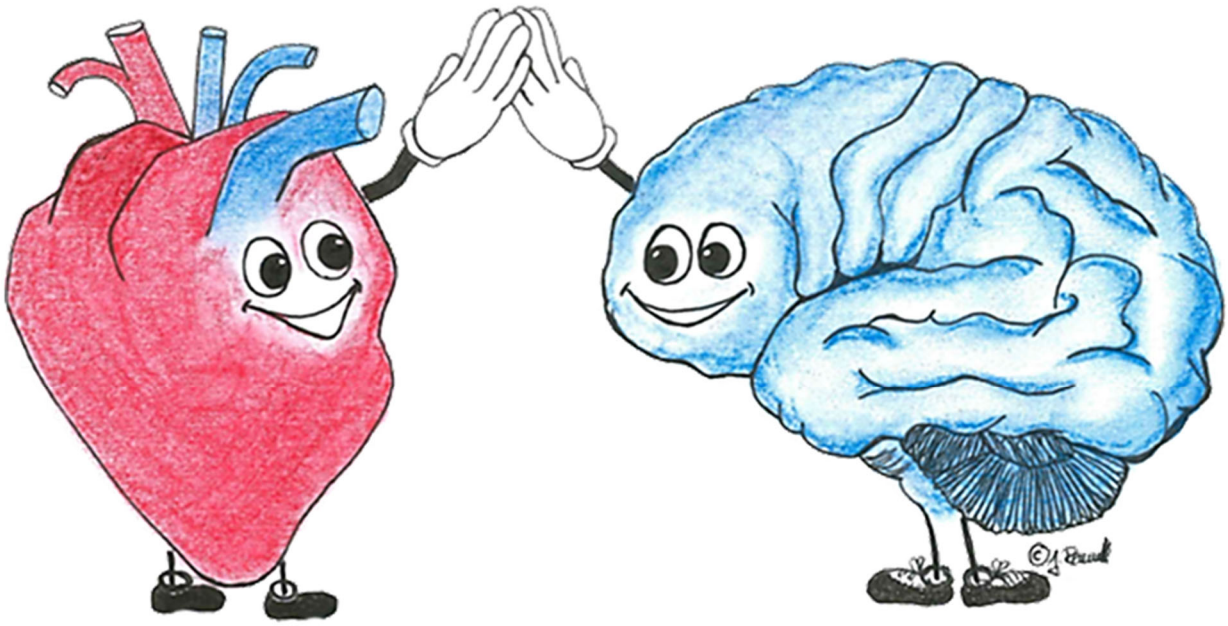
TECHNISCHE UNIVERSITÄT MÜNCHEN

Lehrstuhl für Präventive Pädiatrie

Fakultät für Sport- und Gesundheitswissenschaften

„Neuromental-health Aspekte von Patienten mit angeborenem Herzfehler“

"Neuromental-health aspects in patients with congenital heart defects"



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„Neuromental-health Aspekte von Patienten mit angeborenem Herzfehler“

Julia Remmele, M.Sc.

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Prüfer*innen der Dissertation:

1. Prof. Dr. Renate M. Oberhoffer-Fritz
2. Prof. Dr. Jochen Weil

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Gender-Erklärung

In der Dissertation werden geschlechtsspezifische Begriffe verwendet (vorwiegend maskulin, bspw. Patient), um den Textfluss zu erleichtern bzw. die Lesbarkeit zu erhöhen. Zudem wird der Begriff der gesundheitsspezifischen Lebensqualität mit HrQoL (health-related quality of life) abgekürzt, um eine bessere Lesbarkeit, übereinstimmend mit der Abkürzung in den Publikationen, herzustellen.

Zusammenfassung

Insbesondere das Jugend- und frühe Erwachsenenalter spielt bei Patienten mit angeborenem Herzfehler (AHF) eine entscheidende Rolle. In dieser Phase des Lebens müssen sie beginnen, die Verantwortung für ihren Alltag zu übernehmen, berufliche Entscheidungen treffen, der Auszug von den Eltern hinein in ein autonomes Leben. Hierzu zählen auch das selbstständige vereinbaren von Terminen bei auf AHF spezialisierten Kardiologen und das Wahrnehmen dieser Kontrolltermine. Dies stellt in der alltäglichen Praxis jedoch häufig ein Problem dar, das unter anderem durch das Phänomen des sogenannten „loss to follow-up“ zum Ausdruck kommt.

Im ersten Schritt dieser Dissertation, wurden in einer national repräsentativen Studie, klinische Daten von Patienten mit AHF analysiert, um einen Einblick in den klinisch relevanten Gesundheitszustand der Patienten mit AHF im Transitionsalter in Deutschland zu gewinnen. Es konnte gezeigt werden, dass Jugendliche und junge Erwachsene mit AHF bereits während der Transitionsphase bis zu 4 kardiale und bis zu 7 extrakardiale erworbene Nebendiagnosen aufwiesen. Insbesondere neurologische Diagnosen hatten die höchste Prävalenz bei extrakardialen erworbenen Nebendiagnosen.

Basierend auf diesen Resultaten und aufgrund zahlreicher Studien bei Neugeborenen und Kindern, die eine verzögerte bzw. defizitäre Entwicklung in den Bereichen Kognition, Motorik und Sprachentwicklung nachweisen konnten, konzentrieren sich die Publikationen II und III auf neuromental-health Aspekte (NMHA) bei Erwachsenen mit AHF (EMAH). Die Ergebnisse aus Publikation II und III zeigten normale Intelligenzquotienten (IQ) bei EMAH, wobei weder der AHF Schweregrad, noch das Alter zum Zeitpunkt der ersten Operation am offenen Herzen mit dem IQ assoziiert waren. Gesundheitsbezogene Lebensqualität (HrQoL) war signifikant geringer als die der Referenz in fast allen Dimensionen, außer „bodily pain“ und „mental health“.

Zusammenfassend konnte die klinische Notwendigkeit einer erfolgreichen Transition für Jugendliche und junge EMAH aufgezeigt werden, nicht nur in Bezug auf die Prävention von erworbenen Diagnosen, sondern auch in Bezug auf HrQoL. Die Ergebnisse weisen zudem auf eine normale Intelligenz bei EMAH hin, unabhängig vom AHF Schweregrad. Abschließend wird das prospektive Zwillingstudiendesign (Publikation IV) vorgestellt, das den tatsächlichen Einfluss des AHF auf die kognitiven und motorischen Fähigkeiten, HrQoL und mentale Gesundheit prüfen soll.

Summary

Adolescence and early adulthood in particular play a crucial role for patients with congenital heart defect (CHD). In this phase of life, they must begin to take responsibility for their daily lives, make career decisions, and move away from their parents and into an autonomous life. This includes arranging appointments with CHD-specialized cardiologists and keeping these appointments. However, this often poses a problem in everyday practice, which is expressed, besides other issues, by the phenomenon of the so-called "loss to follow-up".

In the first step of this dissertation, clinical data of patients with CHD were analysed in a nationally representative study to gain insight into the clinically relevant health status of patients with CHD in transition age in Germany. It could be shown that adolescents and young adults with CHD already had up to 4 cardiac and up to 7 extracardiac-acquired secondary diagnoses during the transition phase. In particular, neurological diagnoses had the highest prevalence among extracardiac-acquired secondary diagnoses.

Based on these results and several studies in newborns and children showing delayed or deficient development in the areas of cognition, motor skills and language development, publications II and III focus on neuromental-health aspects (NMHA) in adults with CHD (ACHD). The results from publications II and III showed normal IQ scores in ACHD, with neither CHD severity nor age at first open heart surgery associated with IQ. Health-related quality of life (HrQoL) was significantly lower than the reference in almost all dimensions except „bodily pain“ and „mental health“.

In summary, the clinical requirement for successful transit for adolescents and young ACHD was demonstrated, not only in terms of prevention of acquired secondary diagnoses but also in terms of HrQoL. The results also indicate normal intelligence in ACHD, independent of CHD severity. Finally, the prospective twin study design is presented to test the actual impact of CHD on cognitive and motor skills, HrQoL and mental health.

Danksagung

Mein großer und herzlicher Dank geht an meine Doktormutter, Frau Prof. Dr. Renate Oberhoffer-Fritz, für die Unterstützung dieser Arbeit mit medizinischem Rat, hilfreichen Vorschlägen und Kommentaren, und die herzliche Zusammenarbeit.

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Außerdem möchte ich mich bei allen Freunden und Kollegen, Schwestern und Ärzten sowie den Patienten des Deutschen Herzzentrum München bedanken, ohne deren Unterstützung, diese Arbeit nicht möglich gewesen wäre.

Ein besonderer Dank geht an das Nationale Register für angeborene Herzfehler e.V., Dr. Ulrike Bauer mit all ihren Mitarbeitern, für die wertvolle Zusammenarbeit und großartige Unterstützung, vielen Dank.

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All meinen Freunden und meiner Familie möchte ich danken, für seelisch-moralische Unterstützung während dieser Zeit und den Glauben an mich.

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Abkürzungsverzeichnis

AHF	angeborene Herzfehler
BCAS	The Boston Circulatory Arrest Study
bzw.	beziehungsweise
d.h.	das heißt
DGK	Deutsche Gesellschaft für Kardiologie - Herz- und Kreislaufforschung e. V.
DGPK	Deutsche Gesellschaft für Pädiatrische Kardiologie und Angeborene Herzfehler e.V.
DGTHG	Deutsche Gesellschaft für Thorax-, Herz und Gefäßchirurgie
DHM	Deutsches Herzzentrum München
EMAH	Erwachsene mit angeborenem Herzfehler
GIQ	Gesamt Intelligenz Quotient
HrQoL	gesundheitsbezogene Lebensqualität
IQ	Intelligenzquotient
NMHA	neuromental-health Aspekte
NRAHF	Nationales Register für angeborene Herzfehler e.V.
SD	Standardabweichung
SF-36	Medical Outcomes Study Questionnaire Short Form 36 Health Survey
TGA	Transposition der großen Arterien
UVH	univentrikuläres Herz
WAIS-IV	Wechsler Adult Intelligence Scale-Fourth Edition

1 Einleitung

Das reine Überleben von Patienten mit angeborenem Herzfehler (AHF) ist dank der erheblichen Fortschritte in der Kinderkardiologie, der Herzchirurgie und der Nachsorge in den letzten Jahrzehnten weitgehend gesichert (1-3). Mehr als 95% der Kinder mit AHF erreichen das Erwachsenenalter (4), sodass die Zahl der Erwachsenen mit angeborenem Herzfehler (EMAH) die der Kinder bei weitem übertrifft (5-7). Neben neuen Herausforderung in der Patientenbetreuung und insbesondere der Nachsorge (8), treten zunehmend entwicklungsspezifische Fragestellungen auf und die gesundheitsbezogene Lebensqualität (HrQoL) von Patienten mit AHF gewinnt an Bedeutung (9-11). Insbesondere das Jugend- und junge Erwachsenenalter sind zentrale Schlüsselstellen, die es zu beachten gilt, da in dieser Lebensphase die größten Veränderungen, im Sinne einer eigenständigen Lebensführung, zu treffende berufliche Entscheidungen und Verantwortung für die eigenen Termine, stattfinden (10).

Neuro-mental health Aspekte (NMHA), in dieser Arbeit ist das ein Überbegriff für kognitive Fähigkeiten und HrQoL, treten ebenso mehr in den Fokus. Denn auch NMHA wirken sich auf die Lebensplanung und Perspektiven aus (12). Bereits pränatal konnten strukturelle Hirnveränderungen festgestellt werden, wie geringere Hirnvolumina, die mit Entwicklungsauffälligkeiten assoziiert sind (13). In anderen Publikationen werden ebenfalls über geringeres Hirnvolumen, Läsionen der weißen und grauen Substanz sowie Erweiterungen der äußeren und inneren Liquorräume des Gehirns berichtet (14-17). Diese hirnstrukturellen Veränderungen konnten in den genannten Studien zudem mit Einschränkungen bzw. Verzögerungen in den Bereichen Sprachentwicklung, kognitiven und motorischen Fähigkeiten im Neugeborenen- bis Kindesalter in Verbindung gebracht werden. Es liegen auf dem Gebiet der „neurodevelopmental Outcomes“ lediglich zwei longitudinale Studien mit längerem Follow-up vor, die Boston Circulatory Arrest Study (BCAS) und die Aachen Study (18). Hierbei wurden Kinder mit einer Transposition der großen Arterien (TGA) über einen Zeitraum von bis zu 16 Jahren bei der BCAS bzw. 10 Jahren in der Aachen Study wiederholt getestet. Die BCAS berichtet über Einschränkungen und reduzierte Ergebnisse gegenüber den Normwerten in vielen Bereichen der „neurodevelopmental Outcomes“ über alle Messzeitpunkte hinweg (19-21). Die Aachen Study kommt zu ähnlichen Resultaten, sie konnten ebenfalls über alle Messzeitpunkte hinweg,

reduzierte oder defizitäre neurodevelopmental Resultate bei Kindern mit TGA feststellen (22-24). Neben der Tatsache, dass diese beiden Studien den Forschungsgrundstein zu „neurodevelopmental Outcomes“ bei Patienten mit AHF gelegt haben, wurden in beiden Studien ausschließlich Patienten mit TGA im Verlauf getestet und analysiert. Zudem enden beide Studien im Kindes- bzw. Jugendalter. Die Frage verbleibt, wie sich diese Auffälligkeiten auf das spätere Erwachsenenalter der EMAH auswirken. Es ist bislang sehr wenig bekannt über die NMHA bei EMAH, in einem Kollektiv das alle AHF-diagnosen einschließt (18).

2 Zielsetzung

Im Rahmen dieses Promotionsstudiums wurden wissenschaftliche Untersuchungen zur klinischen Forschung sowie zur Epidemiologie/Gesundheitsforschung bei Patienten mit angeborenen Herzfehlern durchgeführt.

Die für die Dissertation eingeschlossenen Publikationen I, III und IV wurden in internationalen medizinischen Fachzeitschriften veröffentlicht und haben ein peer-review Verfahren durchlaufen. Publikation II befindet sich im Einreichungsverfahren.

Die Dissertation ist in einem schrittweisen Design erstellt. Die Eingangsanalyse, Publikation I, fokussiert auf die Frage, wie es um den klinischen Gesundheitszustand von Jugendlichen und jungen Erwachsenen mit AHF im Transitionsalter zwischen 15 und 25 Jahren bestellt ist.

In Publikation II und III, liegt daraus resultierend der Schwerpunkt auf NMHA, den kognitiven Fähigkeiten und der HrQoL von erwachsenen Patienten mit AHF.

Als Schlussfolgerung und Perspektive dieser Dissertation, folgt zusätzlich Publikation IV, ein Studienprotokoll zu dem prospektiven Studiendesign der Zwillingsstudie „Same Same, but different?“. Ziel der Zwillingsstudie ist es, durch das gewählte Studiendesign Störgrößen (sogenannte Confounder) weitest möglich zu reduzieren und die in den Publikationen I-III gefundenen Ergebnisse eingehend zu überprüfen sowie den tatsächlichen Einfluss des AHF auf NMHA, kognitive Fähigkeiten und HrQoL zu quantifizieren.

3 Hintergrund

3.1 Historische Meilensteine der Kardiologie und Entwicklung der Kinderkardiologie

Der junge Fachbereich Kardiologie in der Medizin hat in seiner Entwicklung einen langen Weg zurückgelegt, von der ersten Beschreibung eines AHF durch Leonardo Da Vinci, bis hin zur erfolgreichen Behandlung von Patienten mit AHF, mit einer dramatischen Verringerung der Morbiditäts- und Mortalitätsraten und einer höheren Lebenserwartung bis heute (2, 3, 25). Einige Beispiele für die medizinische Entwicklung der Kardiologie sind in Tabelle 1 dargestellt.

Tabelle 1: *Timeline einiger wissenschaftlicher Erkenntnisse und Entwicklungen auf dem Gebiet der Kardiologie sowie der angeborenen Herzfehler* (modifiziert nach Marian, 2017 (26), Meyer-Lenz und Weil 2021 (27))

1513	Leonardo Da Vinci: anomalus pulmonary venous return	Erste Dokumentation AHF
1842	Crawford W. Long: Äther als Anästhetikum in der Chirurgie	
1852	London Hospital for Sick Children	Erste Kinderklinik
1870	Adolph Fick und Arthur Grollman: Herzzeitvolumen	
1895	Wilhelm Konrad Röntgen: Röntgenaufnahme	Erstes Röntgengerät
1929	Werner Forssman: Rechtsherzkatheteruntersuchung	Erste Katheteruntersuchung
1933	John H. Gibbons: Herz-Lungen-Maschiene (HLM)	Erste HLM erfunden
1938	R.E. Gross and J.P. Hubbard: Chirurgische Ligatur eines PDA	
1944	Alfred Blalock und Helene Taussig: Blalock-Taussig shunt Crafoord and Nylin: Resektion einer Aortenisthmusstenose	
1952	W.H. Muller und J.F. Dammann: Banding einer Pulmonalarterie	
1953	John H. Gibbons: ASD-Verschluss mit HLM Wilfred G. Bigelow: Hypotermie bei Operationen am offenen Herzen I.G.Edler und C.H. Hertz: Echocardiographie	Erster HLM Einsatz
1955	C.W. Lillehei: cross circulation	Schlüsseljahre der Kinderkardiologie mit dem routinemäßigen Einsatz der HLM in der Kinderchirurgie (in Rochester)
1956	R.A. DeWall: Pumpen-Oxygenator-System	
1960	R.R. Lower und N.E. Shumway: Orthotopische Herztransplantation	
1966	Christian Bernard: Herztransplantation W.J. Rashkind und W.W. Miller: Ballonatriumseptostomie als eine Palliation bei einer Transposition der großen Arterien.	
1967	W. Portsmann, L. Wierny, H. Warnke: katherinterventioneller Verschluss eines PDA	
1968	Francis Fontan: erste Fontan-Palliation bei Trikuspidalatresie	
1970	Beginn der offiziellen Etablierung der Kinderkardiologie als „Subspezialität der Pädiatrie“ in Deutschland	
1975	Adib Jatene: Arterielle Switch-Operation	
1976	Terry King: katheterinterventioneller Verschluss eines ASD II	
1982	Robert Jarvik: Erste Implantation eines dauerhaften Kunstherzens	
1988	W.F. Bernhard: Langzeitimplantation eines linksventrikulären Unterstützungssystems	
2010	Pediatric Heart Network Investigators: Erste randomisierte Studie beim hypoplastischen Linksherzsyndrom	

AHF: angeborene Herzfehler; PDA: Persistierender Ductus arteriosus Botalli; ASD: Vorhofseptumdefekt; HLM: Herz-Lungen-Maschiene.

Neben diesen Meilensteinen an Errungenschaften in der kardiologischen Historie, entwickelte sich die Kinderkardiologie und etablierte sich mehr und mehr als hochspezialisierte Fachdisziplin. Nach dem Vorbild und Dank des translationalen Austausches unter anderem mit London, entstand in der Kinderklinik Göttingen eine der ersten AHF Abteilungen in Deutschland (27). Mit dem Fortschreiten von medizinischen Errungenschaften im Bereich von Diagnostik, Behandlung, insbesondere dank der Kinderherzchirurgie, konnten zunehmende Zahlen von Kindern behandelt werden und es entwickelte sich eine neue Richtung hin zu spezialisierten Kliniken, den Herzzentren. In Deutschland wurde 1973 das Deutsche Herzzentrum München gegründet, das erste seiner Art in Europa, gefolgt vom Deutschen Herzzentrum Berlin 1986 (27). Eine neue Ära hochspezialisierter, an einem Ort gebündelter interdisziplinärer Expertise begann. Im Laufe der Zeit entstanden deutschlandweit bis heute 35 Herzzentren (Deutscher Herzbericht 2019 (5)).

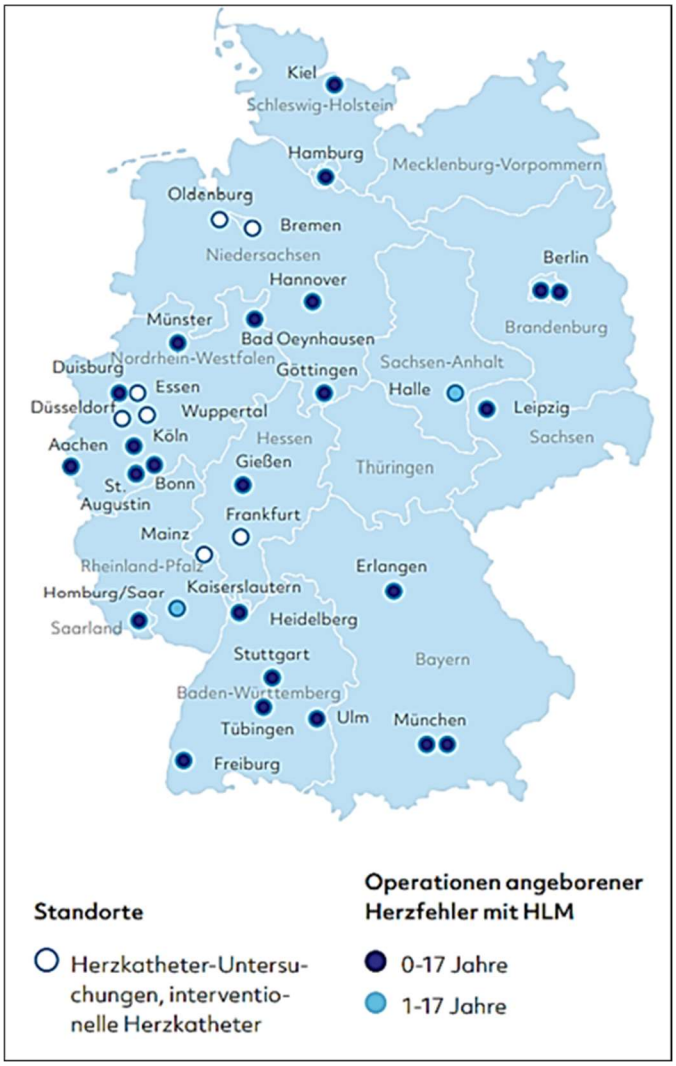


Abbildung 1: *Verteilung der Standorte von Herzzentren in Deutschland*, aus Deutscher Herzbericht 2019 (Darstellung auf Grundlage von Daten der DGPK, der DGTHG und der DGK(5))

Das führte zu einer rasanten Erfolgsgeschichte in den Bereichen Diagnostik, operativer, medikamentöser und katheterinterventioneller Behandlung sowie in der Nachsorge von Patienten mit AHF.

Parallel dazu entwickelten sich zur Unterstützung der Familien und betroffenen Patienten eine Vielzahl von Eltern- und Patientenverbänden, wie zum Beispiel den Bundesverband Herzkranke Kinder e. V. (BVHK). Insgesamt gibt es neben regionalen organisierten Gruppen, grob 13, große deutschlandweit agierende Verbände bzw. Vereine (www.kompetenznetz-ahf.de (28)). Auch in der Medizin entstanden Fachgesellschaften in Deutschland, um einen interdisziplinären Austausch zwischen Medizinern, Wissenschaft und Patientenvertretern sicher zu stellen. Die wichtigsten sind die Deutsche Gesellschaft für Pädiatrische Kardiologie und angeborene Herzfehler e.V. (DGPK), Deutsche Gesellschaft für Thorax-, Herz und Gefäßchirurgie

(DGTHG), Deutsche Gesellschaft für Kardiologie – Herz – und Kreislaufforschung e.V. (DGK).

Dank dieser Entwicklungen erreichen heute mehr als 95% der Kinder mit AHF das Erwachsenenalter (3, 4, 26, 29, 30) und eine neue Herausforderung entstand mit dem Umstand der langfristigen Betreuung und Versorgung von Patienten mit AHF. Die Patienten Versorgung in Deutschland ist prinzipiell gesetzlich geregelt. Erreichen Patienten die Volljährigkeit muss ein Wechsel von der pädiatrischen in die Erwachsenenversorgung erfolgen, die sog. Transition (Fünftes Sozialgesetzbuch (SGB V)). Da Patienten mit AHF in der Nachsorge und Langzeitverlauf andere Probleme, Komplikationen und Bedürfnisse mit sich bringen, etablierte sich eine Zusatzausbildung zur Behandlung von Erwachsenen mit AHF (EMAH) (31). Henning, 2020, beschreibt die besonderen Bedürfnisse von EMAH proportional im Vergleich mit Erwachsenen ohne AHF mit einer zwei- bis viermal höheren medizinischen Versorgungsnotwendigkeit (32). Die EMAH-Zertifizierung für Kinderkardiologen und Kardiologen, soll die bestmögliche Versorgung der Patienten auch außerhalb von spezialisierten Herzzentren, bei niedergelassenen Kardiologen vor Ort sicherstellen.

Das Konzept der interdisziplinären Versorgung von EMAH Patienten besteht aus der hausärztlichen Versorgung durch Allgemeinmediziner, Internisten, Kinder- und Jugendärzte, die in Abstimmung mit den regionalen EMAH-Zentren die Grundversorgung sicherstellen sollen (31). Eine weitere Aufgabe der regionalen EMAH-Zentren ist es, als eine Art Bindeglied zwischen Patienten/Hausärzten und hochspezialisierten Maximalversorgern zu agieren (siehe Abbildung 2).

