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Congenital heart defects and growth restriction of the newborn : population-based studies

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Ali Ghanchi. Congenital heart defects and growth restriction of the newborn : population-based studies. Human health and pathology. Université Paris Cité, 2022. English. NNT : 2022UNIP5134 . tel-04731162

HAL Id: tel-04731162

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**Université
Paris Cité**

École doctorale Pierre Louis de Santé Publique : Épidémiologie et Sciences de l'information
Biomédicale (ED 393)

Laboratoire Centre de Recherche Épidémiologie et Statistiques, Inserm UMR 1153 (CRESS)

Équipe de recherche en épidémiologie obstétricale, périnatale et pédiatrique (EPOPé)

**Congenital Heart Defects and Growth Restriction of the Newborn:
Population-based studies**

Thèse de doctorat en santé publique : spécialité épidémiologie clinique

Présenté et soutenu publiquement le 02 Décembre 2022 par

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Congenital Heart Defects and Growth Restriction of the Newborn: Population-based studies

Abstract

Congenital heart defects (CHD) and Growth Restriction of the Newborn (GRN) are two important causes of infant morbidity and mortality and long-term adverse outcomes. CHD comprises 9 per 1000 live births while GRN affects approximately 10% of all pregnancies. Newborns with CHD are more likely to have GRN and have a worse prognosis than infants with CHD who do not have GRN. There are important gaps in the literature on the relation between CHD and GRN and this thesis is intended to address some of the unresolved questions in the literature. The specific questions addressed were:

- i)** What is the risk of GRN in newborns with CHD?
- ii)** To what extent does the probability and severity of GRN vary according to CHD subtypes?
- iii)** What is the risk of mortality and short-term morbidity in newborns with CHD and GRN?

In order to do so, we conducted two systematic reviews and an analysis of a prospective, population-based cohort of children born with isolated CHD (i.e. CHD not associated with other anomalies) born in the Greater Paris Region (Paris and its surrounding suburbs), the EPICARD study.

A satisfactory definition of GRN has been subject of many articles and a definite consensus has not emerged. However, in practice, almost all empirical studies of fetal growth restriction or that of the GRN use their imperfect proxies, the Small for Gestational Age (SGA), defined as births with <10th percentile birth weight of a reference population birthweight curve. Hence, the SGA in the reference (general) population is 10%.

In the first systematic review of 1783 potential publications, 38 studies were found to be relevant to the study question. A random-effects meta-analysis based on data from 18 studies with sufficient data found that the pooled proportion of SGA for all CHD was 20% (95% CI 16%-24%) and 14% (95% CI 13%-16%) for isolated CHD. The proportion of SGA varied considerably across different types of CHD and ranged from a low of 12% (95% CI 7%–18%) for isolated atrial septal defects to 30% (95% CI 24%–37%) for Tetralogy of Fallot (ToF).

Our analysis of the EPICARD cohort found that the overall risk of SGA for isolated CHD was 13% (95% CI, 12–15%), i.e. 30% higher than what would be expected in the general population.

The risk of severe SGA (<3rd percentile) was 5% (95% CI, 4–6%) as compared with the expected 3% in the general population. There were substantial differences in the risk of overall SGA and more so severe SGA across the different CHD.

The highest risk of SGA occurred for ToF (adjusted OR 2.7, 95% CI, 1.3–5.8) and operated ventricular septal defect (VSD) (adjusted OR 2.1, 95% CI, 1.1–3.8) as compared with the control group of minor (non-operated) VSD.

In the third study, a systematic review of 2053 potentially relevant publications included seven studies specifically about the adverse outcomes in newborns with SGA and CHD. The most frequent outcome studied was mortality. We were not able to perform a meta-analysis of these data as there was an insufficient number of studies and the available data had important limitations. This systematic review suggested however, that newborns with CHD and SGA are at substantially higher risks of mortality, necrotizing enterocolitis and neurological impairment.

A better understanding of the complex relations between CHD and GRN is important for optimal care of newborns with CHD. Our results provide additional information that may help in this process and elucidate the pathways that lead to GRN due to the specific pathophysiological mechanisms associated with different types of CHD. Our findings also underscore the need for future work in this area, including the extent to which the effect of GRN on short- and long-term outcomes may vary across different types of CHD, and, whether GRN may be on the causal pathway between CHD and outcomes of the newborns with CHD, including their possibly suboptimal post-natal growth.

3921 / 4000 characters (spaces included)

Key words: Congenital heart defects (CHD) ; Growth restriction of the newborn (GRN); population based studies, prevalence ; systematic review and meta-analysis ; ordinal logistic regression ; small for gestational age (SGA) ; fetal growth restriction (FGR); mortality ; morbidity ;

Les cardiopathies congénitales et le retard de croissance du nouveau-né : les études en population

French Abstract

Résumé court en français

Les cardiopathies congénitales (CC) et le retard de croissance du nouveau-né (RCN) sont deux causes importantes de mortalité, morbidité infantiles et issues défavorables sur le long terme. Les nouveau-nés avec une CC ont plus fréquemment un RCN et un mauvais pronostic médical par rapport aux enfants nés avec une CC mais sans RCN. Cette thèse a pour but de répondre à des questions de recherche suivantes :

- i. Quel est le risque pour un enfant né avec une CC d'avoir un RCN ?
- ii. Est-ce que la probabilité et la sévérité des RCN varient-elles en fonction des différentes CC ?
- iii. Quel est le risque de mortalité et de morbidité à court terme chez les enfants nés avec une CC et un RCN ?

Nous avons effectués deux revues systématiques de la littérature ainsi qu'une analyse de données à partir d'une cohorte prospective d'enfants nés avec une CC isolée (non associée à d'autres anomalies congénitales) en Ile de France (Paris et ses banlieues proches), l'étude EPICARD.

Il n'y a aucun consensus universellement reconnu de RCN et en pratique, la plupart des études empiriques sur le RCN utilisent le petit poids pour l'âge gestationnel (PAG) comme un synonyme proche. Ce dernier est défini comme un poids de naissance < 10^{ème} percentile sur une courbe de poids de naissance dans une population de référence. Ainsi PAG dans la population générale est de 10%.

La première revue systématique de la littérature a identifié 38 études pertinentes parmi les 1783 publications potentielles. La méta-analyse menée en utilisant un modèle à effet aléatoire sur 18 études a montré que la proportion de PAG pour toutes CC confondues était de 20% (95% CI 16%-24%) et de 14% (95% CI 13%-16%) pour les CC isolées.

La proportion de PAG variait considérablement selon les différents types de CC avec des proportions allant de 12% (95% CI 7%–18%) pour la communication intra-auriculaire isolée à 30% (95% CI 24%–37%) pour la Tétralogie de Fallot (ToF).

L'analyse des données de la cohorte EPICARD a retrouvé un risque global de PAG dans les CC isolées de 13% (95% CI, 12–15%), ce qui correspond à un excès de risque de 30% par rapport à ce qu'on attend dans la population générale. Le risque de PAG sévère était de 5% (95% CI, 4–6%) contre 3% attendu dans la population générale. Il y avait également des différences importantes dans le risque de PAG, surtout PAG sévère, entre les différentes CC. Comparé au groupe témoin composé d'enfants avec une communication interventriculaire (CIV) mineure (non-opérée), le risque de PAG était le plus élevé pour la ToF (OR ajusté 2,7 ; 95% CI 1,3–5,8) et la CIV opérée (OR ajusté 2,1 ; 95% CI 1,1–3,8).

Dans notre troisième étude, nous avons conduit une revue systématique de la littérature et identifiées 2053 publications potentiellement pertinentes dont sept spécifiquement sur les issues défavorables chez les enfants nés avec une CC et PAG. L'issue la plus étudiée était la mortalité. Par manque d'études et de données, nous n'avons pas pu faire une méta-analyse. Néanmoins, il ressort de ces études que les enfants nés avec une CC et un PAG sembleraient avoir un risque accru de mortalité, d'entérocolite ulcéro-nécrosante néonatale et d'atteintes neurologiques.

Une meilleure compréhension des relations complexes entre CC et RCN est importante afin de fournir des soins optimaux aux enfants nés avec une CC. Nos résultats fournissent des renseignements supplémentaires pour comprendre les mécanismes causaux aboutissant à un RCN dû aux mécanismes physiopathologiques spécifiquement associés aux différentes CC.

Nos travaux ont également soulevés la nécessité de conduire des recherches complémentaires dans ce domaine, et notamment pour comprendre dans quelle mesure l'effet de RCN sur des issues défavorables à court et à long terme pourrait varier selon le type de CC ; ainsi que de savoir si le RCN figure parmi les cheminements causaux entre les CC et les issues des nourrissons nés avec une CC y compris la possibilité d'une croissance postnatale suboptimal.

3991/4000 caractères espaces compris

Mots clés : Les cardiopathies congénitales (CC) ; le retard de croissance du nouveau-né (RCN) ; les études en population ; prévalence ; revue systématique et méta-analyse ; régression logistique ordinaire ; petit poids pour âge gestationnel (PAG) ; le retard de croissance intra-utérine (RCIU) ; mortalité, morbidité

Résumé substantiel en française

Les cardiopathies congénitales (CC) et le retard de croissance intra utérin ?? (RCIU) restent, malgré des améliorations importantes dans leur prise en charge, deux causes importantes de morbidité et de mortalité infantiles mais aussi sur le long terme. Les CC touchent près de 1% de toutes les naissances confondues et sont un groupe d'anomalies congénitales très hétérogène en terme de prévalence, d'origine embryologique, de gravité et d'issue. Il existe de nombreuses CC et les sous-groupes plus fréquents incluent dans cette thèse sont les communications intraventriculaire (CIV), la coarctation de l'aorte (CoA) l'hypoplasie du cœur gauche (HLHS) la Tétralogie de Fallot (ToF), la transposition de grandes vaisseaux (TGV) ainsi que retours veineux pulmonaire veineux anormal total (RVPAT)

Une définition satisfaisante de RCN a été le sujet de beaucoup de publications mais aucun consensus universellement reconnu n'a été obtenu. Pourtant en pratique, la plupart des études empiriques sur le retard de croissance intra-utérine ou RCN utilisent un synonyme proche, le petit pour l'âge gestationnel (PAG), défini comme un poids de naissance < 10^{ème} percentile d'une courbe de poids de naissance dans une population de référence. Ainsi la fréquence du PAG dans la population générale est de l'ordre 10%. En revanche, il existe une proportion de PAG qui n'ont pas un RCN (PAG constitutionnel) et inversement.

Les nourrissons nés avec une CC ont plus fréquemment un RCN et un plus mauvais pronostic médical par rapport aux enfants nés avec une CC sans RCN. On pense qu'ils sont « doublement pénalisés » par la combinaison des deux pathologies, dont l'association semble plus fréquente que par leurs seules prévalences individuelles, mais à ce jour il existe peu de données sur ce sujet. D'autre part la cause physiopathologique de cette association est incertaine. On pense que l'association entre CC et RCN pourrait être le résultat d'une cause commune avec effet direct ou indirect et différents mécanismes selon les diverses cardiopathies. Il existe des manques importants dans la littérature concernant cette relation entre CC et RCN et cette thèse a pour but de répondre à certaines questions non résolues et plus particulièrement les questions de recherche suivantes :

- iv. Quel est le risque pour un enfant né avec une CC d'avoir un RCN ?
- v. Est-ce que la probabilité et la gravité des RCN varient en fonction des différentes CC ?
- vi. Quel est le risque de mortalité et de morbidité à court terme chez les enfants nés avec une CC et un RCIU ?

Afin de répondre à ces questions, nous avons effectués deux revues systématiques de la littérature ainsi qu'une analyse de données à partir d'une cohorte prospective d'enfants nés avec une CC isolée (non associée à d'autres anomalies congénitales).

La première revue systématique de la littérature a identifiée 38 études pertinentes parmi les 1783 publications potentielles. Pour cette étude, nous avons utilisés les mots clefs pour interroger 2 bases de données (Pubmed et Embase) jusqu'au 31/03/2019 et deux chercheurs indépendants ont effectué la requête en utilisant un formulaire d'extraction prédéterminé. Le *Critical Appraisal Skills Programme* (CASP) a été utilisé pour évaluer le risque de biais dans les différentes études. On a retrouvé un faible risque de biais pour quatre études et il y avait peu d'études qui avaient pris en compte les potentiels facteurs de confusion. La méta-analyse menée en utilisant un modèle à effet aléatoire sur 18 études a montré que la proportion de PAG pour toutes les CC confondues était de 20% (95% CI 16%-24%, I^2 97.5%) et de 14% (95% CI 13%-16%, I^2 74%) pour les CC isolées. La proportion de PAG variait considérablement selon les différents types de CC avec des proportions allant de 12% (95% CI 7%–18%) pour la communication intra-auriculaire isolée à 30% (95% CI 24%–37%) pour la ToF. La plupart des études étaient menées aux Etats-Unis et 60% étaient des études en population. Puisque les sous-groupes incluait également des anomalies génétiques, nous ne pouvons pas déterminer l'étiologie de l'augmentation dans la proportion de PAG. C'est la raison pour laquelle, nous avons menés une étude sur une cohorte française avec des cardiopathies isolées.

L'étude EPICARD était une étude en population qui incluait tous les enfants nés avec un CC en Ile de France (Paris et ses banlieues proches) entre 2005 et 2008 (N=2348 nés vivants). Cette cohorte était suivi pendant 8 ans avec un recueil des données à des intervalles réguliers (1 an, 3ans, 8 ans). Notre étude sur la cohorte EPICARD avait pour objectif de déterminer le risque de RCN pour les enfants nés avec un CC, pour les différents types de CC. Nous avons étudié 5 types de CC (ToF, CIV, TGV, CoA, et CIV) et notre population d'étude a englobé 1789 enfants avec un CC isolé. Nous avons utilisé une régression logistique ordinaire pour déterminer le risque cumulé de PAG. L'analyse des données de la cohorte EPICARD a retrouvé un risque global de PAG dans les CC isolées de 13% (95% CI, 12–15%), ce qui correspond à un excès de risque de 30% par rapport à ce qu'on attend dans la population générale. Le risque de PAG sévère (défini par un poids < 3^{ème} centile) était de 5% (95% CI, 4–6%) contre 3% attendu dans la population générale. Il y avait également des différences importantes dans le risque de PAG, surtout PAG sévère, entre les différentes CC. Comparé au groupe témoin composé d'enfants avec une communication interventriculaire (CIV) mineure (non-opérée), le risque de PAG était

le plus élevé pour la ToF (OR ajusté 2,7; 95% CI 1,3–5,8) et la CIV opérée (OR ajusté 2,1; 95% CI 1,1–3,8). Cette étude a permis d'élaborer quelques hypothèses physiopathologiques pour expliquer l'augmentation du risque de RCN observé. Nous proposons qu'une anomalie hémodynamique pourrait être à l'origine soit par hypoperfusion sanguine (par exemple CIV opéré) ou soit par hypoxémie lié aux shunts dans la circulation fœtale qui augmentent le débit du sang désoxygéné malgré un hémodynamique sub normale (par exemple ToF). Nous demeurons perplexes concernant les résultats dans les TGV qui, selon notre hypothèse étiologique (de l'hypoxémie), devraient avoir une plus haute proportion de PAG par rapport à ce que nous avons observé. Une explication de ce phénomène pourrait être qu'il existe des mécanismes compensatoires dans la circulation fœtale ou soit dans le placenta. En revanche nous n'avons pas trouvé une association entre risque élevé de PAG et TGV, CoA et les ventricules uniques. Nous n'avons pas pu explorer le mécanisme d'une circulation fetal anormale en raison des limitations dans nos données. Toutefois ce modèle pourrait également expliquer une augmentation de risque de morbidité par exemple par hypoperfusion sanguine dans les HLHS (expliquer) : nous supposons qu'il y ait une redistribution du débit sanguin pour préserver le cerveau (« *brain sparing effect* ») avec par conséquent une hypoperfusion intestinale aboutissant au PAG (en raison d'une hypoperfusion des organes endocriniens). Par ce même mécanisme nous supposons qu'il pourrait y avoir un risque augmenté d'entérocolite ulcéro-nécrosante. C'est la raison pour laquelle nous avons mené une autre revue systématique pour mieux comprendre l'impact du PAG sur le pronostic.

Dans notre troisième étude en utilisant la même méthodologie de requête et les mêmes critères de sélection que dans notre première publication nous avons identifié 2053 publications potentiellement pertinentes en ce qui concerne l'issue de ces nouveaux-nés. Notre meta-analyse comportait finalement 11 études sur le petit poids à la naissance (PPN) car nous avons élargir le critère de sélection de PAG à PPN en général pour augmenter le nombre d'études incluables. En effet, en ce qui concerne le PAG, nous n'avons retrouvé que sept études spécifiquement sur les issues défavorables. Notre méta-analyse sur le PPN en utilisant un modèle à effet aléatoire a démontré que les enfants nés avec une cardiopathie opère et PPN ont une mortalité de 37% (95%CI 27%-47%, I² 96%) La mortalité variait selon les types de cardiopathie, HLHS et RAVAP avait la plus élevée suivi par TGV et CoA (expliquer). Il y avait plus de mortalité dans les études en population par rapport aux études monocentriques (50% (63% -36% vs 10 % (4%-16%). Nous supposons que ces résultats pourraient avoir un lien avec un biais de survie et de sélection. Concernant les études portant uniquement sur les enfants nés avec une CC et un PAG,

ces enfants sembleraient avoir un risque accru de mortalité, d'entérocolite ulcéro-nécrosante néonatale et d'atteintes neurologiques. Nous ne pensons pas que le faible nombre d'études sur le PAG et les CC était due à un biais de publication puisque le graphique en entonnoir et le test d' Egger étaient négatifs concernant CC et PAG ?.

Pour résumer le travail de thèse, nous avons trouvé que la proportion de RCN basé sur le proxy du PAG dans les enfants nés avec un CC était deux fois plus élevée comparée à la population générale. Il existe des variations importantes dans la proportion de PAG selon les différentes CC. Pour la CIV mineure, la proportion de PAG était comparable à la population générale, pour d'autres notamment la ToF, la proportion de PAG était trois fois plus élevée que la valeur attendue. Finalement il semble que les enfants nés avec un CC et PAG ont un risque de mortalité et de la morbidité accru y compris entérocolite ulcéro-nécrosante ainsi que les altérations neurocognitives.

Pour expliquer nos résultats nous proposons deux mécanismes physiopathologiques. Soit la CC induit le PAG, soit un facteur intermédiaire aboutit au PAG et à la CC en même temps mais il est également possible que le mécanisme puisse varier selon le type de CC. En ce qui concerne l'hypothèse où la CC induit le PAG, nos résultats des variations de PAG selon le type de CC soutiennent cette idée. D'autres auteurs (Rizzo *et al*, Lutin *et al*. Et Al Nafsi *et al*.) prônent également cette hypothèse pour expliquer le PAG dans l'hypoplasie du cœur gauche basé sur les résultats d'imagerie de la circulation foetale. Story *et al*. met en avant des variations dans le taux d'oxygénation sanguine pour expliquer les différences de PAG pour différentes CC. Une hypothèse soutenue par Donfrio *et al* et par leurs études avec des Doppler foetaux. A contrario, plusieurs auteurs ont émis l'hypothèse que le placenta est un facteur intermédiaire qui aboutit au PAG et à la CC simultanément. Jones *et al* ont fait des analyses histoplacentaires sur les enfants nés PAG avec une hypoplasie du cœur gauche. Ils ont trouvé qu'une augmentation en leptine placentaire était responsable de la CC ainsi que d'une diminution de l'angiogenèse placentaire. D'autres explications pourraient être génétique /épigénétique ou environnementales (par exemple la consommation du tabac)

Les implications cliniques de cette thèse sont que nos résultats pourraient aider les cliniciens à mieux conseiller les patientes pendant la diagnostique prénatal ainsi qu'à mieux organiser la prise en charge postnatale des enfants nés un PAG et une CC.

