should be informed by exploratory cross-sectional studies in order to identify potential predictors. Theoretical models, such as the dual-risk model or differential susceptibility provide us with the necessary frameworks to develop and test specific hypotheses we need for explaining these complex dynamics. Studies on developmental dynamics in healthy children might help us identify universal mechanisms at play. Comparing the population of children with CHD to other medically at-risk groups, e.g., premature infants, allows us to study differences and similarities and can also inform the development of research questions and hypotheses. Our final goal should be an evidence-based theoretical model of developmental delays in children with CHD as basis for the development of neuroprotective strategies, including intervention and preventive efforts.

Aim of the dissertation

The general aim of this dissertation is to further the understanding of developmental dynamics in children with CHD, by advancing research methodology in this field with an approach that integrates insights from both medical and psychological research. The presented studies have to be considered as the very first step towards establishing an interdisciplinary clinical research unit (CRU) for developmental dynamics in children with CHD.

To gain insights into educational levels and employment status of grown-ups with congenital heart defects (GUCHD), we analysed data from the German National Register for Congenital Heart Defects. Hereby, we explored if educational level and employment status is associated with the severity of CHD.

Secondly, in the ongoing **L**ong-term **EA**rly **DE**velopment **R**esearch in **C**ongenital **H**eart **D**isease (LEADER-CHD) study, we investigate the developmental dynamics in children after corrective surgery for the most common heart defects (TGA, TOF, and VSD) longitudinally, with repeated assessments throughout the first three years of life. By measuring medical risk factors and person-related variables, and additionally by investigating child temperament and the quality of the parent-child interaction as predictors for the cognitive, motor, and language development, we aim to advance insights into the full spectrum of developmental outcomes in this population.

Thirdly, in the LEADER-CPR pilot study, our primary goal was to evaluate the feasibility of the Bayley Scales of Infant and Toddler Development- 3rd Edition (BSID-III) in infants after cardiopulmonary resuscitation. In this population, we expect severe neurological impairments in some children, which potentially impede standardized developmental assessment. Missing data for children with the most severe neurological impairments might bias results. However, no previous studies have reported on this issue. As a secondary goal, we descriptively analysed the developmental status in infants after CPR as assessed with the BSID-III.

1.4. Methods

Study 1- Study on educational levels and employment status in adults with CHD

Study design and participants. In this exploratory cross-sectional study, we analysed data from an online survey conducted by the National Register for Congenital Heart Disease (NRCHD). All patients who were registered with in the NRCHD by the end of 2015 with e-mail address and who were aged ≥ 18 years were eligible for the survey (N = 3874), of which 1458 participated. Patients older than 65 years were excluded from the analysis (N = 13) and medical data were missing for 237 participants, leading to a sample size of N = 1198.

Outcome measures. Educational level was assessed by one item in the online survey with nine answer categories, ranging from no school-leaving certificate to graduation from an advanced technical college/university, as well as additional options of “still going to school” and “others”. Employment status was assessed by one item in the online survey with nine answer categories: pupil, apprentice, student, part-time job, full-time job, job seeking, self-employed, retired and others.

Statistical analysis. For analysis, educational level was summarized into four categories: low (no school-leaving certificate or completed secondary modern school), medium (intermediate school-leaving certificate), high (completed high-school or vocational degree), and others (still attending school or other degree). Employment status was summarized into four categories: in training (pupil, trainee, student), employed (part-time, full-time or self-employed), unemployed (job-seeking or pensioner), and others. Severity of CHD was categorized into simple, moderate, complex and unclassified/other according based on guidelines by Warnes and colleagues[66]. The χ^2 - test was used for all groups- and subgroups comparisons.

Study 2- Protocol of the LEADER-CHD study

Study design and participants. In this ongoing single-centre prospective cohort study, 180 children with TGA, TOF or VSD who undergo corrective surgery at our institution before the age of 10 months will be included. Inclusion criteria are (1) diagnosis of TGA, TOF or VSD, (2) corrective surgery at 10 months, and (3) one parent is a native German speaker. Exclusion criteria are (1) genetic syndromes or phenotypic anomalies that might influence the cognitive/motor development, (2) birth weight under 2.5 kg, (3)

gestational age less than 37 weeks, (4) drug/alcohol abuse/dependence in the history of the mother, and (5) CPR ≥ 5 min before the age of 12 months. Cognitive, motor, and language development of the children is assessed at ages 12, 24, and 36 months; pre-, peri- and postoperative medical variables are derived from patient files and examination record from the child's general practitioner. At each appointment, parents fill out a demographic questionnaire and a questionnaire about post-acute rehabilitation care and use of early support services. At the first appointment, parents additionally fill out a questionnaire on child temperament, the Infant Behaviour Questionnaire-Revised, Short Version (IBQ-R-SV)[67] and a 20-minute free-play video-observation is conducted and coded with the Emotional Availability Scales[68,69].