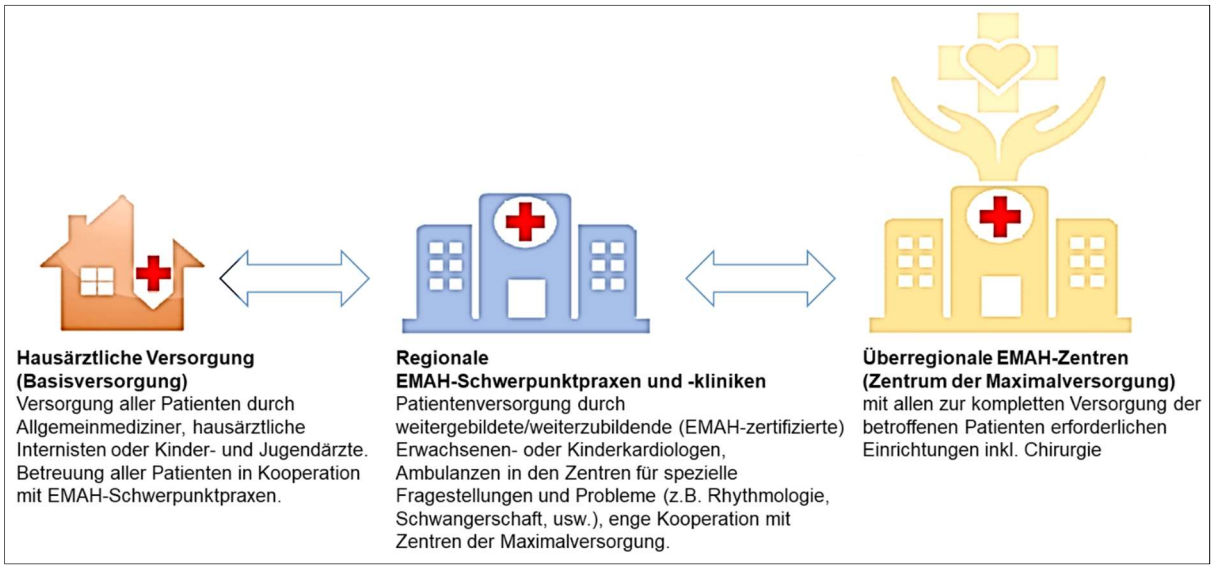


Abbildung 2: *Versorgungsstruktur von EMAH-Patienten nach den Empfehlungen*, modifiziert nach Kaemmerer et al. (31)

Waren in den Anfängen die Patienten mit AHF ausschließlich Kinder, von denen in den 1960er Jahren noch ein Viertel im frühen Säuglingsalter verstarb sowie ein weiteres Viertel im Kindesalter (33), drehte sich der Verteilungsbaum bis heute auf den Kopf. Nach aktuellem Stand sind 2/3 der Patienten mit AHF in der westlichen Bevölkerung erwachsen (34). Eine neue Problematik im klinischen Alltag tritt auf, denn rund 30-60% der Patienten mit AHF gehen während der Transition in die Erwachsenenversorgung aus der medizinischen Betreuung verloren (32, 35) und werden erst wieder von Spezialisten gesehen, wenn ihre Gesundheitssituation eskaliert ist (36). Auch wenn es in Deutschland eine flächendeckende Versorgungsstruktur gibt, so sind dennoch schätzungsweise 200.000 EMAH nicht in eine spezialisierte Nachsorge eingebunden (8, 37).

Genau an diesem Punkt setzt diese Dissertation an; denn nach wie vor sind detaillierte Beweggründe für das beschriebene Patientenverhalten eher spekulativ. Daher fokussiert sich die erste eingebundene Publikation, auf die medizinische Situation der Patienten mit AHF im Transitionsalter. Diese repräsentative Analyse wurde durchgeführt mit medizinischen Daten von Patienten aus ganz Deutschland, die im Nationalen Register für Angeborene Herzfehler angemeldet sind.

3.2 Nationales Register für angeborene Herzfehler

Obwohl AHF die häufigste angeborene Fehlbildung beim Menschen sind, bedarf es bei einer Gesamtprävalenz von rund 1% (38) mehr als nur monozentrischer Daten, um belastbare wissenschaftliche Aussagen und Erkenntnisse über Patienten mit AHF gewinnen zu können. Entsprechend wurde von den drei deutschen Fachgesellschaften für Herzmedizin (DGPK, DGTHG und DGK), 2003 das **N**ationale **R**egister für **a**ngeborene **H**erz**f**ehler (NRAHF) als gemeinnütziger, wissenschaftlicher Verein initiiert, um multizentrische Daten für die Forschung zu sammeln und zur Verfügung zu stellen.

Wird in Deutschland ein Kind mit AHF geboren, besteht für die Eltern die Möglichkeit, ihr Kind im NRAHF anzumelden. Diese Registrierung ist freiwillig, kostenlos und die Mitgliedschaft kann jederzeit ohne Angabe von Gründen widerrufen werden. Bei Erreichen der Volljährigkeit entscheiden die Patienten selbst, ob sie im NRAHF registriert bleiben möchten. Nach der Registrierung erhalten Patienten und Angehörige regelmäßig laienverständliche Informationen über den Stand der Forschung auf dem Gebiet von AHF und können freiwillig an Studien und Patientenbefragungen teilnehmen. Patienten haben darüber hinaus die Möglichkeit, eine Bioprobe (Speichel, Blut, Gewebe) abzugeben, sodass Wissenschaftler genetische Ursachen von AHF untersuchen können (36). Das NRAHF arbeitet eng mit Ärzten und Wissenschaftlern an Universitätskliniken, Herzzentren sowie mit niedergelassenen Kinderkardiologen und Kardiologen, aber auch mit Vertretern von Patientenorganisationen zusammen. Die medizinische Datenbank des NRAHF enthält Versorgungsdaten der Patienten aus medizinischen Berichten (z. B. Arztbriefe, Operationsberichte). Diese Daten werden von geschulten medizinischen Dokumentaren und Fachärzten erfasst, auf Plausibilität geprüft und gegebenenfalls korrigiert und aktualisiert. Abbildung 3 zeigt die detaillierte Struktur und Organisation des NRAHF.

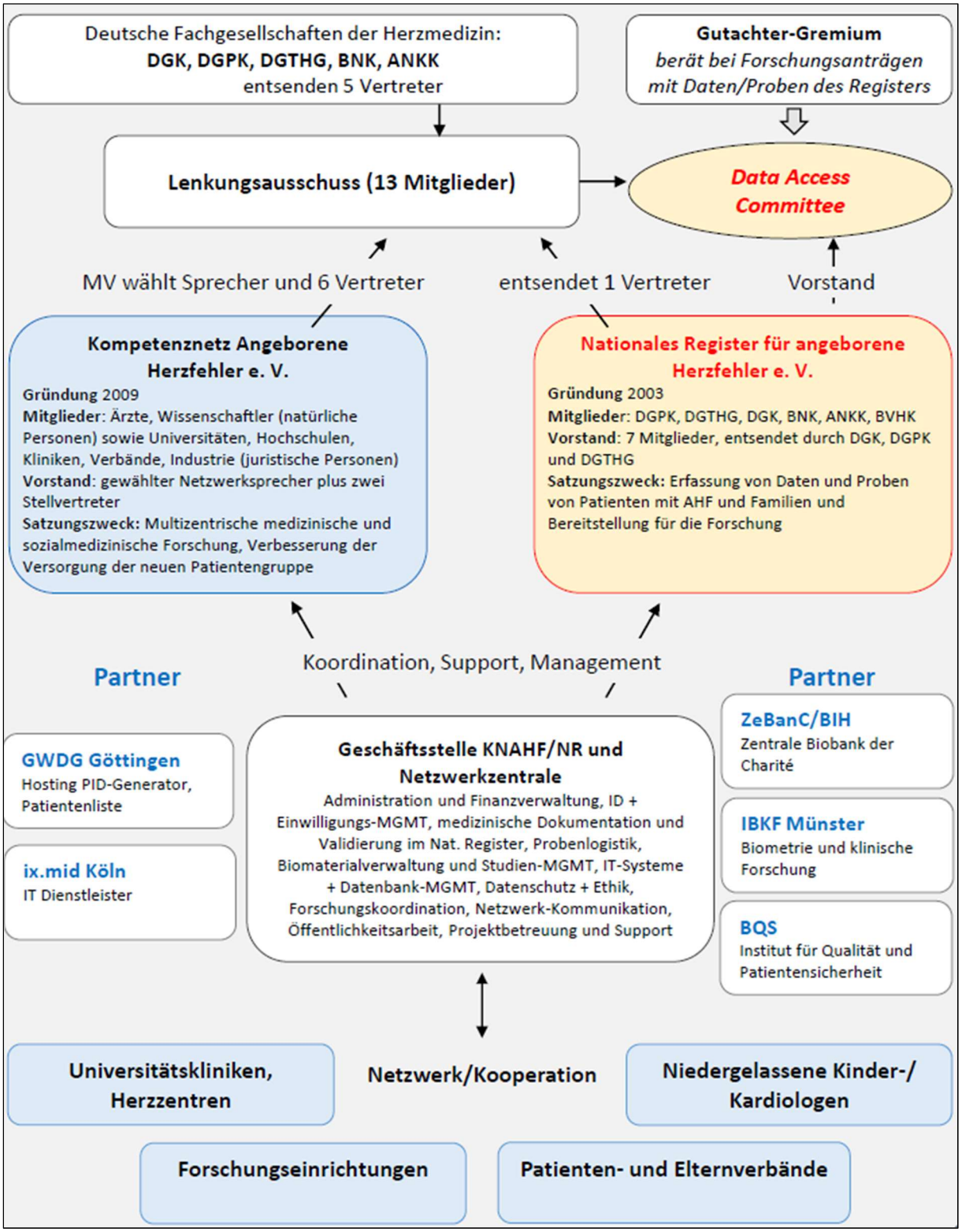


Abbildung 3: *Organigramm des Nationalen Registers für angeborene Herzfehler* (Quelle: Dr. Bauer und PD Dr. Pickardt vom Kompetenznetz für Angeborene Herzfehler e.V. / NRAHF)

DGK = Deutsche Gesellschaft für Kardiologie - Herz- und Kreislaufforschung e. V., DGPK = Deutsche Gesellschaft für Pädiatrische Kardiologie und Angeborene Herzfehler e.V., DGTHG = Deutsche Gesellschaft für Thorax-, Herz- und Gefäßchirurgie, BNK = Bundesverband Niedergelassener Kardiologen, ANKK = ArbeitsgemeinschaftNiedergelassener Kinderkardiologen, BVHK = Bundesverband Herzkranke Kindere.V, ZeBanC= zentrale Biobank

Derzeit sind im NRAHF rund 56.000 Patienten aller Herzfehlerschweregrade und Altersgruppen registriert und somit ist es das größte AHF-Register in Europa (39). Der multizentrische Forschungsansatz des NRAHF ermöglicht eine bundesweite retrospektive, repräsentative Datenanalyse von AHF-bezogenen medizinischen Daten. Wie Helm et al. 2015 zeigen konnten, ist das NRAHF aufgrund seiner Repräsentativität für solche Fragestellungen besonders geeignet (39). Die etablierte Infrastruktur des NRAHF erlaubt die Speicherung der Daten im Rahmen des spezifischen Datenschutzkonzepts, das beim Berliner Beauftragten für Datenschutz und Informationsfreiheit registriert ist (Nr. 531.390). Für retrospektive Forschungsvorhaben, die in oder mit Daten aus dem NRAHF durchgeführt werden, liegt die generelle Zustimmung der Ethikkommission der Charité - Universitätsmedizin Berlin vor. Für Patienten identifizierende Studien, Befragungen und prospektive Studien ist ein Ethikvotum ein zu holen (siehe Abbildung 4).

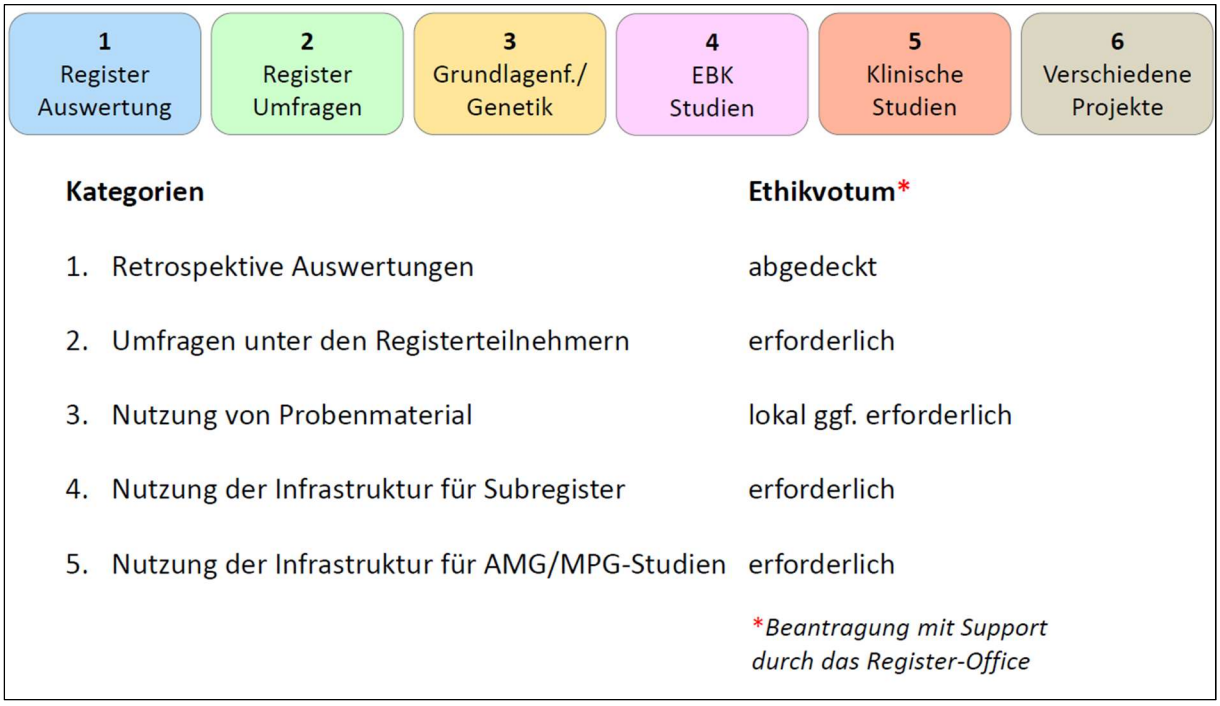


Abbildung 4*: Kategorien von Forschungsvorhaben mit dem NRAHF* (Quelle: Dr. Bauer und PD Dr. Pickardt vom Kompetenznetz für Angeborene Herzfehler e.V. / NRAHF)

Das NRAHF hat, wie dargestellt, zahlreiche Kooperationspartner und forscht erfolgreich deutschlandweit an mehr als 60 Standorten sowie international unter anderem mit Wissenschaftlern aus Großbritannien, Griechenland, Australien, Finnland und Portugal (siehe: www.kompetenznetz-ahf.de/forscher/forschen-mit-uns/wer-forscht-mit-dem-register/ (40)). Basierend auf der Registerarbeit konnten im Laufe der

Zeit wertvolle Erkenntnisse sowohl zu den Herzfehlern, ihren Behandlungsmöglichkeiten als auch zur Lebens- und Behandlungssituation, der Patientenperspektive und den Patientenbedürfnissen gewonnen werden. So konnte seit der Registerentstehung bereits eine Vielzahl relevanter wissenschaftlicher Fachpublikationen veröffentlicht werden (261 Publikationen, https://www.kompetenznetz-ahf.de/wir/publikationen/; Stand 07.11.2022 (41)).

3.3 Herz und Hirn

Im Rahmen der Organogenese laufen Teile der Entwicklung von Herz und Hirn in der 5.-8. Woche der Embryonalentwicklung parallel (40). Die Neurulation beginnt bei der menschlichen Embryonalentwicklung mit der Ausbildung der Neuralplatte aus einem der drei Keimblätter, dem Ektoderm. Zunächst bilden sich ab dem 18. Lebenstag erste Vertiefungen, die das Neuralrohr bilden, dem Vorläufer des Rückenmarks. Dann entwickeln sich drei Ausstülpungen am oberen Ende des Neuralrohrs, die sogenannten Hirnbläschen (40). Durch enorme Zelleinwanderung in die Hirnbläschen beginnen sich diese von der Struktur des späteren Rückenmarks deutlich zu unterscheiden (Abbildung 5). In der 6. Woche lassen sich erste Anlagen von Hirnstrukturen wie Pons, Cerebellum, Thalamus, Basalganglien und Großhirnrinde abgrenzen.

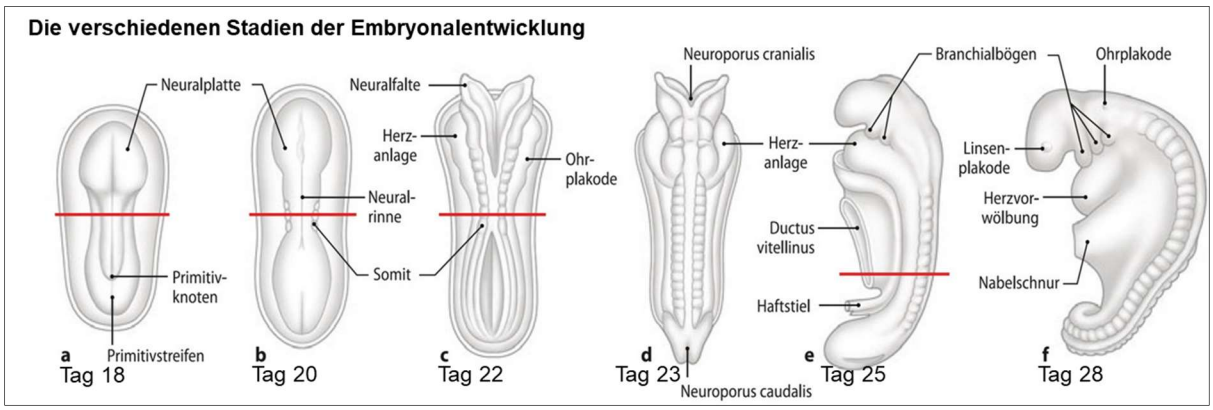
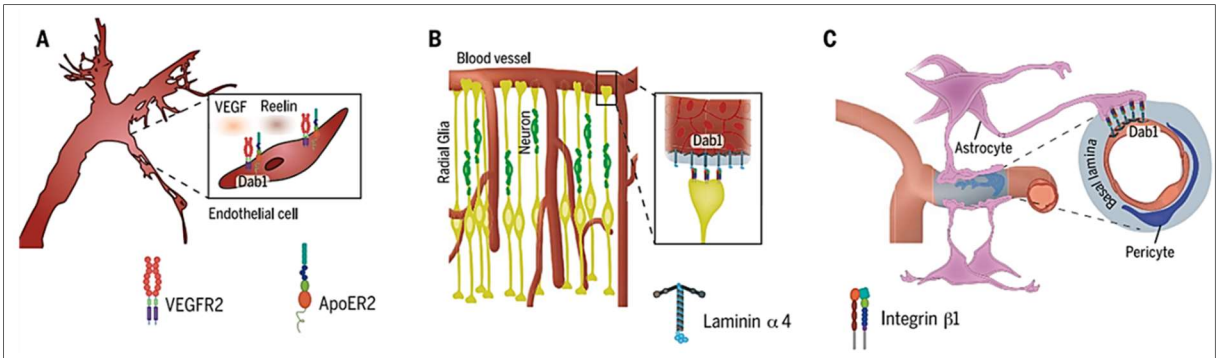


Abbildung 5: *Stadien der Embryonalentwicklung*, modifiziert nach Zilles et al. 2010 (40)

Bereits ab dem 22. Tag der Embryonalentwicklung wird das kardiovaskuläre System aktiviert, das Herz beginnt zu schlagen und übernimmt die Aufgabe des Sauerstofftransportes (40). Abgesehen von ihren Stoffwechselfunktionen wird angenommen, dass die Gefäßbahnen auch als Nischen und Gerüste für die neuronale Migration dienen, sowohl während der Entwicklung als auch während der adulten Neurogenese (41). Zusätzlich werden neben Sauerstoff verschiedene Nährstoffe, Transmitter und Hormone an ihren Ziel-Wirkort transportiert. Diese zellulären Botenstoffe sind für die normale Entwicklung des Gehirns von großer Bedeutung, durch ihre modulierende und orchestrierende Wirkung (42). Der komplexe Aufbau der neurovaskulären Einheit wird durch Vernetzung zwischen Neuronen, Gliazellen und Endothelzellen gesteuert. Hierbei besitzt beispielsweise das Hormon Reelin eine steuernde Funktion, da es mit seiner proangiogenen Aktivität die Kommunikation

zwischen Endothelzellen und Glia sicherstellt, um die neuronale Migration und Bildung der Bluthirnschranke zu steuern (siehe Abbildung 6) (43).



Instruktive Funktionen von vaskulärem Dab1 an der neurovaskulären Schnittstelle.
(**A**) ApoER2 und Dab1 steuern die Proliferation von Endothelzellen und die Ausdehnung der Filopodien von Spitzenzellen während der ZNS-Vaskularisierung, indem sie mit dem VEGFR2-Signalweg kommunizieren. (**B** und **C**) Vaskuläres Dab1 steuert auch die radiale Gliaorganisation und die neuronale Migration in der sich entwickelnden Großhirnrinde (**B**) und die Entwicklung der Blut-Hirn-Schranke (**C**). In beiden Fällen reguliert die Dab1-Signalübertragung in der Vaskulatur die Ablagerung von Laminin-α4 und damit die Aktivierung von Integrin-β1 in Gliazellen.

Abbildung 6: *Interaktion vom Herzkreislaufsystem auf Hirnentwicklung*, modifiziert nach Segarra et al.2018 (43)

Unipotente und multipotente Stammzellen des Gehirns, sogenannte radiale Gliazellen (Abbildung 6 B) entwickeln sich aus dem Neuroektoderm, das die Neuralplatte formt. Sie haben wegweisende Funktionen für die spätere Ausdifferenzierung des Gehirns und die Architektur der Blut-Hirn-Schranke. Sie bilden u.a. den Ursprung von Neuronen, und differenzieren sich in die verschiedenen Gehirnzellen (Astrozyten, Oligodendrozyten) aus (42).

Das hochkomplexe Zusammenspiel von Herz und Hirn, verdeutlicht potenzielle Komplikationen, die durch eine Funktionsstörung der Herz-Kreislauf-Zirkulation, ausgelöst durch einen AHF, auftreten können. Bereits pränatal kann sich die veränderte Hämodynamik negativ auf die Hirnentwicklung auswirken, durch Sauerstoffmangel oder Minderdurchblutung beispielsweise kann es zur Entstehung von kortikalen Nekrosen führen, wohingegen akute schwere Mangel eher mit Stammganglionnekrosen assoziiert sind (44). Insbesondere die Zellen der zentralen Hirnregionen (weiße Substanz und Stammganglien) sind besonders vulnerabel bei dem sich entwickelnden Gehirn (44, 45). Eine durch den AHF induzierte Hypoxämie kann sich zu verschiedenen Zeitpunkten negativ auf die Hirnentwicklung auswirken: während der Schwangerschaft, v. a. im letzten Trimenon, zum Zeitpunkt des schnellen Gehirnwachstums (46, 47), perioperativ und postoperativ (48).

Abbildung 7 zeigt Risikofaktoren zu den verschiedenen Zeitpunkten der Hirnentwicklung und -reifung, die durch den Herzfehler und dessen Behandlung auftreten können.

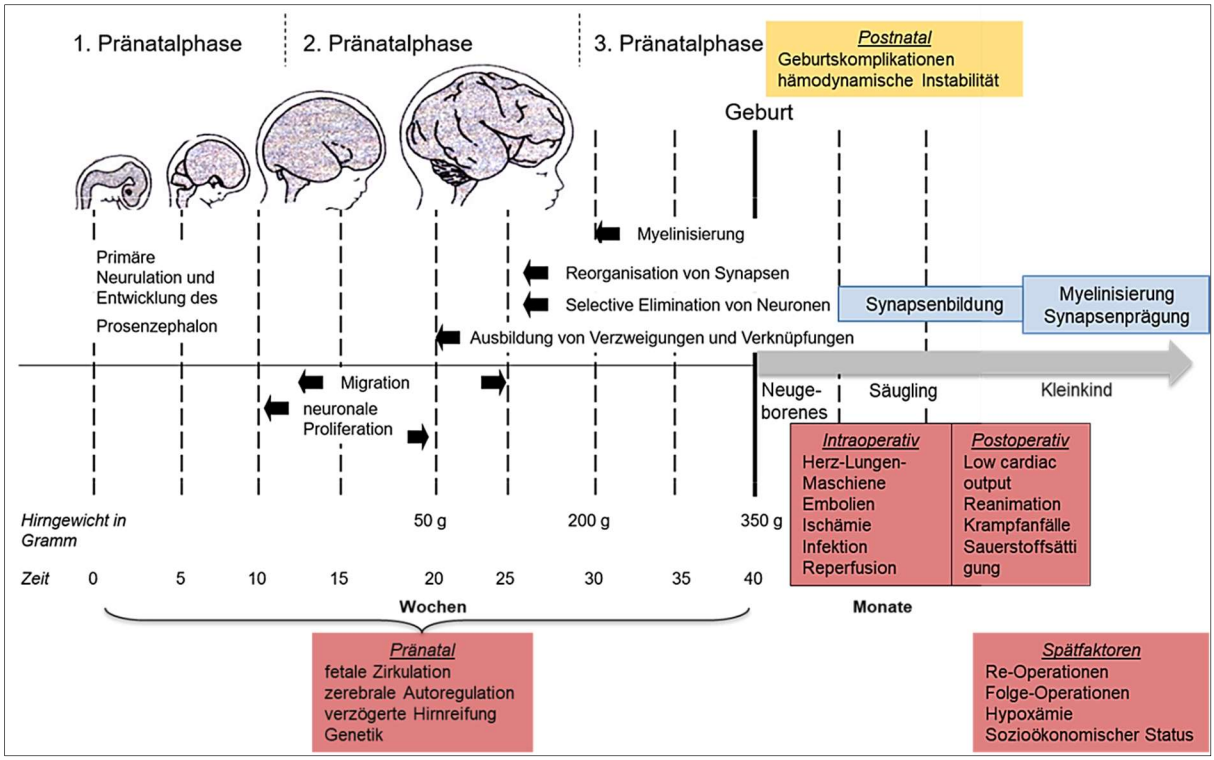


Abbildung 7: *Strukturelle Hirnentwicklung und potentielle AHF induzierte Komplikationen*; modifiziert nach Lagercrantz et al. 2010 (49) und Prof. Dr. Bettina Reich

Als die Überlebensraten bei Kindern mit AHF, mit sehr guten kardialen Ergebnissen, deutlich stiegen, zeigten sich Entwicklungsdefizite und Verzögerungen in deren Entwicklung (50, 51). Parallel zur Optimierung der kardiochirurgischen Eingriffe und perioperativen Behandlung starteten, erste Multizentrums-Studien zum Thema Entwicklung und Outcome von Kindern mit AHF, rund um die Arbeitsgruppe Bellinger und Newburger aus Boston. Mit ersten Publikationen 2003 zum Thema der visuell-räumlichen Verarbeitungsfähigkeit bei Kindern mit d-TGA nach Switch-Operation am offenen Herzen und Assoziationen mit postoperativer Krankenhausliegezeit (52, 53). International etablierten sich verschiedene Forschergruppen, die sich mit der Hirnentwicklung bei Patienten mit AHF befassten und diese von der Neonatalzeit über das Säuglings- bis ins Kindesalter verfolgten. Sie kamen zu dem Schluss, dass es zu Verzögerungen in der Hirnreifung und Entwicklung der Kinder kommt und diese insbesondere bei komplexen Herzfehlern stärker ausgeprägt sind (50, 52, 54-61).