Les forces de cette thèse sont que nos revues systématiques ont été menées avec une méthodologie robuste et répliquable par une équipe pluridisciplinaire. Notre étude en population

sur les CC isolés a pu analyser l'effet de la CC sur la croissance sans les associations avec d'autres anomalies génétiques. Notre utilisation de la régression logistique ordinale a permis d'analyser les PAG modérés et sévères dans le même modèle et d'augmenter la puissance de cette analyse. Les limites sont la validité externe de nos résultats dans des pays en voie de développement, la limitation dans les données récoltées (pour les revues systématiques et les études en population) ainsi que la limitation aux enfants nés vivants uniquement (un biais de sélection par rapport aux morts nés et aux interruptions médicales de grossesses). Finalement nous ne pouvons pas non plus explorer plus en détail les mécanismes physiopathologiques à l'origine des CC et des PAG.

Ainsi nos perspectives de recherche sont d'analyser la mortalité des enfants nés avec une CC et un PAG à 8 ans dans la cohorte EPICARD. Nous aimerions compléter les données qui pourraient expliquer l'étiologie physiopathologiques avec des échographies /Doppler, des analyses anatomopathologiques des placenta ainsi que des mesures plus détaillées à la naissance des enfants nés avec un CC et PAG.

Une meilleure compréhension des relations complexes entre CC et RCN est importante afin de fournir des soins optimaux aux enfants nés avec une CC. Nos résultats apportent des renseignements complémentaires pour comprendre les mécanismes causaux aboutissant à un RCN dû aux mécanismes physiopathologiques spécifiquement associés aux différentes CC. Nos travaux ont également soulevé la nécessité de conduire des recherches complémentaires dans ce domaine, et notamment pour comprendre dans quelle mesure l'effet du RCN sur les issues défavorables à court et à long terme pourrait varier selon le type de CC ; ainsi que de savoir comment RCN participe au lien entre les CC et des issues moins favorables, y compris par la possibilité d'une croissance postnatale suboptimale.

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List of abbreviations

ACC-CHD	Anatomical and clinical classification of CHD
ART	Assisted reproductive technology
ASD	Atrial septal defect
AS	Congenital Aortic stenosis
AVSD	Atrioventricular septal defects
CA	Congenital anomalies
CASP	Critical Appraisal Skills Programme
CI	Confidence intervals
CHD	Congenital heart defects
CoA	Coarctation of the aorta
DROV	Double outlet right ventricle
EFW	Estimated fetal weight
EPICARD	<i>Epidémiologie des CARDiopathies congénitales</i>
EUROCAT	European Surveillance of Congenital Anomalies
FGR	Fetal growth restriction
FUH	Functional univentricular heart
GRN	Growth restriction in the newborn
HLHS	Hypoplastic left heart syndrome
IPCCC	The International Pediatric and Congenital Cardiac Code
IUGR	Intra uterine growth restriction
LBW	Low birth weight
MeSH	Medical Subject Heading
OR	Odds ratio
PFO	Patent foramen ovalis
PS	Pulmonary stenosis
RR	Risk ratio
SGA	Small for Gestational Age
TA	Tricuspid atresia
TAPVR	Total anomalous pulmonary venous return
TGA	Transposition of the great arteries
ToF	Tetralogy of Fallot
TOPFA	Termination of pregnancy for fetal anomaly
VLBW	Very low birth weight
VSD	Ventricular septal defect

Acknowledgements

I would like to start by thanking all the people who have supported me throughout this long arduous journey towards a PhD, and who have made this thesis possible.

I would like to especially thank the following:

Pr. Philippe Acar and Pr. Marie-Victoire Senat for accepting the role of rapporteur for this thesis. It is a great honour and privilege to have your evaluation of my thesis.

Members of the jury committee Dr Chloé Barsinski and Dr Marie-Aline Charles for accepting to participate in my defence.

The Pierre Louis Doctoral School of Public Health for accepting me onto the doctoral programme and for accepting my request to defend my thesis. A special thanks to Magali Moulie

APHP-DRCI who financed my thesis via the Bourse-APHP Sage-femme notably Francois Bassonpierre, Marie-Agnes Lefevre and the 2017 jury consisting of Gearld Breart, Marion Carayol, Christine Etchemendigarary, Patrick Rozenberg, Karine Girard and Grazia Brisset. Thank you for your confidence and for pushing me forwards to pursue another project when the initial one fell apart.

Sophie Guillaume, Vincent-Nicolas Delpech, Yves Ville and Pascal Vouhé who provided their full support for me to leave my day job at Necker to carry out doctoral research full time.

Pierre-Yves Ancel, Director of the EPOPé team and Francois Goffinet who allowed me construct my doctoral project within their unit. For all their support during the dark moments.

My thesis supervisors Laurent Salomon and Babak Khoshnood to whom I'm eternally grateful. Thanking you for supervising the rudimentary beginnings of an idea that evolved finally into this fully blossomed thesis.

Damien Bonnet and Laurence Foix-Hélias for their unwavering support and expert advice from the very beginning of this long journey.

I especially would especially like to thank Catherine Deneux-Tharoux, Corrine Dupont and Anne Rousseau for all their encouragement in seeing this project to its end and their assistance with selecting the jury.

Jérémie Cohen a true gentleman, who kindly stepped in with the supervision of my third and final paper. Without your help all would have been lost and I'm grateful for your guidance.

Nathalie Codet, Sophie Pennec, Denis Basse, Sophie Gouvaert who work tirelessly behind the scenes.

Colleagues and friends who answered endless questions and shared moments on coffee breaks and lunches. In particular, Nathalie Lelong, Rym el Rafei, Isabelle Monier, Aurélien Seco, Nathalie Bertille, Neil Derridj, Adrien Aubert, Monica Saucedo, Alice Hocquette, Pauline BlancPetitjean, Jade Merrier, Anna Vera Seppanen, Makan Rahshenas, Karim Tarabit and my fellow PhD students in the "Young" Researchers' group.

Finally, I want to thank my loving wife and children for their tireless support, patience and understanding with sometimes long working hours and travels and throughout this journey.

Scientific presentations and publications

Scientific presentations

15th European Symposium on Congenital Anomalies: “Current Approaches to Congenital Anomalies” 2nd July 2020. Poster presentation on Children born with Congenital Heart Defects and Growth Restriction at Birth: A Systematic Review and Meta-Analysis accepted. Conference Cancelled because of COVID-19 pandemic

Euroscicon webinar on Heart congress and Obesity. Webinar. 29th September 2020. Oral presentation on Children born with Congenital Heart Defects and Growth Restriction at Birth: A Systematic Review and Meta-Analysis

ICCAP 2021: 25th International Conference on Congenital Anomalies and Pathology 25th – 26th January 2021. Paris, France. Oral presentation on Children born with Congenital Heart Defects and Growth Restriction at Birth: A Systematic Review and Meta-Analysis (best presentation award)

Congrès de la Société Française de la Pédiatrie 19-21 May 2021. Poster publication. Prevalence of growth restriction at birth for newborns with congenital heart defects: A population-based prospective cohort study (EPICARD)

17eme congrès Médico-chirurgical de la FCPC. 29th September -1st October 2021. Oral communication on Prevalence of growth restriction at birth for newborns with congenital heart defects: A population-based prospective cohort study (EPICARD)

50eme journées nationales de la société Française de la Médecine Périnatale (SFPC) 7th -9th October 2021. Oral Communication on Prevalence of growth restriction at birth for newborns with congenital heart defects: A population-based prospective cohort study (EPICARD)

31st World congress on Ultrasound in Obstetrics and Gynecology (ISUOG). 15th -17th October 2021. 2 Poster communications on Children born with Congenital Heart Defects and Growth Restriction at Birth: A Systematic Review and Meta-Analysis and Prevalence of growth restriction at birth for newborns with congenital heart defects: A population-based prospective cohort study (EPICARD)

9th Congress of the European Academy of Paediatric Societies (EAPS). 7th -11th October 2022. Poster communication on Early mortality in infants born with neonatally-operated congenital heart defects and low or very-low birthweight: Systematic review and meta-analysis.

Publications

Ghanchi, A., Derridj, N., Bonnet, D., Bertille, N., Salomon, L. J., & Khoshnood, B. (2020). Children born with congenital heart defects and growth restriction at birth: A systematic review and meta-analysis. *International Journal of Environmental Research and Public Health*, 17(9), 3056.

Ghanchi, A., Rahshenas, M., Bonnet, D., Derridj, N., LeLong, N., Salomon, L. J., ... & Khoshnood, B. (2021). Prevalence of Growth Restriction at Birth for Newborns With Congenital Heart Defects: A Population-Based Prospective Cohort Study EPICARD. *Frontiers in Pediatrics*, 9.

Publications unrelated to this doctoral thesis

Ghanchi, A. (2020). Adaptation of the National Plan for the Prevention and Fight Against Pandemic Influenza to the 2020 COVID-19 epidemic in France. *Disaster medicine and public health preparedness*, 14(6), 805-807.

Ghanchi, A. (2021). Adaptation of coronavirus disease (COVID-19) protocols to a Parisian maternity unit during the 2020 pandemic: A managerial perspective. *Disaster Medicine and Public Health Preparedness*, 15(2), e36-e39.

Chapter 1: Introduction

Congenital anomalies (CA) can be broadly defined as structural malformations, chromosomal anomalies, and syndromes occurring in the early stages of embryonic development that may be diagnosed prenatally or postnatally(1). Overall, CA represent relatively frequent events (6% of all births) (2) They are a major cause of mortality, childhood morbidity and long-term disability. The scholarly activities concerned with CA comprise a complex set of scientific questions and public health challenges. A rich mix of disciplines as diverse as genetics, embryology, pathology, physiology, public health, epidemiology, biostatistics but also social sciences. can and do address important questions concerning fetuses and newborns with CA.

There is great heterogeneity within CA and most CA are rare diseases (prevalence < 1 per 2500 births as per the European definition of what comprises a rare disorder)(3,4). Their study represents important conceptual and empirical challenges. In this context, it is essential that we understand whether and to what extent results a given study on a specific type or subgroup of CA may or may not be applicable to other CA. This heterogeneity is also particularly true in the case of CHD. Indeed, they represent a very heterogeneous group of malformations in terms of their prevalence, embryological origin, pathophysiology, severity, clinical management and outcomes.

Congenital heart defects (CHD)

CHD are the most frequent group of congenital anomalies and account for approximately 1% of all births(3,5,6) They comprise a large spectrum of malformations that affect the structure of the heart and are prenatal in origin. By definition, they exclude patent ductus arteriosus, cardiac tumors, cardiomyopathies and arrhythmias(7). Isolated CHD are defined as CHD not associated with chromosomal anomalies, malformations from other systems and / or syndromes.(6-8)

There are important geographic and temporal differences in the prevalence of CHD. However, at least some of these differences are due to diagnosis, coding and data collection issues.

There are also important differences in the practices and policies with regard to prenatal diagnosis and termination of pregnancy for fetal anomalies across countries, which can in turn result in differences in the live birth prevalence of CHD across countries and over time

Normal heart and pathophysiology of CHD

The heart is a four chambered pump that circulates oxygenated and deoxygenated blood to the lungs, brain and the rest of the body. The four chambers can be divided into two parts consisting of an atria and ventricle joined together by valves that ensure unidirectional blood flow. The right side of heart is composed of the right atrium and ventricle separated by the tricuspid valve. Deoxygenated blood from the vena cava enters the right atrium and is pumped by right ventricle to the lungs via the pulmonary artery.

The left side of the heart is composed of the left atrium and ventricle separated by the mitral valve. Oxygenated blood from the lungs enters the left atrium and is pumped by the left atrium to the head and body via the aorta. The aorta exits the left heart between the bifurcation of the main pulmonary artery, with the aortic arch looping over the left pulmonary artery. Both the right and left sides of the heart are separated by interatrial and interventricular septa.

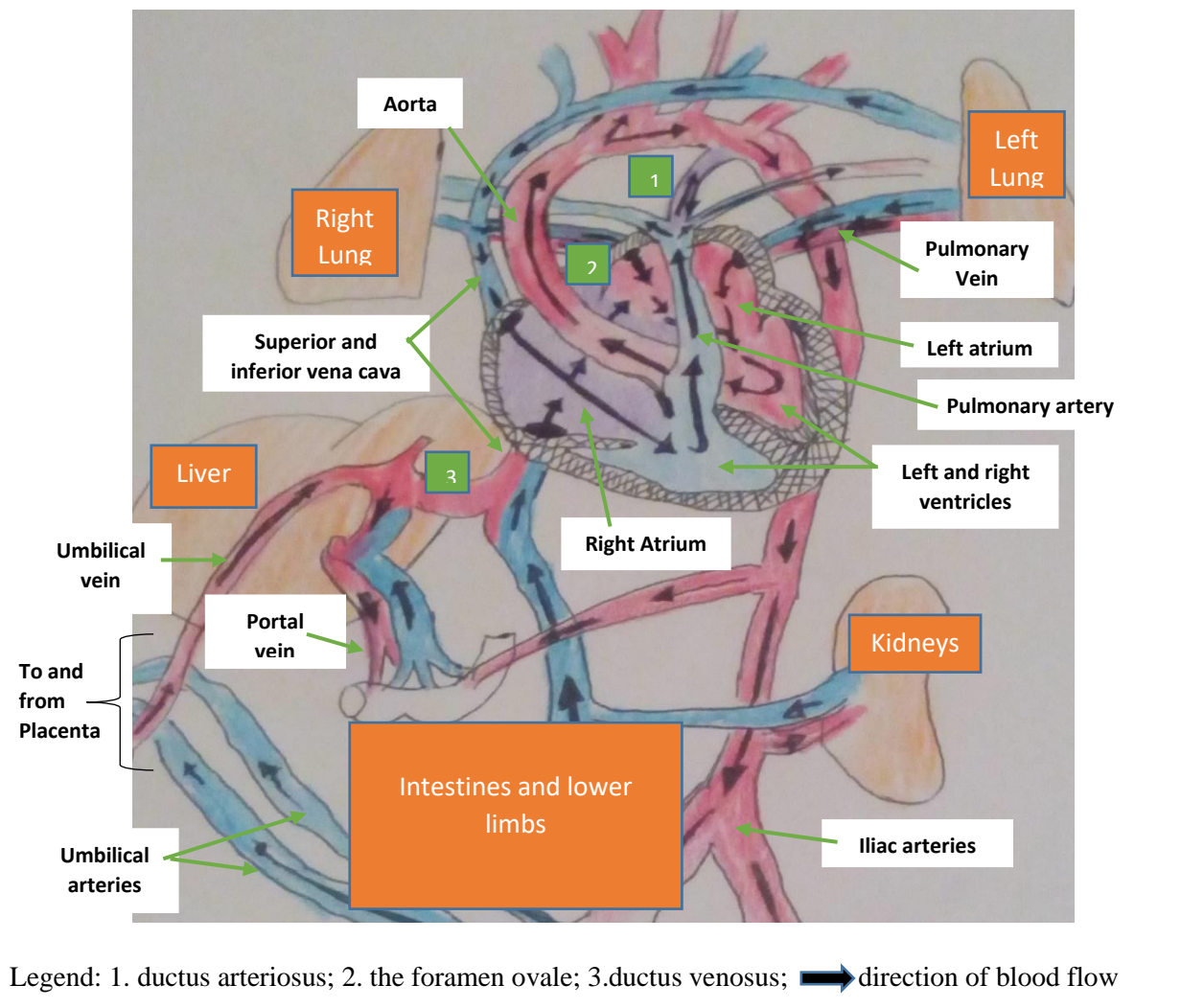
Normal intra and extra-uterine circulation.

In normal fetal circulation, once embryological cardiogenesis is completed, oxygenation of tissues occurs through the placenta, bypassing the lungs. Three shunts are essential to intra-uterine life; i) the ductus arteriosus, ii) the foramen ovale and iii) the ductus venosus (Figure 1) (9) .

From the internal iliac arteries, deoxygenated blood flows to the umbilical arteries which enter the placenta. Gaseous and nutrient exchanges occur in the placenta through which oxygenated blood leaves through the umbilical vein.(9,10) Approximately 30% of oxygenated blood in the umbilical vein is shunted through the ductus venosus joining the inferior vena cava and enters directly into the right side of the heart(9,10). The rest of the oxygenated blood in the umbilical vein enters the liver via the portal vein and then becomes the hepatic vein as oxygenated blood leaves this organ. The hepatic vein also joins the inferior vena cava which also follows directly into the right side of the heart (9,10).

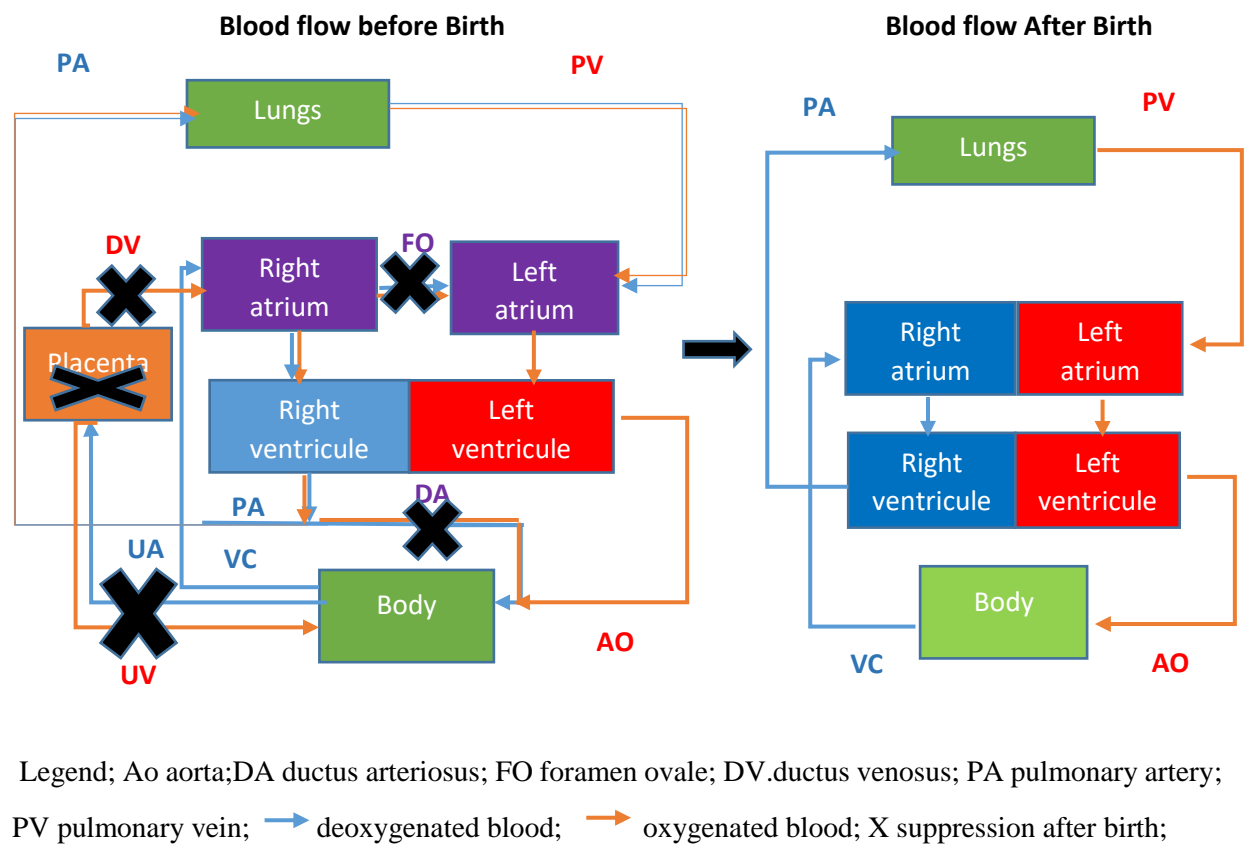
The foramen ovale joins the right and left atria. This allows oxygenated blood from the right atrium to circulate directly into the left atrium bypassing the lungs and the right ventricle. Blood then flows into the left ventricle and the rest of the body as it exits the heart via the aorta. A portion of the blood is also pumped into the right ventricle where it enters the pulmonary arteries (9,10).