Outcome measures. Primary outcome measure is the cognitive, motor, and language development, which is measured with the German version of the Bayley Scales of Infant and Toddler Development- 3rd Edition (BSID-III)[70,71]. The BSID-III is the most widely used developmental assessment for infants[72,73]. It is comprised of five subtests: fine and gross motor skills (which can be summarised into a composite motor score), receptive and expressive language (which can be summarised into a composite language score), and cognition. Secondary outcome measures are death of the child and child temperament at 12 months.

Statistical analysis. After study conclusion, differences between groups will be analysed with repeated-measures ANOVAS. Cognitive, motor, and language scores will be entered as dependent variables; time (12, 24, and 36 months) will be entered as within-subjects factor and group (VSD, TGA, and TOF) will be entered as between-subjects factor. Time point of surgery will be entered as covariate. Medical, person-related, and environmental predictors of cognitive, motor, and language scores at each time point will be analysed by multiple regression analyses. Differences in temperament between groups will be explored with an analysis of covariance, with group (VSD, TGA, and TOF) entered as factor and confounding variables (time point of surgery, gender) entered as covariates. Secondary multilevel analyses will be used to explore differential developmental trajectories and potential predictors for different pathways.

Study 3- LEADER-CPR Pilot Study

Study design and participants. In this single-centre cross-sectional pilot study, children with cardiovascular disease who were younger than 24 months at recruitment,

who had experienced a CPR event before the age of 12 months and who were treated at our institution were included. Inclusion criteria were (1) cardiovascular disease, (2) CPR ≥ 5 minutes (3) survival to follow up and (4) age ≤ 24 months at recruitment. Exclusion criteria were (1) neither parents are native German speakers and (2) diagnosed/suspected genetic syndrome or phenotypic anomaly associated with developmental deficits. Cognitive, motor, and language development in the children was assessed at age 12 months (if the child's age was < 12 months) or 24 months (if the child's age was ≥ 12 months). Pre-, peri-, and postoperative medical variables were derived from patient files and examination record from the child's general practitioner. Demographic variables, information on post-acute rehabilitation care and use of early support services were assessed by use of questionnaires.

Outcome measures. Primary outcome measure is the cognitive, motor, and language development, as assessed with the BSID-III.

Statistical analysis. We limited our statistical approach to descriptive analyses because of the small sample size and the exploratory nature of this study. Data are reported as mean (M), standard deviation (SD) or percentages (%).

1.5. Results

Study 1- Study on educational levels and employment status in adults with CHD

Sample characteristics. The participants had a mean age of 30 years (SD = 11), 54.5 % were female. Of all 1198 participants, 30 % had simple CHD, 38.6 % had a moderate CHD, and 28.3 % had a complex CHD, while 3.1 % fell in the unclassified category. Overall, 8.5 % reported a low educational level, 27.2 % a medium educational level, 59.4 % a high educational level, and 4.8 % fell in the “others” category. When it comes to employment status, 34.6 % reported to be in training, 51.5 % employed, 7.8 % unemployed, and 6.5 % fell in the “others” category.

Associations between CHD severity and educational level. We found a significant association between CHD severity and educational level ($p < 0.01$), in that individuals with more severe CHD reported lower educational levels. In subgroup analyses, individuals with simple CHD differed significantly from individuals with moderate CHD ($p < 0.01$) and complex CHD ($p < 0.001$) in their educational levels. However, differences in educational levels between moderate and complex CHD were not significant ($p = 0.635$). To illustrate, individuals with a simple CHD showed the highest percentage of high educational levels (66.9 %), and second-to-lowest percentage of low educational levels (4.2 %), topped only by the unclassified CHD group (2.7 %). Individuals with a complex CHD showed the highest percentage of low educational levels (12.1 %) and the lowest percentage of high educational levels (54.3 %).