Hinzu kamen bildgebende Verfahren, die Erklärungen für zugrundeliegende Pathomechanismen lieferten, woher die Entwicklungsdefizite rühren könnten. Abbildung 8 zeigt neben einem normalen Schädel-MRT verschiedene hirnstrukturelle Veränderungen, welche bei Patienten mit AHF vermehrt auftreten können (14-17, 62, 63). Diese Studien konnten auch eine Assoziation der hirnstrukturellen Veränderungen mit neurokognitiven Entwicklungsdefiziten herstellen, die sich am häufigsten bei Kindern mit komplexe AHF finden lassen. Außerdem wurden verschiedene Behandlungsparameter des AHF, wie zum Beispiel Krankenhausliegedauer, Bypass-Zeit aber auch Anzahl von Operationen und katherterinterventionellen Eingriffen als beeinflussende Faktoren identifiziert (50).

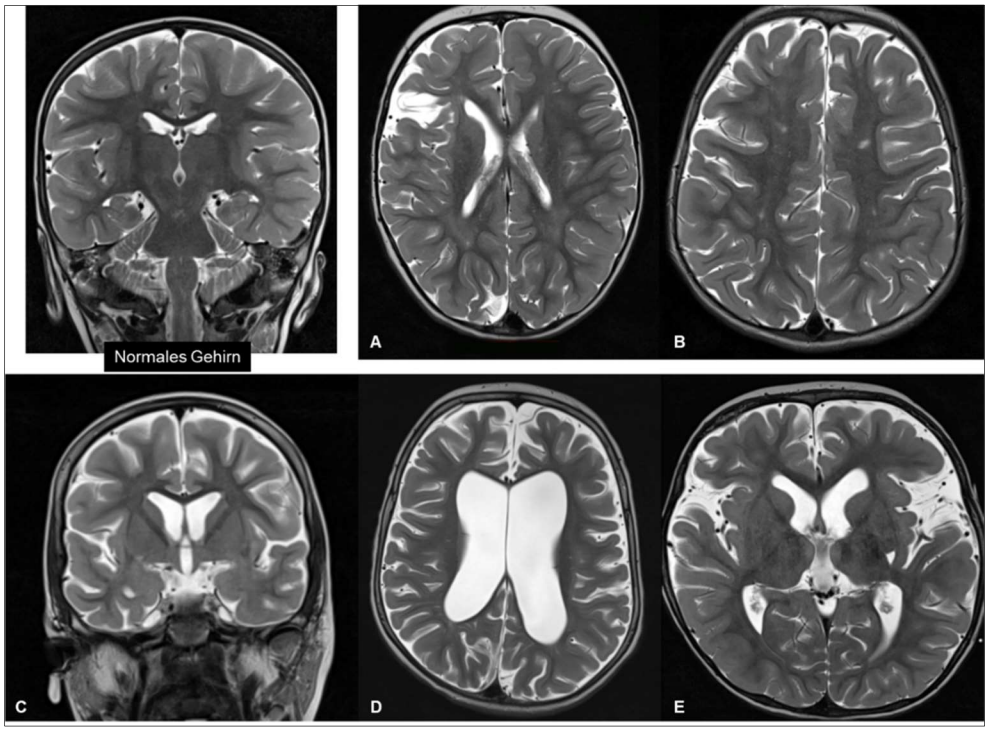


Abbildung 8: *Hirnstrukturelle Veränderungen / Läsionen bei Patienten mit AHF;* Quelle: mit Erlaubnis von Prof. Dr Bettina Reich (A: Mediainfarkt rechts fronto-parietal; B: Läsionen der zentralen weißen Substanz, sog. White mater injury; C und D: erweiterte innere und äußere Liquorräume; E: Erweitertere externe Liquorräume mit noch nicht geschlossener Sylvischer Furche).

Durch rezidivierende und kumulative Risikofaktoren während der Entwicklung können Patienten mit komplexen AHF lebenslang Probleme zeigen, die ihre Schulbildung, den Alltag und damit auch die Lebensqualität negativ beeinflussen können. Viele Outcome-Studien haben sich bisher auf kürzere Nachbeobachtungszeiträume von Kleinkindern und Schulkindern fokussiert. Und es liegen kaum Studien vor, die die Relevanz der Entwicklungsverzögerungen im Jugend- und Erwachsenenalter untersuchen (7, 10, 18). Es ist unklar, wie sich die Entwicklungsbeeinträchtigungen im Verlauf bis ins

Erwachsenenalter darstellen. Fraglich ist, ob aufgrund der Neuroplastizität des Gehirns -teilweise- eine Adaptation der motorischen und kognitiven Fähigkeiten stattfindet (64).

Über die kognitiven Fähigkeiten von EMAH, die mit standardisierten Intelligenztests erhoben wurden, ist wenig bekannt. Da die kognitiven Fähigkeiten die individuellen Lebensperspektiven und -pläne sowie die HrQoL beeinflussen können (12), zielen die Publikationen II und III der vorliegenden Dissertation darauf ab, EMAH hinsichtlich ihrer kognitiven Fähigkeiten und der Assoziationen mit HrQoL zu untersuchen und zu analysieren.

4 Methoden

Die vorliegende Dissertation fokussiert als Ausgangspunkt Patienten mit AHF im Transitionsalter, sowie darauf aufbauend NMHA, die kognitiven Fähigkeiten und die HrQoL, von jungen EMAH. Im Folgenden werden die Messinstrumente zur Erfassung der kognitiven Fähigkeiten und der HrQoL vorgestellt, die Studiendesigns der Einzelpublikationen im Überblick dargestellt und die verwendeten statistischen Verfahren erläutert.

4.1 Kognitive Fähigkeiten - Wechsler Intelligenztest

Der Begriff der Intelligenz (wörtlich „wählen zwischen …“ von lateinisch *inter* „zwischen“ und *legere* „lesen, wählen“ bzw. *intellegere* „erkennen“, „einsehen“; „verstehen“) fand seinen Ursprung um 1900 als Fachbegriff in der Psychometrie (65). Geprägt wurde der Begriff inhaltlich durch den Franzosen Alfred Binet und die Engländer Louis Leon Thurstone und Charles Spearman. Im Auftrag der französischen Regierung und als Teil der *„Société Libre pour l'Etude Psychologique de l'Enfant",* entwickelte Alfred Binet (1857–1911) den ersten einsatzfähigen Intelligenztest bereits 1904, gemeinsam mit seinem Schüler Théodore Simon: den Binet-Simon-Test (65, 66). Es war Binet sehr wichtig, dass sein Test lediglich Kindern zugutekam, die einen erhöhten Förderbedarf haben und keinesfalls als ein kategorisierendes Messinstrument verallgemeinert wird (65). Bereits mit dem Tod Binets adaptierte der Kalifornier Lewis Terman, von der Stanford University, den Test und stellte ihn als numerischen Maßstab für vererbte Intelligenz unter dem Namen Stanford-Binet-Intelligenztest vor (67). Ein nächster wegweisender Entwicklungsschritt war es die Testinterpretation dem Alter anzupassen. Dies verwirklichte William Stern indem er eine Formel erdachte, *Intelligenzalter geteilt durch Lebensalter multipliziert mit 100*, somit war Intelligenzquotient (IQ) entstanden (68, 69). Bei Erwachsenen war das jedoch schwierig, da das Alter konstant steigt, der IQ jedoch nicht. Dieses Problem löste David Wechsler indem er 1932 den Abweichungs-IQ einführte. Hierbei wird der Testwert mit dem Mittelwert einer repräsentativen gleichaltrigen Norm, unter Berücksichtigung der Streuungsverhältnisse verglichen (70). Bereits 1939 entwickelte der US-amerikanische Psychologe David Wechsler mit der Bellevue Intelligence Scale I und II einen standardisierten Test zur Messung der Intelligenz. Wechsler selbst definierte 1956 Intelligenz wie folgt: „Intelligenz ist die zusammengesetzte oder globale Fähigkeit des Individuums, zweckvoll zu handeln, vernünftig zu denken und sich mit

seiner Umgebung wirkungsvoll auseinanderzusetzen“ (Wechsler, 1956, S. 13 (71)). Wechsler stellte 1955 seinen Intelligenztest für Erwachsene, die Wechsler Adult Intelligence Scale (WAIS) vor (72). Im zeitlichen Verlauf wurden die Items und Normen der WAIS immer wieder aktualisiert. Die heute aktuelle Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) (73) stellt den Goldstandart in der Erhebung von Intelligenz bei Erwachsenen dar (74). Die weltweit etablierte Testbatterie der WAIS-IV wurde im Jahr 2013 für die deutsche Normalbevölkerung mit einer Normierungsstichprobe von 1.664 Teilnehmern validiert und aktualisiert (75). Diese Norm stellt für die eingeschlossenen Studien die Referenz dar.

Die WAIS-IV umfasst 10 Kerntestungen zur Berechnung des Gesamt Intelligenz Quotient (GIQ). Der GIQ repräsentiert das allgemeine intellektuelle Niveau. Zudem lassen sich vier spezifische Intelligenzbereiche abbilden:

- Das Sprachverständnis umfasst die Fähigkeiten in den Bereichen der sprachlichen Begriffsbildung, dem sprachlichen Schlussfolgern und dem erworbenen Wissen (kristalline Intelligenz, d.h. abhängig von Wissen und Erfahrung).
- Das wahrnehmungsgebundene logische Denken gibt Auskunft über das wahrnehmungsgebundene und fluide Schlussfolgern sowie das räumliche Vorstellungsvermögen und die visuo-motorische Integration (fluide Intelligenz: abstraktes Denken, Problemlösung, Geduld, Mustererkennung als Ausdruck der Hirnvernetzung).
- Das Arbeitsgedächtnis prüft die Fähigkeit, Informationen vorrübergehend im Gedächtnis zu behalten, um damit beispielsweise Handlungen zu planen oder durchzuführen und ein Ergebnis zu produzieren; außerdem werden Aufmerksamkeit, mentale Kontrolle, Konzentration und Schlussfolgern geprüft.
- Die Verarbeitungsgeschwindigkeit beschreibt die Fähigkeit einfache visuelle Informationen schnell und korrekt zu erfassen, um sie dann in eine Abfolge zu bringen oder zu unterscheiden. (73)

Im WAIS-IV-Test wird eine Beeinträchtigung der kognitiven Fähigkeiten als ein erreichter IQ definiert, der negativ mehr als eine Standardabweichung (SD) von der Norm abweicht (durchschnittlicher IQ = 100, Abweichungs-IQ = ±1SD; IQ-Normalbereich = 85-115 IQ-Punkte). Auch in der Kinderkardiologie finden die Wechsler-Versionen für Kinder und Jugendliche häufig Anwendung (52, 54-56, 58, 60, 61).

4.2 Gesundheitsbezogene Lebensqualität - SF-36

Es ist bekannt, dass viele Faktoren das persönliche Empfinden von Lebensqualität beeinflussen. Auch Lebens- und Umweltsituationen können eine wichtige Rolle spielen und gelten als relevante Einflussfaktoren (76). Es ist nicht ohne Einschränkungen möglich/sinnvoll, die Lebensqualität von Menschen aus verschiedenen Ländern zu vergleichen, da die Lebenssituationen oftmals nur bedingt vergleichbar sind, was sich unter Umständen erheblich auf Lebensziele und Bedürfnisse auswirken kann. Das Gleiche gilt für soziale oder gesellschaftliche Faktoren (z. B. kulturelle und religiöse Einflüsse), die die Wahrnehmung dessen prägen, was erstrebenswert ist und was nicht (77). Zudem ist bekannt, dass der wirtschaftliche Status, die berufliche Beschäftigung und die Familienverhältnisse Auswirkungen auf die Lebensqualität haben (76). Ein anderer Ansatz besagt, dass Lebensqualität nicht zwischen verschiedenen Individuen vergleichbar ist, sondern nur bei einer Person zu verschiedenen Zeiten gemessen und verglichen werden kann (78). Der amerikanische Medical Outcomes Study Questionnaire Short Form 36 Health Survey (SF-36) umfasst forschungsbasierte Parameter, die für gesundheitsbezogene Lebensqualität (HrQoL) definiert wurden. Aufgrund seiner psychometrischen Qualität und Wirtschaftlichkeit ist der SF-36 ein international führendes Instrument zur Erfassung der HrQoL (79) und stellt einen Konsens im Forschungsbereich der Lebensqualität dar.

Der SF-36 ist ein in acht Abschnitte unterteilter Fragebogen zu allgemeinen gesundheitsbezogenen Lebensqualitätsmessungen (80). Die gewichteten Summen der Fragen, die sowohl dichotom als auch Likert-skaliert sind, ergeben für jeden Abschnitt skalierte Werte zwischen 0 (schlechtester Gesundheitszustand) und 100 (bester Gesundheitszustand). Der SF-36 beruht auf Selbstauskünften der Patienten innerhalb eines 4-Wochen-Fensters. Er ist in verschiedenen Bereichen des Gesundheitswesens sehr gut etabliert, um den Gesundheitszustand einzelner erwachsener Patienten zu bewerten und die Krankheitsbelastung zu überwachen und zu vergleichen (79). Die deutsche Version des SF-36 wurde von Bullinger und Kirchberger validiert. Zudem steht der SF-36 in über 170 Sprachen zur Verfügung und ist daher ein weltweit verwendeter, gut etablierter Fragebogen (79). Die aktuellsten Normdaten für Deutschland stammen aus einer Erhebung von 2013 (81). Die Normdaten wurden den Studienteilnehmern nach Alter und Geschlecht zugeordnet.

4.3 Studiendesign

In Tabelle 2 werden die 4 Publikationen dieser Dissertation in einer kurzen Übersicht dargestellt.

Tabelle 2: Studiendesign der ausgewählten Publikationen

Studie	Studiendesign	Studien-population	Zielgrößen	Statistische Auswertung
I	*Cross-sectionale Registerstudie*	N = 8.834 46 % ♀ Ø 20.3±3.1 Jahre Jugendliche und junge Erwachsene mit verschiedenen AHF	•Prävalenz von extrakardial und kardial erworbenen Nebendiagnosen additiv zum AHF	•deskriptive Statistik •Shapiro-Wilk-Test •Student‘s t-Test •χ^2 -Test und Fischers Exakten
II	*Cross-sectionale Observations-studie*	N = 78 50% ♀ Ø 34.1±12.9 Jahre Erwachsene mit verschiedenen AHF	•Kognitive Fähigkeiten •HrQoL •Unterschiede zwischen Herzfehlergruppen	•deskriptive Statistik •Kolmogorov-Smirnov Test •Student‘s t-Test •Pearson Korrelation •GLM •Lineare Regressionsmodelle
III	*Cross-sectionale Observations-studie*	N = 44 48% ♀ Ø 34.7±11.9 Jahre 22 erwachsene Fontan-Patienten vs. 22 azyanotische EMAH	•Kognitive Fähigkeiten und HrQoL im direkten Herzfehlergruppen vergleich	•deskriptive Statistik •Shapiro-Wilk-Test •Student‘s t-Test •Pearson Korrelation •Multivariate Regressionsmodelle
IV	*Prospektive Observations-studie*	Zwillinge national G-Poweranalyse N = 54 Paare geplant N = 129 Paare	•Kognitive Fähigkeiten •Motorische Fähigkeiten •Mentale Gesundheit •Lebensqualität	•Darstellung der geplanten Analysen in Abbildung 2 der Publikation IV (Studienprotokoll)

4.4 Daten und Datenauswertung

Die Studien, die in diese Dissertation eingebunden sind, wurden in Anlehnung an die Deklaration von Helsinki (Revision 2013) durchgeführt. Entsprechend wurden alle Patienten ausführlich über die freiwillige Teilnahme und den Inhalt der Studien informiert und gaben ihre schriftliche Einwilligung zur Teilnahme sowie der anonymen wissenschaftlichen Veröffentlichung ihrer Daten. Datenerhebung und Datenverarbeitung erfolgten gemäß der Bundes- und Landesdatenschutzgesetze.

Für die retrospektive Analyse der Registerdaten zum Thema Transition (Publikation I), liegt die generelle Zustimmung der Ethikkommission der Charité - Universitätsmedizin Berlin vor, wie in Abschnitt 3.2 beschrieben. Die Genehmigungen der lokalen Ethikkommission der TU München (Projektnummer 350/18 S; zur Studie von Publikation II und III) und der Ethikkommission der Charité - Universitätsmedizin Berlin (EA2/086/18) zur Durchführung der Zwillingsstudie „Same Same, but different?“ (Publikation IV Studienprotokoll) wurden eingeholt.

Die Patientendaten wurden sowohl monozentrisch (Deutsches Herzzentrum München) als auch multizentrisch deutschlandweit erhoben. Zu den Analysen von unterschiedlichen AHF-Schweregraden wurde die Schweregradeinteilung von Warnes et al. (82) verwendet (Einteilung in simple, moderate und komplexe AHF).

Zudem wurden primäre kardiale Diagnosen und erworbene kardiale sekundäre Diagnosen unter Verwendung des International Paediatric and Congenital Cardiac Code (IPCCC) (83) sowie der ICD-10-Klassifikation für extrakardial erworbene Diagnosen (84) klassifiziert. Die detaillierte Schweregradeinteilung nach Warnes et al., die IPCCC-Diagnosen und die ICD-10-Diagnosen sind im Anhang von Publikation I ausführlich dargestellt.

Die deskriptiven Statistiken wurden in absoluten und relativen Häufigkeiten für kategoriale Variablen und in Mittelwerten und SD für metrische Variablen berechnet. Die Unterschiede zwischen den Gruppen wurden bei nominalen Variablen mit dem $\chi 2$-Test überprüft, es sei denn, der erwartete Wert lag unter 5. In diesem Fall wurde der Fischers Exakter Test anstelle des $\chi 2$-Tests verwendet. Nach positiver Prüfung der Normalverteilung mit dem Shapiro-Wilk-Test oder Kolmogorov-Smirnov-Test, wurde der Student's t- Test für Vergleiche von Mittelwerten verwendet. Regressions- und Korrelationsmodelle wurden verwendet, um Zusammenhänge zwischen Messungen und Patientendaten zu ermitteln. Die ANOVA ermöglicht hierbei die Berücksichtigung

von Alter und Geschlecht und wurde für Zwischengruppenunterschiede durchgeführt. Alle Analysen wurden mit der Software SPSS V.20, V.25 oder V.28 (SPSS Inc., Chicago, Illinois, USA) oder der R-Software V. 3.3.1, V. 4.1.1 durchgeführt. Das Niveau der statistischen Signifikanz wurde zweiseitig und mit einem p-Wert < 0,05 festgelegt.

5 Wissenschaftliche Publikationen

Die Transition beschreibt die Phase des Übergangs von der pädiatrischen Versorgung hin zur adulten Versorgung von chronisch Kranken. Insbesondere für Patienten mit AHF spielt eine lebenslange, angemessene Versorgung durch spezialisierte Kardiologen eine entscheidende Rolle, da AHF Patienten ein erhöhtes Risiko für erworbene Nebendiagnosen haben, additiv zu den Risiken die mit dem Alter einhergehen. In dieser entscheidenden Phase tritt in der Praxis jedoch häufig das Phänomen des „loss to follow-up“ auf und Patienten tauchen erst wieder in spezialisierten Zentren auf, wenn ihre Gesundheitssituation eskaliert ist.

Daher sollen mit Publikation I, in einem ersten Schritt, folgende Fragen beantwortet werden:

=> Wie geht es den Jugendlichen und jungen EMAH aus medizinischer Perspektive im Transitionsalter?

=> Welche Herzfehlergruppen sind besonders auffällig?

=> Welche erworbenen Nebendiagnosen treten zusätzlich zum AHF mit welcher Prävalenz auf?

5.1 Publikation I Transition

„Endangered patients with congenital heart defect during transition—Germany-wide evaluation of medical data from National Register for Congenital Heart Defects (NRCHD)“

Autoren:

Julia Remmele, Sandra Schiele, Renate Oberhoffer-Fritz, Peter Ewert, Ulrike M. M. Bauer, Paul Christian Helm

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I Konzeption und Gestaltung: **JR**, PCH

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IV Sammlung und Zusammenstellung der Daten: **JR**, PCH, UMMB

V Analyse und Interpretation der Daten: **JR**, PCH, SS

VI Verfassen des ersten Manuskripts: **JR**, PCH, SS

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VIII Überarbeitung nach der peer-review Beurteilung: **JR**

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Original Article on Current Management Aspects in Adult Congenital Heart Disease (ACHD): Part IV

Endangered patients with congenital heart defect during transition—Germany-wide evaluation of medical data from National Register for Congenital Heart Defects (NRCHD)

Julia Remmele[1,2]^, Sandra Schiele[1], Renate Oberhoffer-Fritz[2]^, Peter Ewert[1,3]^, Ulrike M. M. Bauer[4]^, Paul Christian Helm[4]^

[1]Department of Congenital Heart Disease and Pediatric Cardiology, German Heart Center Munich, Technical University of Munich, Munich, Germany; [2]Institute of Preventive Pediatrics Technical University Munich, Munich, Germany; [3]DZHK (German Centre for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany; [4]National Register for Congenital Heart Defects, DZHK (German Centre for Cardiovascular Research), Berlin, Germany

Contributions: (I) Conception and design: J Remmele, PC Helm; (II) Administrative support: R Oberhofer-Fritz, P Ewert, S Schiele; (III) Provision of study materials or patients: UMM Bauer, PC Helm; (IV) Collection and assembly of data: UMM Bauer, PC Helm, J Remmele; (V) Data analysis and interpretation: J Remmele, PC Helm, S Schiele; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Julia Remmele, MSc. Department of Congenital Heart Disease and Pediatric Cardiology, German Heart Center Munich, Technical University of Munich, Lazarettstraße 36, 80636 München, Germany. Email: remmele@dhm.mhn.de.

Background: Appropriate care over the entire lifespan is essential in the population with congenital heart defect since the number of patients with congenital heart defect is increasing steadily worldwide. More than 90% survive into adulthood nowadays. The transition from pediatric to adult care in patients with congenital heart defect is a major challenge in clinical practice and often fails. Patients with congenital heart defect are generally at higher risk for different acquired secondary diagnoses. This cross-sectional retrospective study analysed data from the German National Register for Congenital Heart Defects to gain insight into the clinically relevant health-status of the transition population among congenital heart defect patients in Germany.

Methods: Adolescents and young adults with congenital heart defect between the ages of 15 to 25 years (which have been defined as the transition generation) were identified using the National Register of Congenital Heart Defects medical database. Out of 55,687 patients with congenital heart defect, 8,834 adolescents and young adults with congenital heart defect [4,063 female (46.0%); 20.3±3.1 years] were included in the statistical analyses. Statistical analyses were conducted using the student's *t*-test, χ^2-test and Fisher's exact test.

Results: Severity of congenital heart defect: simple (23.4%), moderate (45.1%) and complex (31.5%). Most common congenital heart defect: atrial septal defects (14.9%) followed by ventricular septal defects (12.8%) and tetralogy of Fallot (10.5%). Most frequent acquired cardiac diagnosis: arrhythmia (25.5%) followed by secondly pulmonary hypertension (4.5%) and thirdly systemic arterial hypertension (3.6%). Almost 10% had chromosomal abnormalities and other genetic syndromes. Patients had neurological defects overall with 7.3%, followed by musculoskeletal defects with 6.9% and psychological disorders with 5.6%.

Conclusions: Adolescents and young adults with congenital heart defect need to bridge the gap between pediatric and adult cardiology as they already show up to 4 cardiac and up to 7 extracardiac acquired secondary diagnoses during the transition period. Otherwise, early detection of an acquired secondary diagnosis, which affects the lives of young adults with congenital heart defect, fails with all its consequences.

^ ORCID: Julia Remmele, 0000-0002-0887-3231; Renate Oberhoffer-Fritz, 0000-0002-3166-0488; Peter Ewert, 0000-0003-0253-1190; Ulrike M. M. Bauer, 0000-0002-6317-3609; Paul Christian Helm, 0000-0002-1868-4266.