Figure 1: Fetal heart and intrauterine blood circulation (9)



The ductus arteriosus joins the pulmonary arteries to the aorta. Hence, oxygenated blood bypasses the lungs and flows directly into the aorta. The shunting of oxygenated blood via the foramen ovale and the ductus arteriosus is facilitated by high vascular resistance in the lungs. This is because the alveoli are closed in the non-functional lungs during intrauterine life. At birth, the alveoli expand as the lungs become functional, vascular resistance decreases, which causes the prostaglandins levels to decrease, which in turn results in the closure of the ductus arteriosus. Normally, the foramen ovale and the ductus venosus also close at birth (Figure 2) (9,10)

Figure 2: Schematic diagram of the physiological changes that occur at birth so that the heart is fully functional at birth to pump blood around the body and maintain extra-uterine life (10).



CHD subtypes: A brief survey of some of the major defects

This section describes some of the major forms of CHD, which were studied in this thesis. They illustrate the great heterogeneity that exists across different CHD.

Ventricular septal defect

Ventricular Septal Defect (VSD) is an interventricular communication due to a defect in the septal wall between the left and right ventricles(9,11). This results in a pathological left to right shunt with detrimental effects being dependent on pulmonary artery vascular resistance and the size and location of the VSD. The formation of the interventricular septum occurs around the fifth week of cardiogenesis and is due to both the folding of the primitive heart and fusion of the muscular, outlet and inlet septa(9,11,12). Any disruption that may occur during this complex physiological process may result in either perimembranous VSD, outlet VSD, Atrioventricular canal VSD or muscular VSD(12).

The different types differing according to the location of the interventricular communication(11). Furthermore VSD may also be present in other CHD for example Tetralogy of Fallot etc. Clinical manifestations of VSD vary according to their size with small VSD often being asymptomatic. Medium and large VSD are initially characterized by tachypnea, dyspnea, difficulties in feeding and poor weight gain. However untreated, over time the shunt may be reversed resulting in congestive heart failure.(11)

Coarctation of the Aorta

Coarctation of the aorta (CoA) is the result a narrowing in the aorta usually in the area of the ligamentum arteriosum of the aortic arch(13). It is thought that the narrowing of the aortic lumen is due to ductal tissue which progressively closes the ductus arteriosus to form the ligamentum arteriosum.

Consequently there are three types of CoA categorized according to its proximity to the ligamentum arteriosum and include preductal CoA, ductal CoA and post ductal CoA (13). As a result symptoms vary according to the location and degree of the aortic constriction in addition to the type of CoA.

Although CoA may be asymptomatic in a number of cases, complications may be due cardiac muscle hypertrophy and insufficient blood flow to the extremities resulting in dyspnea, difficulties feeding and a failure to thrive in infants(13). While insufficient blood flow to the extremities may result in unequal pulse between limbs.

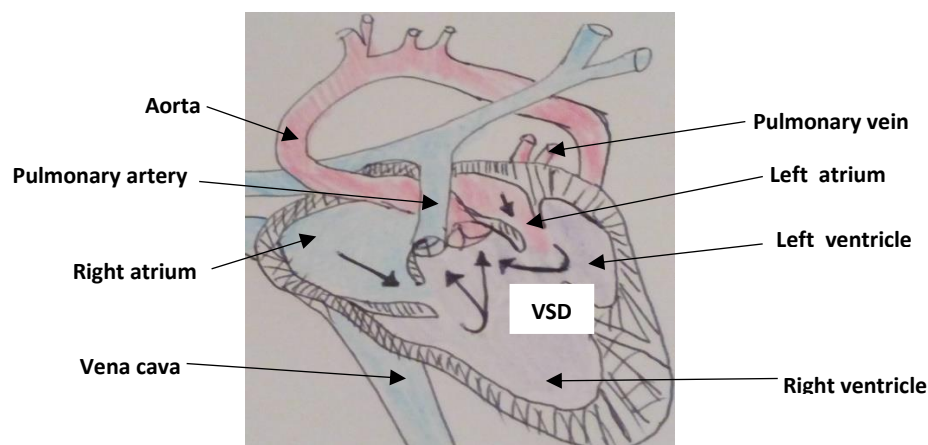
Double-outlet right ventricle

Double outlet right ventricle (DORV) is where both the aorta and pulmonary arteries (known collectively as great arteries) are connected to the right ventricle(14,15). As there is no longer an outlet for blood to exit the left ventricle, there is usually an interventricular communication that allows blood to enter the right ventricle. The embryological etiology of DORV is complex and is likely the result of multiple abnormalities that occur simultaneously as the primitive right ventricle divides and is remodeled into the pulmonary artery and the aorta and migration of the endocardial cushions into the semilunar valves, conal septum (14,15)

DORV is a heterogeneous group malformations of ventriculo-arterial connections with types depending on the size of the great arteries, how these vessels are connected to the right ventricle, the extent of the VSD and circulation of blood into great arteries.(14) Common variants include subaortic VSD DORV (figure 3), subpulmonary VSD DORV, Non committed VSD DORV and

Doubly Committed VSD DORV(14). Other rare variants include DORV with an intact interventricular septum resulting in a hypoplastic left ventricle and Fallot type which includes pulmonary stenosis in addition to the presence of the VSD. As a result of these variations clinical symptoms of DORV are extremely variable although cyanosis and tachypnea are often present. Symptoms may also be further complicated by the presence of other CHD, extra congenital anomaly, chromosomal anomaly and or syndromes (14,15)

Figure 3: Cross sectional view of DORV heart (14)



Legend: → blood flow; VSD ventricular septal defect

Hypoplastic left heart syndrome

Hypoplastic left heart syndrome (HLHS) is a range of malformations caused by a cascade of multiple anomalies during cardiogenesis that result in the left side of the heart being underdeveloped (12,16). In addition to hypoplasia of the left ventricle, atresia or hypoplasia of the aorta, aortic valve and/ or the mitral valve may also be present(16). As the great vessels are normally connected, the heart is unable to pump oxygenated blood through the aorta. Shortly after birth, the right side of the heart is able to sustain life because oxygenated blood bypasses the left ventricle through the patent ductus arteriosus and the foramen ovale(16). However as the patent ductus arteriosus and foramen ovale physiologically closes shortly after birth, HLHS is fatal in the absence of medical and surgical intervention. Prior to death, other clinical manifestations of HLHS include cyanosis, dyspnea and weak peripheral pulses(16).

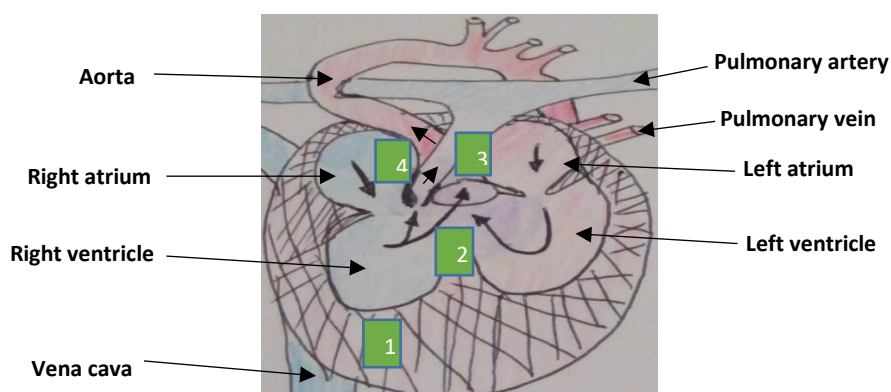
Tetralogy of Fallot

Tetralogy of Fallot (ToF) is a combination of the following four separate CHD that occur concomitantly(9). These include i) pulmonary stenosis (PS) ii) VSD iii) dextroposition of the aorta (i.e. an overriding aorta that is positioned directly over the VSD and connected to both ventricles instead of over the left ventricle) and iv) right ventricle hypertrophy (figure 4)(17,18). ToF is caused by an anomaly during cardiogenesis. Normally, the aortic pulmonary septum executes a spiral of 180° and swings into line with the superior margin of the intra ventricular septum(12).

An anomaly during this process results in PS, VSD and an overriding aorta while these malformations increase resistance in blood flow through the right outflow tract resulting in a hypertrophied right ventricle(9) .

The overall consequence of these four combined malformations is that the blood is insufficiently oxygenated and clinical symptoms depend on the severity of the right outflow tract obstruction and individual CHD (e.g. type of PS and VSD, the precise location of the overriding aorta and degree of right ventricle hypertrophy)(17,18). Consequently there a number of different types of ToF, while ToF may also combine with other CHD (e.g. Atrial Septal Defects,ASD also known as pentology of Fallot)(18). Cyanosis is often present to varying degrees (either persistently or during episodic hypercyanotic spells) in addition to this dyspnea, tachypnea, syncope, difficulties in feeding, poor weight gain and clubbing of fingers and toes may also be present in certain cases(17,18).

Figure 4: Cross sectional view of ToF heart(9,18)

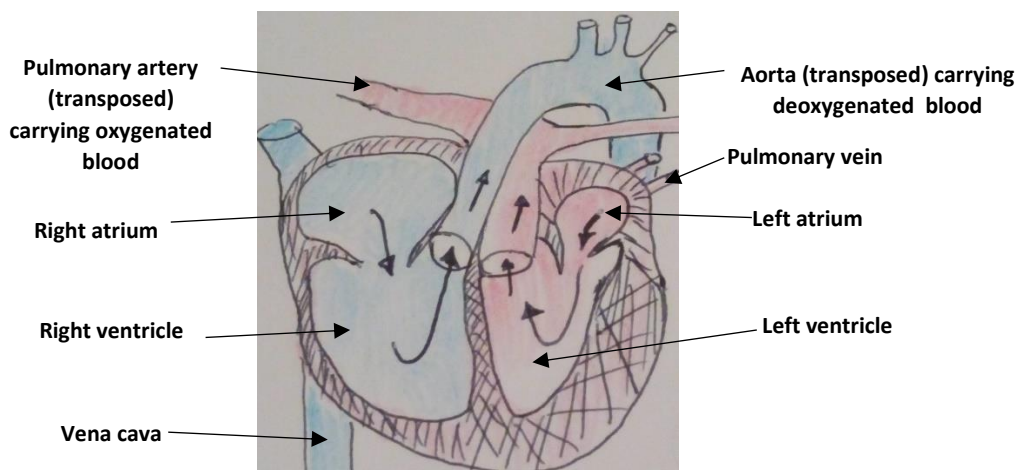


Legend: → blood flow; 1. Hypertrophied right ventricle; 2 Ventricular septal defect; 3 overriding aorta directly over VSD; 4. pulmonary stenosis

Transposition of the great arteries

Transposition of the great arteries (TGA) occurs as the result of a failure of the aorticopulmonary septum fails to spiral correctly approximately around the 5 week of embryological development resulting in a permutation of the great arteries (pulmonary artery and aorta) (12,19). Consequently TGA is defined by the presence of atrioventricular concordance and ventriculoarterial discordance (i.e. the pulmonary artery exits the left ventricle and the aorta leaves the right ventricle, figure 5), while variations in the spatial arrangement between the aorta and pulmonary artery result in a number of different types(9,18,19). TGA may also be combined with other CHD being present simultaneously such as VSD, ASD, aortic stenosis (AS) or other defects of adjacent structures/ vessels etc (9,18,19).

Figure 5: Cross sectional heart with TGA (9,18)



Legend: —→ blood flow

The main clinical manifestation of TGA is cyanosis (9,18). The extent of the blue coloration of the skin and mucus membranes varies according to the degree of mixing between oxygenated and deoxygenated blood and presence of other CHD. Other symptoms also include tachypnea, dyspnea, tachycardia and/or feeding difficulties(19).

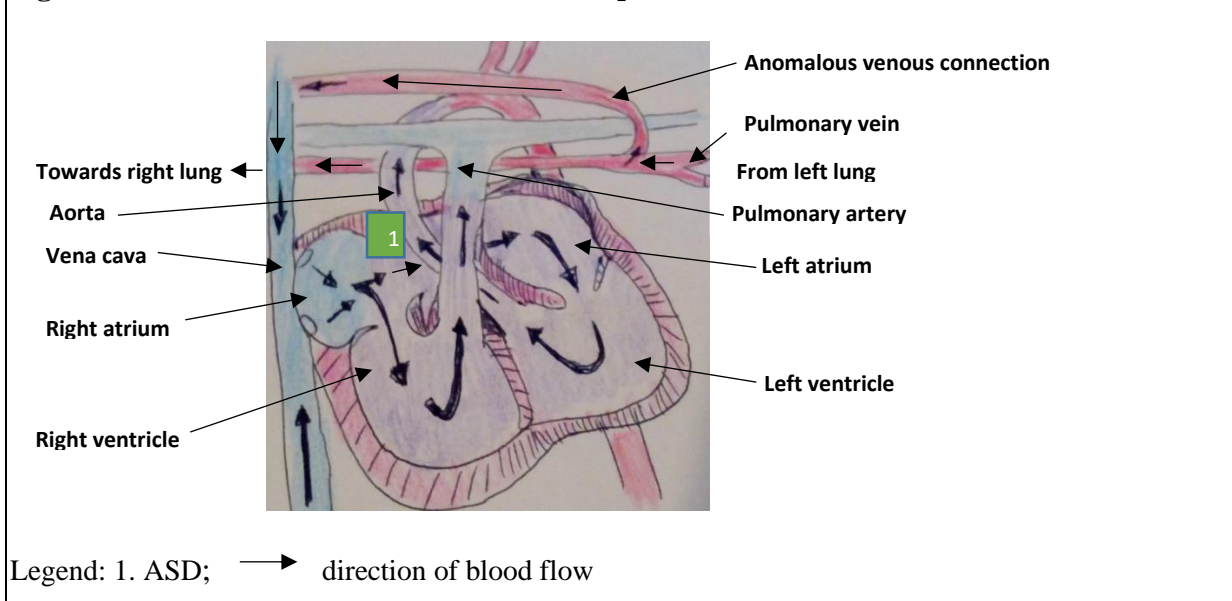
Total anomalous pulmonary venous return

Total anomalous pulmonary venous return (TAPVR) is characterized by an anomalous connection of all four pulmonary veins either indirectly (via the systemic venous circulation) or directly into the right atrium(20,21).

Consequently, oxygenated blood is mixed with deoxygenated blood in the right side of the heart instead of arriving directly into the left atrium. Therefore, to sustain life, blood must be shunted either through an ASD or patent ductus arteriosus(20,21).

TAPVR is the result of an anomaly in the formation of the pulmonary venous system early in cardiogenesis after the fusion of umbilical veins from the chorion, vitelline veins from yolk sac and cardinal veins from the embryo(12,21). These three veins flow into the sinus venosus of the primitive heart, which later develops into the right atrium. As the lungs and heart develop simultaneously, the common pulmonary vein (from which the four pulmonary veins later develop) involutes into the left atrium and is progressively separated from the systemic venous vascular system. However, the disruption of this physiological process leads to a persistence of the systemic venous connection and result in TAPVR (Figure 6)(12). There are four types of TAPVR which correspond to the level at which the pulmonary venous connection was unable to fully separate from the systemic venous system during morphogenesis(20,21).

Figure 6: Cross sectional view of a heart with Supracardiac TAPVR (20)



Clinical manifestations of TAPVR depend in part on the presence of pulmonary venous obstruction caused by their excessive length, hepatic sinusoids (low pressure vascular channels) and/or narrowing that increases venous blood pressure(20,21).

This results in pulmonary hypertension, pulmonary edema, right ventricle hypertrophy and eventually right side congestive heart failure. Severe cyanosis maybe present in addition to dyspnea and tachypnea(20,21). In the absence of pulmonary venous obstruction, TAPVR maybe initially asymptomatic however progressive cyanosis, failure to thrive, feeding and respiratory difficulties develop over time(20,21).

Congenital Heart Defects and Growth Restriction in the Newborn

Fetal growth restriction

Growth restriction in the fetus, common terms in the literature include Intrauterine Growth Retardation/Restriction (IUGR) or Fetal Growth Restriction (FGR), occurs when the rate of intrauterine growth is not sufficient for the fetus to attain its full growth potential(22,23). The latter may be affected by environmental and genetic factors(22,23). Attainment of full growth potential is empirically assessed by constructing “customized” growth curves of weight by gestational age(23,24). The customized growth curves are variably based on fetal sex, ethnicity, maternal height, parity or other characteristics and use different reference populations.(24,25)

Most commonly a 10th percentile cut-off is used and fetuses (or newborns) with weights below the 10th percentile of the gestational age-based growth curve are defined as being Small for Gestational Age (SGA); those below the 3rd percentile are classified as severe SGA (23,26). In some studies, the cut-off used is two standard deviations below the mean but this is far less common(26).

An alternative approach is to use prescriptive international intrauterine growth charts(24,27). This consists of establishing universal standardized biometrics and growth trajectory of the human fetus under optimal conditions as the reference population(24,27). This approach is based on the assumption that all fetal growth will be similar across different geographic locations if environmental constraints that affect growth are reduced to a minimum.(24,27) This approach has a potential limitation as it does not allow for “constitutionally” small newborns. Furthermore, there may be newborns who are not SGA but who nevertheless have clinical signs of growth restriction (24,27)

An international study using the Delphi method came to the conclusion that FGR should exclude cases with congenital anomalies(22). It was also agreed that there are two types of FGR, early and late FGR, which should be measured using fetal ultrasound(22). Gordijn *et al* recommended that synonyms especially IUGR should not be used to avoid confusion (22).

IUGR implies a geographical location (i.e. that restricted/retarded growth occurs in the uterus) to describe the *location* in which a pathology occurs and not the *individual* affected by the pathology(22). Furthermore, IUGR does not fully describe the semantics of physiopathology because it incorrectly implies that retarded growth can be caught up given the appropriate conditions. However due to pathology, catch-up growth does not occur in fetuses unable to fully attain their biological growth potential(22).

In practice, repeated measures are required to detect abnormal growth rates(25). There are also discrepancies between estimated fetal weight (EFW) and actual fetal weight due to measurement and statistical errors in ultrasound measures. Hence, a precise measurement of the weight occurs shortly after birth at which time one may have a precise assessment of whether the newborn has growth restriction(22,23,25).