Associations between CHD severity and employment status. We found a significant association between CHD severity and employment status ($p < 0.01$), in that individuals with more severe CHD more often reported to be unemployed. In subgroup analyses, individuals with simple CHD differed significantly from individuals with complex CHD in their employment status ($p < 0.01$), while all other differences in employment status between CHD groups were not significant. To illustrate, individuals with a simple CHD had the highest percentage in the category “employed” (53.8 %) and the lowest percentage in the category “unemployed” (4.2 %), while individuals with a complex CHD had the highest percentage in the category “unemployed” (12.1 %) and second to lowest percentage in the category “employed”, topped only by the unclassified CHD group.

Study 2- Protocol of the LEADER-CHD study

No results are presented in this dissertation, as the data collection is ongoing. The published study protocol is part of this dissertation.

Study 3- LEADER-CPR Pilot Study

Sample characteristics. Of 20 eligible patients, five patients were not included because the families declined participations or contact could not be established. Three patients were not included because of severe neurological impairments. One family dropped out during the first developmental assessment, resulting in N = 11 children (55 % female), of which nine children had a CHD, one child had dilative cardiomyopathy, and one child had myocarditis. No patient had documented developmental deficits prior to resuscitation. Four children were assessed at age 12 months; seven children were assessed at age 24 months.

Feasibility of assessment procedure. In three of the cases, standardized BSID-III assessment procedure was not accomplishable because of visual/hearing or motor impairments and accordingly, results were not quantified. Acceptance of the study procedures was good; all parents wanted to be informed about their child's BSID-III test result.

Developmental status. Mean scores were lower than -1SD on all composite scales, indicating below-average performance (composite cognitive scale: M = 79.4, SD = 24.3; composite motor scale: M = 75.4, SD = 28.6; composite language scale: M = 69.6, SD = 26.6). On each composite score, 50 % of the children scored average and 50 % scored below -2SD. On a subtest level, average mean scores were observed for the subtest fine motor skills (M = 7.5, SD = 4.8) and below-average mean scores on all other subtests, with lowest mean scores on the subtest gross motor skills (M = 4.8, SD = 4.9).

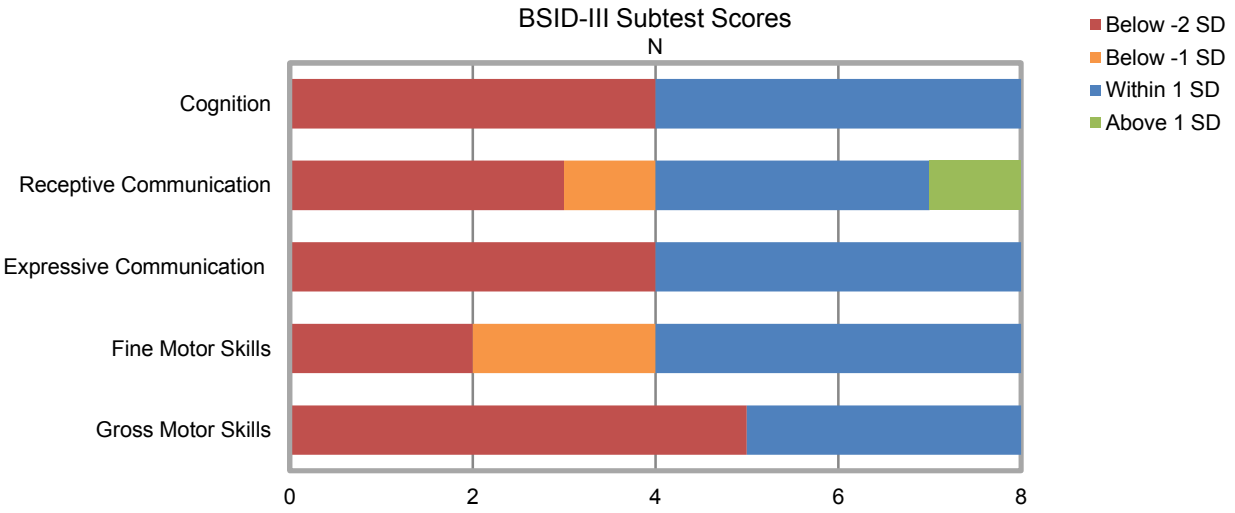

Figure 1. Frequencies of BSID-III subtest scores of the total group (N = 8). Subtest scores are scaled to a mean of 10 and standard deviation of 3 in the normative sample.