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Introduction

As a result of improved medical treatment and care for patients with congenital heart defect (CHD), the number of CHD patients, and especially adolescent and adult patients with CHD, is increasing rapidly during the last decades (1). It was estimated in 2015 by the International Society for Adult Congenital Heart Disease (ISACHD) that worldwide, there are around 12 to 34 million adults with a congenital heart defect (ACHD) (2) and 2.3 million of them in Europe (3).

As most of the patients are not cured but palliated, appropriate and specialized CHD care during their whole lifespan is essential. A major challenge in clinical practice is their transition from pediatric to adult CHD care, since ageing CHD patients are at high risk for cardiac secondary diagnoses (SD), like arrhythmias, systemic and pulmonary arterial hypertension, thromboembolic events, infective endocarditis (4), as well as non-cardiac diseases. Many young ACHD, even with severe diagnoses, are lost to cardiological follow-up care, as they have to become responsible for their healthcare, struggle for independence, lack of compliance or knowledge, or simply move to a new environment after finishing school (5-7). Failure of the transition process may lead to delayed recognition of evolving cardiac and non-cardiac problems, which complicates subsequent patient management (6). Therefore, we need to pay special attention to this patient group reaching adulthood and becoming responsible for themselves. To improve the organisation of care for adolescents and young ACHD in Germany and to establish the right link to specialised institutions in the transition phase, it is important to know the current situation in Germany, the number of affected patients, their diagnoses and the challenges adolescents and young ACHD face. The data on young adults with CHD are continuously changing (4).

In this cross-sectional register study, we analysed data from February 2020 of adolescents and young ACHD registered in the National Register for Congenital Heart Defects (NRCHD) to obtain more detailed information on the health-related status of the transition population of adolescents and young ACHD in Germany. This study analysed data from the German NRCHD to gain insight into the clinically relevant health-status of the transition population among CHD patients in Germany. To answer the question of whether patients with CHD in Germany of transition-age are in such good health that the loss of follow-up does not pose a threat to their health or there is an urgent need for improvements. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/cdt-21-66).

Methods

NRCHD

The NRCHD was initiated in 2003 by the three German professional associations of heart medicine [Deutsche Gesellschaft für Pädiatrische Kardiologie (DGPK), Deutsche Gesellschaft für Thorax-, Herz und Gefäßchirurgie (DGTHG), Deutsche Gesellschaft für Kardiologie (DGK)] as a non-profit, scientific association and is currently funded by the German Centre for Heart and Circulatory Research [Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK)]. Currently, the NRCHD has about 56,000 patients with CHD of all severity classes and age groups registered. The NRCHD is thus the largest CHD register in Europe (8). The multi-centre research approach of the NRCHD makes a nationwide retrospective and prospective representative data analysis and evaluation of CHD related medical data possible. As Helm *et al.* (2015) could show, the NRCHD is particularly suitable for such questions due to its representativeness (8). The established data infrastructure of the NRCHD allows data to be stored within the framework of a specific data-protection concept, which is registered with the Berlin Official for Data Protection and Freedom of Information (Nr. 531.390). General approval of the ethical review board of the Charité – Universitätsmedizin Berlin is given for all research conducted within the scope of the NRCHD.

When a child is born with CHD in Germany, the

parents have the opportunity to register their child in the NRCHD. This registration is voluntary, free of charge and membership can be revoked at any time without stating reasons. After registration patients and relatives regularly receive information in layman's terms about the state of research in the field of CHD, and they can voluntarily participate in studies and patient surveys. They also have the opportunity to give a biospecimen (saliva, blood) so that scientists can investigate possible genetic causes of CHD. The NRCHD cooperates closely with patient organizations, resident pediatric cardiologists and cardiologists, hospitals, university clinics and special heart centres. NRCHD's medical database is based on patient data from medical reports (e.g., doctor's letters, operation reports). These medical patient data are collected by specially trained medical documentaries and medical specialists and checked for plausibility and, if necessary, corrected and regularly checked for topicality. Patients whose medical data were not classified as sufficiently secured/up-to-date at the time the data analyses were carried out were excluded from the analyses. The underlying medical documents are usually primarily cardiological medical reports. Information about, for example, drastic, non-medical or life events is only available to the NRCHD if this has also been noted in the medical records. The collected and evaluated medical data correspond to the highest standard for the evaluation of decentralized, multi-centre evidence-based data analysis.

Study population

Adolescents and young ACHD between 15 and 25 years of age (which have been defined as the transition generation) were identified using the NRCHD medical database on 12 February 2020. Out of a total of 55,687 registered patients with CHD, 11,262 (20.2%) were identified between the age of 15–25 years [5,233 female (46.5%)]. After deceased patients had been excluded and the clinically proven completeness of the data had been verified, 8,834 adolescents and young ACHD [4,063 female (46.0%)] remained for statistical analysis. The Bethesda classification by Warnes *et al.* was used to categorise the severity of the CHD (9). The severity groups, simple, moderate and complex CHD were compared regarding the prevalence of SD of clinical interest across the severity groups during the transition phase.

The primary cardiac diagnosis, as well as the cardiac acquired SD, was defined and classified by using the International Paediatric and Congenital Cardiac Code (IPCCC) (10) as well as the ICD-10 classification for extracardiac acquired diagnosis (11). The detailed classification of the CHD severity (available at https://cdn.amegroups.cn/static/public/cdt-2020-achd-31-1.pdf), the IPCCC diagnoses (available at https://cdn.amegroups.cn/static/public/cdt-2020-achd-31-2.pdf) and the ICD-10 diagnoses (available at https://cdn.amegroups.cn/static/public/cdt-2020-achd-31-3.pdf) can be found in the Appendix. In the context of this work, the term acquired SD serves as an overarching term that includes sequelae, residual disease as well as comorbidities.

Statistical analyses

For categorical variables, descriptive statistics were calculated in absolute and relative frequencies (%), in numerical variables means and standard deviations. The Shapiro-Wilk test was used to test for normal distribution and group comparison was performed using student's *t*-test, χ^2-test as well as Fisher's exact test.

Alpha error adjustment in multiple comparisons was not performed due to the explorative and descriptive nature of the study, and to avoid overlooking potential influencing factors (12). Statistical analyses were conducted using the software SPSS V.25 (SPSS Inc., Chicago, Illinois, USA). The level of statistical significance was determined two-sided and with a P value <0.05.

Results

The majority of adolescents and young ACHD were of moderate CHD severity (45.1%) followed by complex CHD (31.5%) and simple CHD (23.4%), with a close to an identical mean age of 20.3±3.1 years (*Table 1*). Female overall accounted for 4,063 (46.0%) adolescents and young ACHD with significantly more female patients in the simple CHD group (55.9%) compared to the moderate (45.9%) and complex (38.7%) severity groups (P<0.001). Overall, the most common defects were 1,317 (14.9%) atrial septal defects (ASD) followed by 1,129 (12.8%) ventricular septal defects (VSD) then 929 (10.5%) tetralogy of Fallot (TOF). The most common CHD diagnoses in patients with simple CHD was ASD (36.4%), coarctation of the artery (CoA) (18.1%) in patients with moderate CHD and univentricular heart (UVH) (26.0%) in the complex CHD patient group (*Table 1*).

Further details on surgical and interventional procedures are shown in *Table 1*. Regarding structural heart defect

Table 1 Descriptive data of the transition generation of CHD patients in Germany

Variable	Total number of patients	Simple severity by Warnes *et al.*	S *vs.* M P value	Moderate severity by Warnes *et al.*	M *vs.* C P value	Complex severity by Warnes *et al.*	S *vs.* C P value
Number of Patients	8,834	2,067 (23.4%)	–	3,987 (45.1%)	–	2,780 (31.5%)	–
Age (years)	20.3±3.1	20.1±3.1	0.086	20.3±3.1	0.857	20.3±3.1	0.086
Sex, female (%)	4,063 (46.0%)	1,156 (55.9%)	<0.001#	1,832 (45.9%)	<0.001#	1,075 (38.7%)	<0.001#
Most frequent CHD-diagnoses (>10% of the group)*	VSD: 1,317 (14.9%); ASD: 1,129 (12.8%); TOF: 929 (10.5%)	ASD: 735 (36.4%); VSD: 615 (29.8%); AoV: 252 (12.2%)	–	CoA: 723 (18.1%); VSD: 577 (14.5%); AVSD: 429 (10.8%)	–	UVH: 722 (26.0%); TGA: 605 (21.8%); TOF: 504 (18.1%)	–
Number of surgeries[a]	3.3±2.7 (1/22)	1.3±0.6 (1/3)	<0.001#	2.3±1.7 (1/22)	<0.001#	4.6±3.0 (1/22)	<0.001#
Age at first surgery	2.0±3.0	3.7±3.7	<0.001#	2.7±4.4	<0.001#	1.2±3.2	<0.001#
Number of catheter interventions[a]	2.1±2.1 (1/24)	1.1±0.3 (1/3)	<0.001#	1.5±1.2 (1/24)	<0.001#	2.8±2.6 (1/24)	<0.001#
Age at first catheter intervention	5.5±5.8	7.3±4.7	<0.001#	6.3±6.1	<0.001#	4.6±6.0	<0.001#
Prematurity	339 (3.8%)	82 (4.0%)	0.804	153 (3.8%)	0.838	104 (3.7%)	0.685

*, Appendix A (available at https://cdn.amegroups.cn/static/public/cdt-2020-achd-31-1.pdf) with detailed information on the classification by Warnes *et al.*; [a], following the definition of the International Paediatric and Congenital Cardiac Code (IPCCC); #, P<0.05. CHD, congenital heart defect; S, simple; M, moderate; C, complex; P, level of significance with P≤0.05; VSD, ventricular septum defect; ASD, atrial septum defect; CoA, coarctation of the artery; UVH, univentricular heart; TGA, transposition of the great arteries; AoV, aortic valve stenosis; AVSD, atrioventricular septal defect; TOF, tetralogy of Fallot.

groups, septal defects/vascular malformations showed 40.6% the highest proportion followed by left heart obstruction with 19.7% overall (*Table 2*). An accurate allocation of heart defect groups adapted from Schumacher *et al.* can be found in Appendix B (available at https://cdn.amegroups.cn/static/public/cdt-2020-achd-31-2.pdf) (13).

As shown in *Table 1*, there was no difference in the severity of CHD in preterm births.

Almost 9.4% [832] of the patients had chromosomal abnormalities and other genetic syndromes, with trisomy 21 (55.5%) being the most frequent, followed by DiGeorge syndrome (*Table 3*).

Cardiac acquired SD

The most frequent cardiac acquired SD was arrhythmia with 2,225 (25.5%) cases in the transition group and with a frequency that more than doubles from severity class to severity class (*Table 3*). With 43.8% arrhythmia occurred the most often in the right heart obstruction group followed by patients with UVH 35.6% (*Table 2*).

Secondly, pulmonary hypertension occurred in 401 (4.5%) cases and thirdly systemic arterial hypertension in 316 (3.6%) adolescents and young ACHD. Concerning pulmonary hypertension highest prevalence was shown in patients with septal defects/vascular malformation at 6.9% followed by UVH patients at 6.0%. Systemic arterial hypertension showed the highest prevalence in patients with left heart obstruction at 11.3% followed by UVH patients at 4.0% (*Table 2*).

Extracardiac acquired SD

In extracardiac acquired SD patients had neurological SD overall in 643 (7.3%) cases, followed by musculoskeletal SD with 607 (6.9%) and psychological SD with 497 (5.6%). Further details on extracardiac acquired SD are shown in *Table 3*. The highest prevalence of extracardiac acquired SD were shown in UVH patients in all analysed aspects except in metabolic SD left heart obstruction patients had a higher prevalence, in "ear, nose and throat" SD had a higher prevalence in patients with right heart obstruction, and "lung" SD in patients with "other" as defect group (*Table 2*).

Figure 1 shows the cardiac acquired SD with their prevalence among the CHD severity classes with a frequency of up to 4 cardiac acquired SD. *Figure 2* shows the prevalence of extracardiac acquired SD among the severity classes and a frequency of up to 7 extracardiac

Table 2 Prevalence of extracardiac and cardiac acquired secondary diagnoses according to heart defect groups*

Variable	Septal defects/vascular malformation	Right heart obstruction	Left heart obstruction	Transposition of great arteries	Univentricular heart	Other
Total number 8,834, n (%)	3,586 (40.6)	1,538 (17.4)	1,736 (19.7)	701 (7.9)	722 (8.2)	551 (6.2)
Prevalence of extracardiac acquired secondary diagnoses, n (%)						
Lung	146 (4.1)	60 (3.9)	65 (3.7)	24 (3.4)	51 (7.1)	42 (7.6)^
Renal	44 (1.2)	41 (2.7)	34 (2.0)	9 (1.3)	32 (4.4)^	6 (1.1)
Liver	8 (0.2)	14 (0.9)	10 (0.6)	3 (0.4)	35 (4.8)^	1 (0.2)
Gastroenterological	73 (2.0)	27 (1.8)	31 (1.8)	5 (0.7)	38 (5.3)^	7 (1.3)
Metabolic	148 (4.1)	57 (3.7)	96 (5.5)^	15 (2.1)	25 (3.5)	14 (1.5)
Endocrinologic	116 (3.2)	46 (3.0)	36 (2.1)	5 (0.7)	27 (3.7)^	8 (1.5)
Neurological	179 (5.0)	149 (9.7)	100 (5.8)	58 (8.3)	118 (16.3)^	39 (7.1)
Psychological	152 (4.2)	106 (6.9)	100 (5.8)	34 (4.9)	69 (9.6)^	36 (6.5)
Musculoskeletal	189 (5.3)	144 (9.4)	98 (5.6)	38 (5.4)	94 (13.0)^	44 (8.0)
Haematologic	64 (1.8)	30 (2.0)	29 (1.7)	10 (1.4)	47 (6.5)^	10 (1.8)
Peripheral vascular	16 (0.4)	17 (1.1)	13 (0.7)	5 (0.7)	26 (3.6)^	2 (0.4)
Neoplasm/oncological	11 (0.3)	4 (0.3)	4 (0.2)	1 (0.1)	5 (0.7)^	1 (0.2)
Eye	51 (1.4)	22 (1.4)	24 (1.4)	9 (1.3)	24 (3.3)^	12 (2.2)
Ear, nose and throat	48 (1.3)	42 (2.7)^	29 (1.7)	14 (2.0)	19 (2.6)	9 (1.6)
Gynaecological, obstetrics	8 (0.2)	6 (0.4)	8 (0.5)	0	4 (0.6)^	2 (0.4)
Prevalence of cardiac acquired secondary diagnoses, n (%)						
Heart failure	22 (0.6)	7 (0.5)	22 (1.3)	8 (1.1)	13 (1.8)	12 (2.2)^
Arrhythmia	693 (19.3)	674 (43.8)^	265 (15.3)	209 (29.8)	257 (35.6)	127 (23.0)
Coronary artery disease	3 (0.1)	1 (0.1)	2 (0.1)	5 (0.7)	1 (0.1)	5 (0.9)^
Pulmonary hypertension	248 (6.9)^	45 (2.9)	50 (2.9)	9 (1.3)	43 (6.0)	6 (1.1)
Systemic arterial hypertension	30 (0.8)	24 (1.6)	197 (11.3)^	19 (2.7)	29 (4.0)	17 (3.1)
Thrombo-embolic events	31 (0.9)	47 (3.1)	29 (1.7)	18 (2.6)	81 (11.2)^	8 (1.5)
Infective endocarditis	29 (0.8)	45 (2.9)^	16 (0.9)	10 (1.4)	3 (0.4)	6 (1.1)

*, the one-to-one classification according to the IPCCC can be found in Appendix B (available at https://cdn.amegroups.cn/static/public/cdt-2020-achd-31-2.pdf); ^, the highest prevalence rates. IPCCC, International Paediatric and Congenital Cardiac Code.

acquired SD.

Discussion

An estimated 1.35–1.5 million children worldwide are born with CHD every year, 45% of them with moderate or complex CHD, 55% with simple CHD (14). All kinds of CHD increased in adults to 55% of all patients with CHD from the year 2000 to 2010 in Quebec with an increased prevalence of severe CHD (1). In our present nationwide study, results for Germany show a larger proportion of adolescents and young ACHD in the moderate and complex severity class of CHD than in the simple heart defects group. Plausible reasons for the increased prevalence of severe CHD in adolescents and young adults are improvements in diagnostic procedures, interventional and medical treatments that have led to reduced mortality in recent decades.

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Table 3 Prevalence of acquired secondary diagnoses in the CHD transition population

Diagnoses	Total number of patients (n=8,834)	Simple severity (n=2,067)	S *vs.* M P value	Moderate severity (n=3,987)	M *vs.* C P value	Complex severity (n=2,780)	S *vs.* C P value
Acquired cardiac diagnoses, n (%)							
Heart failure	84 (1.0)	0	<0.001#	37 (0.9)	0.005#	47 (1.7)	<0.001#
Arrhythmia	2,225 (25.5)	185 (9.0)	<0.001#	873 (21.9)	<0.001#	1,167 (42.0)	<0.001#
Coronary artery disease	17 (0.2)	3 (0.2)	1.000[a]	6 (0.2)	0.221	8 (0.3)	0.372[a]
Pulmonary hypertension	401 (4.5)	0	0.001#	23 (0.6)	<0.001#	378 (13.6)	<0.001#
Systemic arterial hypertension	316 (3.6)	15 (0.7)	<0.001#	202 (5.1)	0.003#	99 (3.6)	<0.001#
Thrombo-embolic events	214 (2.4)	4 (0.2)	<0.001#	45 (1.1)	<0.001#	165 (5.9)	<0.001#
Infective endocarditis	109 (1.2)	0	0.011[a]#	12 (0.3)	<0.001#	97 (3.5)	<0.001#
Chromosomal anomalies and other genetic syndromes, n (%)							
Total	832 (9.4)	114 (5.5)	–	475 (11.9)	–	243 (8.7)	–
Trisomy 21	462 (55.5)	74 (64.9)	–	275 (57.9)	–	113 (46.5)	–
DiGeorge 22q11	138 (16.6)	5 (4.4)	–	53 (11.2)	–	80 (32.9)	–
Williams-Beuren	39 (4.7)	1 (0.9)	–	36 (7.6)	–	2 (0.8)	–
Noonan	35 (4.2)	5 (4.4)	–	27 (5.7)	–	3 (1.2)	–
Other	158 (19.0)	29 (25.4)	–	84 (17.7)	–	45 (18.5)	–
Acquired extracardiac diagnoses*, n (%)							
Lung	388 (4.4)	57 (2.8)	0.013#	160 (4.0)	<0.001#	171 (6.2)	<0.001#
Renal	166 (1.9)	15 (0.7)	0.003#	66 (1.7)	<0.001#	85 (3.1)	<0.001#
Liver	71 (0.8)	2 (0.1)	0.241[a]	11 (0.3)	<0.001#	58 (2.1)	<0.001#
Gastroenterological	181 (2.0)	19 (0.9)	0.010#	70 (1.8)	<0.001#	92 (3.3)	<0.001#
Metabolic	355 (4.0)	70 (3.4)	0.081	172 (4.3)	0.615	113 (4.1)	0.221
Endocrine	238 (2.7)	25 (1.2)	<0.001#	110 (2.8)	0.192	91 (3.3)	<0.001#
Peripheral vascular	79 (0.9)	1 (0.1)	0.004#	20 (0.5)	<0.001#	58 (2.1)	<0.001#
Neoplasm/oncological	26 (0.3)	8 (0.4)	0.356	10 (0.3)	0.772	8 (0.3)	0.551
Neurological	643 (7.3)	67 (3.2)	<0.001#	229 (5.7)	<0.001#	347 (12.5)	<0.001#
Psychological	497 (5.6)	73 (3.5)	0.007#	202 (5.1)	<0.001#	222 (8.0)	<0.001#
Gynaecological, obstetrics	28 (0.3)	4 (0.2)	0.783[a]	10 (0.3)	0.098	14 (0.5)	0.079
Musculoskeletal	607 (6.9)	72 (3.5)	<0.001#	229 (5.7)	<0.001#	306 (11.0)	<0.001#
Haematological	190 (2.2)	29 (1.4)	0.934	57 (1.4)	<0.001#	104 (3.7)	<0.001#
Ear, nose and throat	161 (1.8)	22 (1.1)	0.068	66 (1.7)	0.006#	73 (2.6)	<0.001#
Eye	142 (1.6)	26 (1.3)	0.816	53 (1.3)	0.003#	63 (2.3)	0.010#

*, Appendix C (available at https://cdn.amegroups.cn/static/public/cdt-2020-achd-31-3.pdf) with detailed allocation based on ICD-10 categorization; [a], the expected value was below 5, therefore, the Fischer's exact test was used instead of χ^2; #, P<0.05. n, number; CHD, congenital heart defect; S, simple; M, moderate; C, complex; P, level of significance with P≤0.05.

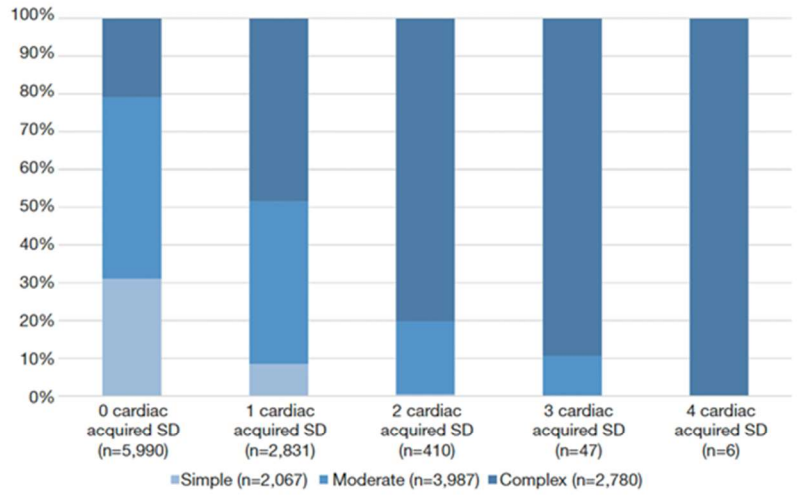

Figure 1 Distribution of cardiac acquired secondary diagnoses within the CHD severity class displayed in percentages. SD, secondary diagnosis; n, number; CHD, congenital heart defect.

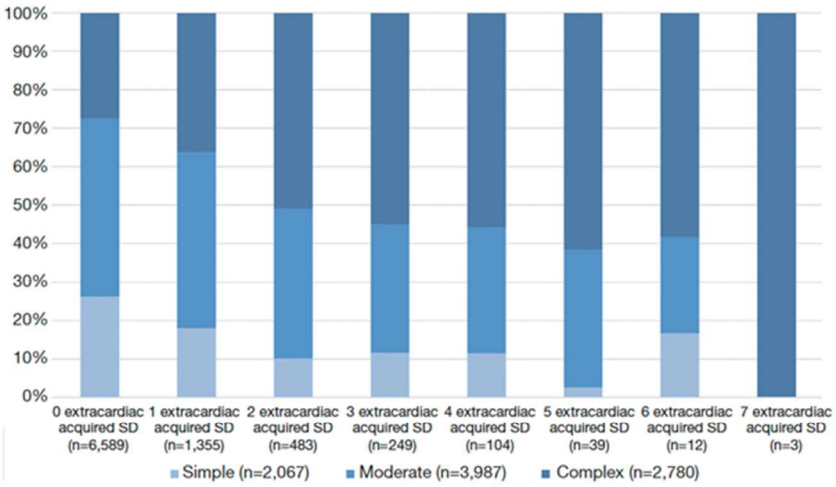

Figure 2 Distribution of extracardiac acquired secondary diagnoses within the CHD severity class displayed in percentages. SD, secondary diagnosis; n, number; CHD, congenital heart defect.

Regarding preterm birth rates, there is an increase during the last decades in Europe (15) which accounts for 5–12%. CHD is one of the most frequent malformation causing preterm birth with two times higher frequency than full-term infants (16). Therefore, we decided to include this clinical parameter in the baseline characteristics. Interestingly, in our study population, there was no difference in the preterm birth rates between the different severity groups. With about 4%, the preterm birth rate was even lower than in the normal German population [1990: 7.2%, 2010: 8.6%; (17)].

Cardiac acquired SD

In our transition group, even though the patient cohort was still young, more than a quarter of all investigated

patients had arrhythmia. Arrhythmias were significantly increased from 9% in simple CHD to 42% in adolescents and young ACHD with complex CHD. The largest proportion of arrhythmia patients occurred in the group of right heart obstruction CHD (43.8%) followed by patients with univentricular circulation (35.6%). The majority of patients showed a complete right bundle branch block (42.3%) followed by 1st degree atrioventricular block (9.8%). Arrhythmias are known to be the main reason for the hospitalization of ACHD and they are an increasingly frequent cause of mortality (18,19).

Cardiac acquired SD, such as coronary artery disease and heart failure, are quite important to treat adequately, as they often occur in ACHD (20) and are strong predictors of poor outcome (21). But not in our transition group, this may depend on these cardiac acquired SDs occur in older ages. Whereas almost 14% with complex CHD was suffering from pulmonary hypertension. In our study, thrombo-embolic events and infective endocarditis occurred significantly more often, the higher the severity class. In summary, in patients with simple CHD, the most important cardiac acquired SD is arrhythmia. Whereas all other cardiac acquired diagnoses we investigated were not relevant for this patient group at this age or rather, they lead to the patients moving to higher severity class, e.g., development of Eisenmenger syndrome (9).

Patients with complex CHD do have more cardiac acquired diagnoses even at an adolescent age, the most frequent still being arrhythmia. However, even in this patient group, pulmonary hypertension, thromboembolic events, systemic arterial hypertension and infective endocarditis are relevant cardiac acquired SD (*Figure 1*).