An international group of experts coined the term “Growth Restriction in the Newborn (GRN) to describe “FGR observed at the time of birth” (28). GRN is defined based on the following criteria(28):

1. Birthweight <3rd percentile on sex specific population-based or customized growth charts or
2. The presence of at least three out of the five following criteria:
 - Birthweight <10th percentile on population based or customized growth charts
 - Head circumference <10th percentile
 - Length <10th percentile
 - Prenatal diagnosis of fetal growth restriction
 - Information on maternal pathology during pregnancy (e.g. hypertension or pre-eclampsia)

CHD and GRN

The possible association between CHD and GRN may be due to either direct and/or indirect causal effects of the CHD on fetal growth or they may both be due to a common cause(29).

These are not mutually exclusive possibilities and both may be relevant for a given case. CHD associated with GRN is likely to present more severe cases as both pathologies may result in short- and long-term adverse developmental effects.

There is a paucity of literature on the relation between CHD and growth restriction in the fetus resulting in GRN(29). The available information suggests that associations exist between the two. However, there are important shortcomings, including lack of standard definitions for growth restriction, the limited data available from population-based studies and differential assessment of for the most part short-term outcomes(29). Moreover, the heterogeneity of CHD in its relation to GRN has been little studied. Many studies have not studied CHD that is not associated with genetic abnormalities, which further complicates the interpretation of available studies(29).

The first paper of the thesis provides a summary of the available data using a systematic review and meta-analysis of the available literature (29).

Research questions, Specific Aims and Outline of the thesis

The specific research question addressed in this doctoral project were as follows:

- 1) What is the risk of GRN in newborns with CHD?**
- 2) To what extent does the probability and severity of GRN vary according to CHD subtypes?**
- 3) What is the risk of mortality and short-term morbidity in newborns with CHD and GRN?**

In order to do so, we conducted two systematic reviews and a prospective, population-based cohort of children born with isolated CHD (not associated with other anomalies) born in the Greater Paris Region (Paris and its surrounding suburbs), the EPICARD study.

After the first introductory chapter presented above, the rest of the thesis is organized as below Chapter 2 describes the methods used to carry out a systematic review and meta-analysis, as well as, the statistical analysis of the EPICARD data using ordinal logistic regression.

Chapter 3 presents two articles, which addressed the first two questions above, as published in peer reviewed journals. The chapter ends with the current draft of the manuscript addressing the third question, which is to be submitted shortly.

Finally, Chapter 4 discusses the results and their implications, and briefly outlines a few perspectives for future research on this topic.

Chapter 2: Methods

The aim of part one of this chapter is to present the methods used in a systematic review and meta-analysis. The second part briefly presents the statistical modelling of data in the Paper 2, which used ordinal logistic regression.

Part 1: Systematic review and meta-analysis: State of the art

Formulation of the research questions and establishing the search protocol

Following the Cochrane methodological approach, research questions were established beforehand using an unambiguously explicit structured question to help focus the search and define the search strategy.(30,31)

We used the term FGR defined as the failure of a fetus to attain expected growth as the initial object of our searches(22,23). The initial search found a reference to GRN, which was also included in the search strategy. We also searched for the most often used proxy of FGR and GRN, namely SGA (birthweight <10th percentile for gestational age based on a reference population)(26). We also included another definition of FGR (<2 SD of the mean birthweight)(22).

The protocols for both our systematic reviews were published on the University of York Centre for reviews and dissemination PROSPERO international prospective register of systematic reviews (Appendices 1 and 2) (32,33)

Conducting the search of the literature

A search of two bibliographic databases (Pubmed and Embase) without any limitations of date or language for both systematic reviews were carried out. Keywords and medical subject headings that were validated by a library scientist were used and the same search algorithm was used for both systematic reviews. To avoid the possibility of introducing bias in our searches, we did not use web of science, google scholar or other search engines because they retrieve records using only keywords(30,31). Thereby resulting in different numbers of retrievable publications varying on the on the researcher, keyword used, keyword order and/or spacing.

During the two literature searches, titles and abstracts were first screened for their pertinence to inclusion criteria using Rayaan web application(34). The second step of the triage was the full text review and articles were excluded according to the criteria outlined in advance in both search protocols(30,31).

In our first systematic review, we excluded articles on CHD and low birth weight only or CHD and single umbilical artery, conference abstracts, absence of SGA data, use of a matched case control study as the study design, use of estimated fetal weight from ultrasound data, and SGA outcomes in the offspring of women born with CHD(29).

In our second systematic review, we excluded articles that included extra-cardiac anomalies and/or syndromes, did not contain any data on SGA or did not report on the outcomes. We also had to eliminate irretrievable articles(33).

Throughout the whole process of both systematic reviews, two blinded reviewers conducted the search, extracted data and assessed the quality of included studies. This was carried out to reduce as much as possible the effect of reviewer bias on findings, ensuring their neutrality of and objectivity as much as possible(30,31). Conflicts between the two were arbitrated by a third senior reviewer. Furthermore, our literature review consisted of a multidisciplinary team that were able to pool their individual expertise together especially with regards to assessing the quality of included studies and the statistical analysis of extracted data.

Quality assessment

Quality assessment of studies was carried out using the Critical Appraisal Skills Programme (CASP) cohort study checklist. The CASP cohort study checklist contains 12 questions divided into three sections that enabled a structured approach to finding evidence, determine possible sources of bias, and evaluate internal and external validity of each study (35).

We specifically adapted the questionnaire used by the two blinded reviewers for both systematic reviews to research questions paying particular attention to selection and measurement biases. Although there are many other methods of evaluating bias (e.g. the use of scales/scores for different assessment criteria which enables an overall score to be given for each individual study and allows the comparison between different studies), we deemed that the CASP cohort study checklist was the most appropriate and internationally recognized method of evaluating bias in the included studies (36,37).

This is because a number of the following reasons; i) the scoring thresholds may be arbitrary resulting in a possible source of bias in itself; ii) Scores are based on what is reported in the study and not what weather the methods used were actually appropriate to either the study design or research question; iii) Scoring methods have been found to be unreliable in tests of validity, while scores may affect transparency and peer review (as the allocation of scores maybe given according to opaque/unknown criteria); iv) Overall scores assign different weights to each different study which may be also difficult to justify (30,36).

Extraction of data

For each systematic review, two predetermined forms were used to help reduce the risk of human error in the extraction of data and minimize bias(30,31)These tables were elaborated during the planning phase of each systematic review protocol and included a variety of themes specific to the research question for each systematic review. For example, study characteristics (study location, number of subjects, year etc.), CHD /subtype, definitions of SGA/FGR, data sources, study exclusion criteria, and SGA proportions (adverse outcome was also included in the second systematic review). Challenges in the extraction of data were mainly in the use of differing definitions, use of the terms FGR and SGA interchangeably, missing data and incomprehensible presentation of data. This was overcome by either contacting the authors of studies directly for complementary information or a consensus between the two reviewers

Statistical methods for meta-analysis

This section briefly describes general principal underlying a meta-analysis then the specific methods used to combine proportions reported by individual studies in the first systematic review. A meta-analysis was not possible for the second systematic review on the outcomes of CHD and growth restriction because of insufficient data.

A meta-analysis is the combination of results from two or more studies using of a variety of statistical techniques to obtain an overall weighted average of effect size(30,38,39). There are a number of different methods in which weight is attributed however the underlying idea behind a meta-analysis is that studies with a bigger effect size observed in a larger population sample will have a greater contribution to the overall summary effect because of a larger allocated weight (30,38,40).

A random effects model was used for this meta-analysis. This assumes that the effect size (i.e. magnitude of difference between the results of studies) varies randomly between the different studies. In other words, that heterogeneity is present and is an intrinsic part of the pooled result (41,42). Consequently, combining different effect sizes does not produce one “true effect” value, instead it is the normally distributed random effect sizes from studies around the mean “true effect” value (41–43). As a result, inter study variation is unlikely to be due to chance and more likely due to the individual characteristics of included studies. Therefore, the allocation of weights to different studies does not vary only according to sample size but instead takes into consideration the inverse variance and heterogeneity parameter(41,42). This provides the random effects model with greater flexibility and may improve external validity as it takes into account both intra- and inter- study variations(40,41,43).

Allocation of weight

The allocation of weight in the meta-analysis depends on the type of model (fixed or random effects) and type of data used to express effect size in included studies(30,43). For a random effects model used in our meta-analysis, the inverse variance method was used because it is appropriate for both dichotomous and continuous variables and when there are few studies with large populations (41,42). The inverse variance method allocates weight to each study in the meta-analysis using the inverse variance of the effect size estimate, thereby reducing the variance of the weighted average and improving the precision of the combined effect estimate (30,43).

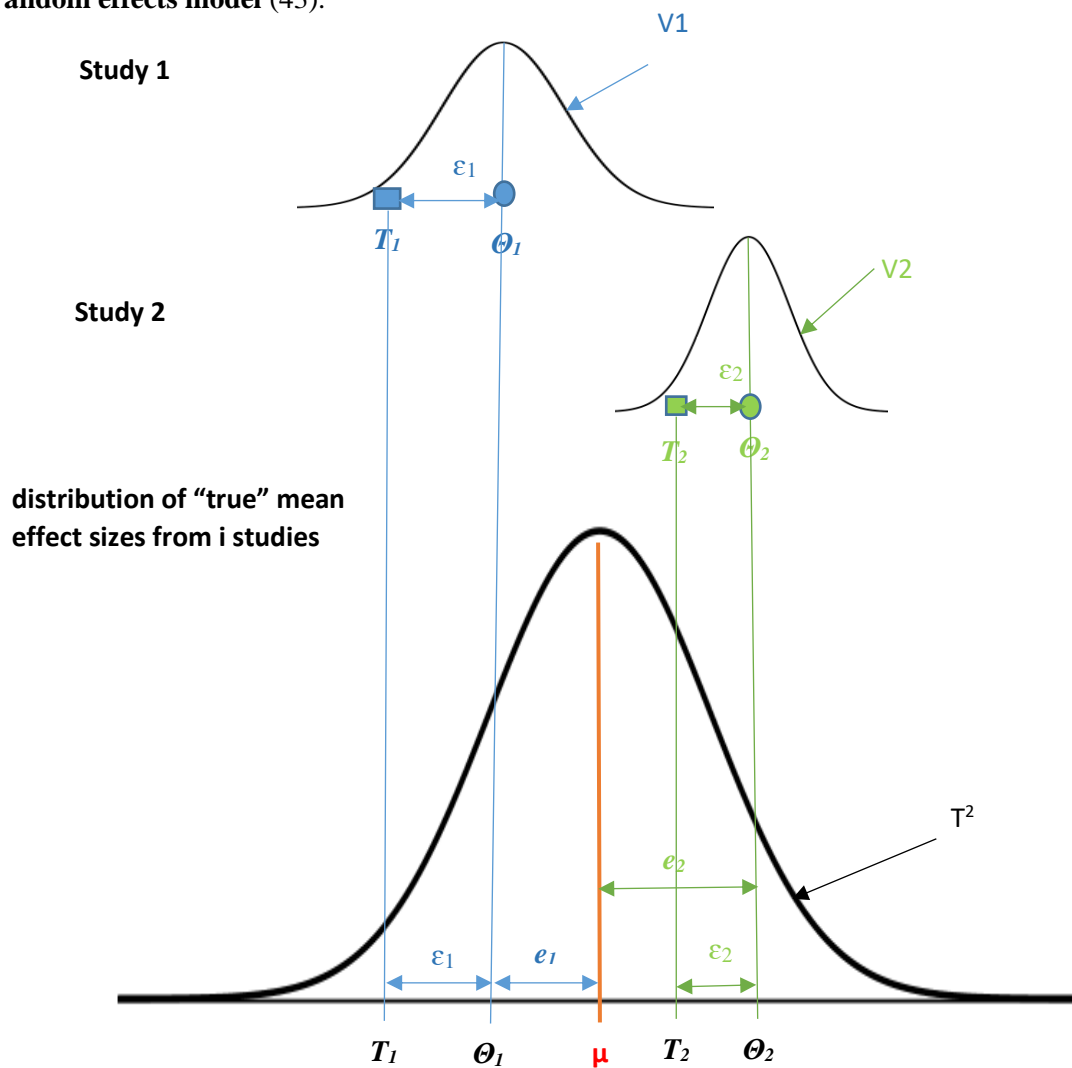
Consequently the variance of study i about $\mu = V_i + T^2$ and inverse variance weighting of studies in a random effects model is therefore (30,43,44):

$$\text{weight assigned to each study in a random effects model } (w_i) = \frac{1}{V_i + \tau^2}$$

While the mean true effect size (μ), observed mean for i studies (T_i) and intra study variance (ϵ_i) are observable, the inter study variance (τ^2) has to be estimated. The most commonly used method for estimating τ^2 is to use the DerSimonian and Laird method which takes into consideration the total variance (Q), the expected variance if all the studies had the same true effect size (df) and a common scaling factor of the sum of the squared weights in the following computations (30,43,44) :

$$\tau^2 = \left(\frac{Q - df}{c} \right)$$

Figure 7: Schematic illustration of the distribution of variance from different results using a random effects model (43).



Legend: observed mean for studies 1 and 2 (T_1 and T_2), common “true effect size” for studies 1 and 2 (θ_1 and θ_2), mean distribution of the “true effect size” (μ), intra study variance of studies 1 and 2 (ϵ_1 and ϵ_2), inter study variance of studies 1 and 2 (e_1 and e_2), variance of studies 1 and 2 (V_1 and V_2), variance of the “true effect sizes” from i studies (T^2)

Meta-analysis of proportions

As the unit of measure from studies included in our systematic review was proportions of CHD, the meta-analysis had to be adapted to take this into consideration. This is because proportions differ from other measures of effect size (e.g. OR etc) in that mathematically they range only between zero and one and that the sum of different proportions must always add up to one (38). There are three methods of estimating intra study variance (V_i) for studies that use proportion data (38,45).

For our meta-analysis on the proportion of CHD and GRN, we used the Freeman and Tukey double arcsine transformation (t) as follows (38,45):

$$t = \sin^{-1} \sqrt{\frac{n}{N+1}} + \sin^{-1} \sqrt{\frac{n}{N+1}} \quad \text{with the variance of } t = \frac{1}{N+0.5}$$

Where N is the sample size of study i and n is the number of people in a given category

This method was deemed most appropriate because it resolves issues of variance instability and allows the inclusion of studies with proportions close to the extremes of zero and one(38,45).

Heterogeneity

We used different methods to assess statistical heterogeneity, which included: i) visual inspection of the overlap of effect size confidence intervals from different studies in the Forest plot (the greater the overlap, the lower the statistical heterogeneity); ii) χ^2 test of heterogeneity and iii) the I^2 statistic which provides a quantification of the degree of heterogeneity present in studies using the following formula that takes into consideration the χ^2 (Q) and its degrees of freedom (df) (30,46).

$$I^2 = \left(\frac{Q - df}{Q} \right) \times 100\%$$

Part 2: Ordinal Logistic Regression

Ordinal logistic regression allows a more efficient analysis of ordinal (e.g., none, mild, moderate, severe) outcomes. It is a generalization of the binary logit models and most often assumes proportional odds to calculate the odds of having at least one of multiple outcomes based on the cumulative odds for an outcome with $k+1$ categories (47–49):

$$\text{Odds}(Y \leq j) = \frac{P(Y \leq j)}{1 - P(Y \leq j)}, \quad j = 1 \dots k$$

This can be re-expressed using the logit (log odds) function as:

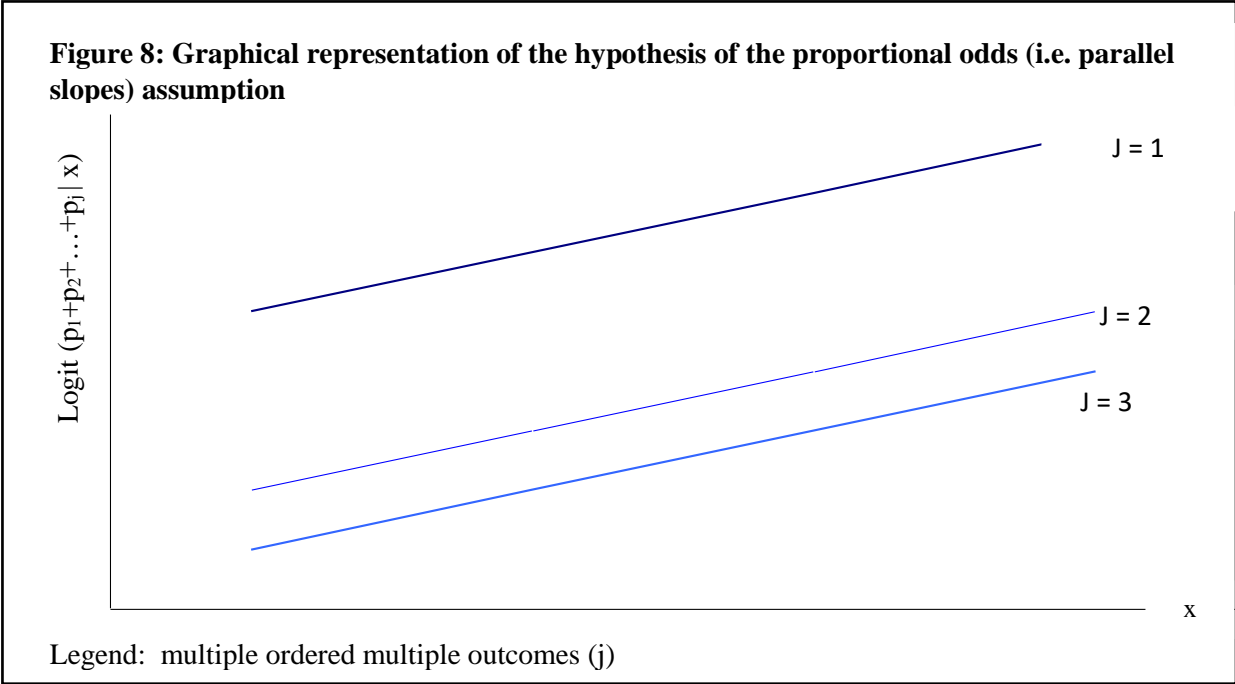
$$\text{logit}(Y \leq j) = \ln \left(\frac{P(Y \leq j)}{1 - P(Y \leq j)} \right), \quad j = 1 \dots k$$

$$\text{logit}(Y \leq j) = \alpha_j + X' \beta$$

Where $P(Y \leq j) = P_1 + P_2 + \dots + P_j$: is the cumulative probability of the event, α_j the unknown intercept parameters and $\beta = (\beta_1, \beta_2 \dots \beta_k)$ is a vector of unknown regression coefficients.

In the proportional odds model, regression coefficients (β 's) do depend on j , which is an index for the ordered outcomes.(47–49) As a result, the logit for each category has its own α_j term but the same vector of coefficients β . This means that the effect of the predictor variable is the same for different logit functions, implying that the model assumes that the relationship between x and y is independent of j (47–49). In other words, in the proportional odds logit model, the slopes that correspond to the model coefficients are parallel to one another because the k odds for each cut-off category j differ only with regards to the intercept α_j (Figure 8)(47–49).

Non-proportional logit models have been developed. However, in our study, the χ^2 test for the proportional odds assumption suggested that this was a reasonable assumption(47–49).