1.6. Discussion

This dissertation has the general aim of furthering the understanding of developmental dynamics in children with CHD, by preparing and developing longitudinal studies informed by insights from medical and psychological research. Our goal is the establishment of an interdisciplinary clinical research unit (CRU) for developmental dynamics in children with CHD. More studies are currently being prepared or ongoing, which will serve as the basis for initial multicentre studies.

In our study on educational level and employment status of adults with CHD, we found systematic differences in educational levels and employment status depending on CHD severity. Individuals with simple CHD showed the highest percentages of employment and high educational levels, whereas individuals with complex CHD showed relatively lower percentages of employment and high educational levels. If these differences can be attributed to cognitive deficits that manifest themselves in academic and or work-related problems, or to other factors, such as ongoing medical complexities and associated physical limitations, remains to be investigated. Importantly, with a response rate of less than 50 %, these exploratory results are prone to selection bias and need to be replicated in confirmatory research. In particular, prospective studies are needed that directly link cognitive development to academic and/or professional achievement in this population, to ascertain whether difficulties in these domains are indeed consequence of developmental deficits.

By conducting the longitudinal LEADER-CHD study, we want to contribute to insights into the developmental dynamics of children after corrective surgery for TGA, TOF and VSD in the first three years of life. Investigating three different heart defects allows us to directly compare their cognitive, motor, and language capacities at each time point, as well as their development across time. By measuring different medical, person-related, and environmental risk factors, we are able to not only discern the unique contribution of risk factors to development at each time point, but also see how these risk factors predict development across time and thus get a better idea of the temporal dynamics. Specifically, we will be able to look at predictors for different change patterns across time, potentially identifying high-risk children within this at-risk group. By measuring child temperament and the quality of the parent-child interaction, we will be able to investigate differential susceptibility in this special population. Finally, by conducting

additional exploratory analyses, we will also gain insight into potential underlying mechanisms, thus generating hypotheses for subsequent longitudinal research.

In our LEADER-CPR pilot study, the primary goal was to evaluate the feasibility of the Bayley Scales of Infant and Toddler Development- 3rd Edition (BSID-III) in children after CPR, as we expect severe neurological impairments in some children might impede standardized developmental assessment. Importantly, in three of the included cases, deviation from the BSID-III standardized procedure was necessary because of visual/hearing or motor impairments and therefore, results were not quantified. Additionally, three patients were not enrolled in the study because of severe neurological impairments. Altogether, this reflects 30 % of the study population, which highlights the necessity to find alternatives for developmental assessment in hearing, visual and/or motor impaired infants in order to avoid biased results. Importantly, half of the patients did not show developmental delays based on the BSID-III assessment, with high stability across developmental domains, whereas individuals who showed impaired functioning on one domain showed impaired functioning also on the other domains. How these differences in outcome may be explained is subject of an ongoing longitudinal study on developmental dynamics in infants after CPR.

Importantly, these studies are the first step in researching developmental dynamics in children with CHD. One important limitation of the presented studies is the reliance on the BSID-III as a dependent variable. While this instrument is vastly used in developmental research, it may be useful to use instruments that differentiate different neurocognitive domains (e.g., executive functioning, attention or working memory), as well as different aspects of language and motor development for more in-depth research on developmental dynamics in this population. Above that, the BSID-III does not assess the social and emotional development, which might also be compromised in children with CHD but is understudied so far. Another important limitation of our longitudinal LEADER-CHD study is the assessment of development once a year, and the restriction of the study to the first three years of life. The smaller the time lapse between assessments, the clearer the picture of developmental trajectories, as more data points are available for each study participant for modelling intra-individual variance. Investigating different time scales and age groups in different longitudinal studies might be a feasible strategy for future research, with some studies focusing on short-term variations and other studies focusing on long-term development. Integrating

insights from these different efforts will give us a clearer picture of developmental dynamics. Finally, we will expand the ongoing project as there are many more presentations of CHD to consider, in particular patients with uni-ventricular physiologies, who have a high burden of neurological injury[74-76].

In conclusion, research on child development is a complex endeavour, forcing us to leave the realm of certainty and simple cause-and-effect relationships, as summarized in the introduction. We have to integrate insights from different scientific disciplines and advanced research methods in order to arrive at an evidence-based model of developmental delays in children with CHD. We should take on this challenge, because it is a vital prerequisite for the development of efficacious preventive and intervention programs. Investing in these children means investing in the future. Our aim should be that every child with CHD has the same opportunities in life as every other child.