Extracardiac acquired SD

It was investigated whether extracardiac acquired SD already play a role in adolescents and young ACHD going through the transition period. Common extracardiac acquired SD in ACHD are renal disease (22), lung disease (23), liver disease, neoplasms (catheter- and imaging-related), as well as psychological (anxiety, depression, neurocognitive delays) and pregnancy-related issues (24). Regarding the extracardiac acquired SD in our transition group, the most common acquired diagnoses of the adolescent and young ACHD involved the neurological (7.3%) or musculoskeletal (6.9%) system (both including developmental delays).

With the third-highest proportion of extracardiac acquired SD, psychological disorders, including neurocognitive delays (5.6%), are significant for adolescent and young ACHD followed by the lungs and the metabolic system.

Whereas gynecologic and obstetrical issues are known to be important problems for females with CHD (25), they didn't play a major role in our transition group. The young age of our transition group could be one reason, as obstetric problems do not occur until the first birth in the mid-20s to 30s (26). Almost all acquired extracardiac acquired SD became more frequent, the higher the severity class.

As *Table 2* shows patients with UVH presenting the highest prevalence in close to all extracardiac acquired SD. Except in metabolic SD, the group of left-heart obstructions showed the highest prevalence. Neidenbach *et al.* (2018), in their study cohort of ACHD with an age range of 15.5 to 80.0 years, reported metabolic comorbidities in 44% ACHD (25). This is in strong contrast to our younger transition group with a prevalence of 4% overall. This implies that the transition age plays an increasingly important role, as it is the chance to avoid this 40% increase in metabolic diseases.

Fortunately, oncological diseases were rare in our transition group and their prevalence did not vary between the CHD severity classes. A recent NRCHD-register study from 2016 showed that malignancies were the cause of death in 5% of ACHD (27), but in our study, the age range was limited due to the focus on transition-aged CHD patients. Another reason for the low incidence of oncological SD is the fact that most patients possibly develop thyroid cancer later than 20 years after exposure to low-dose radiation (28).

Concerning extracardiac acquired SD, it can be summarised that; on the one hand, the transition group under consideration already had up to seven extracardiac acquired SD (*Figure 2*). Also, the transition group showed most of the extracardiac acquired SD, which mostly occur in older age, lower prevalent, but existing. Especially neurological SD often occur in combination with psychological components and musculoskeletal limitations. For other extracardiac acquired SD especially in metabolic diseases, the transition age seems to be an important approach for preventive strategies to avoid a loss to follow-up.

The current medical care situation in Germany was investigated in 2017 by a survey in ACHD; most of the patients stated that they were mainly treated by an ACHD clinic (25%), a pediatric cardiologist in private practice (33%), or an adult cardiologist in private practice (32%). But there were almost 10% of the surveyed patients were not treated by any of the former physicians for their CHD. In the group of simple CHD, this number even went up to

18% (29). Seidel *et al.* were also found to report very similar results in a recent publication in 2020 (30). Our study data prove that there is a need for structured programmes that enable and/or ensure a successful transition as was recommended in the latest European Society of Cardiology (ESC) guidelines on ACHD (31). There are transition projects around the world, e.g., structured education programs (32), nurse-led interventions improving CHD knowledge (33) or the development of a mobile app to reach children and young adults (34), and they show promising results. Further development to establish a smooth and well-functioning transition process in Germany is still needed.

Conclusions

As this NRCHD analysis showed, adolescents and young ACHD had up to four cardiac acquired SD and up to seven extracardiac acquired SD. These findings show the clinical relevance of this transition phase for adolescents and young ACHD and underlines the importance of this age as a suitable starting point for targeted prevention strategies. For adolescents and young ACHD, there is an urgent need to bridge the gap between paediatric and adult cardiology and to find sustainable strategies to not lose these young patients in this transitional phase. Otherwise, early detection of acquired SD, which affects the lives of adolescents and young ACHD, will fail with all its consequences.

Limitations

Due to the registration process of the NRCHD, we included only patients with clinically apparent CHD and available medical data. This may lead to an underrepresentation of simple, clinical unapparent CHD and we cannot rule out that the rate of moderate and complex CHD is overestimated.

This study is a cross-sectional retrospective registry study, therefore, relations of cause and effect cannot be concluded. As previous studies also showed differences due to study setting and location, the results should be generalized to patients beyond Germany only with caution.

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Footnote

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***Appendix A:* CHD severity classification by Warnes et al.**

SIMPLE	MODREATE	COMPLEX
• Native disease • Isolated congenital aortic valve disease • Isolated congenital mitral valve disease (e.g., except parachute valve, cleft leaflet) • Isolated patent foramen ovale or small atrial septal defect • Isolated small ventricular septal defect (no associated lesions) • Mild pulmonic stenosis • Repaired conditions • Previously ligated or occluded ductus arteriosus • Repaired secundum or sinus venosus atrial septal defect without residua • Repaired ventricular septal defect without residua	• Aorto-left ventricular fistulae • Anomalous pulmonary venous drainage, partial or total • Atrioventricular canal defects (partial or complete) • Coarctation of the aorta • Ebstein's anomaly • Infundibular right ventricular outflow obstruction of significance • Ostium primum atrial septal defect • Patent ductus arteriosus (not closed) • Pulmonary valve regurgitation (moderate to severe) • Pulmonic valve stenosis (moderate to severe) • Sinus of Valsalva fistula/aneurysm • Sinus venosus atrial septal defect • Subvalvar or supravalvar aortic stenosis (except HOCM) • Tetralogy of Fallot • *Ventricular septal defect with* . Absent valve or valves . Aortic regurgitation . Coarctation of the aorta . Mitral disease . Right ventricular outflow tract obstruction . Straddling tricuspid/mitral valve . Subaortic stenosis	• Conduits, valved or nonvalved • Cyanotic congenital heart (all forms) • Double-outlet ventricle • Eisenmenger syndrome • Fontan procedure • Mitral atresia • Single ventricle (also called double inlet or outlet, • common or primitive) • Pulmonary atresia (all forms) • Pulmonary vascular obstructive diseases • Transposition of the great arteries • Tricuspid atresia • Truncus arteriosus/hemitruncus • Other abnormalities of atrioventricular or ventriculo arterial connection not included above (i.e., crisscross heart, isomerism, heterotaxy syndromes, ventricular inversions)

Appendix B: Allocation of the International Paediatric and Congenital Cardiac Codes into heart defect groups adapted from Schumacher et al.

The International Paediatric and Congenital Cardiac Code (IPCCC)	
Septal defects / vascular malformation	
IPCCC	**Principal cardiac diagnoses**
01.01.16	Partially anomalous pulmonary venous connection of Scimitar type,
04.06.00	Totally anomalous pulmonary venous connections: supracardiac,
04.07.01	Partially anomalous pulmonary venous connection(s),
04.08.05	Totally anomalous pulmonary venous connection,
04.08.10	Totally anomalous pulmonary venous connections: intracardiac,
04.08.20	Totally anomalous pulmonary venous connections: infracardiac,
04.08.30	Totally anomalous pulmonary venous connections: mixed,
05.04.01	Interatrial communication ('ASD'),
05.04.02	Atrial septal defect (ASD) within oval fossa (secundum),
05.04.03	Spontaneous closure of atrial septal defect (ASD) within oval fossa (secundum),
05.05.00	Sinus venosus defect (ASD),
05.05.03	Interatrial communication (ASD) through coronary sinus orifice,
06.06.00	Atrioventricular septal defect (AVSD),
06.06.01	Partial atrioventricular septal defect (AVSD) with isolated atrial component (primum ASD),
06.06.08	Atrioventricular septal defect (AVSD) with isolated ventricular component,
06.06.09	Complete atrioventricular septal defect (AVSD) with atrial and ventricular components,
06.06.10	Intermediate atrioventricular septal defect (AVSD) with atrial and ventricular components and separate atrioventricular valvar orifices,
07.10.00	Ventricular septal defect (VSD),
07.10.01	Perimembranous ventricular septal defect (VSD),
07.10.12	Ventricular septal defect (VSD) with malaligned outlet septum,
07.11.01	Muscular ventricular septal defect (VSD),
07.12.00	Subarterial (outlet) ventricular septal defect (VSD),
07.12.01	Doubly committed subarterial ventricular septal defect (VSD),
07.14.02	Communication between left ventricle + right atrium (Gerbode defect),
07.14.05	Inlet ventricular septal defect (VSD),
07.15.01	Ventricular septal defect(s): haemodynamically insignificant,
07.15.04	Multiple ventricular septal defect (VSD)s,
07.16.01	Spontaneous closure of ventricular septal defect (VSD),
09.01.01	Common arterial trunk (truncus arteriosus),
09.04.01	Aortopulmonary window,
09.08.01	Major systemic-to-pulmonary collateral artery(ies) (MAPCA(s)),
09.09.08	Pulmonary artery from ascending aorta (hemitruncus),
09.17.02	Aorto: left ventricular tunnel,
09.19.01	Arteriovenous fistula (malformation),
09.27.21	Patent arterial duct (PDA),
05.06.01	Common atrium (virtual absence of atrial septum),
09.19.05	Pulmonary arteriovenous fistula (malformation),
Right heart obstruction	
IPCCC	**Principal cardiac diagnoses**
01.01.01	Tetralogy of Fallot,
01.01.06	Pulmonary atresia + ventricular septal defect (VSD) (including Fallot type),
01.01.07	Pulmonary atresia + intact ventricular septum,
01.01.17	Double outlet right ventricle: Fallot type (subaortic or doubly committed ventricular septal defect & pulmonary stenosis),
01.01.20	Atrioventricular septal defect and Tetralogy of Fallot,
01.01.25	Pulmonary atresia + ventricular septal defect (VSD) + systemic-to-pulmonary collateral artery(ies) (MAPCA(s)),

06.01.03	Tricuspid valvar dysplasia,
06.01.34	Ebstein malformation of tricuspid valve,
07.03.01	Double chambered right ventricle,
07.05.01	Right ventricular outflow tract obstruction,
09.05.04	Congenital pulmonary valvar stenosis,
09.05.11	Pulmonary atresia,
09.05.12	Pulmonary atresia: imperforate valve,
09.05.25	Absent pulmonary valve syndrome: Fallot-type,
09.05.92	Pulmonary stenosis,
09.07.13	Supravalvar pulmonary trunk stenosis,
09.07.26	Solitary arterial trunk (absent intrapericardial pulmonary arteries),
09.10.01	Pulmonary arterial stenosis,
09.10.06	Peripheral pulmonary arterial stenoses or hypoplasia: at-beyond hilar bifurcation,
09.10.07	Central pulmonary arterial stenosis or hypoplasia: proximal to hilar bifurcation,
09.10.11	Pulmonary arterial hypoplasia,
06.01.92	Tricuspid stenosis,
09.05.32	Bicuspid pulmonary valve,
09.10.10	Discontinuous (non-confluent) right and left pulmonary arteries,
Left heart obstruction	
IPCCC	**Principal cardiac diagnoses**
01.01.33	Left heart obstruction at multiple sites (including Shone syndrome),
05.02.01	Cor triatriatum (divided left atrium),
06.02.07	Congenital mitral valvar stenosis,
07.09.00	Subaortic stenosis,
07.09.01	Left ventricular outflow tract obstruction,
07.09.03	Subaortic stenosis due to fibromuscular shelf,
09.15.01	Congenital aortic valvar stenosis,
09.15.12	Eccentric opening of tricuspid aortic valve,
09.15.21	Unicuspid aortic valve
09.15.22	Bicuspid aortic valve,
09.15.92	Aortic stenosis,
09.16.00	Supravalvar aortic stenosis,
09.16.02	Ascending aorta hypoplasia,
09.29.01	Aortic coarctation,
09.29.11	Aortic arch hypoplasia (tubular),
09.29.16	Descending-abdominal aorta hypoplasia (middle aortic syndrome),
09.29.31	Interrupted aortic arch,
10.10.20	Hypertrophic cardiomyopathy,
05.02.02	Supravalvar or intravalvar mitral ring,
06.02.56	Parachute malformation of mitral valve,
Transposition of great arteries	
IPCCC	**Principal cardiac diagnoses**
01.01.02	Transposition of great arteries (TGA) (concordant atrioventricular & discordant ventriculo-arterial connections) & intact ventricular septum,
01.01.03	Congenitally corrected transposition of great arteries (discordant atrioventricular & ventriculo-arterial connections),
01.05.01	Transposition of great arteries (discordant ventriculo-arterial connections) (TGA),
Univentricular heart	
IPCCC	**Principal cardiac diagnoses**
01.01.04	Double outlet right ventricle,
01.01.09	Hypoplastic left heart syndrome,
01.01.14	Double inlet atrioventricular connection (double inlet ventricle),
01.01.18	Double outlet right ventricle: transposition type (subpulmonary ventricular septal defect),

01.01.19	Double outlet right ventricle: with non-committed ventricular septal defect,
01.01.22	Functionally univentricular heart,
01.04.03	Double inlet right ventricle,
01.04.04	Double inlet left ventricle,
01.05.03	Double outlet left ventricle,
02.03.05	Solitary ventricle of indeterminate morphology,
06.01.01	Tricuspid atresia,
06.02.01	Mitral atresia,
06.07.26	Atrioventricular septal defect (AVSD) with ventricular imbalance,
09.15.03	Aortic atresia,
09.45.11	Coronary fistulas within right ventricle ('sinusoidal'),
09.46.06	Right ventricle dependent coronary circulation,
Other	
IPCCC	**Principal cardiac diagnoses**
04.01.01	Left superior caval vein (SVC) persisting to coronary sinus,
05.03.00	Atrial septum abnormality,
05.03.03	Aneurysm of fossa ovalis
06.01.00	Tricuspid valvar abnormality,
06.01.25	Congenital tricuspid regurgitation,
06.02.00	Mitral valvar abnormality,
06.02.25	Congenital mitral regurgitation,
06.02.35	Mitral valvar prolapse,
06.02.36	True cleft of mitral leaflet (without atrioventricular septal defect),
07.06.00	Left ventricular abnormality,
07.06.13	Left ventricular aneurysm,
07.08.05	Noncompaction cardiomyopathy
07.20.00	Ventricular septal abnormality,
07.20.01	Aneurysm of membranous septum,
09.05.00	Pulmonary valvar abnormality,
09.05.22	Congenital pulmonary regurgitation,
09.09.06	Anomalous origin of left pulmonary artery from right pulmonary artery (pulmonary arterial sling),
09.10.00	Pulmonary arterial abnormality,
09.15.00	Aortic valvar abnormality,
09.15.07	Congenital aortic regurgitation,
09.16.09	Ascending aorta dilation,
09.16.10	Ascending aorta abnormality,
09.18.01	Aortic sinus of Valsalva aneurysm,
09.20.20	Distal systemic arterial abnormality,
09.28.00	Aortic arch abnormality,
09.28.09	Double aortic arch,
09.28.15	Right aortic arch,
09.30.00	Aortic arch branch abnormality,
09.30.02	Aberrant origin right subclavian artery,
09.31.00	Vascular ring,
09.41.01	Anomalous origin of coronary artery from pulmonary arterial tree,
09.42.00	Anomalous aortic origin or course of coronary artery,
09.45.01	Coronary fistula,
09.46.00	Coronary arterial abnormality,
09.46.01	Coronary arterial aneurysm(s),
10.13.02	Idiopathic (primary) pulmonary hypertension,
11.06.16	Congenital complete heart block,
11.07.01	AV reciprocating (reentry) tachycardia: manifest preexcitation in sinus rhythm (Wolff Parkinson White),

11.07.06	Accessory pathway: retrograde conduction only (concealed: no preexcitation sinus rhythm),
11.07.11	Manifest accessory pathway,
11.12.01	Prolonged QT interval,
02.01.02	Dextrocardia: heart predominantly in right hemithorax,
04.01.00	Superior caval vein (SVC) abnormality,
04.04.00	Coronary sinus abnormality,
07.01.10	Arrhythmogenic right ventricular cardiomyopathy,
09.15.30	Aortic valvar prolapse,
09.27.00	Arterial duct (ductus arteriosus) abnormality,

Appendix C: Allocation of extracardiac acquired secondary diagnoses by ICD-10

Acquired extracardiac secondary diagnoses based on International Classification of Diseases and Health Related Problems		
System	**ICD-10 Code**	**ICD-10 Definition**
-Lung	J09-J99, excl. J30-J39	Diseases of the respiratory system
-renal	N00-N29	Diseases of the genitourinary system
-liver	K70-K77	Diseases of liver
-gastroenterological	K00-K93	Diseases of the digestive system
-metabolic	E08-13, E65-88	Overweight, obesity and other hyperalimentation
-endocrine	E00-E89	Endocrine and nutritional diseases
-peripheral vascular	I00-I99, excl. I20-I52	Diseases of the circulatory system
-neoplasm/oncological	C00-C96, D00-D49	Neoplasms
-neurological	G00-G99	Diseases of the nervous system
-psychological	F01-F99	Mental, Behavioral and Neurodevelopmental disorders
-gynaecological, obstetrics	O00-O99	Pregnancy, childbirth, and the puerperium
-musculoskeletal	M00-M99	Diseases of the musculoskeletal system and connective tissue
-haematological	D50-D89	Diseases of the blood and bloodforming organs
-ear, nose and throat	H60-H95, J00-J06, J30-J39	Diseases of the ear, mastoid process and upper respiratory system
-eye	H00-H59	Diseases of the eye and adnexa

In den jungen Jahren der Transition zeigten die Patienten mit AHF, über alle Herzfehlergruppen hinweg, eine Prävalenz von 7,3% für eine erworbene neurologische Nebendiagnose. Diese Prävalenz steigt bis 16,3% an bei Patienten mit einem univentrikulären Herz (UVH). Basierend auf den Ergebnissen der Evaluierung der Transitionsphase bei Patienten mit AHF, knüpfen die nachfolgenden Publikation II und III an.

In verschiedenen Studien bei Kindern mit AHF werden Zusammenhänge zwischen beeinträchtigten kognitiven und motorischen Fähigkeiten beschrieben, die mit Beschäftigungsmöglichkeiten sowie den Bildungsabschlüssen, aber auch der Lebensqualität in Verbindung gebracht werden.

Daher wurden in Publikation II, folgende Fragen zu NMHA erörtert:

=> Wie ist es bei EMAH um die kognitiven Fähigkeiten bestellt?

=> Wie ist es bei EMAH um die Lebensqualität bestellt?

=> Gibt es Assoziationen oder Interaktionen zwischen Lebensqualität, der Kognition und der Herzfehlerschwere?

5.2 Publikation II Neuromental-health Aspekte bei Erwachsenen mit AHF

„Neuromental-health aspects in adults with congenital heart disease after open heart surgery during childhood“

Autoren:

Julia Remmele, Milka Pringsheim, Nicole Nagdyman, Renate Oberhoffer-Fritz, Peter Ewert

Under review

Anteilserklärung Julia Remmele an der Publikation:

I Konzeption und Gestaltung: **JR**, NN, MP

II Administrative Unterstützung: ROF, PE

III Bereitstellung von Studienmaterialien oder Patienten: **JR**, NN, MP

IV Sammlung und Zusammenstellung der Daten: **JR**, NN, MP

V Analyse und Interpretation der Daten: **JR**

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VII Endgültiges Verfassen und Genehmigung des Manuskripts: Alle Autoren.

VIII Überarbeitung nach der peer-review Beurteilung: **JR**

Zudem war **JR** für die Patienten Rekrutierung, die Durchführung und die Auswertung der Tests verantwortlich.

Neuromental-health aspects in adults with congenital heart disease after open heart surgery during childhood

Julia Remmele, MSc[1,2], Milka Pringsheim, MD[1], Nicole Nagdyman, MD[1], Renate Oberhoffer-Fritz, MD[1,2], Peter Ewert, MD[1]

Affiliation:

[1] German Heart Center of Munich, Department of Congenital Heart Disease and Pediatric Cardiology, Munich, Germany

[2] Institute of Preventive Pediatrics Technical University Munich, Munich, Germany

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The authors have no conflicts of interest to declare.

Abstract

Objective:

It is often assumed, that adults with congenital heart defects (ACHD) have an impairment regarding their cognitive function and decreased health-related quality of life (HrQoL). In particular, it seems reasonable to assume that cyanosis may have a potential impact on cognitive function as well as surgical or drug treatment into adulthood. This study assesses neuromental-health aspects (NMHA) such as cognitive function and HrQoL in ACHD patients.

Patients and Methods:

Seventy-eight ACHD patients (female n=39 (50%); mean age at assessment 34.1±12.9 years; cyanotic CHD n=49 (62.8%) with a cyanosis duration of 159.8±196.2 month) who underwent open heart surgery as first intervention were asked to participate during routinely follow-up in 2018. NMHA were measured using Wechsler Intelligence Scale IV for cognitive function and the Medical Outcomes Study Questionnaire Short Form 36 Health Survey (SF-36) to assess HrQoL in ACHD.

Results:

IQ measures showed significant differences comparing never cyanotic and with a cyanotic phase in verbal comprehension (p=0.013). There was no association of cognitive function with cyanosis duration, number of surgery or catheter interventions, CHD severity and the timeframe of the first surgery. The group of early surgery showed significantly better results in the domain physical function (p=0.040) of HrQoL and in comparison with their assigned reference, both groups showed significantly reduced results in all domains except in bodily pain and mental health. Finally, full-scale IQ correlates with physical function in HrQoL.

Conclusions:

The results show positive news with normal cognitive function in ACHD. HrQoL was weak in comparison with the reference and there is an urgent need to improve the well-being of our ACHD with structured programmes, e.g. including physical activity programmes. This growing ACHD population should be focused in order of their needs and problems medical ones on one hand and on the other hand psychosocial matters.

Introduction

The first 3 years of life are very important in terms of child development. During this period, the typical developmental milestones are of greatest interest to be able to intervene with therapies if required (1, 2). The physical activities of a newborn are important to give the impulse for activating neurons, which is the base for building a neuronal network in the brain (3). The more frequently and diversely these neurons are used, the better and faster the connection via synaptic junctions will be established. Therefore motoric activity is important for development, especially in the first year of life because during this time the brain is particularly malleable and easily changeable (4). Some of the motions and movements that are not experienced during this age period are hard to recover or reinforce later (4). The necessary interruptions during this period by open heart surgery have a greater influence on the developing child with a congenital heart defect (CHD). The procedure under sedation, with the use of a heart-lung machine, the subsequent hospitalisation time and further treatment in the hospital are in themselves a massive interruption of early childhood development. Especially in children with CHD, from newborns to infancy, numerous studies have shown impairments in the development of speech, motor skills and cognitive function or executive function (5-12). Thanks to advances in pediatric cardiology, cardiac surgery or catheter interventions and aftercare during the last decades, mortality has dramatically decreased (13-15). Today more than 95% of children with CHD reach adulthood in western civilisation (16). This growing adult congenital heart disease (ACHD) population, is often assumed to have impairments regarding their cognitive function and decreased health-related quality of life (HrQoL). In particular, it seems reasonable to assume that cyanosis may have a potential impact on cognitive function as well as surgical or drug treatment into adulthood. To our best knowledge, less is known about neuromental-health aspects (NMHA) in an ACHD population including all kinds of CHD who underwent open heart surgery during childhood. Therefore, in this study, we investigated ACHD with all types of CHD after open heart surgery during their childhood regarding their cognitive function and HrQoL. We hypothesized that (I) the age at first surgery earlier or beyond the age of 3 years is associated with cognitive function as well as (II) cyanosis duration, number of surgeries and catheter interventional treatments and (III) potential associations between cognitive function and HrQoL in ACHD.

Patients and Methods

Study subjects

During 2018 seventy-eight ACHD patients (female n=39 (50.0%); mean age at assessment 34.1±12.9 years) with all kinds of CHD were routinely asked to complete IQ tests and fill in the SF-36 questionnaire during routine follow-up for this cross-sectional study. Inclusion criteria were legal age (>18 years), no interventional treatment or surgery during the past six months and surgical treatment of the CHD, exclusion was catheter-interventional treatment only in this analysis. Out of 100 ACHD patients, 2 patients were not interested and 4 reported time problems, 94 were willing to participate. Additionally, 16 patients were excluded due to they have had no surgery but catheter interventional repair. The severity class of CHD was split into simple, moderate and complex based on the American College of Cardiology (ACC) definition by Warnes et al. (17). The ACHD were divided into two categories; firstly, patients with one or more open heart surgery between newborn time and 3 years of age, secondly patients who underwent open heart surgery after the age of 3 years. The term cyanosis duration was defined from the date of birth until definitive or palliative repair, additionally for still cyanotic ACHD patients from the date of birth until the date of the test, in the case of Eisenmenger syndrome from the date of diagnosis until the date of the test. All patients gave written informed consent to participate voluntarily and agreed to the anonymous publication of their data. The study was following the Declaration of Helsinki (revision 2013). Approval from the local ethics board was obtained (Project Number 350/18 S).

Cognitive function

The current Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) (18) represents the gold standard in the assessment of cognitive function in adolescents and adults from 16 to 90 years (19). The WAIS-IV provides information about the intelligence quotient (IQ), once as the Full-Scale IQ (FSIQ) with four specific domains of intelligence; Verbal Comprehension (VC), Perceptual Reasoning (PR), Processing Speed (PS) and Working Memory (WM). The IQ scores are calculated out of 10 different core tests with different weights and adjusted for age by using the WAIS-IV software. Cognitive impairment is defined as an achieved IQ that deviates negatively

by more than one standard deviation (SD) from the norm (average IQ = 100, deviation-IQ = ± 1SD; IQ normal range = 85-115 IQ points) (18).
Additionally, the Wechsler Intelligence Scales for children are widely used in paediatric cardiology to identify impairments or changes in cognitive function (6, 7, 9, 20, 21) and therefore provide good opportunities for comparisons. The globally established test battery of the WAIS-IV was validated and updated in 2013 for the German normal population with a norming sample of 1,664 participants (22).