Chapter 3: Results

In this chapter, the results of different studies are presented in detail and provide an answer to the research questions that are discussed in the introduction. The first paper presents the findings of a systematic review on the prevalence of children born with CHD and GRN, the second paper presents the results of a population-based prospective cohort and finally this chapter ends with the findings from another systematic review on the outcomes of children born with CHD and GRN

Paper 1: Children born with Congenital Heart Defects and Growth restriction at Birth: A systematic review and meta-analysis

Objectives

The objective of this first systematic review and meta-analysis was to provide a thorough review of the literature on the prevalence of children born with CHD and growth restriction at birth.

Methods

Using the methods described in the last chapter, a search protocol was predetermined prior to the review and published on the PROSPERO international prospective register of systematic reviews (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=131079 , Appendix 1) (33)

This systematic review aimed to answer the two following questions:

- i) What proportion of children born with CHD are growth restricted at birth?
- ii) To what extent does the risk and severity of growth restriction at birth vary according to CHD subtype?

As the term GRN is relatively recent, the search parameters concentrated on the association between SGA and CHD in the literature (from inception until 31st March 2019). It was assumed that SGA to be a close proxy for GRN. To increase the exhaustiveness of the search, no language restrictions were applied and search terms included keywords and Medical Subject Headings (MeSH) terms. Two blinded reviewers carried out the search with conflicts being resolved by a third senior independent reviewer.

Selection of included studies

The search of Pubmed and Embase databases identified 1783 potentially relevant publications of which 72 articles were assessed for eligibility after the removal of duplicates and screening of titles and abstracts (figure 9).

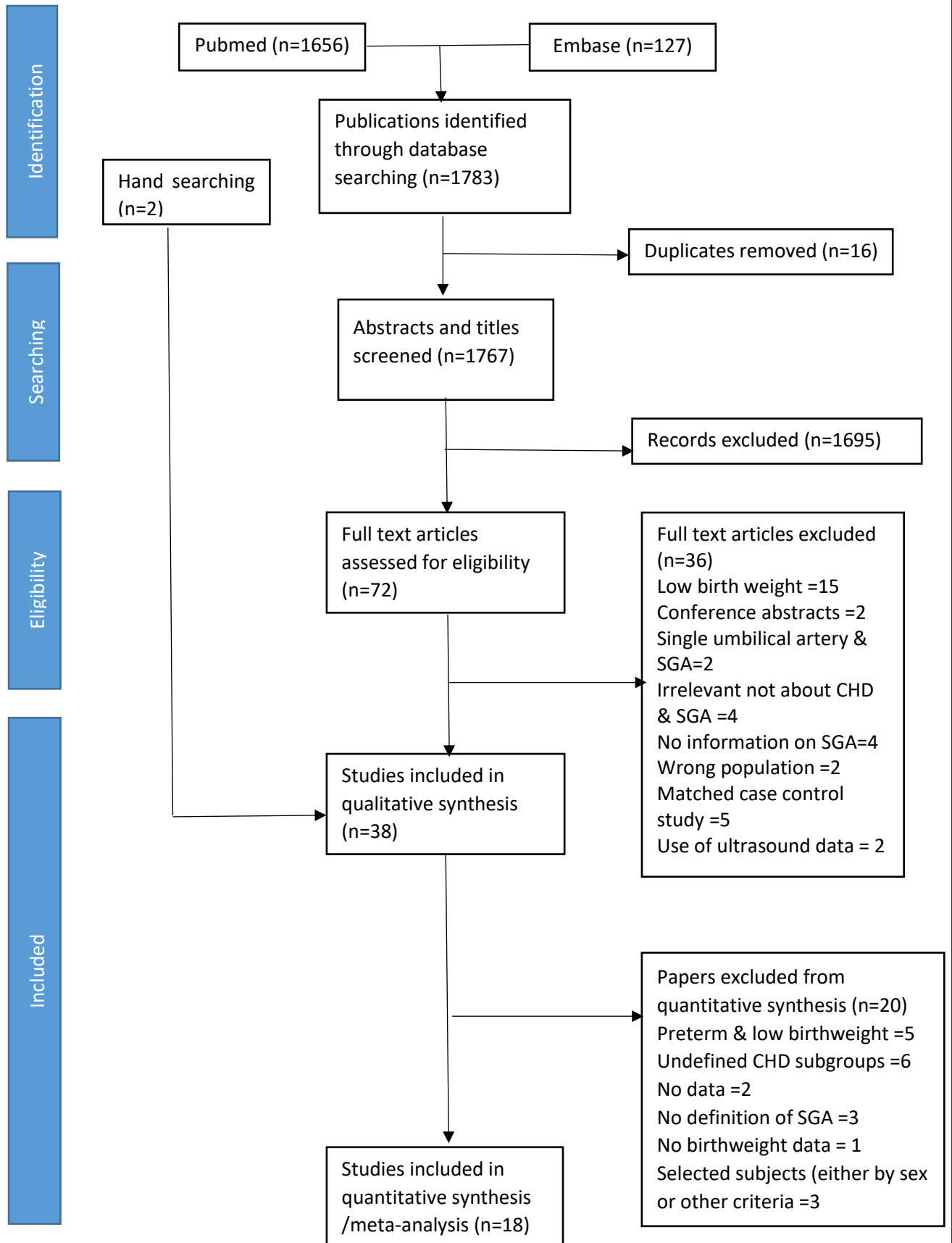
Full text review removed 36 articles irrelevant to the subject in hand and included publications on low birth weight, single umbilical artery and SGA, conference abstracts, no data on SGA and CHD prevalence, the use of ultrasound data, matched case control study and analyses carried out on the wrong population. A further two studies were found through hand searching of reference lists. In total, it was found that 38 studies were found to be relevant to the research questions of which 18 citations

Results

Study characteristics of included studies

The study characteristics of included studies are found in Table 1. This shows that from the 38 included studies on CHD and SGA, 23(60.5%) studies were published after the year 2010 and the majority were conducted in the United States (68.5%). The population study size ranged from 16 to 99,786. Some studies were restricted to preterm births or very low birth weight infants even though by far most studies included all gestational ages. It was found that the reference population used to compare SGA varied greatly according to the year and location of the study, with over 19 growth curves cited. The most frequent reference curve used was by Alexander *et al.* cited by six studies (15.8%) that used American cohorts. Moreover, definitions of SGA also varied.

Figure 9: Flow chart to indicate the selection of studies



Study characteristics of included studies

There were 22 studies (57.9%) that used the <10th percentile cut-off threshold definition, 7 studies (18.4%) used the 3rd percentile cut-off threshold definition and 9 studies (23.7%) did not define the percentile cut-off threshold used. Six studies (27.2%) did not report explicitly the use of gestational age or a reference population in their definition of SGA, whereas another 6 studies (27.2%) studies considered gender in addition to gestational age in the definition of SGA. It was found that 3 studies (7.9%) used the term FGR even though the actual outcome was SGA.

There was also variation between studies with regards to the types of CHD used with some of the 38 included studies using multiple CHD. It was found that 23 studies comprised all CHD (i.e. included genetic anomalies, extra-cardiac anomalies and/or syndromes) and 10 isolated CHD only. In addition to this, 12 specific subgroups were studied with the majority of studies on hypoplastic left heart syndrome (HLHS) and Tetralogy of Fallot (ToF) (10 publications). Certain studies also included a selected set of newborns with CHD, e.g., those operated for critical CHD. While only one study examined SGA for isolated CHD subgroups.

Table 1: Number of citations according to different study characteristics

Characteristics of study	Number of Publications
Year of Publication (n=38)	
1970-1979	3 (7.9%)
1980-1989	1 (2.6%)
1990-1999	3 (7.9%)
2000-2009	8 (21.1%)
2010-2019	23 (60.5%)
Country (n=38)	
USA	26 (68.5%)
Sweden	4 (10.5%)
China	3 (8%)
Italy	1 (2.6%)
West Germany	1 (2.6%)
Chile	1 (2.6%)
France	1 (2.6%)
UK	1 (2.6%)
Definition of SGA according to percentile (n=38)	
10th percentile (consensus definition of SGA)	22(57.9)
3rd percentile	7 (18.4)
undefined percentile	9(23.7)
Consensus definition of SGA: 10th percentile compared to (n=22)	
no comparaisou	6 (27.2)
according to gestational age and sex	6 (27,3)
according to gestational age	4(18.2)
according to gestational age, sex and race	3 (13.7)
according to gestational age and race	2 (9.1)
according to gestational age, race, sex and single or multiple gestation	1 (4.6)
Birthweight data provided for SGA (n=38)	35 (92.1)
SGA 1st aim of study (n=38)	17 (44.7)
CHD*	
All	23
Isolated	10
CHD Subtypes*	
Hypoplastic Left Heart Syndrome (HLHS)	10
Tetrology of Fallot (ToF)	10
Ventricular septal defect (VSD)	10
Coarctation of the Aorta (CoA)	8
Transposition of the great arteries (TGA)	7
Atrioventricular septal defect (AVSD)	7
Atrial septal defect (ASD)	7
Tricuspid atresia (TA)	3
Common truncus arteriosus (CAT)	3

Legend: SGA small for gestational age; * percentages not provided because multiple CHD included in certain studies

Observed proportions of SGA in isolated CHD, and specific CHD subgroups reported in studies

It was observed that the proportions of SGA in all, isolated, and subgroups of CHD varied greatly across the 38 studies included in this systematic review. It was found that four studies on isolated CHD reported same proportion of SGA i.e., 15%. The proportion of SGA observed in individual studies also varied greatly for various CHD subgroups. For HLHS, this was between 3% and 37%; for ToF 8% and 67%; for VSD 10% and 40% and for CoA 5% and 57%.

Evaluation of bias

Using the Critical Appraisal Skills Program (CASP) cohort study checklist, the risk of bias was evaluated in the 38 included studies (35). It was found that four studies had a lower risk of bias. However most studies were to some extent subject to selection and measurement bias, especially with regards to diagnosis of CHD using a validated diagnostic method. Few studies took into consideration the effects of confounding factors (e.g., parity, ethnicity, maternal disease, maternal smoking, etc.) Confidence intervals for SGA proportions were not provided in any study. Notwithstanding differences in geographic locations and reference populations, external validity criterion was met for most studies as they were population-based

Results of the Meta-analysis using a random effects model.

A total of 18 studies contained sufficient data for a meta-analysis, which was done using a random effects model via the Simonian and Laird inverse variance method after Freeman–Tukey double arcsine transformation (38).

The pooled proportion of SGA in all CHD was 20% (95% CI 16%–24%) and 14% (95% CI 13%–16%) for isolated CHD (figure 10). Proportions of SGA varied across different CHD ranging from 30% (95% CI 24%–37%) for Tetralogy of Fallot to 12% (95% CI 7%–18%) for isolated atrial septal defect (table 3). Based on two studies that used the 3rd percentile, the proportion of severe SGA (birthweight <3rd percentile) for all CHD was 6% (95% CI 6–7%).

Figure 10: Forest plot of proportions of SGA in all and isolated CHD according to 10th percentile cutoff threshold

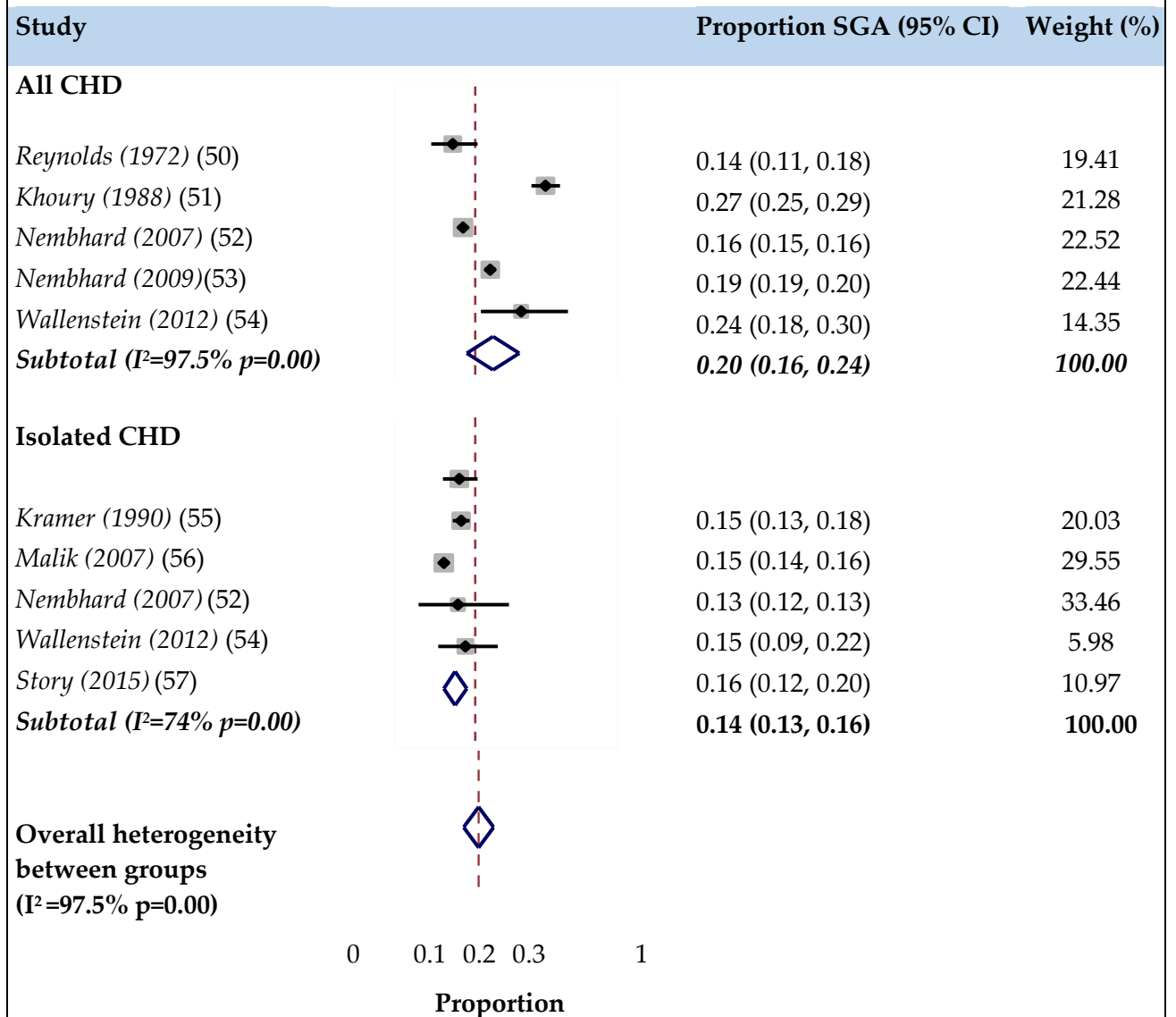


Table 2: Meta-analysis of proportions of SGA in different CHD subgroups (including genetic anomalies, extra cardiac anomalies and/or syndromes) using the 10th percentile cutoff threshold

Subgroup	Author	Pooled proportion (95% CI)	% Weight
HLHS			
Total pooled result		21	(19 - 23)
	<i>Khoury (1988) (51)</i>	23	(15 - 33) 7.36
	<i>Nembhard (2009) (53)</i>	23	(18 - 28) 22.81
	<i>Williams (2010) (58)</i>	20	(17 - 24) 48.79
	<i>Swenson (2012)(59)</i>	19	(15 - 24) 21.04
ToF			
Total pooled result		30	(24-37)
	<i>Khoury (1988) (51)</i>	34	(25 -43) 29.05
	<i>Nembhard (2009) (53)</i>	26	(23 - 30) 48.18
	<i>Swenson (2012)(59)</i>	36	(25 - 48) 22.77
TGV			
Total pooled result		17	(13-22)
	<i>Khoury (1988) (51)</i>	17	(11 - 23) 28.79
	<i>Nembhard (2009) (53)</i>	20	(17 -24) 41.34
	<i>Swenson (2012)(59)</i>	13	(8 -18) 29.87
VSD			
Total pooled result		19	(18- 20)
	<i>Khoury (1988) (51)</i>	27	(24- 31) 13.1
	<i>Nembhard (2009) (53)</i>	17	(16- 19) 86.9
CoAo			
Total pooled result		22	(19- 25)
	<i>Khoury (1988) (51)</i>	28	(21- 36) 19.06
	<i>Nembhard (2009) (53)</i>	20	(17- 24) 80.94
AVSD			
Total pooled result		27	(21 - 32)
	<i>Khoury (1988) (51)</i>	28	(20 - 38) 37.3
	<i>Williams (2010) (58)</i>	25	(18 - 33) 53.51
	<i>Swenson (2012)(59)</i>	32	(15 - 54) 9.19
TA			
Total pooled result		27	(21 - 35)
	<i>Williams (2010) (58)</i>	30	(22 - 39) 74.84
	<i>Swenson (2012)(59)</i>	21	(10 - 37) 25.16
CAT			
Total pooled result		23	(17 - 30)
	<i>Khoury (1988) (51)</i>	24	(11 - 41) 19.66
	<i>Nembhard (2009) (53)</i>	25	(17 - 34) 64.1
	<i>Swenson (2012)(59)</i>	18	(6 - 37) 16.24

Legend: HLHS hypoplastic left heart syndrome, ToF Tetralogy of Fallot, VSD ventricular septal defect, CoAo Coarctation of the Aorta, TGV transposition of great vessels, AVSD atrioventricular septal defect, TA tricuspid atresia, CAT common truncus arteriosus

Conclusion

This systematic review and meta-analysis found that the prevalence of SGA in all CHD was 20% (95% CI 16%–24%) and 14% (95% CI 13%–16%) for all isolated CHD. It was also found that the relatively new term “GRN” to designate growth restriction in the newborn observed at the time of birth did not appear in the literature *per se* and that certain authors mislabeled the terms SGA and FGR or used them interchangeably to imply GRN in some studies. Although there were very few studies that were on severe SGA (birthweight <3rd percentile, which is almost equivalent to GRN) and CHD in the literature, based on the pooled results of two studies, the prevalence of severe SGA in all CHD was 6% (95% CI 6–7%). The majority of studies on specific CHD subgroups included genetic anomalies, extracardiac anomalies and /or syndromes and we were unable to determine the proportion of SGA in isolated specific CHD. Nevertheless it appears that there is a discordance in the proportion of SGA according to type of specific CHD. It was found that ToF had the highest proportion of SGA (30%, 95% CI 24%–37%) while the lowest proportion of SGA was in isolated ASD (12%, 95% CI 7%–18%).

In conclusion, from this systematic review we found overall that the proportion of SGA and severe SGA in all CHD was 2-fold higher whereas that of isolated CHD was as 1.4-fold higher than the expected proportion in the general population. These findings may provide a clue to the physio-pathological mechanisms for the increased prevalence of SGA and we were able to investigate knowledge gaps in further detail using a prospective population based cohort. The results of this complementary study are presented in the next section of this chapter.