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2. Eidesstattliche Versicherung

„Ich, Hannah Ferentzi, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Development of Children with Congenital Heart Disease“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

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Datum Unterschrift

3. Anteilserklärung an den erfolgten Publikationen

Hannah Ferentzi hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Constanze Pfitzer, Paul C. Helm, Lisa-Maria Rosenthal, Christoph Walker, Hannah Ferentzi, Ulrike M. M. Bauer, Felix Berger, Katharina R. L. Schmitt, Educational level and employment status in adults with congenital heart disease, Cardiology in the Young, 2018.

Beitrag im Einzelnen: Schreiben und Editieren des Manuskripts.

Publikation 2: Hannah Ferentzi*, Constanze Pfitzer*, Lisa-Maria Rosenthal, Felix Berger, Katharina R. L. Schmitt, 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.
*contributed equally

Beitrag im Einzelnen: Konzeption der Studie inklusive Entwicklung der Problem- und Fragestellung, des Studiendesigns, der Forschungshypothesen und des Datenanalyseplans in interdisziplinärer Zusammenarbeit, sowie Schreiben und Editieren des Manuskripts, Formalisierung des Inklusionsablauf (daraus entstanden Graphik 1), Datenerhebung (Fragebögen, BSID-III Erhebungen, Video-Observation) und Datenadministration, Überarbeitung des Manuskripts im Review-Prozess, Korrektur der Druckfahne.

Publikation 3: Hannah Ferentzi*, Constanze Pfitzer*, Lisa-Maria Rosenthal, Felix Berger, Katharina R. L. Schmitt, Peter Kramer, Developmental outcome in infants with cardiovascular disease after cardiopulmonary resuscitation: a pilot study, Journal of Clinical Psychology in Medical Settings, 2019.
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Beitrag im Einzelnen: Konzeption der Studie inklusive Entwicklung der Problem- und Fragestellung, des Studiendesigns, der Forschungshypothesen und des Datenanalyseplans in interdisziplinärer Zusammenarbeit, sowie Datenerhebung, Datenadministration, Datenanalyse (Daten zu den demographischen Angaben, zur Versorgungssituation und zu den Entwicklungstestergebnissen, inklusive Erstellung der Tabellen 1, 2 und der Grafik 2), Schreiben und Editieren des Manuskripts, Überarbeitung des Manuskripts im Review-Prozess, Korrektur der Druckfahne.

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Unterschrift, Datum und Stempel des betreuenden Hochschullehrers/der betreuenden Hochschullehrerin

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Unterschrift des Doktoranden/der Doktorandin

4. Ausgewählte Publikationen als Promotionsleistung

Publikation 1

Pfitzer C, Helm PC, Rosenthal L-M, Walker C, Ferentzi H, Bauer UM, Berger F, Schmitt KR.

Educational level and employment status in adults with congenital heart disease.

Cardiology in the Young 2018;28:32-8.

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Publikation 2

Ferentzi H*, Pfitzer C*, Rosenthal L-M, Berger F, Schmitt KR.

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.

*contributed equally

Open Access Protocol

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

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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] Decelerated brain development is a predisposing factor for white matter injury, which is often present in newborns with CHD.[31] In addition, infarction, ischaemic strokes and cerebral haemorrhage are frequently observed after corrective 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 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 corrective 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 in earlier research.[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,