Health-related quality of life

The Medical Outcomes Study Questionnaire Short Form 36 Health Survey (SF-36) is based on patient self-report within the last 4-weeks and has been proven in various healthcare settings to assess or monitor HrQoL outcomes in adult patients (23). The SF-36 asks for information from patients on eight different dimensions of health-HrQoL (vitality, physical function, physical pain, general health perception, physical role function, emotional role function, social role function, and mental health). The questionnaire consists of Likert-scale questions as well as dichotomous questions; scaled values from 0 to 100 (poor to best health) are calculated for each dimension. The German version was validated by Bullinger and Kirchberger (24) and was implemented in this study. Based on Ellert and Kurth 2013, the ACHD were assigned the sex and age-specific norm data of the German population of the SF-36 for comparison (25).

Data analyses

Descriptive statistics were calculated in absolute and relative frequencies (%) for categorical variables, and means and SD for numerical variables. After testing normal distribution using Kolmogorov-Smirnov Test (26), Student's t-test was used for comparisons of means as well as paired Student's t-test. Linear regression model, general linear model and Pearson correlation were used to determine relationships between measurements and patient data.
All analyses were performed using the software SPSS V.27 (SPSS Inc., Chicago, Illinois, USA) or R software V. 3.3.1. Pirate plots were used for visualization of the data which represent the mean, confidence interval, raw data and density distribution. The level of statistical significance was determined as two-sided and with a p-value < 0.05.

Results

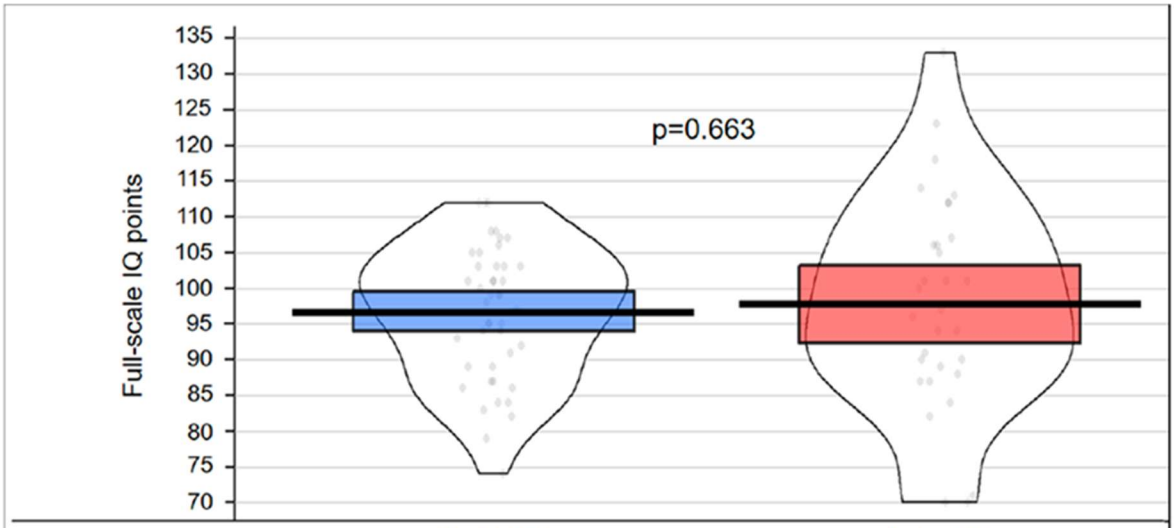
In total, the ACHD group is perfectly balanced in terms of sex but not in subgroups; the Early OP group shows more male patients at 53.3% and the Late OP group more females at 54.5%. The huge majority showed complex CHD followed by moderate CHD and the minority with simple CHD. Additionally, differences between the groups in terms of 'Age at first surgery' or cyanosis duration (Table1).

Table 1: Anthropometric data and group characteristics

	Total N=78	**Early OP n=45**	**Late OP n=33**
Age (years)	34.1±12.9	29.2±9.5	40.9±13.9
Sex	39 ♀ / 39 ♂ (50% / 50%)	21 ♀ / 24 ♂ (46.7% / 53.3%)	18 ♀ / 15 ♂ (54.5% / 45.5%)
CHD severity	Simple 11.5% Moderate 20.5% Complex 67.9%	Simple 4.4% Moderate 22.2% Complex 73.3%	Simple 21.2% Moderate 18.2% Complex 60.6%
Cyanosis duration (month)	159.8±196.2	52.8±51.3	280.9±228.3
Number of surgeries	3.1±11.7	3.6±2.3	2.3±1.5
Number of catheter-intervention	1.6±1.6	1.7±1.7	1.5±1.5
Age at first surgery (years)	6.8±11.7	0.45±0.5	15.4±14.1

n: number; CHD: congenital heart defect.

The cognitive function of the whole ACHD cohort showed a mean of 97.1±12.0 FSIQ. In a direct comparison between Early OP and Late OP groups, there was no significant difference found either in FSIQ or in subscales of the WAIS (Figure1).



IQ domain	Early OP (±SD)	p-value	Late OP (±SD)
Verbal comprehension IQ	97.7 ± 9.8	0.701	98.8 ± 14.1
Perceptual reasoning IQ	95.9 ± 11.4	0.409	98.5 ± 16.3
Working memory IQ	97.7 ± 13.5	0.923	97.4 ± 13.4
Processing speed IQ	99.5 ± 12.0	0.744	98.5 ± 14.8

Figure 1: Student's t-test for group comparison of IQ scores
IQ: Intelligence quotient; SD: standard deviation; level of significance p< 0.05.

The duration of cyanosis showed no significant association with all IQ scales in a linear regression model, but a significant difference was found in verbal comprehension by comparing patients with a cyanotic phase or never been cyanotic (p = 0.013). Furthermore, a general linear model showed no statical significant association with CHD severity, the number of surgeries and the number of catheter interventions for all IQ scales.

The Early OP group showed significantly better results in the HrQoL domain of physical function and better results without statistical significance in most of the HrQoL domains (Table 2).

Table 2: HrQoL in total and in comparison between both groups with student's t-test

HrQoL domain	Total N=78	Early OP n=45	Late OP n=33	p-value
Physical function	72.9 ± 28.8	78.6 ± 22.8	64.6 ± 34.4	**0.040**
Role limitations physical	71.2 ± 39.2	70.4 ± 40.2	72.5 ± 38.5	0.820
Bodily pain	77.4 ± 33.7	79.5 ± 33.4	75.6 ± 34.6	0.644
Energy vitality	55.6 ± 21.6	57.1 ± 21.8	53.5 ± 21.4	0.486
Social function	83.0 ± 23.7	86.8 ± 19.3	77.3 ± 28.5	0.095
Role limitations emotional	79.9 ± 38.0	79.1 ± 38.5	81.1 ± 37.8	0.821
Mental health	71.8 ± 16.7	73.2 ± 16.2	69.7 ± 17.6	0.381
General health perceptions	61.1 ± 23.3	62.4 ± 24.0	59.1 ± 22.5	0.567

HrQoL: Health-related quality of life; n: number; OP: operation/surgery; level of significance $p < 0.05$.

By comparing both groups with their sex and age-specific reference values using a paired sample t-test significant impairments occurred except in the dimensions of bodily pain and mental health in both groups as well as social function in the Early OP group and Role limitations emotional in the Late OP group (Figure 2).

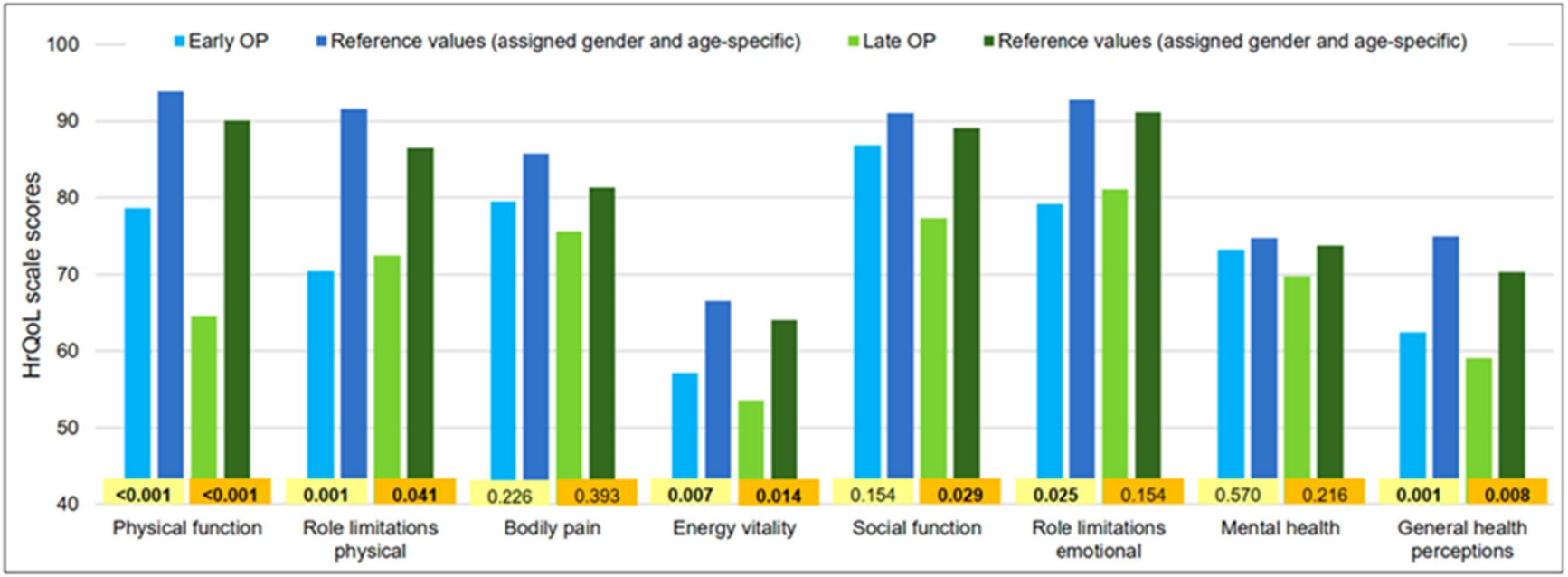


Figure 2: Group comparison with reference values of HrQoL by paired sample t-test
HrQoL: Health-related quality of life; OP: operation/surgery; level of significance $p < 0.05$.

The dimensions of 'physical function' and 'role limitations physical' significantly correlated with FSIQ in the Early OP group but no correlation in the group of Late OP (Table 3).

Table 3: Pearson correlation of FSIQ with all dimensions of HrQoL

		Physical function	Role limitations physical	Bodily pain	Energy vitality	Social function	Role limitations emotional	Mental health	General health perceptions
Early OP	PC-FSIQ	0.310	0.371	0.303	0.009	0.098	0.113	0.185	0.151
	p-value	**0.046**	**0.016**	0.054	0.952	0.538	0.475	0.240	0.340
Late OP	PC-FSIQ	0.308	0.082	0.128	0.100	0.348	0.249	0.280	0.354
	p-value	0.111	0.679	0.532	0.620	0.075	0.202	0.157	0.070

OP: operation/surgery; PC-FSIQ: Pearson correlation coefficient with full-scale intelligence quotient; level of significance $p < 0.05$.

Discussion

This study investigated neuro-mental health aspects in ACHD to gain an impression of cognitive function and HrQoL when patients after open heart surgery reached adulthood. Especially in older ACHD patients, the duration of cyanotic conditions was often longer, due to limited diagnostic possibilities and a later surgical correction. Thus, the question can be asked which constellation has the greater influence on NMHA; the first surgery in the vulnerable first three years of life, which are so crucial for development, or the duration of cyanosis. Based on this the focus is on the two groups of Early OP (first surgery between 0 to 3 years) and the group of Late OP (first surgery beyond the age of 3 years).

The majority showed complex CHD followed by moderate than simple CHD, this is due to inclusion criteria. Based on the literature on children and adolescents with CHD, the included ACHD with predominantly complex CHD should therefore have reduced IQ scores (27-31). However, this was not the case, as a general linear model did not show significant associations of CHD severity with all domains of the WAIS-IV which is contractionary with the results of children and adolescents (30, 32-34). Also, in the model, the number of surgeries and the number of catheter interventional treatments had no association with cognitive function. Kessler et al. 2020 described structural brain abnormalities (e.g. multifocal microhemorrhages) which were significantly associated with complex CHD but they reported no association with the IQ outcomes using the WAIS-IV short form (32) and in line with Schaefer et al. 2013 CHD complexity was not associated with neurodevelopmental outcome (35). That means they do not have a structural explanation only differences in the severity of CHD but as Kessler et al. 2020 mentioned in their limitations, 15 young ACHD cases have to be interpreted with caution (32). Additionally, they reported an overall mean IQ of 98.51±11.21 (n=65) which is quite similar to our overall results of FSIQ 97.1±12.0 (n=78), the approximately ten years difference between these study populations can be left out of consideration, as age is taken into calculation in the evaluation of the WAIS-IV from the outset (18).

Regarding differences between Early OP and Late OP, both groups showed almost the same results from the FSIQ across all subscales. This means that despite the early massive interruption of development by open heart surgery, the consequences are not transferred to adult age in ACHD or there is some catch-up development over

time. Interestingly separating both groups into ‚had a period of cyanosis' and ‚never had been cyanotic' significant differences in IQ scale verbal comprehension occurred with better results in ‚never had been cyanotic'. But there was no association between IQ scores and cyanosis duration, even though no significant in the regression model slight tendency occurred in terms of processing speed with the longer ACHD suffer from cyanotic conditions the slower they are in processing speed (p=0.053). Klouda et al. also reported on difficulties respectively impairments in information processing speed, psychomotor speed and reaction time in ACHD with complex CHD (36) but our study results must be compared cautiously since different measurements came to use. Overall ACHD patients needed to be intensively included in larger studies to better understand brain-related changes since they e.g. are at higher risk for neurocognitive decline or early onset of dementia (37-39).

The other part of NMHA is HrQoL, besides pure functioning of the brain self-reported HrQoL is an important tool to get insights into the patient's needs and worries and is quite easy to assess for follow-up of the patients by using SF-36 questionnaire e.g. in the waiting room. Our study population showed significantly different results in the SF-36 domain physical function in the direct comparison of Early OP and Late OP, in addition, the Early OP group showed better results in most of the HrQoL domains but without significance. Since the Early OP group is approximately 10 years younger this may explain the difference in physical function in this comparison. On the other hand, it is quite interesting that both OP groups did not show more differences as it is well known that the HrQoL decreases with increasing age (25). Therefore the next step of comparing both OP groups with their sex and age-specific reference value revealed alarming results. As Figure 2 shows, ACHD performed significantly reduced in all areas of the HrQoL except mental health and bodily pain. Additionally, the Early OP had no significant difference with their reference in case social function, this may be related to being at this age social contacts or interactions are more in the focus of activities than in older ages. And in terms of Late OP, there was no significant difference in role limitations emotional in comparison with their assigned reference. Interestingly the FSIQ correlates significantly with the dimension of physical function and role limitations physical and this is in the Early OP group only. It is known that more physical activity is associated with increased HrQoL even in ACHD patients (40). The contradictory results on HrQoL and physical activity in ACHD cause-effect constructs have already been discussed and various explanatory models were used

(41-43). In addition, it is known that a higher level of education is associated with better physical activity (32), which in turn may explain the significant correlation of the FSIQ with the physical function and role limitations physical dimensions in our ACHD. Since the contradictory results on HrQoL in patients with CHD were previously discussed in terms of lack of general definition of HrQoL, different measurements as well as different settings even with different explanations like the sense of coherence, changing expectations and awareness of illness during ageing (44-47) it is in need to identify the HrQoL status and changes to get the chance for intervention early, interdisciplinary but primarily adapted to the specific needs of the patients. If ACHD already deviates from the sex and age-specific reference in many domains, an earlier approach needs to be found, such as through continuous questionnaire analysis over the years, to be able to react to changes appropriately and on time.

Conclusion

Concerning the hypothesis, we found no association of cognitive function with cyanosis duration, number of surgery or catheter interventions, CHD severity and the timeframe of the first surgery in ACHD and greatly normal IQ scores. HrQoL was weak in comparison with the reference and there is an urgent need to improve the well-being of our ACHD with structured programmes, e.g. including physical activity programmes. This growing ACHD population should be focused in order of their needs and problems medical ones on one hand and on the other hand psychosocial matters.

Limitations

The significant differences between both groups must be interpreted with caution since both groups showed normal results within the frame of normative data. The evaluation of the detailed surgery data is not feasible as complete data is not available for all patients, since not all of the surgeries were performed at the same hospital or in the same country.

Ethics and dissemination

Approval from the local ethics board of the Technical University of Munich was obtained (Project Number 350/18 S). The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Patienten mit univentrikulärem Herz (UVH) haben basierend auf beiden vorangegangenen Studien ein deutlich höheres Risiko für eine Vielzahl von Nebendiagnosen, insbesondere neurologischer Art. Zudem werden in zahlreichen Publikationen signifikante Einschränkungen in der Entwicklung im Kindes- und Jugendalter beschrieben, meist in Kombination mit kognitiven Limitationen insbesondere bei komplexen AHF.

Mit Publikation III wurde in einer Subgruppenanalyse den Fragen nachgegangen:

=> Haben erwachsene UVH Patienten schlechtere kognitive Fähigkeiten als Patienten mit einfachem Herzfehler?

=> Ist die Lebensqualität von erwachsenen UVH Patienten schlechter als die von Patienten mit simplen AHF?

=> Gibt es Assoziationen oder Interaktionen zwischen Lebensqualität und Kognition beider Patientengruppen?

5.3 Publikation III Fontan vs. azyanotische AHF in Kognition und HrQoL

„Kognitive function in adults with Fontan Palpation vs. acyanotic CHD patients and Assoziation with health-related quality of life“

Autoren:

Julia Remmele, Milka Pringsheim, Nicole Nagdyman, Renate Oberhoffer-Fritz, Peter Ewert

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Anteilserklärung Julia Remmele an der Publikation:

I Konzeption und Gestaltung: **JR**, NN, MP

II Administrative Unterstützung: ROF, PE

III Bereitstellung von Studienmaterialien oder Patienten: **JR**, NN, MP

IV Sammlung und Zusammenstellung der Daten: **JR**, NN, MP

V Analyse und Interpretation der Daten: **JR**

VI Verfassen des ersten Manuskripts: **JR**

VII Endgültiges Verfassen und Genehmigung des Manuskripts: Alle Autoren.

VIII Überarbeitung nach der peer-review Beurteilung: **JR**

Zudem war **JR** für die Patienten Rekrutierung, die Durchführung und die Auswertung der Tests verantwortlich.

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Cognitive function in adults with Fontan palliation versus acyanotic CHD patients and association with health-related quality of life

Julia Remmele[1,2], Milka Pringsheim[1], Nicole Nagdyman[1], Renate Oberhoffer-Fritz[1,2] and Peter Ewert[1]

[1]German Heart Center of Munich, Department of Congenital Heart Disease and Pediatric Cardiology, Munich, Germany and [2]Institute of Preventive Pediatrics Technical University Munich, Munich, Germany

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Author for correspondence:
Julia Remmele, Department of Congenital Heart Defects and Pediatric Cardiology, German Heart Center of Munich, Lazarettstrasse 36, 80636 Munich, Germany.
Tel: +49 89 1218 1570.
E-mail: remmele@dhm.mhn.de

Abstract

Background: Impairments and developmental delay are often reported in infants and young children with CHD. However, currently, there is no data regarding cognitive abilities assessed by standardised intelligence tests in adults with CHD. This study assesses the cognitive function in Fontan patients compared with acyanotic CHD patients whether restrictions in cognitive function are present in adulthood and its association with health-related quality of life. *Methods:* Forty-four adult CHD (female n = 21 (47.7%); mean age 34.7 ± 11.9 years), 22 with Fontan circulation and 22 with acyanotic CHD, underwent the Wechsler Intelligence Scale for adults as patients during routine follow-up in 2018. The Medical Outcomes Study Questionnaire Short-Form 36 Health Survey (SF-36) assessed health-related quality of life. *Results:* Fontan patients showed significantly better results in the FSIQ ($p = 0.020$) and perceptual reasoning ($p = 0.017$) in comparison with patients with acyanotic CHD. All adult CHD patients showed normal IQ in subscales and full-scale IQ (FSIQ). In health-related quality of life, no association with cognitive function was found and no significant difference between both CHD groups, but trends to reduced values in acyanotic adult CHD. *Conclusions:* Interestingly, our study results in adult Fontan patients showed that it is possible to live an adult life with normal cognitive function and good health-related quality of life with a univentricular heart. Thus, this study could be a guidepost for more in-depth studies on cognitive function in Fontan survivors. In addition, the focus should be on health-related quality of life of adult CHD with simple CHD in particular, since a reduced health-related quality of life is not only medically based.

Introduction

During the last years, mortality in children and adolescents with CHD has rapidly decreased.[1,2] Life expectancy is increasing due to the significant advances in paediatric cardiology, cardiac surgery, and aftercare in the last decades.[3–5] For this growing adult congenital heart disease population, it is a question of how to prevent, reduce, or delay them in terms of comorbidities, as they are known to have a generally increased risk of morbidities, including neurologically acquired diagnoses in particular.[1] Regarding the close interaction of the heart and the brain focus shifts on the heart–brain axis as an important neurodevelopmental factor in the CHD population.[6] Some studies in neonates, infants, and children show structural brain abnormalities such as reduced brain volume, white matter, and grey matter lesions, and outer and inner liquor space enlargement.[7–12] All of these studies pointed out a significant association of these brain-related findings with developmental delay in young children with most of them having complex CHD.

That leads to the assumption patients with complex CHD do have lifelong problems due to their CHD. So far, most of the studies investigated children and fewer adolescents, which means right now there was not enough follow-up time for children with CHD to find out the relevance when they reach adulthood.

However, less is known about cognitive function assessed by standardised intelligence tests in adult CHD patients. Since cognitive function causes individual life perspectives and plans and their health-related quality of life,[13] this study aimed to assess and compare adult CHD patients with Fontan circulation and adult CHD patients with acyanotic CHD in terms of cognitive function and associations with health-related quality of life.

Patients and Methods

Study subjects

In 2018, patients with all kinds of CHD were routinely asked to complete an intelligence test and fill in the SF-36 questionnaire during their routine appointment at the German Heart Center Munich. Forty-four adult CHD patients (female n = 21 (47.7%); mean age at assessment 34.7 ± 11.9 years) were included in this subgroup analysis. Inclusion criteria were an age of at least 18 years and no interventional treatment or surgery during the past 6 months which potentially affects their cognition. Acyanotic CHD was defined based on the underlying leading CHD diagnosis,[14] and none of the included patients had already developed a cyanotic condition (e.g., Eisenmenger syndrome). The severity class of CHD was categorised as simple, moderate, and complex based on the American College of Cardiology (ACC) definition.[15] The variable cyanosis duration was defined from the day of birth to the day of completion of the Fontan circulation. The study was following the Declaration of Helsinki (revision 2013). Approval from the local ethics board was obtained (Project Number 350/18 S). Patients voluntarily agreed to participate and to the anonymous publication of their data by giving their written informed consent.

Cognitive function

Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV)[16] was administered to all patients. This worldwide established test was validated in 2013 for the German norm population of 1664 participants.[17] These national test norms serve the comparison in this study. It is the most commonly used test to assess cognitive function in adolescents and adults from 16 to 90 years. It includes 10 core subtests to calculate the Full-Scale Intelligence Quotient (FSIQ) with four specific domains of intelligence; Verbal Comprehension (VC), Perceptual Reasoning (PR), Processing Speed (PS), and Working Memory (WM) each of them also calculated into IQ points. In this test, impairment is defined as an intelligence quotient (IQ) achieved which is below more than one standard deviation (SD) of the norm (100 IQ points ± 1SD). The versions for children and adolescents have been frequently used in paediatric cardiology populations as well.[18]

Health-related quality of life (SF-36)

The Medical Outcomes Study Questionnaire Short-Form 36 Health Survey (SF-36) is a set, subdivided into eight sections (vitality, physical function, bodily pain, general health perceptions, physical role functioning, emotional role function, social role function, and mental health) of generic health-related quality-of-life measures.[19] Out of each section scaled scores with a range from 0 (negative health) to 100 (positive health) represent the weighted sums of the Likert-scaled questions. The SF-36 relies upon patient self-reporting within a 4-week window. It is quite well established in various health care sections to assess or monitor adult patient outcomes. The German version was validated by Bullinger and Kirchberger[19] and was deployed in this study. The SF-36 is used to evaluate individual patients' health status and monitor and compare disease burden with an acceptable internal consistency[20]; therefore, it is a worldwide used well-established questionnaire. It was used in this study as it was the most recent normal value for Germany taken from a 2013 survey.[21] The norm data were assigned to our participants according to age and sex.

Data analyses

Descriptive statistics were calculated in absolute and relative frequencies (%) for categorical variables, and means and SD for numerical variables. Shapiro–Wilk test was performed to prove normal distribution. The Student's t-test was used for group comparison as well as regression and correlation models to find associations between measurements and patients' data. The analysis was made with adjustments for age and sex. All analyses were performed using the software SPSS V.20 (SPSS Inc., Chicago, Illinois, United States of America) or R software V. 3.3.1. Pirate plots were used for visualisation of the data which represent the mean, confidence interval, raw data, and density distribution. The level of statistical significance was determined two-sided and with a p-value < 0.05.

Results

Both groups show the same number of patients with more male adult CHD (64%) in the Fontan group and more female adult CHD in the acyanotic group (59%). Most of the Fontan patients were palliated with total cavopulmonary connection with about 55% followed by the Fontan Björk procedure with about 34%. In four cases, the Fontan patients had the right ventricle as their systemic ventricle (Table 1).

Fontan-specific data on oxygen saturation, blood pressure, and body composition at the date of the test are given in Table 2. Additionally, detailed information on the underlying cardiac diagnosis in Fontan patients is in Table 3.