Review

Children Born with Congenital Heart Defects and Growth Restriction at Birth: A Systematic Review and Meta-Analysis

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Received: 30 March 2020; Accepted: 20 April 2020; Published: 28 April 2020



Abstract: Newborns with congenital heart defects tend to have a higher risk of growth restriction, which can be an independent risk factor for adverse outcomes. To date, a systematic review of the relation between congenital heart defects (CHD) and growth restriction at birth, most commonly estimated by its imperfect proxy small for gestational age (SGA), has not been conducted. Objective: To conduct a systematic review and meta-analysis to estimate the proportion of children born with CHD that are small for gestational age (SGA). Methods: The search was carried out from inception until 31 March 2019 on Pubmed and Embase databases. Studies were screened and selected by two independent reviewers who used a predetermined data extraction form to obtain data from studies. Bias was assessed using the Critical Appraisal Skills Programme (CASP) checklist. The database search identified 1783 potentially relevant publications, of which 38 studies were found to be relevant to the study question. A total of 18 studies contained sufficient data for a meta-analysis, which was done using a random effects model. Results: The pooled proportion of SGA in all CHD was 20% (95% CI 16%–24%) and 14% (95% CI 13%–16%) for isolated CHD. Proportion of SGA varied across different CHD ranging from 30% (95% CI 24%–37%) for Tetralogy of Fallot to 12% (95% CI 7%–18%) for isolated atrial septal defect. The majority of studies included in the meta-analysis were population-based studies published after 2010. Conclusion: The overall proportion of SGA in all CHD was 2-fold higher whereas for isolated CHD, 1.4-fold higher than the expected proportion in the general population. Although few studies have looked at SGA for different subtypes of CHD, the observed variability of SGA by subtypes suggests that growth restriction at birth in CHD may be due to different pathophysiological mechanisms.

Keywords: congenital heart defects; small for gestational age; systematic review; meta-analysis; population-based study

1. Introduction

Congenital heart defects (CHD) are the most common group of congenital anomalies with a live birth prevalence of 8.2 per 1000 births in Europe [1]. Despite considerable progress in medical and surgical management of CHD, they remain the most important cause of infant death by malformation. One study suggested that there were approximately 260,000 deaths due to CHD in 2017 [2]. However,

the survival rate is much higher in high resource countries and a recent review found that 85% of children with CHD reach adulthood [3].

Growth restriction at birth, often measured by its imperfect proxy small for gestational age is an important risk factor for perinatal mortality, morbidity, and long-term adverse outcomes, including an increased risk of diabetes, hypertension, and cardiovascular disease later in life.

Therefore, growth restriction in a newborn with a CHD may represent a “double jeopardy” with risks related to CHD combined with those associated with growth restriction. Moreover, differences in the proportion of CHD subtypes with growth restriction may provide clues about possible pathophysiological mechanisms of the relation between growth restriction and CHD.

To date, no systematic review of the relation between CHD and growth restriction at birth has been conducted. The objective of our study was to conduct a systematic review and meta-analysis of the relation between growth restriction at birth and CHD.

2. Methods

This study is reported in accordance to Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines [4]. The review protocol was registered on the PROSPERO: International Prospective Register of Systematic Reviews website [5]. As data sources originated from previously published studies in the public domain, ethical approval for this study was not requested [6].

2.1. Search Strategy

A comprehensive literature search was carried out on Pubmed/Medline and Embase databases with the assistance of a specialized documentalist. Medical Subject Headings (MeSH)/Medical Embase Medical Headings (EMTREE) and keywords that included different synonyms for CHD, CHD subtypes, small for gestational age (SGA), fetal growth restriction (FGR)/intrauterine growth retardation (IUGR) and low birth weight were combined together using Boolean operators. The search was carried out from inception until 31/03/2019 and no language preferences were applied. A manual search of references in included articles was carried out to complete the search.

2.2. Study Selection

Titles and abstracts of retrieved studies were screened independently by two blinded reviewers (AG and ND) using Rayaan web application [7]. Excluded articles were about CHD and low birth weight only, conference abstracts, CHD and single umbilical artery, absence of SGA data, matched case control studies, use of estimated fetal weight from ultrasound data, and SGA outcomes in the offspring of women born with CHD.

2.3. Data Extraction

A predetermined data extraction form was designed and used independently by the two reviewers (AG and ND). Extracted data for each study included study characteristics, object of study, SGA outcomes, data sources, exclusion criteria, and SGA proportions. Authors of studies were contacted to request further information or clarification of results.

2.4. Evaluation of Bias

The Critical Appraisal Skills Programme (CASP) cohort study checklist evaluated the risk of bias in studies included in this review [8]. The checklist contains 12 questions divided into three sections that enable a structured approach to finding evidence, determine possible sources of bias, and evaluate internal and external validity of each study. We adapted this checklist to our study question paying particular attention to selection and measurement biases.

Throughout the entire process (article selection, data extraction, and evaluation of bias) discrepancies were resolved through end result discussion. Any further disagreements between the two reviewers (AG and ND) were resolved by a third reviewer (BK).

2.5. Definitions

CHD was defined as children born with structural heart defect and excluded patent ductus arteriosus, cardiac tumors, cardiomyopathies, and arrhythmias. Isolated CHD was defined as CHD not associated with chromosomal anomalies, malformations from other systems or syndromes. Due to data availability, we used SGA as an imperfect measure of growth restriction at birth. We used the consensual definition of SGA, defined as birthweight <10th percentile according to gestational age and compared to a standard population [9]. Studies were grouped according to birthweight percentile cut-off rather than labels assigned by the different authors.

2.6. Statistical Analysis

A meta-analysis of pooled proportions (with their 95% confidence intervals) was carried out using a random effects model with inverse variance weighting, using the Simonian and Laird method [10,11]. Freeman–Tukey double arcsine transformation was used to limit the effects of over-weighting caused by studies with a variance close to zero for estimating the confidence intervals for the pooled estimate [10,11]. The I^2 statistic assessed statistical heterogeneity between groups. Principal analysis concerned all/isolated CHD using the SGA defined using the 10th percentile cutoff threshold. Additional analyses were conducted for CHD subtypes and for severe SGA using the 3rd percentile. Sensitivity analysis was carried by restricting the analysis to only population-based studies. The meta-analysis was performed using STATA 12.1 software (StataCorp LP, College Station, TX, USA). We considered p -values < 0.05 as statistically significant.

3. Results

The database search identified 1783 potentially relevant publications of which 72 articles were assessed for eligibility. An additional two studies were found through hand searching of reference lists [12,13]. In total 38 studies were found to be relevant to the study question of which 18 citations contained sufficient data for a meta-analysis (Figure 1).

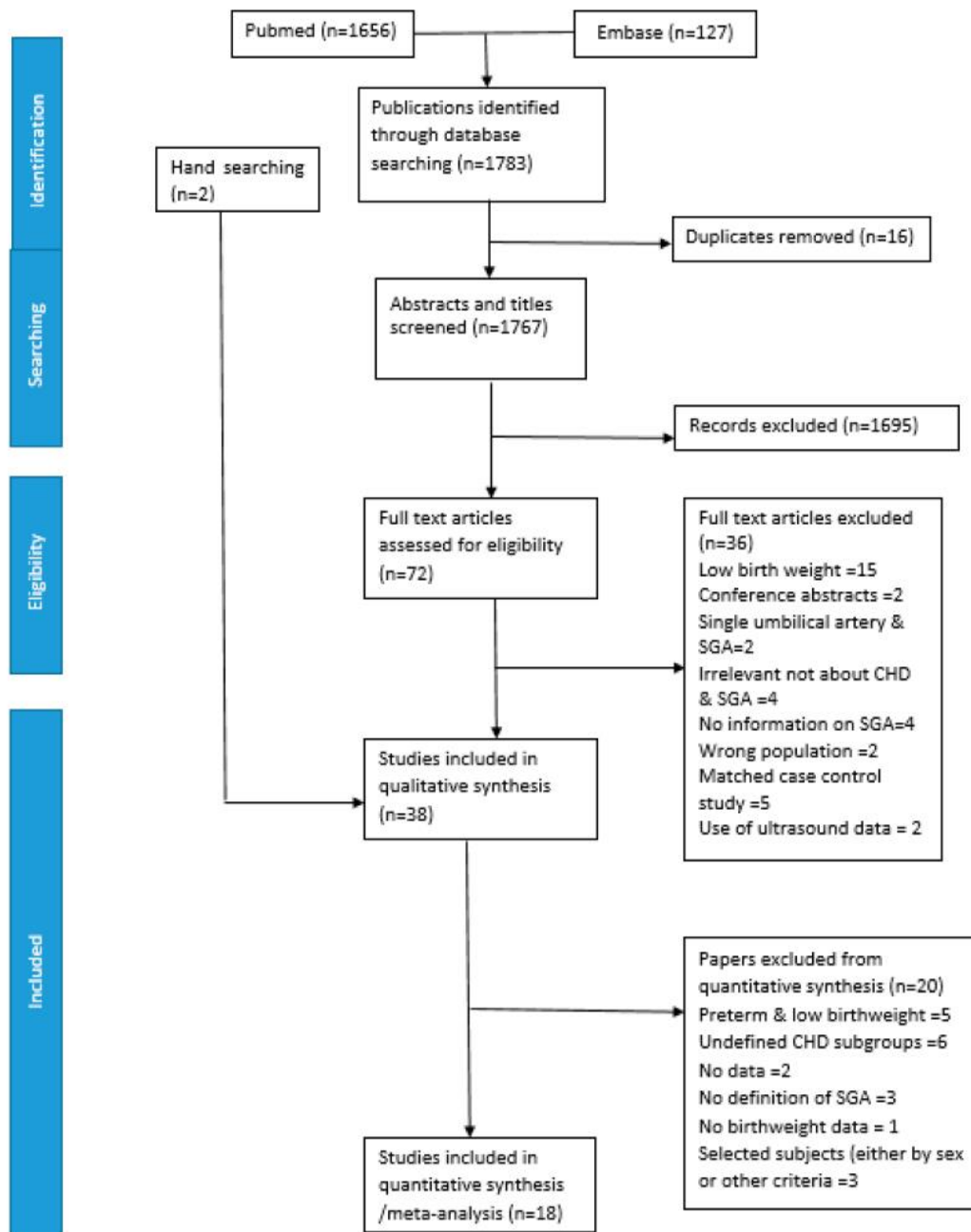


Figure 1. Flow chart to indicate the selection of studies.

3.1. Study Characteristics

Characteristics of the studies according to year of publication, country and objective of the study are shown in Table 1. Publication years ranged from 1972 to 2018 and 23 (60.5%) studies were published between 2010 and 2019. Sample sizes of patients with CHD ranged from 16 to 99,786. Twenty-six studies (68.5%) were based on US cohorts. The reference populations varied greatly based on geographical location and the year of study. Overall, 19 different reference populations were cited. The most frequent was growth curve by Alexander et al., which was used in six American studies while eight (21%) studies did not state which reference population was used.

Table 1. Number of citations according to different study characteristics.

Characteristics of Study	Number of Publications	Number of Publications in MA
Year of Publication (n = 38)		(n = 18)
1970–1979	3 (7.9%)	2 (11.1%)
1980–1989	1 (2.6%)	1 (5.6%)
1990–1999	3 (7.9%)	2 (11.1%)
2000–2009	8 (21.1%)	6 (33.3%)
2010–2019	23 (60.5%)	7 (38.9%)
Country (n = 38)		(n = 18)
USA	26 (68.5%)	14 (77.8%)
Sweden	4 (10.5%)	1 (5.6%)
China	3 (8%)	1 (5.6%)
Italy	1 (2.6%)	0
France	1 (2.6%)	0
Chili	1 (2.6%)	0
UK	1 (2.6%)	1 (5.6%)
Definition of SGA according to percentile (n = 38)		(n = 18)
10th percentile (consensus definition of SGA)	22 (57.9%)	14 (77.8%)
3rd percentile	7 (18.4%)	4 (22.2%)
Undefined percentile	9 (23.7%)	0
Consensus definition of SGA: 10th percentile: (n = 38)		(n = 14)
No comparison	6 (27.2%)	4 (28.6%)
According to gestational age and sex	6 (27.3%)	4 (28.6%)
According to gestational age	4 (18.2%)	3 (21.4%)
According to gestational age, sex and race	3 (13.7%)	1 (7.1%)
According to gestational age and race	2 (9.1%)	2 (14.3%)
According to gestational age, race, sex, and single or multiple gestation	1 (4.6%)	0
Birthweight data provided for SGA	35 (92.1%)	18 (100%)
Characteristics of Study	Number of Publications	Number of Publications in MA
SGA 1st aim of study	17 (44.7%)	13 (72.2%)
CHD		
All	23	8
Isolated	10	7
CHD subtype		
HLHS	10	8
ToF	10	7
CoAo	8	7
TGV	7	7
AVSD	7	7
ASD	7	6
TA	3	3
CAT	3	3

Legend: MA—meta-analysis; SGA—small for gestational age; CHD—congenital heart defect; HLHS—hypoplastic left heart syndrome; ToF—Tetralogy of Fallot; VSD—ventricular septal defect; CoAo—coarctation of the aorta; TGV—transposition of great vessels; AVSD—atrioventricular septal defect; ASD—atrial septal defect; TA—tricuspid atresia; CAT—common truncus arteriosus.

Of the 38 studies included in the systematic review, 22 (57.9%) used birthweight <10th percentile for definition of SGA; 17 (44.7%) studies were designed specifically to study SGA and CHD as their primary objective. Six studies (27.2%) did not report explicitly the use of gestational age or a reference population in their definition of SGA, whereas six studies (27.2%) studies considered gender in addition to gestational age in the definition of SGA (Table 1). Three (7.9%) studies used the term FGR even though the actual outcome was SGA.

Twenty-three (60.5%) studies comprised all CHD and 10 (26.3%) isolated CHD only. In addition, 12 specific subgroups were studied with the majority of studies on hypoplastic left heart syndrome (HLHS) and Tetralogy of Fallot (ToF) (10 publications).

3.2. Proportion of SGA in All CHD, Isolated CHD, and Subgroups Reported by Individual Studies

As shown in Table 2, the proportions of SGA in all, isolated, and subgroups of CHD varied greatly across the studies in the systematic review. It was found that four (10.5%) studies on isolated CHD reported same proportion of SGA i.e., 15%. The proportion of SGA varied between 3% and 37% for HLHS 8% and 67% for ToF and 10% and 40% for ventricular septal defects and 5% and 57% for coarctation of the aorta (CoAo).

Some studies were restricted to preterm births or very low birth weight infants even though by far most studies included all gestational ages. Certain studies included a selected set of newborns with CHD, e.g., those operated for critical CHD. Only one study examined SGA for isolated CHD subgroups [14].

Table 2. Summary of key characteristics of individual studies.

Author	Country	Definition of SGA	CHD	CHD (n)	SGA (%)
Archer (2011) [23]	USA	<10th P ⁰ according to GA, maternal race, gender, and type of gestation	All	99,786	21
Bain (2014) [24]	USA	<10th P ⁰ according to GA, gender, race	All	98,523	24
Calderon (2018) [25]	France	<10th P ⁰ according to GA and gender	All	419	14
Cedergren (2006) * [26]	Sweden	<2SD below mean birth weight according to GA	All	6346	7
			Isolated	5338	6
Chu (2015) [27]	USA	ICD?	All	28,806	6
Cnota (2013) [28]	USA	<10th P ⁰ according to GA, gender, race	HLHS	33	No data
Joelsson (2001) [29]	Sweden	Not stated	PAIVS	84	14
El Hassan (2008) [30]	USA	ICD	HLHS	5720	3
Fisher (2015) [31]	USA	Not stated	All	235,643	43
Gelehrter (2011) * [32]	USA	<3rd P ⁰ according to GA	HLHS	52	37
			Isolated	454	15
			PA	18	11
			ToF	63	24
			TGV	12	16
Jacobs (2003) * [33]	China	<-2z score from normal mean for age and gender	CoAo	20	20
			VSD	86	12
			ASD	31	23
			PS	52	11
			HLHS	16	31
Jones (2015) * [20]	USA	<10th P ⁰ according to GA and gender	HLHS	16	31
Josefsson (2011) [34]	Sweden	<-2SD of the mean birthweight for gestational length	All	2216	31
Karr (1992) [35]	USA	Not stated	ToF	125	21
Kernell (2014) [36]	Sweden	<-2SD of the mean birthweight for gestational length	All	2689	21
			All	3669	28
			HLHS	91	23
			CAT	34	24
			ToF	110	33
Khoury (1988) * [12]	USA	<10th P ⁰ according to GA, race and gender	TGV	167	17
			CoAo	139	28
			VSD	833	27
			ASD	409	30
			i.ASD	26	11
AVSD	103	28			

Table 2. Cont.

Author	Country	Definition of SGA	CHD	CHD (n)	SGA (%)						
Kramer (1990) * [37]	West Germany	<10P ⁰	Isolated	843	15						
			ToF	81	26						
			TGV	60	15						
			AS	45	8						
			CoAo	69	13						
			VSD	236	13						
			ASD	70	17						
Levin (1975) [38]	USA	Not stated	All	37	43						
			VSD	5	40						
			AoA	3	70						
			All	2178	6						
			HLHS	163	6						
			TA	64	5						
			TAPVR	58	3						
Levy (1978) * [39]	USA	<2SD below mean birth weight of control group	ToF	156	7						
			TGV	217	2						
			AS	43	2						
			CoAo	136	6						
			VSD	313	10						
			ASD	59	8						
			AVSD	107	8						
Li (2009) [21]	China	Not stated	PS	81	5						
			PAIVS	64	6						
			All	274	5						
			Lupo (2011) [40]	USA	<10th P ⁰ according to GA and gender	Ebstein	175	19			
						Malik (2007) * [16]	USA	<10th P ⁰ according to GA and gender	Isolated	3395	15
									All	9645	19
			HLHS	283	23						
Nembhard (2009) * [41]	USA	<10th P ⁰ using race specific growth curve	CAT	112	25						
			ToF	602	26						
			Ebstein	61	15						
			TGV	472	20						
			CoAo	592	20						
			VSD	5528	17						
			ASD	467	28						

Table 2. Cont.

Author	Country	Definition of SGA	CHD	CHD (n)	SGA (%)
Nembhard (2007) * [17]	USA	<10th P ^o using race specific growth curve	All	12,964	16
			Isolated	10,870	13
Oyarzún (2018) [22]	Chile	Not stated	Isolated	46	26
Pappas (2012) [42]	USA	<10th P ^o	All	110	27
Polito (2013) [43]	Italy	<3rd P ^o	All	70	17
			AS	433	14
Reynolds (1972) * [13]	USA	<10th P ^o according to GA	AS	21	38
			Isolated	1299	12
			HLHS	96	20
			CAT	113	18
			ToF	119	7
			Ebstein	57	5
Rosenthal (1991) * [14]	USA	<10th P ^o according to GA	TGV	103	10
			CoAo	470	11
			VSD	130	12
			ASD	44	18
			PS	167	14
			All	230	25
Sochet (2013) [44]	USA	<10th P ^o according to GA	Isolated	6863	16
Steurer (2018) * [45]	USA	<10th P ^o according to GA and sex	Isolated	308	16
Story (2015) * [46]	UK	<10th P ^o	All	753	21
			HLHS	261	19
			TA	38	16
			CAT	28	21
			DROV	54	24
			TAPVR	35	26
Swenson (2012) * [47]	USA	<10th P ^o	ToF	70	36
			TGV	181	13
			IAA	44	36
			AVSD	25	32

Table 2. Cont.