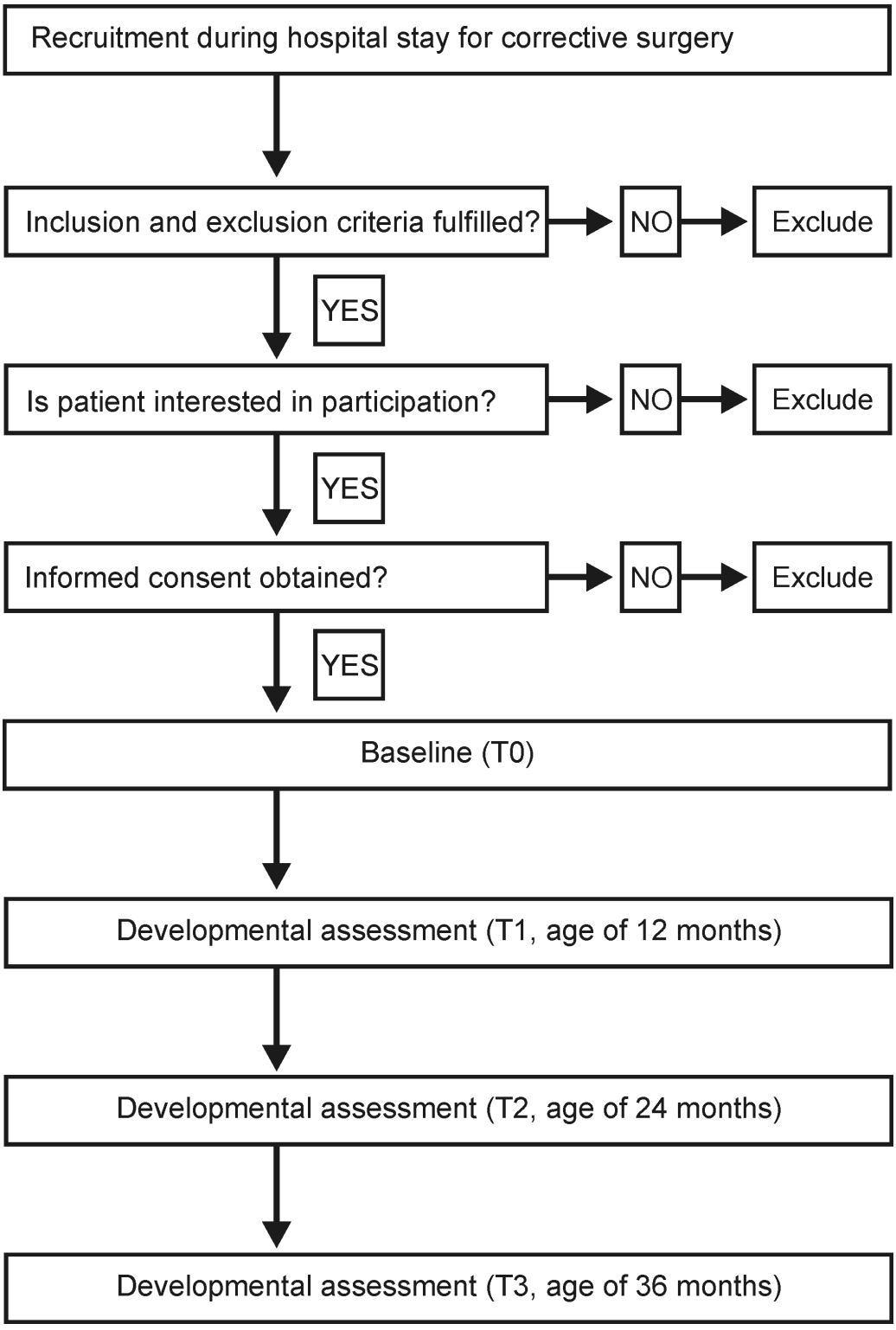

Figure 1 Flow chart of inclusion process and measurement time points.

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.

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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.

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Publikation 3

Ferentzi H*, Pfitzer C*, Rosenthal L-M, Berger F, Schmitt KR, Kramer P.

Developmental outcome in infants with cardiovascular disease after cardiopulmonary resuscitation: a pilot study.

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5. Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

6. Publikationsliste

Publikation	Impact Factor
1. Pfitzer C*, Ferentzi H*, Rosenthal L, Kramer P, Berger F, & Schmitt KR (in press). First steps to a clinical research unit for developmental research in pediatric cardiology: conception and progress of the LEADER project (Long Term Early Development Research) in congenital heart disease. Cardiology in the Young. *contributed equally	0.987
2. Ferentzi H*, Pfitzer C*, Rosenthal L-M, Berger F, Schmitt KR, Kramer P. Developmental outcome in infants with cardiovascular disease after cardiopulmonary resuscitation: a pilot study. Journal of Clinical Psychology in Medical Settings 2019:1-9. *contributed equally	1.893
3. Sepke M, Ferentzi H, Disselhoff VSU, Albert W. Exploring the developmental tasks of emerging adults after paediatric heart transplantation: a cross-sectional case control study. BMJ Open 2018;8:e022461.	2.413
4. Ferentzi H*, Scheibner H*, Wiers R, Becker ES, Lindenmeyer J, Beisel S, Rinck M. Retraining of automatic action tendencies in individuals with obesity: A randomized controlled trial. Appetite 2018;126:66-72. *contributed equally	3.174
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