All adult CHD patients showed normal IQ scores in subscales and full-scale score. Fontan patients showed significantly better results in the full-scale IQ as well as in subscale perceptual reasoning in comparison with patients with acyanotic CHD. Figure 1 shows the IQ results of the subscales of both groups.

The significant difference between groups in FSIQ is shown in Figure 2 by pirate plots serving detailed information on the results of each group. There were no significant associations found in terms of sex differences, number of surgeries or catheter interventions, or cyanosis duration with the IQ score.

In terms of health-related quality of life, no significant difference was found between both CHD groups, but partly obviously trends to reduced values in the acyanotic CHD group (Fig 3). Furthermore, no significant association between IQ scores and health-related quality of life was found.

Discussion

Cognitive function

Since there is a close connection of an abnormal cognitive function with overall quality of life, employment opportunities as well as educational attainments, it is important to follow this in patients with CHD into adulthood.[13] Neonates and infants are most often reported with neurodevelopmental delays, especially in patients with complex CHD.[22–25] Hypoxaemia during pregnancy, perioperative as well as postoperative, haemodynamic changes, and early surgeries are related to adverse effects on brain development and neurodevelopment.[26] For example, because of the enormous advantages in medicine and surgical procedures, surgeries with cardiopulmonary bypass have become a widespread, low-risk standard procedure; in Germany alone, around 3852 children (newborns up to the age <18 years) underwent heart surgery with cardiopulmonary bypass in 2019.[27] In addition to the benefits,

Table 1. Group characteristics.

Variables	Fontan patients n = 22	Acyanotic CHD patients n = 22
Age (years)	32.9 ± 9.3	36.5 ± 14.1
Sex	8 ♀ / 14 ♂ (36.4% / 63.6%)	13 ♀ / 9 ♂ (59.1% / 40.9%)
Fontan type/CHD type	7 Björk (33.8%) 2 Linz (9.1%) 12 TCPC (54.5%) 1 Modified Fontan (4.5%)	7 atrial septum defects (31.8%) 3 aortic valve stenosis (13.6%) 3 coarctation of the aorta (13.6%) 2 ventricular septum defects (9.1%) 2 EBS (9.1%) 5 Other (22.7%)
Systemic ventricle	18 left ventricle (81.9%) 4 right ventricle (18.1%)	22 left ventricle (100%)
TCPC type	Extra cardiac tunnel (58.3%) Intra atrial tunnel (25%) Atrial fenestration (16.7%)	
Cyanosis duration (month)	99.4 ± 73.1	
Surgeries	3.55 ± 2.1	1.10 ± 1.3
catheter intervention	1.86 ± 1.4	0.75 ± 0.8
Age at first intervention (years)*	2.1 ± 3.7	21.1 ± 22.4

*Surgery or catheter intervention.
Cn = number; TCPC = total cavopulmonary connection; EBS = Ebstein's anomaly

Table 2. Fontan patients.

Fontan type	Age at first surgery (years)	Age at Fontan completion (years)	Oxygen saturation	RRsys (mmHg)	RRdia (mmHg)	Hight (cm)	Weight (kg)	BMI
Linz	8.9 ± 10.9	12.3 ± 6.1	92.0 ± 0	123.0 ± 0	71.5 ± 3.5	166.5 ± 0.7	67.5 ± 6.4	24.4 ± 2.5
Björk	1.7 ± 1.7	8.5 ± 6.2	94.0 ± 1.5	121.6 ± 12.0	67.9 ± 7.4	172 ± 11.4	67.4 ± 15.7	22.6 ± 4.2
TCPC l	0.7 ± 1.7	7.0 ± 8.0	94.1 ± 3.0	123.9 ± 13.1	68.8 ± 10.0	174.3 ± 10.7	70.3 ± 11.1	23.0 ± 1.8
TCPC r	3.0 ± 2.5	9.6 ± 1.3	91.8 ± 1.3		78.3 ± 7.4			

(*Continued*)

Table 3. Detailed cardiac diagnosis in Fontan patients.

Cardiac diagnosis in Fontan patients	Number of patients
Dysbalanced atrioventricular septal defect	2 (9.1%)
Double-inlet left ventricle	5 (22.7%)
Tricuspid atresia	11 (50%)
Double-inlet left ventricle, L-TGA	1 (4.6%)
Hypoplastic left ventricle	1 (4.6%)
TGA, hypoplastic right ventricle	1 (4.6%)
TGA, severe sub- and valvular pulmonary stenosis	1 (4.6%)

TGA = transposition of the great arteries; L-TGA = corrected transposition of the great arteries.

however, there are also side effects that can affect the lungs, kidneys, liver, or brain. Studies from the early 2000s reported neurological deficits in up to 80% of adults after heart surgery with cardiopulmonary bypass.[28–31] This does not seem to apply to children with CHD, Gunn et al. investigated the neurodevelopmental status after early heart surgery of 130 children at the age of 2 years in a direct comparison of CHD surgery with cardiopulmonary bypass and surgery without cardiopulmonary bypass. They found no significant differences in terms of the cardiopulmonary bypass use or aortic clamp on its own but reported repeated surgeries as a high-risk factor for neurodevelopment impairments.[32] In our study, number of surgeries or interventions did not show a relation with cognitive function in adulthood. Our study population of adult CHD patients showed no impairment in cognitive function compared with the german norms. Interestingly, Fontan patients had partly significant higher scores than patients with acyanotic CHD, although the control group had the first intervention or surgery at a significantly later time, that is, after the critical developmental age. Our results are not in line with other studies, but since most of them focus on younger CHD patients it is hardly comparable. Based on advances, different technics came to use to get an improved knowledge of the developing brain and its relations to CHD. More recent studies focus on neurodevelopmental outcomes combined with brain imaging using MRI to identify differences that can explain the neurodevelopmental delay in neonates and young CHD patients. They reported a high incidence of white

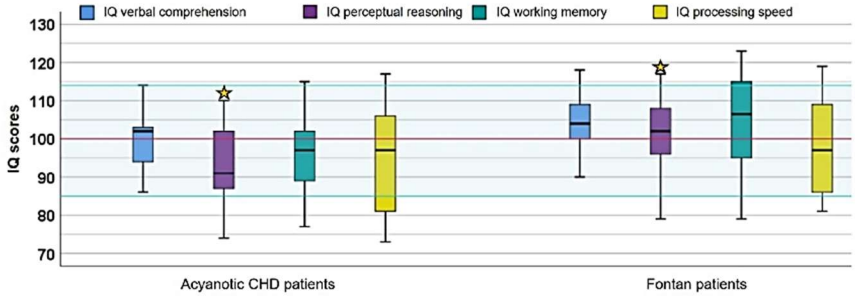

Figure 1. Subscale scores of the Wechsler Intelligence Test. IQ: Intelligence quotient; * significant difference between the groups with a level of significance $p < 0.05$.

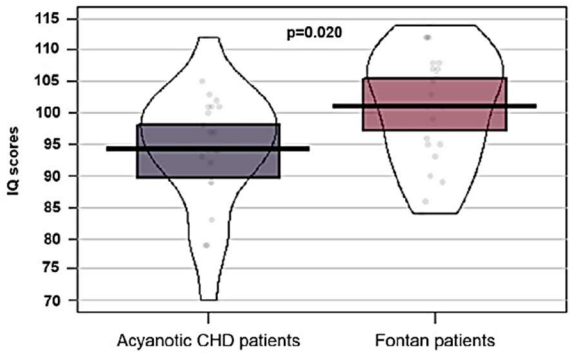

Figure 2. The FSIQ in comparison depicted with pirate plots. IQ: Intelligence quotient; level of significance $p < 0.05$.

matter lesions.[9,33–36] Additionally, Claessens et al. reported impaired cortical volume and brain gyrification in patients with univentricular heart circulation and white matter development resembling premature birth[10,37] changes that can predict developmental problems. Most of the studies in adolescents with CHD reported on executive function problems with reduced working memory and additionally, Fontes et al. on volume changes of the hippocampus with a structure–function relation of hippocampal subfields in this context in adolescents with complex CHD.[38] In another study, functional MRI was used which brought out a reduced prefrontal inhibition in patients with CHD compared to a healthy control group and a correlation with executive functioning.[39] However, besides all these advanced findings resulting from technical possibilities, it remains unclear what this means for our growing group of adult CHD. It remains unclear what impact the differences/abnormalities found will ultimately have on the function of the mature brain in adult CHD, due to the enormous neuroplasticity of the developing child's brain.[40]

In our study cohort, there was no impairment in cognitive function, and one reason might be that none of the patients in this study had been diagnosed with neuro events like ischaemic stroke. Of course, that does not mean they do not exist but it seems the brain found adaption mechanisms to enable normal cognitive function. It would be most interesting to do MRI with our Fontan cohort to find out whether there are still existing changes or undiagnosed lesions. On the one hand, it can be discussed whether MRI findings in neonates and young children with CHD present some kind of pathophysiology due to less oxygen or changes in the blood flow. For example, reported in the literature is liquor space enlargements associated with neurodevelopmental delay,[7,8] which may be due to a higher rate of ultrafiltration in the brain to prevent oxygen deficiency in the growing brain. On the other hand, a recently published work by Ehlert et al. reported reduced fractional anisotropy of the brain in both patients with cyanotic CHD and with acyanotic CHD as well in comparison with healthy controls in adolescents, especially in the frontal lobe which is associated with working memory.[41] It would be interesting if these changes of the brain still exist in older ages of our adult survivors or what kind of adaption mechanism leads the brain to normal function. MRI studies on adult CHD survivors may promise an improvement in understanding brain adaptions due to the underlying CHD.

Health-related quality of life

The adult CHD patients of both groups showed normal to good self-reported health-related quality of life measured with the SF-36 in this study without significant differences between both groups. This is in line with a recent study reporting on a large cohort of about 4000 patients with all kinds of adult CHD.[42] They also pointed out that health-related quality of life is not dependent on the complexity of the underlying CHD. With a closer look at the descriptive data (Fig 3), there were differences, without statistical significance but of interest, in the dimensions of physical role functioning, physical function, and bodily pain with worse results in patients with simple to moderate CHD, especially in comparison with normal data. Since patients with complex CHD usually have to be treated surgically postnatally and are now more often diagnosed during pregnancy than in previous decades, families have time to cope with the diagnosis. Furthermore, the need for repeated surgeries in the case of Fotan patients leads to those patients having to live with CHD from the beginning. They had to find coping strategies within their family as well as for their own, which leads to a higher sense of coherence with more mindfulness.[43] In a recently published study, Moons et al. reported on the positive association of sense of coherence with QoL in a large study with 15 enrolled countries and concluded strategies to improve SOC may improve QoL.[44] However, the enhanced sense of coherence develops during childhood through the successful application of generalised resistance resources.[45] This implies that when patients experience new, life-altering situations due to CHD later in life, we need to accompany them to help them develop their coping strategies and improve their health-related quality of life. Further studies on adult CHD patients, especially those underinvestigated with a simple CHD, should be invited to get more knowledge about their needs and worries since they do not have regular appointments like patients with moderate or complex CHD. Once this has been done, the next step is to develop

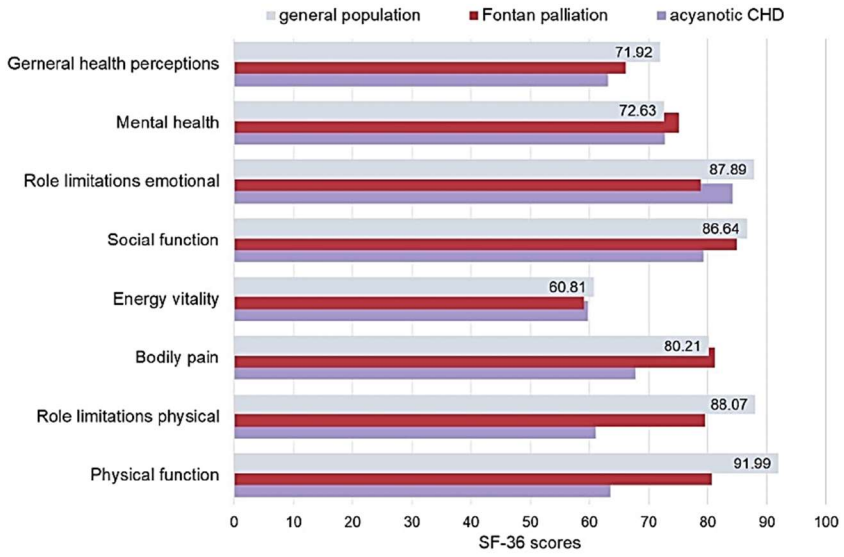

Figure 3. HrQoL scores in comparison.

programmes that support and strengthen patients in dealing with their CHD.

Conclusion

This study in adult Fontan patients showed that it is possible to live an adult life with normal cognitive function and good health-related quality of life with a univentricular heart. Thus, this study could be a guidepost for more in-depth studies on cognitive function in Fontan survivors. Since these results are not in line with other studies on Fontan patients at younger ages, further studies are needed on older Fontan survivors or long-term studies that follow the newborn patients into older ages. Additionally, various newer MRI or functional MRI techniques should be increasingly used in studies in adult CHD to understand the adaptive mechanisms that take place to allow the brain to function and to compare them with neonatal findings.

In addition, the focus should be on health-related quality of life of adult CHD with simple CHD in particular, since a reduced health-related quality of life is not only medically based. However, when the acyanotic group was compared with the norm values, the results were partly significant worse in the acyanotic CHD group, which necessitates further studies on the health-related quality of life of patients with acyanotic CHD.

Limitations

The significant differences between both groups must be interpreted with caution, since both groups showed normal results within the frame of normative data. The evaluation of the detailed surgery data is not feasible as complete data are not available for all patients, since not all of the surgeries were performed at the same hospital or in the same country. In addition, this is a single-centre experience; even though the sample size is small, it is a considerable sample of Fontan patients at this age.

Ethics and dissemination. Approval from the local ethics board of the Technical University of Munich was obtained (Project Number 350/18 S). The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Resultierend aus den vorangegangenen drei Publikationen und als schlussfolgerndes Studiendesign, wurde die deutschlandweite prospektive Observationsstudie „Same Same, but different?“ konzipiert.

Das Studienprotokoll, zur aktuell noch laufenden Studie, gibt einen Überblick über die technischen Details des Studiendesigns und verschiedene Testungen. Das Studiendesign ermöglicht unter anderem den Ausschluss von Confoundern, die die neurokognitiven Entwicklungsergebnisse sowie die HrQoL von Patienten mit AHF beeinflussen können sowie den tatsächlichen Einfluss des AHF auf NMHA, kognitive Fähigkeiten und HrQoL zu quantifizieren.

5.4 Publikation IV Studienprotokoll „ Same Same, but different?“

„A National Comparative Investigation of Twins With Congenital Heart Defects for Neurodevelopmental Outcomes and Quality of Life (Same Same, but Different?): Protocol for a Prospective Observational Study“

Autoren:

Julia Remmele, Paul Christian Helm, Renate Oberhoffer-Fritz, Ulrike MM Bauer, Thomas Pickardt, Peter Ewert, Oktay Tutarel

JMIR Research Protocols 2021; 2021;10(5):e26404);

doi: 10.2196/26404 (Impact factor: **1,85**)

Anteilserklärung Julia Remmele an der Publikation:

I **JR** und OT konzipierten die Studie, PE unterstützte und supervidierte sie.

II UMMB und TP halfen, die Studie auf die nationale Ebene zu bringen.

III **JR** und PCH definierten die geplanten statistischen Analysen und verfassten den ersten Entwurf mit PE.

IV PE, ROF, UMMB und TP überprüften das Protokoll kritisch und nahmen Änderungen vor.

V Alle Autoren haben die endgültige Fassung kritisch geprüft und genehmigt.

VI **JR** überarbeitete das Manuskript nach der peer-review Beurteilung.

JMIR RESEARCH PROTOCOLS Remmele et al

Protocol

A National Comparative Investigation of Twins With Congenital Heart Defects for Neurodevelopmental Outcomes and Quality of Life (Same Same, but Different?): Protocol for a Prospective Observational Study

Julia Remmele[1,2], BSc, MSc; Paul Christian Helm[3], Dip (Psych), Dr Rer Medic; Renate Oberhoffer-Fritz[2], MD, Prof Dr; Ulrike MM Bauer[3], MD; Thomas Pickardt[3], Dr Biol, PD; Peter Ewert[1,4], MD, Prof Dr; Oktay Tutarel[1,4], MD, Prof Dr

[1]Department of Congenital Heart Defects and Pediatric Cardiology, German Heart Center of Munich, Munich, Germany

[2]Institute of Preventive Pediatrics, Technical University Munich, Munich, Germany

[3]National Register for Congenital Heart Defects, German Center for Cardiovascular Research (DZHK), Berlin, Germany

[4]Partner Site Munich Heart Alliance, German Center for Cardiovascular Research (DZHK), Munich, Germany

Corresponding Author:
Julia Remmele, BSc, MSc
Department of Congenital Heart Defects and Pediatric Cardiology
German Heart Center of Munich
Lazarettstraße 36
Munich, 80636
Germany
Phone: 49 89 1218 1570
Email: remmele@dhm.mhn.de

Abstract

Background: Due to the increased survival rates of patients with congenital heart defects (CHD), associated disorders are an increasing focus of research. Existing studies figured out an association between CHD and its treatment, and neurodevelopmental outcomes including motor competence impairments. All these studies, however, compared their test results with reference values or results of healthy control groups. This comparison is influenced by socioeconomic and genetic aspects, which do have a known impact on neurodevelopmental outcomes.

Objective: This study protocol describes a setting that aims to find out the role of CHD and its treatments on neurodevelopmental outcomes, excluding socioeconomic and genetic aspects. Only a twin comparison provides the possibility to exclude these confounding factors.

Methods: In a German-wide prospective cohort study, 129 twin siblings registered in the National Register for Congenital Heart Defects will undergo testing on cognitive function (Wechsler Intelligence Tests age-dependent: Wechsler Adult Intelligence Scale, fourth edition; Wechsler Intelligence Scale for Children, fifth edition; and Wechsler Preschool and Primary Scale of Intelligence, fourth edition) and motor competence (Movement Assessment Battery for Children, second edition). Additionally, the self-reported health-related quality of life (KINDL-R for children, Short Form 36 for adults) and the parent-reported strength and difficulties of the children (Strength and Difficulties Questionnaire, German version) will be assessed by standardized questionnaires. CHD data on the specific diagnosis, surgeries, transcatheter procedures, and additional medical information will be received from patient records.

Results: The approval of the Medical Ethics Committee Charité Mitte was obtained in June 2018. After getting funded in April 2019, the first enrollment was in August 2019. The study is still ongoing until June 2022. Final results are expected in 2022.

Conclusions: This study protocol provides an overview of the study design's technical details, offering an option to exclude confounding factors on neurodevelopmental outcomes in patients with CHD. This will enable a specific analysis focusing on CHD and clinical treatments to differentiate in terms of neurodevelopmental outcomes of patients with CHD compared to twin siblings with healthy hearts. Finally, we aim to clearly define what is important to prevent patients with CHD in terms of neurodevelopmental impairments to be able to develop targeted prevention strategies for patients with CHD.

Trial Registration: German Clinical Trials Register DRKS00021087; https://tinyurl.com/2rdw8w67
International Registered Report Identifier (IRRID): DERR1-10.2196/26404

(JMIR Res Protoc 2021;10(5):e26404) doi: 10.2196/26404

KEYWORDS

congenital heart defect; twin siblings with CHD; twin study; neurodevelopmental outcome; same same; cardiology; heart defect; twin

Introduction

Congenital heart defects (CHD) are the most common congenital malformation and are associated with increased morbidity and mortality [1,2]. Based on the medical progress made in recent decades in the fields of prenatal diagnostics, pediatric cardiology, and heart surgery, mortality has been substantially reduced, and life expectancy has increased significantly [1,3,4]. Therefore, currently, more than 90% of children with CHD reach adulthood [1,5-7]. Thus, a major scientific focus lies on the clinical outcome and especially on neurologic concomitant diseases or sequela. Newborns with a CHD are already considered to be at risk of often starting with acidosis and low Apgar levels after delivery. After birth, acute initial oxygen deficiency, low cardiac output, and cyanosis are risk factors as are medical interventions such as surgery, transcatheter interventions, or other invasive medical procedures that may influence the developing brain [8-10].

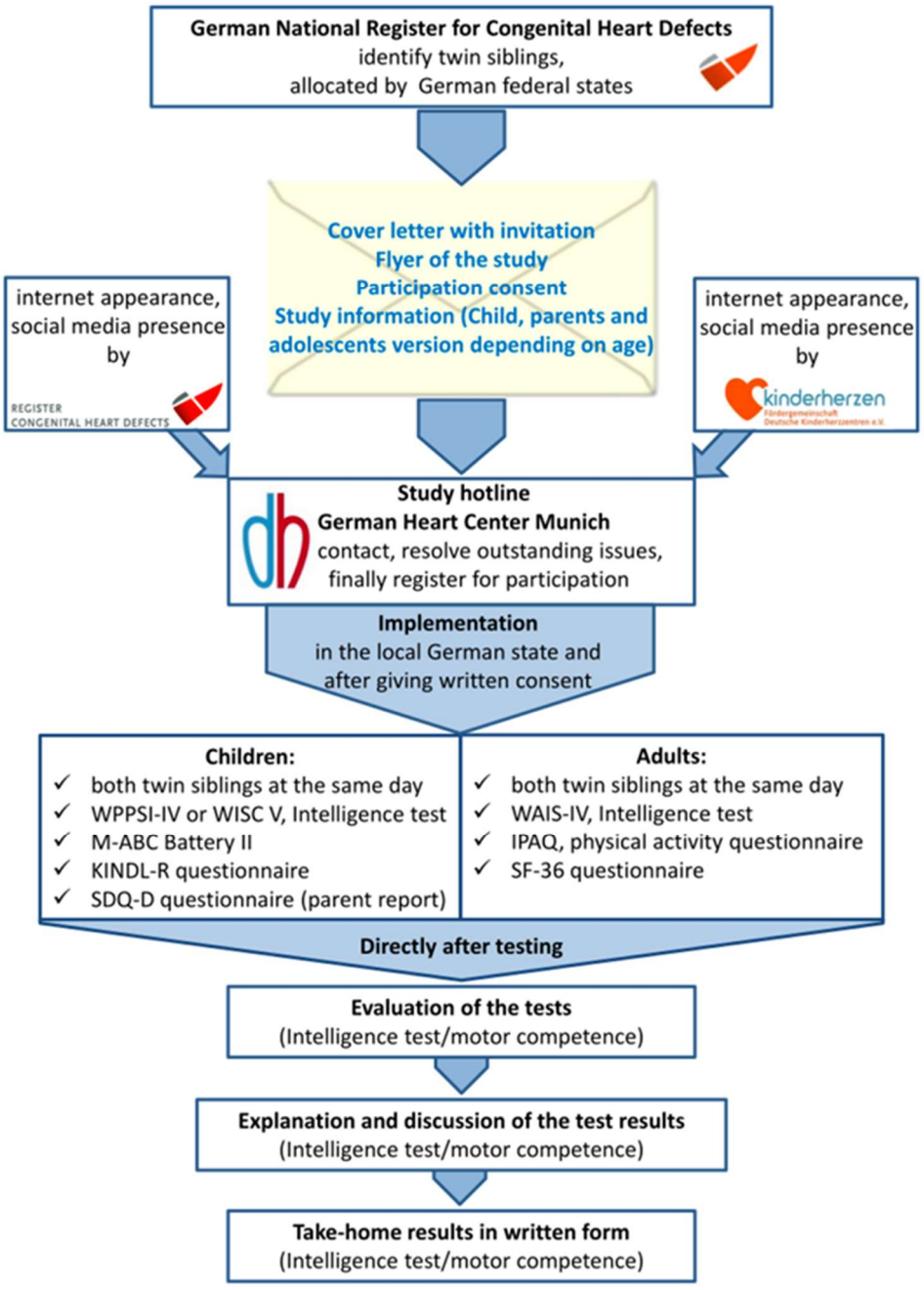
Several studies on patients with CHD after surgery have shown that neurodevelopment, including motor competence, is significantly impaired compared to healthy controls [9,11-14]. Although it seems obvious to consider the heart defect and its treatment consequences as the main cause of this difference, the patient's genetic predisposition, individual support, and socioeconomic factors play a central role in cognitive development as well [15,16]; it is, however, not known to what extent. How would the same child have developed without the CHD? Theoretically, these influences could be differentiated, comparing patients with CHD with healthy volunteers who have the same genetic predisposition and the same socioeconomic environment. In a practical approximation, our study on twins of whom only one sibling has CHD tries to differentiate the influence of heart defects and medical treatment on one hand from genetic predisposition and environmental factors on the other hand, focusing on neurodevelopmental outcome.

Methods

Study

This study is a national, German-wide prospective cohort study investigating twin siblings with at least one having a CHD. They are registered in the National Register for Congenital Heart Defects (NRCHD), the largest register for patients with CHD in Europe [17]. The inclusion takes place by written information sheets and an invitation to participate (see Figure 1). Participation in the study is voluntary and only takes place after the participants or, in the case of minors, their parents have given their written consent.

Figure 1. Flowchart of recruitment and implementation. IPAQ: International Physical Activity Questionnaire; M-ABC: Movement Assessment Battery for Children; SDQ: Strength and Difficulties Questionnaire, German version; SF-36: Short Form 36; WAIS-IV: Wechsler Adult Intelligence Scale, fourth edition; WISC V: Wechsler Intelligence Scale for Children, fifth edition; WPPSI-IV: Wechsler Preschool and Primary Scale of Intelligence, fourth edition.



Participants

The study population consists of patients with CHD and their twin siblings as well as both twins having CHD. To enable the participation of as many twins as possible, to keep the effort for the participants as low as possible, and to offer optimal test conditions with short travel distances and the same test settings, the tests are carried out at regional test facilities performed by one single investigator for all the tests throughout Germany.