Author	Country	Definition of SGA	CHD	CHD (n)	SGA (%)
Wallenstein (2012) * [18]	USA	<10th P ^o	All	193	24
			Isolated	129	15
			All	74	51
			HLHS	11	30
Wei (2015) [48]	USA	Size < 10th P ^o	ToF	12	70
			Ebstein	4	50
			CoAo	7	57
			VSD	6	17
			PAIVS	5	60
Williams (2010) * [49]	USA	<10th P ^o according to GA	HLHS	606	20
			TA	114	30
			AVSD	148	25
Wollins (2001) * [19]	USA	<10th P ^o according to sex and GA	PAIVS	102	25
			CoAo	181	12
Yu (2014) [15]	China	Not stated	All	477	11

Legend: * included in meta-analysis. § Not a population-based study. σ SGA 1st aim of study. SGA—small for gestational age; CHD—congenital heart defect; HLHS—hypoplastic left heart syndrome; ToF—Tetralogy of Fallot; VSD—ventricular septal defect; CoAo—coarctation of the aorta; TGV—transposition of great vessels; AVSD—atrioventricular septal defect; ASD—atrial septal defect; iASD—isolated atrial septal defect; TA—tricuspid atresia; CAT—common truncus arteriosus; PAIVS—pulmonary atresia intact ventricular septum; TAPVR—total anomalous pulmonary venous return; DORV—double outlet right ventricle; IAA—interrupted aortic arch; AoA—aortic atresia; PS—pulmonary stenosis; AS—aortic stenosis; P^o—percentile; GA—gestational age; SD—standard deviation; ICD—international classification of diseases.

3.3. Evaluation of Bias

Studies were evaluated for bias using a modified CASP checklist. Yu et al. was omitted because we could not obtain the full article [15]. All studies addressed a clearly focused issue, however the quality of studies regarding other criteria in the checklist varied greatly. In particular, most studies were to some extent subject to selection and measurement bias, especially with regards to diagnosis of CHD using a validated diagnostic method.

Few studies took into consideration the effects of confounding factors (e.g., parity, ethnicity, maternal disease, maternal smoking, etc.). Four studies were found to have a lower risk of bias [15–18], whereas five others were deemed to have a higher risk of bias [12,19–22]. Confidence intervals (CI) for SGA proportions were not provided in any study. Notwithstanding differences in geographic locations and reference populations, external validity criterion was met for most studies as they were population-based.

3.4. Meta-Analysis

Of the 38 articles in the systematic review, we used 18 (47.4%) in the meta-analysis. The reasons for excluding studies from the meta-analysis are detailed in Figure 1. These included studies of low birth weight and preterm newborns only, unclear definition or of CHD subgroups included, absence of data on birth weight or clear definition of SGA, and studies limited to one gender only.

The pooled proportion of SGA in all CHD was 20% (95% CI 16–24%) and for isolated CHD 14% (95% CI 13–16%) (Figure 2). Limiting the meta-analysis only to population-based studies did not change the results appreciably. Based on two studies that used the 3rd percentile, the proportion of severe SGA for all CHD was 6% (95% CI 6–7%).

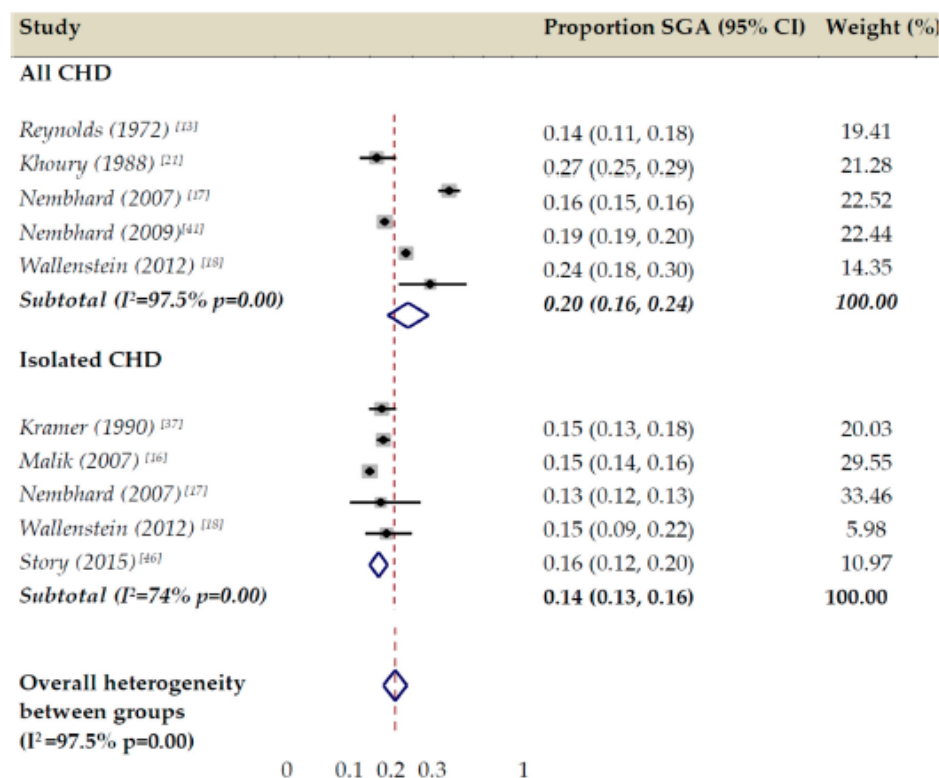


Figure 2. Forest plot of the meta-analysis of proportions of small for gestational age (SGA) in all and isolated congenital heart defects (CHD) according to 10th percentile cutoff threshold.

Table 3 illustrates the results of meta-analysis for subgroups of CHD. Genetic and other anomalies were not explicitly excluded in the studies reporting on subgroups of CHD. Pooled proportion of SGA was 30% for ToF, 21% for HLHS, and 17% for transposition of great vessels (TGV). The proportion of SGA was lowest for isolated atrial septal defects (ASD) with a proportion of 12%.

Table 3. Meta-analysis of proportions of SGA in different CHD subgroups (including genetic anomalies/syndromes) using the 10th percentile cutoff threshold.

Subgroup	Author	Pooled Proportion (95% CI)	% Weight
HLHS			
Total pooled result		21 (19–23)	
	Khoury (1988) [12]	23 (15–33)	7.36
	Nembhard (2009) [41]	23 (18–28)	22.81
	Williams (2010) [49]	20 (17–24)	48.79
	Swenson (2012) [47]	19 (15–24)	21.04
ToF			
Total pooled result		30 (24–37)	
	Khoury (1988) [12]	34 (25–43)	29.05
	Nembhard (2009) [41]	26 (23–30)	48.18
	Swenson (2012) [47]	36 (25–48)	22.77
TGV			
Total pooled result		17 (13–22)	
	Khoury (1988) [12]	17 (11–23)	28.79
	Nembhard (2009) [41]	20 (17–24)	41.34
	Swenson (2012) [47]	13 (8–18)	29.87
VSD			
Total pooled result		19 (18–20)	
	Khoury (1988) [12]	27 (24–31)	13.1
	Nembhard (2009) [41]	17 (16–19)	86.9
CoAo			
Total pooled result		22 (19–25)	
	Khoury (1988) [12]	28 (21–36)	19.06
	Nembhard (2009) [41]	20 (17–24)	80.94
AVSD			
Total pooled result		27 (21–32)	
	Khoury (1988) [12]	28 (20–38)	37.3
	Williams (2010) [49]	25 (18–33)	53.51
	Swenson (2012) [47]	32 (15–54)	9.19
TA			
Total pooled result		27 (21–35)	
	Williams (2010) [49]	30 (22–39)	74.84
	Swenson (2012) [47]	21 (10–37)	25.16
CAT			
Total pooled result		23 (17–30)	
	Khoury (1988) [12]	24 (11–41)	19.66
	Nembhard (2009) [41]	25 (17–34)	64.1
	Swenson (2012) [47]	18 (6–37)	16.24

Legend: HLHS—hypoplastic left heart syndrome; ToF—Tetralogy of Fallot; VSD—ventricular septal defect; CoAo—coarctation of the aorta; TGV—transposition of great vessels; AVSD—atrioventricular septal defect; TA—tricuspid atresia; CAT—common truncus arteriosus.

4. Discussion

4.1. Main Findings and Interpretations

This systematic review and meta-analysis found 38 articles that studied the association between SGA and CHD. The pooled proportion of SGA for all CHD was 20% and for isolated CHD 14%. Given the definition of SGA as the 10th percentile, these results suggest that overall, newborns with CHD have a two-fold greater risk of SGA compared to its theoretical value and those with isolated CHD a 1.4-fold higher risk of SGA. Estimates of SGA in the general population in developed countries are also considerably lower than the pooled proportions in our meta-analysis [50,51]. There was a great deal of variability in the proportion of SGA for different CHD. Tetralogy of Fallot had the highest proportion of SGA whereas isolated ASD had the lowest proportion of SGA. The range of SGA proportions across studies was highly variable for CHD, isolated CHD, or given subgroups of CHD in the 38 studies included in the systematic review. However, this variability decreased substantially for the 18 studies included in the meta-analysis.

Overall, approximately 20%–30% of CHD are due to known chromosomal, genetic, or other anomalies [52,53]. Some of these anomalies, e.g., Down Syndrome, Turner Syndrome may in turn be associated with growth restrictions. Indeed, isolated CHD had a substantially lower proportion of SGA. The issue of associated anomalies complicates the interpretation of differences in subgroups of CHD as they may be more (ToF) or less (HLHS or CoA) associated with other anomalies.

The higher proportion of SGA in newborns with CHD may be caused either by the CHD itself and/or by a common etiological factor (maternal, fetal, placental) that can cause both CHD and growth restriction [12,16,52,54].

With regards to the theory that CHD causes SGA, a number of authors suggest that alterations in fetal hemodynamics and oxygen saturation due to CHD are the root cause of this association [12,14,16,51]. Differences in SGA proportions according to CHD subtypes that we identified in this review support this hypothesis with the proportions of SGA varying from 22% for CoA to 12% in isolated ASD. Wallenstein et al. hypothesized that reduced ventricular function decreases cardiac output resulting in stunted fetal growth [18]. Our findings of increased SGA in HLHS (21%) are consistent with this mechanism. Story et al. maintained that decreased oxygenation in the aortic arch reduces cerebral perfusion and thus causes SGA [46]. Our findings of increased proportions of SGA in transposition of great arteries (TGA) (17%) may be at least in part explained by this mechanism. Sun et al. also found that decreased oxygen consumption is associated with smaller brain sizes in children with CHD [55].

Several authors have hypothesized that the association between SGA and CHD is caused by one or more common etiological factors (maternal, placental, fetal, and/or environmental) that result in both CHD and SGA [20,54]. Malik et al. have proposed that smoking may contribute to a common etiological pathway for CHD and SGA [56]. Although 33 studies (86%) included in our review provided data on maternal smoking only four (11%) took this into consideration in their statistical analysis [14,18,19,26]. Cedergren and Kallen theorized that disturbed placentation caused by abnormal trophoblastic growth in early pregnancy results in both SGA and CHD [26]. While, Jones et al. argued that placental insufficiency is the common causal pathway for HLHS [20]. They asserted that placental insufficiency reduces angiogenesis and villous tree maturation of the placenta, thereby reducing the surface area for gaseous and nutritional exchanges. As a result, SGA is induced directly and indirectly by nutritional deficiency. Their observations of increased placental leptin secretion led them to speculate that a predisposition for HLHS is the result of some kind of compensatory mechanism. Nevertheless, the effect of leptin in myocardial hypertrophy is debatable in the literature [57].

In addition to the two possible physiopathological mechanisms previously discussed, Spiers et al. proposed another, even if a minority position, hypothesis in the literature [12,14,46,58] According to Spiers et al., early FGR during cardiogenesis may result in CHD; in other words, SGA may be the cause of CHD [46,58]. Despite the fact that early FGR is very difficult to diagnose, five authors in this review made reference to this theory to account for the genetic anomalies and syndromes that are associated

with CHD. They used this theory to explain that an intrinsic disturbance in fetal growth could provide a predisposition for CHD. However, to our knowledge little evidence exists to corroborate this theory.

In general, our results raise several questions about the possible underlying mechanisms of the association between SGA and CHD. Few studies were designed to examine this association specifically or to investigate different mechanisms that may explain the association between CHD and SGA. Moreover, the roles of confounding, intermediate (mediating) variables, and possible interactions in the causal pathway(s) between CHD and SGA have not been adequately studied. For example, the role of maternal age, if any, is unclear. While it is well known that maternal age (and parity) are associated with SGA, whether or not maternal age (or parity) in and of itself are risk factors for CHD is not known. Previous studies have provided conflicting results about the possible association between maternal age and CHD even if maternal age is known to be associated with SGA [3,59–62].

The genetic mechanisms potentially related to the association between CHD and SGA appear to be the result of complex, multifactorial interactions between genetics, epigenetics, and the environment that are poorly understood [61–63]. Certain specific isolated CHD subtypes may be caused by point mutations to transcription factors of specific genes (e.g., *IRX4* results in VSD) that affect cardiogenesis. The expression of genes either directly (through methylation or other mechanisms) or indirectly via environmental exposure has been associated with CHD. DNA methylation was one of the first epigenetic mechanisms to be associated with CHD e.g., aberrant methylation of *NKX2-5* and *HAND1* genes has been observed to result in TOF [62]. A hypomethylative state of certain maternal genes may result in CHD being inherited in the offspring [64,65]. Monteagudo-sanchez et al. found that aberrant methylation of placental genes resulted in FGR although to our knowledge no study has yet to investigate hypomethylation of genes that cause both CHD and SGA [64]. Alternatively, chromatin remodeling and histone modification may also result in CHD epigenesis e.g., inactivation of deacetylases 5 and 9 are a feature of lethal VSD [61,62]. Small non-coding RNA may also contribute to the epigenetics of CHD with recent studies indicating that they are highly susceptible to environmental exposures e.g., cigarette smoking [60,65]. Similarly, through the same physiopathological pathways, maternal diabetes and obesity may induce CHD [61]. However, no study has specifically investigated the role of genetics or epigenetics in the association between SGA and CHD.

Another unresolved issue concerns the role of multiple pregnancies and its possible effect in the association between CHD and SGA. Although, Gijtenbeek et al. found in a systematic review that there is more CHD in twin pregnancies, which in turn are known to have higher rates of SGA [66]. Consequently, the link between multiple pregnancy and advanced maternal on CHD and SGA is unclear because to our knowledge few studies have addressed this issue. The key underlying factor between type of pregnancy and CHD-SGA being the placenta which could have a direct or indirect role in this association [20,67–69]. Jones et al. found a physiopathological explanation of SGA in HLHS based on placental histological analysis, a finding corroborated by other authors specializing in placentology rather than our study question [20]. For example, Matthiesen et al. investigated fetal and placental growth using Z scores [70]. Despite finding a slight difference in placental growth for HLHS, Matthiesen et al. observed an association between suboptimal placental weight and impaired fetal growth for TOF, VSD, and double outlet right ventricle [70]. Consequently, they concluded that placental growth is part of the causal pathway of the association between SGA and certain CHD. In conclusion, from our findings and based the literature, we hypothesize that both placental dysmorphology and abnormal fetal hemodynamics could play a role in the association between CHD and SGA. However further study is required to fully investigate this hypothesis.

This systematic review also confirmed ambiguity in the use of FGR and SGA in the literature. Despite the fact that SGA and FGR are quite distinct concepts, the terms were used interchangeably by different authors using a variety of definitions, cutoff thresholds and reference populations to infer the same meaning; SGA often being used as a proxy for FGR. A recent consensus based definition using a Delphi procedure defined FGR using exclusively ultrasound measurements [71]. While an international meeting of experts in 2007 reached a consensus on SGA, defining it as “a weight and/or

length less than minus 2 standard deviations from the mean"; confusion still reigns [72,73]. Once our literature review was completed, we found an article that used the term "growth restriction in the newborn (GRN)" aimed at clarifying the situation [74]. This consensus-based definition, defined GRN as "birthweight < 3rd percentile compared to population or customized charts". Alternatively, the presence of three out of the following five criteria: "birthweight < 10th percentile compared to population or customized references, head circumference < 10th percentile, length < 10th percentile, prenatal diagnosis of FGR, and data on maternal pregnancy pathology" [48]. Of the 38 studies included in our systematic review, seven (18.4%) studies used a definition of SGA as birthweight < 3rd percentile thereby conforming to the recent definition of GRN. Although only two studies could be used in the meta-analysis, the proportion of GRN in all CHD was 6% (95% CI 6%–7%) [26,39,74]. However, we were unable to compare this to the proportion of GRN in the general population from the literature as this is a new concept. For the same reason our search did not find any study on CHD that specifically used the term GRN and further studies on this subject is required.

4.2. Strengths

Strengths of this systematic review are that a thorough search of the literature was carried out by a multidisciplinary team with specializations in pediatric cardiology, obstetrics, epidemiology, and library science. Following good research practice, the study protocol was registered in the PROSPERO database. The abstracts and articles were reviewed by two independent reviewers and data extraction followed standardized procedures. We evaluated the risk of bias using a validated standardized checklist. The set of studies included in the systematic review and particularly in the meta-analysis included many large population-based studies, which strengthened the external validity of the study in high resource countries. Results highlighted differences in the risk of SGA across different CHD subgroups, which can be useful for risk assessment and for generating hypotheses about the relation between CHD and growth restriction.

4.3. Limitations

Our study has certain limitations and caveats. Differences in practices and policies for prenatal diagnosis and termination of pregnancy for fetal anomaly (TOPFA) across populations and over time can result in changes in the proportion of SGA among newborns with CHD. As TOPFA concerns more severe CHD, all else equal, increases in TOPFA is likely to decrease the proportion of SGA among newborns with CHD. This is more likely to be the case for CHD associated with genetic or other severe anomalies.

The long period of time (1972–2018) for the publications included in the review could have affected the results, in part due to TOPFA but also changes in diagnosis of CHD and the and reference populations used for SGA. However, 2/3 of studies were published after 2009 and the meta-analysis results were often comparable for older and more recent studies.

The paucity of data on isolated subgroups of CHD complicated the interpretation of differences in the proportion of SGA across subgroups of CHD. In addition, the use of large and administrative databases in a number of studies could have been a source of inaccuracies because of coding and data entry errors.

As the majority of studies were from high resource, Western countries, (over two thirds of studies came from the USA), the results may not be generalizable to middle- and low-resource countries.

Finally, we did not evaluate publication bias due to the nature of the research question. Publication bias occurs when negative findings are less likely to be published and can be measured via visual inspection of funnel plots and Egger's test. However, because there are no negative results in a prevalence study, we deemed these methods inappropriate for our meta-analysis [75].

5. Conclusions

Overall, the proportion of SGA in all CHD (20%) was 2-fold higher whereas that of isolated CHD (14%) was as 1.4-fold higher than the expected proportion in the general population. Although the available data have important limits, differences in the proportion of SGA for different subtypes of CHD suggest that there are different pathophysiological mechanisms underlying the relation between CHD and growth restriction. Further studies are required to disentangle the mechanisms of the association between CHD and growth restriction and the risks associated with growth restriction for newborns with CHD.

Author Contributions: Conceptualization, B.K. and L.J.S.; methodology, A.G., N.D. and N.B.; software, A.G. and N.B.; validation, L.J.S., D.B. and B.K.; formal analysis, A.G., N.D. and N.B.; investigation, A.G. and N.D.; resources, A.G. and N.D.; data curation, A.G. and N.D.; writing—original draft preparation, A.G. and N.D.; writing—review and editing, A.G., N.D., L.J.S., D.B. and B.K.; visualization, B.K.; supervision, B.K.; project administration, B.K.; funding acquisition, A.G. All authors have read and agreed to the published version of the manuscript.

Funding: Thesis project financed by APHP DRCI and Association pour la Recherche en Cardiologie du Foetus à l'Adulte (ARCFa).

Acknowledgments: Catherine Weil.

Conflicts of Interest: The authors declare that they have no conflict of interest.