Inclusion Criteria

The inclusion criteria were the following: all kinds of CHD (this includes all cardiac diagnoses defined by the International Paediatric and Congenital Cardiac Code [18]), age between

3-99 years, and both twins or their parents agreeing to participate.

Exclusion Criteria

The exclusion criteria were the following: surgery or interventional treatments within the last 6 month, massive mental retardation (to avoid a selection bias, all patients who wish to participate are admitted; if testing is not possible due to massive mental retardation, the twin siblings are excluded from the analysis but recorded as "drop-outs"), other medical examinations on the test day, or insufficient language skills (German).

Procedure

Primary Outcome

Wechsler Intelligence Test

The Wechsler Intelligence Test is designed for three age groups to assess cognitive function. The current version of the Wechsler Preschool and Primary Scale of Intelligence, fourth edition [19] is used for children aged 3-7 years, and the Wechsler Intelligence Scale for Children, fifth edition [20] is intended for children and young people aged 6-16 years. Finally, the Wechsler Adult Intelligence Scale, fourth edition [21] is an intelligence test for adolescents and adults within an age range of 16-99 years.

These tests consist of 10 subtest groups, which results in IQs for the four competence areas (working memory IQ, verbal comprehension IQ, processing speed IQ, and perceptual logical thinking IQ) and a full-scale IQ calculated using the results of all subtest groups.

Motor Competence

For the evaluation of motor competence, the Movement Assessment Battery for Children, second edition (M-ABC 2) [22] is used. It is a standardized test for assessing the motor competence of children aged 3-16.9 years. The M-ABC 2 is divided into three competence groups according to age (first: 3-6 years; second: 7-10 years; third: 11-16 years) and thus adequately records the three competence categories: manual dexterity (consisting of 3 tests), ball skill (consisting of 2 tests), and balance (consisting of 3 tests).

The total test value, consisting of all three areas, represents motor competence [23].

International Physical Activity Questionnaire

To measure adult participants' physical activities in everyday life, the International Physical Activity Questionnaire (IPAQ) [24] for adult patients will be used, due to there being no international standardized motor assessment battery for adults. The test results are categorized into three activity levels:

1. Health-promoting active (vigorous intensity activity on at least 3 days achieving a minimum of at least 1500 metabolic equivalent task [MET] minutes per week or 7 days of any combination of walking, moderate intensity, or vigorous intensity activities achieving a minimum of at least 3000 MET minutes per week)
2. Minimally active (3 or more days of vigorous activity of at least 20 minutes per day; 5 or more days of moderate intensity activity or walking of at least 30 minutes per day; or 5 or more days of any combination of walking, moderate intensity, or vigorous intensity activities achieving a minimum of at least 600 MET minutes per week)
3. Inactive (no activity reported or some activity reported but not enough to meet *health-enhancing physical active* or *minimally active*) [25]

The IPAQ is closely correlated with the results of spiroergometry [25].

Secondary Outcome

KINDL-R Questionnaire to Assess the Health-Related Quality of Life

To assess the health-related quality of life, parents (for preschool age children) and children receive the KINDL-R questionnaire [26], which they fill in independently. This is a multidimensional generic instrument for recording health-related quality of life. There are three versions for the corresponding age groups (first: 3-6 years; second: 7-12 years; third: 13-17 years); these comprise 24 questions, and validation has already been carried out [26].

Short Form 36 Questionnaire for Measuring Health-Related Quality of Life in Adults

The Short Form 36 (SF-36) consists of 36 questions and is a general health questionnaire that allows statements about the patient's health status using means of 8 different dimensions [27]. It makes statements about general health perception (5 questions), physical health (10 questions), limited physical role function (4 questions), physical pain (2 questions), vitality (4 questions), mental health (5 questions), limited emotional role function (3 questions), and social functioning (2 questions).

The possible score ranges from 0 to 100 points. Zero points represent the worst quality of life value in terms of health, while 100 points describe the best possible state of health. Bullinger and Kirchberger [27] validated the German version, and the SF-36 is used to evaluate individual patients' health status and monitor and compare disease burden with an acceptable internal consistency [28]. Therefore, it is used worldwide and is a well-established questionnaire, which is used in various fields of medicine, with great clinical relevance and is available in over 170 languages.

Strength and Difficulties Questionnaire

The Strength and Difficulties Questionnaire, German version (SDQ-D) [29] assesses behavioral problems and strengths in children and young people aged 4-17 years, and it is available in over 75 languages. The two-page parent-reported questionnaire contains a total of 25 characteristics, 10 of which are positive, 14 negative, and 1 neutral, and asks about problematic experiences of the child.

The SDQ-D measures the scales emotional problems, conduct problems, hyperactivity, behavioral problems with peers, and prosocial behavior.

From these scale scores, a total problem score is calculated, ranging in value from 0 to 40. Validation and updating of age-specific German reference values by Robert-Koch Institute published in 2020 [30].

Data Handling

Since the study participants come from the NRCHD and the data processing takes place under the umbrella of the NRCHD, the study is subject to the data protection concept established in the NRCHD. All study participants already have a pseudonym and a randomly generated number as a result of their participation in the NRCHD. The latter is used to identify the questionnaires. The data obtained are stored separately from the personal identifying data under the aforementioned pseudonym. All information and data remain within the jurisdiction of the NRCHD. People outside this area, except for the study directors, have no access to the data. The study director conducts the tests personally.

The collection and storage of all data are carried out following the NRCHD's data protection concept, which is registered with the Berlin Commissioner for Data Protection and Freedom of Information (No. 531.390). The study directors receive the data for statistical evaluation for a limited time and without direct reference to the participating persons. In addition, only NRCHD employees who are bound to secrecy have access to the data. The data collected via German Heart Center Munich are stored on hospital servers and only the research team has access. Data transfer between NRCHD and German Heart Center Munich takes place in person or a password-protected version. The written consent and collected data will be stored separately for 10 years after the end of the study. At the end of the study, both the participants and the funding agency will be informed about the results.

Statistical Analysis

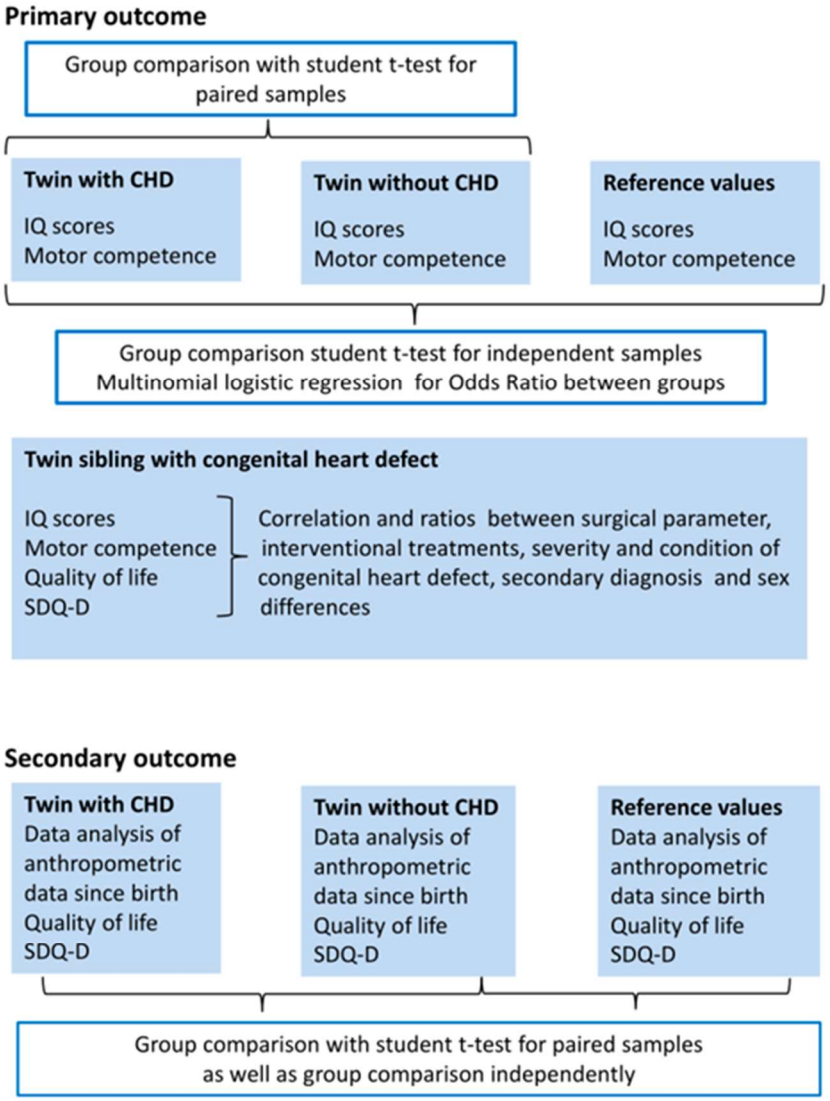
Power Analysis and Sample Size

Due to the explorative character of the study and the, so far, unknown prevalence of CHD in twin siblings in Germany or in any other country, this makes adequate case number planning difficult. Using G*Power analysis for "a priori required sample size" for student *t* test with paired samples with a medium effect size (0.5), a power set to 0.95, and an alpha error probability set to .05, we ended up with a total number of 54 twins. However, this study aims for a total survey of twins with CHD living in Germany. Based on previous experience, a conservative estimate of at least 50% inclusion can be expected, that is, 129 pairs of twins from 259 twins recorded in the NRCHD throughout Germany (as of February 2018).

Primary and Secondary Analysis

The planned primary and secondary analysis are displayed in Figure 2.

Figure 2. Planned statistical analysis. CHD: congenital heart defects; SDQ-D: Strength and Difficulties Questionnaire, German version.



Results

The approval of the Medical Ethics Committee Charité Mitte was obtained on June 26, 2018 (EA2/086/18). After getting funded in April 2019, first enrollment began in August 2019. The study is still ongoing until June 2022. Final results are expected in 2022.

Discussion

This study protocol provides an overview of technical details of the study design, offering an option to exclude confounding factors on neurodevelopmental outcomes in patients with CHD. This will enable a specific analysis focusing on CHD and clinical treatments to differentiate in terms of neurodevelopmental outcomes of patients with CHD compared to twin siblings with healthy hearts. In the end, we aim to clearly define what is important to prevent patients with CHD in terms of neurodevelopmental impairments and to define targeted prevention strategies for patients with CHD.

Acknowledgments

This study is funded by *kinderherzen*, Fördergemeinschaft Deutsche Kinderherzzentren e.V, Germany.

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We would like to thank all the cooperating centers in Germany who support the study and provide us with the premises for testing.

Authors' Contributions

JR and OT came up with the study; PE supported and supervised it. UMMB and TP supported bringing it to the national level. JR and PCH contributed toward statistical analyses and the first draft with PE. PE, ROF, UMMB, and TP critically reviewed the protocol and made amendments. All authors critically reviewed and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

CHD: congenital heart defects
IPAQ: International Physical Activity Questionnaire
MET: metabolic equivalent task
M-ABC 2: Movement Assessment Battery for Children, second edition
NRCHD: National Register for Congenital Heart Defects
SDQ-D: Strength and Difficulties Questionnaire, German version
SF-36: Short Form 36

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6 Zusammenfassende Diskussion

Weltweit werden jedes Jahr rund 1,35 bis 1,5 Millionen Kinder mit AHF geboren, 45 % davon mit mittelschweren oder komplexen AHF, 55 % mit simplen AHF (85). EMAH aller Schweregrade werden zunehmend mehr, zwischen 2000 und 2010 ist die Zahl von EMAH beispielsweise in Quebec auf 55 % aller AHF-Patienten gestiegen, wobei die Prävalenz der schweren AHF gestiegen ist (6). Dieser Trend lässt sich fortlaufend beobachten, sodass in der entwickelten, westlichen Welt mehr als 95% das Erwachsenenalter erreichen (4) und die Zahl der EMAH die der Kinder mit AHF in Deutschland deutlich übertrifft (5).

Grundsätzlich gilt bei Patienten mit AHF, auch wenn der AHF chirurgisch oder katheterinterventionell behandelt wird, ist er nie geheilt; er kann palliiert oder bestenfalls korrigiert werden (86), daher ist aufgrund verschiedener Residuen und Folgeerkrankungen eine lebenslange spezialisierte Versorgung unerlässlich (36, 87, 88). Eine große Herausforderung in der klinischen Praxis ist die Transition, der Übergang von der pädiatrischen zur erwachsenen AHF-Versorgung, da alternde EMAH ein erhöhtes Risiko für kardiale Nebendiagnosen, zusätzlich zur initialen AHF-Diagnose, wie Arrhythmien, systemische und pulmonale arterielle Hypertonie, thromboembolische Ereignisse, infektiöse Endokarditis (89) sowie nicht-kardiale Erkrankungen aufweisen (90). Ein Scheitern des Transitionsprozesses kann zu einer verzögerten Erkennung sich entwickelnder kardialer und nicht-kardialer Probleme / Diagnosen führen, was die weitere Behandlung der AHF-Patienten erschwert (91).

Die Ergebnisse aus Publikation I zur Transition, unterstreichen die dringende Notwendigkeit einer erfolgreichen Transition für junge AHF-Patienten. Denn es konnte gezeigt werden, dass Patienten mit AHF schon in den jungen Jahren der Transition mit einigen durchaus relevanten Nebendiagnosen konfrontiert sind. Bis zu vier kardiale Nebendiagnosen zusätzlich zur AHF-Diagnose wurden identifiziert, zudem bis zu sieben nicht-kardiale Nebendiagnosen. Diese Ergebnisse entsprechen den Resultaten anderer Publikationen zu Nebendiagnosen. Neidenbach et al. 2018, konnten in 95% der EMAH zusätzlich nicht-kardiale Diagnosen nachweisen (90). Bouma et al. 2017, berichten über die veränderte Patientenlandschaft von AHF Patienten sowie den damit einhergehenden Komplikationen und Komorbiditäten (2).

Die vorliegende Studie I zeigte, dass neurologische Nebendiagnosen die höchste Prävalenz der erworbenen Nebendiagnosen darstellen. Neben den

behandlungsspezifischen Parametern (Operation, katheterinterventionelle Behandlung, aber auch medikamentöse Behandlung), sind hämodynamische Änderungen oder Gefäßsystemanomalien/-veränderungen dafür verantwortlich. So konnte bei Patienten mit einer Coarctation der Aorta (CoA) schon im Kindesalter eine Verdickung der Gefäßwand der Carotis-Intima-Media (cIMT) nachgewiesen werden (92). Die cIMT wird als Marker für strukturelle Veränderungen des Gefäßes erhoben und es gibt Evidenz dafür, dass erhöhte cIMT-Werte bei Erwachsenen mit CoA prädiktiv für Myokardinfarkt, zerebrovaskuläre Ereignisse, Aortenaneurysma-Reparatur und Herztod sind (93). Im Kontext von zerebrovaskulären Ereignissen sowie den bereits pränatal veränderten hämodynamischen Bedingungen der Hirnperfusion/-entwicklung, liegt der Schluss nahe, dass es durch die Behandlung des AHF, über erworbene Nebendiagnosen und Entwicklungsdefizite hinaus, zu tiefergreifenden Veränderungen der Hirnfunktion bei EMAH führen könnte. Bislang konnten in Studien hirnstrukturelle Veränderungen wie beispielsweise erweiterte Liquorräume, Läsionen der weißen Substanz bei Kindern nachgewiesen werden, welche auch in Verbindung mit kognitiven und motorischen Entwicklungsdefiziten stehen (14, 16, 17, 63, 94). Im Bereich der kognitiven Fähigkeiten scheint das jedoch im erwachsenen Alter nicht mehr der Fall zu sein. Im Rahmen von Publikation II konnte gezeigt werden, dass EMAH nach einer Operation am offenen Herzen in der Kindheit, im Durchschnitt einen normalen IQ von 97,1±12,0 (n=78) haben. Zu ähnlichen Ergebnissen kamen Kessler et al. 2020, sie berichteten in einer im Mittel 10 Jahre jüngeren Kohorte einen GIQ von 98,51±11,21 (n=65), wobei der Altersunterschied nicht berücksichtigt werden muss, da bei der Auswertung des WAIS-IV das Alter in der Berechnung berücksichtigt wird (73). Im weiteren beschrieben Kessler et al. einen signifikant geringeren GIQ bei Patienten mit komplexen AHF, diese Ergebnisse stehen im Gegensatz zu den Ergebnissen unserer Analyse. Hier unterschieden sich die Patienten in den verschiedenen Schweregradgruppen des AHF nicht. In Publikation III wurde eine detaillierte Subgruppenanalyse durchgeführt, wobei EMAH mit dem schwerwiegendsten AHF, dem UVH, verglichen wurden mit azyanotischen EMAH mit primär simplem Herzfehlerschweregrad. Es zeigten sich signifikant bessere Ergebnisse in der UVH Gruppe im GIQ (p=0,020) und im wahrnehmungsgebundenem logischen Denken (p=0,017) im Vergleich zu Patienten mit azyanotischen AHF. Somit konnte gezeigt werden, dass es möglich ist mit, UVH das Erwachsenenalter zu erreichen und einen normalen IQ zu haben, trotz widriger Entwicklungsbedingungen und mehrfacher Operationen. Des Weiteren konnte gezeigt werden, dass UVH

Patienten sich nicht signifikant von der Gruppe azyanotischer EMAH in Bezug auf die HrQoL voneinander unterschieden. Publikation II zeigte eine signifikant schlechtere HrQoL als die ihnen geschlechts- und altersspezifisch zugeordneten Referenzwerte in allen Bereichen außer „mental health“ und „bodily pain“. Mittels einer Korrelation konnte zudem ein signifikanter Zusammenhang zwischen dem GIQ und den Dimensionen „physical function“ und „role limitation physical“ hergestellt werden. Es ist bekannt, dass mehr körperliche Aktivität bei EMAH mit einer höheren Lebensqualität verbunden ist (95). Die widersprüchlichen Ergebnisse zu HrQoL und körperlicher Aktivität bei EMAH zu Kausal-Konstrukten wurden bereits diskutiert und verschiedene Erklärungsmodelle wurden vorgeschlagen (9, 96, 97). Darüber hinaus ist bekannt, dass ein höheres Bildungsniveau mit einer besseren körperlichen Aktivität verbunden ist (18), was wiederum die signifikante Korrelation des GIQ mit den Dimensionen „physical function“ und „role limitation physical“ in unserer EMAH Studie erklären könnte. Die signifikant reduzierte HrQoL bei EMAH ist insofern verwunderlich, da in einer Vielzahl von Studien am Deutschen Herzzentrum München (DHM), bei Kinder mit AHF eine vergleichbar gute und bessere HrQoL im Vergleich mit den altersentsprechenden Referenzen ermittelt wurden (96, 98-100). Die EMAH der Publikationen II und III waren ebenfalls Patienten, die an das DHM angebunden waren. Neben der Tatsache, dass mit unterschiedlichen Messinstrumenten gemessen wurde (Kinder: KINDL-R; EMAH: SF-36), stellt sich die Frage, wie es zu einer solchen Verschlechterung der HrQoL im Erwachsenenalter kommen kann. Es könnte argumentiert werden, dass verschiedene Coping Strategien nur solange greifen, wie sich die Kinder mit AHF in ihrem familiär geschützten Umfeld befinden und der Effekt nachlässt, sobald sie erwachsen werden. Nach dem Schulabschluss und mit der neuen eigenverantwortlichen Selbständigkeit des Lebens, müssen sich die Patienten mit AHF nun mit der immer schnelleren, leistungsorientierten Gesellschaft auseinandersetzten und es werden ihnen ihre Grenzen deutlicher vor Augen geführt. Andererseits ist es bemerkenswert, dass UVH Patienten keine so deutlichen Einschränkungen der HrQoL zeigten. Hier könnte ein Erklärungsansatz darin liegen, dass sie vom ersten Tag an immer regelmäßige Kontrollen in spezialisierten Zentren haben und sie ihre Lebenspläne kontinuierlich an ihr Wohlergehen adaptieren (9) und so lebenslang in einem kontrollierten, geschützten Umfeld verbleiben. Wie in Publikation I geschildert, könnte aber auch das Problem des „loss to follow-up“ einen Erklärungsansatz liefern. So scheint es plausibel, dass EMAH mit weniger schweren AHF nicht mehr an EMAH-zertifizierte Spezialisten angebunden sind. Sie kommen viel

zu häufig erst nach vermehrtem Auftreten von Komorbiditäten zurück in die spezialisierten Zentren, zu einem Zeitpunkt, zu dem sie die Einschränkungen ihres Lebensalltags bereits deutlich spüren.

7 Schlussfolgerung und Perspektive

Die Bedeutung der Transition und die klinische Relevanz für Jugendliche und junge EMAH konnte klar aufgezeigt werden und unterstreicht die Bedeutung dieses Alters als geeigneten Ausgangspunkt für gezielte Präventionsprogramme. Für Jugendliche und junge EMAH besteht die dringende Notwendigkeit, die Kluft zwischen Kinder- und Erwachsenenkardiologie zu überbrücken und nachhaltige Strategien zu finden, um diese jungen Patienten in dieser Transitionsphase nicht zu verlieren. Dafür bedarf es eines besseren Bewusstseins der EMAH, sich von spezialisierten Zentren oder niedergelassenen EMAH-zertifizierten Ärzten betreuen zu lassen. Andernfalls wird die Früherkennung von erworbenen Morbiditäten, die das Leben von Jugendlichen und jungen EMAH beeinträchtigt, mit all ihren Konsequenzen scheitern. Auch in Bezug auf die HrQoL kann eine erfolgreiche Transition zielführend sein. Es ist notwendig, den HrQoL-Status zu kennen und Veränderungen zu identifizieren, um die Chance für eine frühzeitige, interdisziplinäre, aber vor allem an die spezifischen Bedürfnisse der Patienten angepasste Intervention zu haben. Da EMAH bereits in den meisten Dimensionen der HrQoL von der geschlechts- und altersspezifischen Referenz signifikant abweichen, muss ein früherer Ansatz gefunden werden, z. B. durch eine kontinuierliche Fragebogenanalyse über die Jahre, um auf Veränderungen angemessen und rechtzeitig reagieren zu können.

Entgegen der Entwicklungsstörungen und –verzögerungen im frühen Kindes- und Jugendalter, konnte mit dieser Arbeit nachgewiesen werden, dass EMAH durchaus mit einer normalen Intelligenz das erwachsenen Alter erreichen können. Zudem konnten Trends einer verlangsamten Verarbeitungsgeschwindigkeit hergestellt sowie eine Korrelation von IQ und HrQoL nachgewiesen werden. Dennoch verbleibt die Frage, wie es entgegen der widrigen Bedingungen durch den AHF möglich ist, dass das Gehirn normal arbeitet. Somit kann diese Dissertation ein Wegweiser für weiterführende Studien zu kognitiven Fähigkeiten bei EMAH sein. Es sind weitere Studien mit älteren EMAH oder Langzeitstudien erforderlich, die die neugeborenen Patienten bis ins hohe Alter begleiten. Darüber hinaus sollten verschiedene neuere MRT- oder fMRT-Techniken verstärkt in Studien bei EMAH eingesetzt werden, um die Anpassungsmechanismen zu verstehen, die stattfinden, damit das Gehirn funktionieren kann, und um sie mit neonatalen Ergebnissen zu vergleichen. Darüber hinaus sollte ein Schwerpunkt auf der HrQoL von EMAH mit simplen AHF liegen, da die reduzierte HrQoL nicht rein medizinisch begründet werden kann.

Es ist hinreichend bekannt, dass NMHA stark abhängig von Umwelteinflüssen, den sozioökonomischen Verhältnissen sowie genetischen Veranlagung sind. Daher wurde in diesem Kontext diskutiert, inwiefern der Vergleich mit nationalen Referenzwerten gerechtfertigt wäre. Murphy et al. haben sich für einen Vergleich mit gesunden Geschwistern entschieden und kamen zu dem Resultat, dass junge Patienten mit einer Fallott'schen Tetralogie, bezüglich ihres IQ im Geschwistervergleich schlechter abschnitten als im Vergleich mit den Normwerten (101). Daraus ziehen sie den Schluss, dass Vergleiche mit etablierten Normen die neurokognitiven Schwachstellen möglicherweise unterschätzen könnten. Ein anderer Ansatz ist es, Patienten mit AHF mit Freunden aus ihrem Umfeld mit gleichem Alter und Geschlecht zu vergleichen, um möglichst identische Vorraussetzungen zu schaffen (102). Es verbleiben dennoch auch bei diesem Ansatz genetische und familiäre Aspekte, die sich unterscheiden.

Das schlussfolgernde, prospektive Studiendesign, Publikation IV, von „Same Same, but different?" eröffnet die Möglichkeit, annäherungsweise alle Confounder, wie gentische Veranlagung oder familiäres Umfeld, die die kognitiven Fähigkeiten und HrQoL beeinflussen, zu kontrollieren. Denn nur ein Zwillingsdesign, ein Zwilling mit und ein Zwilling ohne AHF, ermöglicht eine Evaluation, um den tatsächlichen Einfluss des AHF und dessen Behandlung, auf die kognitiven und motorischen Fähigkeiten, HrQoL und mentale Gesundheit zu prüfen. Denn selbst in Ausnahmesituation, wie aktuell die Corona Pandemie, erleben und erfahren sie die Pandemie zum gleichen Entwicklungszeitpunkt. Die derzeit laufende Zwillingstudie (Studienprotokoll = Publikation IV) stellt einen hoch relevanten Baustein für ein besseres Verständnis hinsichtlich der NMHA von Patienten mit AHF dar und verspricht wertvolle Erkenntnisse in Bezug auf den AHF und dessen Auswirkung auf NMHA zu liefern.

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Julia Remmele