Abbreviations

CHD	Congenital heart defects
SGA	Small for gestational age
CASP	Critical Appraisal Skills Programme
HLHS	hypoplastic left heart syndrome
ToF	Tetraology of Fallot
TGV	transposition of great vessels
VSD	ventricular septal defect
CoAo	coarctation of the aorta
AVSD	atrioventricular septal defect
TA	tricuspid atresia
CAT	common truncus arteriosus

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Paper 2: Prevalence of growth restriction at birth for newborns with congenital heart defects: A population-based prospective cohort study EPICARD.

Objectives

Following on from the first previously presented systematic review and meta-analysis, the aims of this study were to assess the overall risk of growth restriction at birth for newborns with isolated CHD and to compare the risk and severity of growth restriction for five major types of CHD in a prospective population based cohort of newborns with CHD (EPICARD).

Methods

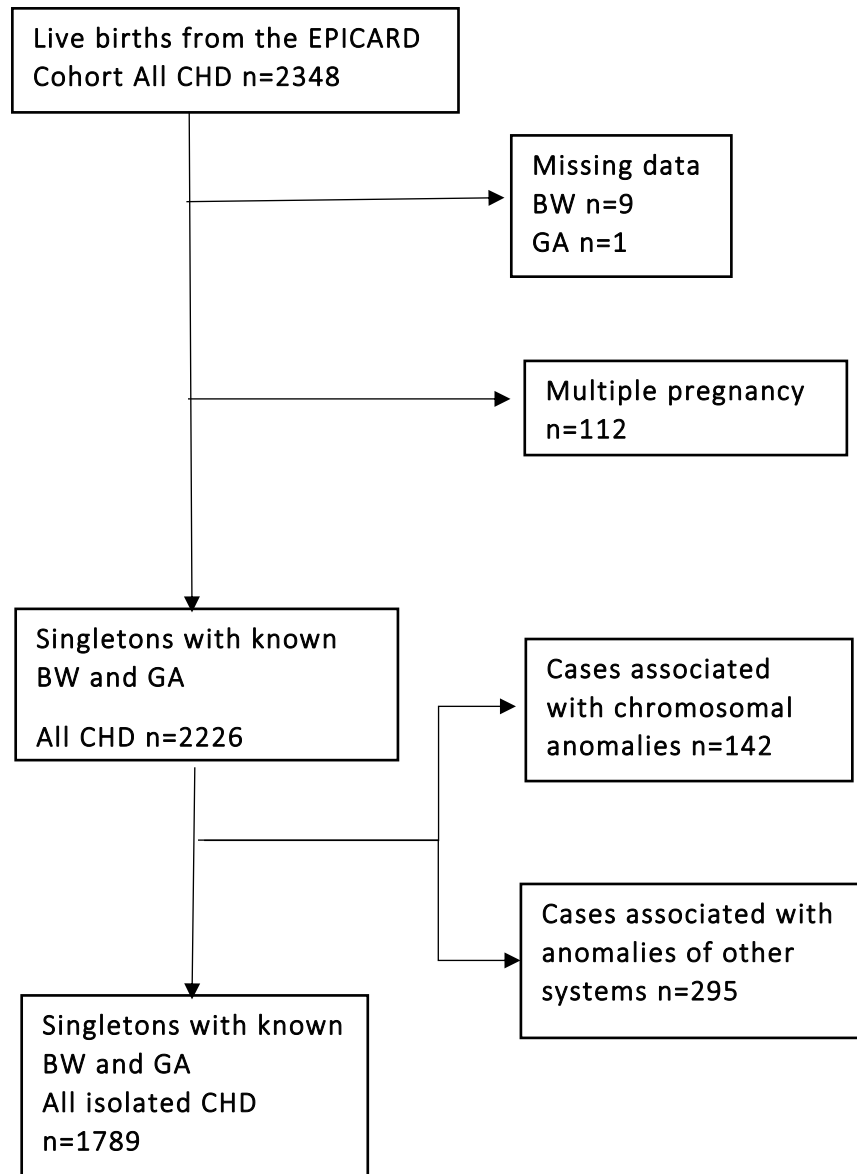
The outcome variable for this study was growth restriction at birth which was measured by its imperfect proxy SGA. This was defined as birthweight < 10th percentile for gestational age and sex according to the EPOPé growth curves while severe SGA was defined using the cut-off birthweight < 3rd percentile and Intermediate SGA as birthweights between the 3rd less than the 10th percentiles (25,26). Not -SGA was defined based on birthweight \geq 10th percentile.

The predictor variable was isolated CHD with minor (non-operated) VSD selected as the control group. Isolated CHD was defined as CHD without chromosomal anomalies, extracardiac anomalies and/or syndromes (6,7). The odds of severe and intermediate SGA were evaluated across five major specific CHD subtypes using ordinal logistic regression that took into account a set of potentially confounding variables that included maternal diabetes, hypertension, smoking, maternal age, geographic origin, parity, prenatal diagnosis, infertility treatments, sex and preterm (< 37 weeks) delivery.

Selection of the study population from the EPICARD Cohort

From the EPICARD cohort of all live births born with CHD in the *Ile de France* region between 2005 and 2008 (N=2,348), we excluded 112 multiple pregnancies and ten subjects with missing data on birthweight and/or gestational age. Newborns with chromosomal anomalies (n=142) or anomalies of other systems and/or genetic syndromes (n=295) were also excluded from the study population. Our final study population comprised 1,789 singleton newborns with isolated CHD and known birthweight and gestational age (Figure 11).

Figure 11: Selection of study population from the EPICARD Cohort of live births born with all CHD.



Legend: CHD congenital heart defects; BW birth weight; GA gestational age

Results

Maternal and fetal characteristics

Table 3 shows the maternal and fetal characteristics of the 1,789 newborns with isolated CHD (not associated with chromosomal or other anomalies) that were included in the study population. Of these, 47% were boys and 11% were born preterm (before 37 weeks). Approximately 3% of mothers reported smoking during pregnancy, 1% had diabetes and 1% reported illicit drug use. Maternal age was 35 years or older for one quarter of women.

One half of women were of French origin and 19% of North African origin. Approximately 7% of the study population were born after infertility treatments and 17% had a prenatal diagnosis of the CHD.

Table 3: Maternal and fetal characteristics of the study population: EPICARD cohort

	N	%	95% CI
Sex			
<i>Male</i>	847	47	45 - 50
Preterm birth (< 37 weeks)			
<i>Yes</i>	192	11	9 - 12
Smoking during pregnancy			
<i>Yes</i>	50	3	2 - 4
Maternal diabetes			
<i>Yes</i>	25	1	1 - 2
Maternal illicit drug use			
<i>Yes</i>	10	1	0 - 1
Maternal age			
< 29	675	38	36 - 40
30-34	650	37	34 - 39
35-39	343	19	18 - 21
> 40	111	6	5 - 7
Parity			
0	638	36	34 - 38
1	545	31	29 - 33
> 2	595	33	31 - 36
Maternal Geographic origin			
<i>France</i>	907	51	49 - 53
<i>North Africa</i>	330	19	17 - 20
<i>Sub Saharan Africa</i>	217	12	11 - 14
<i>Other</i>	329	18	17 - 20
Maternal high blood pressure			
<i>Yes</i>	22	1	1 - 2
Prenatal diagnosis of CHD			
<i>Yes</i>	313	17	16 - 19
Assisted Reproductive Technologies			
<i>Yes</i>	124	7	6 - 8
Small for gestational age			
<i>Normal</i>	1554	87	85 - 88
< 10 th percentile	235	13	12 - 15
3rd - 10th percentile	142	8	7 - 9
< 3rd percentile	93	5	4 - 6
Birth weight (gr)	<i>Mean</i>	<i>SD</i>	
	3175	618.71	3147 - 3204
Total number of patients	1789		

Proportions of SGA, intermediate SGA and severe SGA in isolated CHD for the EPICARD cohort

Table 4 shows the proportions of SGA, intermediate SGA and severe SGA for isolated CHD and isolated specific CHD.

The prevalence of SGA for isolated CHD was 13% (95% CI 12% - 15%) and 5% (95% CI 4% - 6%) for severe SGA. For specific CHD, SGA, ranged from 10% (95% CI 9% - 12%) for minor non-operated VSD to 26% (95% CI 16% - 40%) for Tetralogy of Fallot (ToF). Severe SGA proportions for specific CHD ranged from 4% (95% CI 3% - 5%) for non-operated VSD to 17% (95% CI 9% - 31%) for the ToF.

Table 4: Proportions of SGA (<10th percentile), intermediate SGA (≥ 3rd percentile <10th percentile) and severe SGA (<3rd percentile) for all isolated CHD, major isolated CHD and isolated specific CHD

	SGA				Intermediate SGA			Severe SGA		
	Total	N	%	95% CI	N	%	95% CI	N	%	95% CI
All isolated CHD	1789	235	13	12 - 15	142	8	7 - 9	93	5	4 - 6
All isolated major CHD	493	78	16	13 - 19	51	10	8 - 13	27	6	4 - 8
Specific isolated CHD										
ToF	53	14	26	16 - 40	6	11	5 - 24	8	15	8 - 28
TGA	78	9	12	6 - 21	8	10	5 - 19	1	1	0 - 9
CoA	71	12	17	10 - 28	6	9	4 - 18	6	9	4 - 18
FUH	36	7	19	9 - 36	3	8	3 - 24	4	11	4 - 27
Operated VSD	128	27	21	15 - 29	16	13	8 - 20	11	9	5 - 15
Non-Operated VSD	1063	113	11	9 - 13	69	6	5 - 8	44	4	3 - 6

Legend: CHD congenital heart defects; CoA coarctation of the aorta; FUH functionally univentricular heart; SGA small for gestational age; TGA transposition of the great arteries; ToF Tetralogy of Fallot; VSD ventricular septal defects

The risk of SGA (severe and intermediate vs. non SGA) for different types of isolated CHD

Using ordinal logistic regression, table 5 shows substantial differences in the odds of both intermediate SGA and severe SGA across the five specific CHD. It was found that the odds of overall and severe SGA were substantially higher for operated VSD and for ToF as compared with minor non-operated VSD; the adjusted odds ratios from the ordinal logit model were 2.1 (95% CI, 1.1 - 3.8) and 2.7 (95% CI, 1.3 - 5.8) for operated VSD and ToF, respectively.

Table 5: Odds ratios of SGA (severe and intermediate vs. non SGA) for different types of isolated CHD by ordinal logistic regression

	Crude Odds Ratio	95% CI	Adjusted Odds Ratio**	95% CI
Minor VSD	reference		reference	
Operated VSD	2.8	1.6 - 4.8	2.0	1.1 - 3.8
UVH	2.2	0.9 - 5.1	2.0	0.7 - 5.5
ToF	3.3	1.7 - 6.2	2.7	1.3 - 5.8
TGA	1.1	0.5 - 2.2	1.1	0.5 - 2.5
CoA	1.8	0.9 - 3.4	1.4	0.6 - 3.0

Legend: CI confidence interval; CoA coarctation of the aorta; FUH functionally univentricular heart; TGA transposition of the great arteries; ToF Tetralogy of Fallot; VSD ventricular septal defects
 **Adjusted on diabetes, maternal high blood pressure, maternal smoking during pregnancy, maternal geographic origin, parity, prenatal diagnosis, assisted reproductive therapy, gender and prematurity

Conclusion

This study found that in a large prospective population based cohort of newborns with CHD the prevalence of SGA for isolated CHD was 13% (95%CI 12% - 15%) and 5% (95%CI 4% - 6%) for severe SGA. The risk of growth restriction was substantially higher for certain types of CHD, notably operated VSD and the ToF than what would be expected in the general population

These results may provide a clue for understanding the underlying mechanisms of the relation between alterations in fetal circulation associated with different types of CHD and their effects on fetal growth. Although this knowledge may assist clinicians to better advise patients during prenatal screening and help develop care pathways that may improve medical and surgical management of children with CHD and growth restriction at birth, further knowledge about adverse outcomes would also complement these findings.

Consequently, a second systematic review and meta-analysis was carried out to ascertain the adverse outcomes in infants born with of CHD and GRN in infants. The results of this study are presented in the next section of this chapter.



Prevalence of Growth Restriction at Birth for Newborns With Congenital Heart Defects: A Population-Based Prospective Cohort Study EPICARD

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OPEN ACCESS

Edited by:

Henrique Barros,
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Specialty section:

This article was submitted to
General Pediatrics and Pediatric
Emergency Care,
a section of the journal
Frontiers in Pediatrics

Received: 06 March 2021

Accepted: 30 April 2021

Published: 28 May 2021

Citation:

Ghanchi A, Rahshenas M, Bonnet D,
Derridj N, LeLong N, Salomon LJ,
Goffinet F and Khoshnood B (2021)
Prevalence of Growth Restriction at
Birth for Newborns With Congenital
Heart Defects: A Population-Based
Prospective Cohort Study EPICARD.
Front. Pediatr. 9:676994.
doi: 10.3389/fped.2021.676994

Background and Objectives: Congenital heart defects (CHD) and growth restriction at birth are two major causes of childhood and adult morbidity and mortality. The aim of this study was to assess the overall risk of growth restriction at birth, as measured by its imperfect proxy small (< 10th percentile) for gestational age (SGA), for newborns with CHD.

Methods: Using data from a population-based cohort of children born with CHD, we assessed the risk of growth restriction at birth using SGA and severe SGA (3rd percentile). To compare the odds of SGA and severe SGA across five specific major CHD, we used ordinal logistic regression using isolated, minor (non-operated) ventricular septal defect (VSD) as the control group.

Results: The overall proportion of SGA for "isolated" CHD (i.e., those not associated with other anomalies) was 13% (95% CI, 12–15%), which is 30% higher than what would be expected in the general population (i.e., 10%). The risk of severe SGA was 5% (95% CI, 4–6%) as compared with the expected 3% in the general population. There were substantial differences in the risk of overall SGA and more so severe SGA across the different CHD. The highest risk of SGA occurred for Tetralogy of Fallot (adjusted OR 2.7, 95% CI, 1.3–5.8) and operated VSD (adjusted OR 2.1, 95% CI, 1.1–3.8) as compared with the control group of minor (non-operated) VSD.

Conclusion: The overall risks of both SGA and severe SGA were higher in isolated CHD than what would be expected in the general population with substantial differences across the subtypes of CHD. These results may provide a clue for understanding the underlying mechanisms of the relation between alterations in fetal circulation associated with different types of CHD and their effects on fetal growth.

Keywords: small for gestational age, congenital heart defects, population-based cohort, prevalence, ordinal logistic regression

INTRODUCTION

Congenital heart defects (CHD) are the most frequent group of congenital anomalies with a prevalence of about 1% of all births (1, 2). Newborns with CHD are at a higher risk of growth restriction at birth (3–5). The latter may be an independent risk factor for adverse outcomes in newborns with CHD (5).

By far most of the previous studies that investigated the relation between CHD and growth restriction were hospital-based and population-based studies remain rare (3). Some of the literature has the shortcoming of including CHD associated with chromosomal or other anomalies without separate analyses of “isolated” CHD (not associated with chromosomal or other anomalies). Hence, the effects associated with the CHD *per se* are not always clear. Moreover, the specific effects of different types of CHD on the risk of growth restriction has not been adequately studied. Such an analysis may provide clues about the possible underlying mechanisms of the associations between CHD and growth restriction.

We used data from a population-based, prospective cohort study of more than 2,000 newborns with CHD to: (i) Assess the overall risk of growth restriction at birth for newborns with isolated CHD and to: (ii) Compare the risk and severity of growth restriction for five major types of CHD.

MATERIALS AND METHODS

Data Source

The EPICARD study was a population based prospective cohort of children born with CHD in the Greater Paris area (Paris and its surrounding suburbs) of France carried out between 2005 and 2008.

All cases (live births, terminations of pregnancy for fetal anomaly, TOPFA and fetal deaths) diagnosed prenatally or up to 1 year of age were eligible for inclusion. Diagnoses of CHD and associated comorbidities (i.e., genetic, extra cardiac anomalies and/or syndromes) were confirmed by specialized pediatric cardiologists. Detailed description of the EPICARD cohort has been provided elsewhere (6).

From the EPICARD cohort of all live births ($N = 2,348$), we excluded 112 multiple pregnancies and ten subjects with missing data on birthweight and/or gestational age. Newborns with chromosomal anomalies ($n = 142$) or anomalies of other systems and/or genetic syndromes ($n = 295$) were also excluded from the study population. Our final study population comprised 1,789 singleton newborns with isolated CHD and known birthweight and gestational age (Figure 1).

Outcome and Predictor Variables

The outcome variable, Small for Gestational Age (SGA) was defined as sex- and gestational age-specific birthweight <10th percentile based on the EPOPE population-based growth curves (7). We defined severe SGA using the cut-off birthweight <3rd

Abbreviations: CHD, Congenital Heart defects; VSD, Ventricular Septal Defects; CoA, Coarctation of the Aorta; ToF, Tetralogy of Fallot; TGA, Transposition of the Great Arteries; FUH, Functionally Univentricular Heart; SGA, Small for Gestational Age; TOPFA, Termination of Pregnancy for Fetal anomaly.

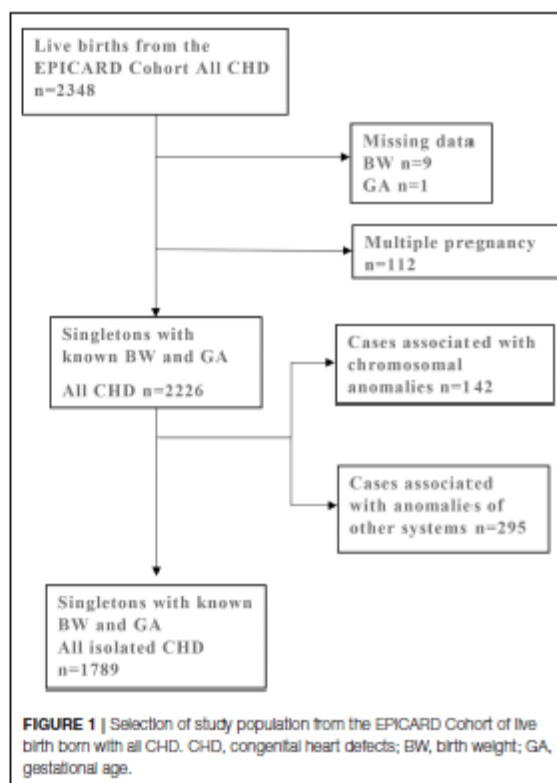


FIGURE 1 | Selection of study population from the EPICARD Cohort of live birth born with all CHD. CHD, congenital heart defects; BW, birth weight; GA, gestational age.

percentile and Intermediate SGA as birthweights between the 3rd < 10th percentiles. Not -SGA was defined based on birthweight \geq 10th percentile (8).

The main predictor variable of interest was type of CHD. We also took into account a set of potentially confounding variables including maternal diabetes, hypertension, smoking, maternal age, geographic origin, parity, prenatal diagnosis, infertility treatments, sex and preterm (< 37 weeks) delivery.

Statistical Analysis

As the outcome variable comprised ordered outcomes (severe SGA/intermediate SGA/Not SGA) we used ordinal logistic regression for the statistical analysis. The proportional odds assumption for the ordinal logit models was tested and the models were found to be consistent with a proportional odds model.

The proportional odds model considers the cumulative probability of an individual event and all other events that are ordered before it (Box 1) (9, 10). Whereas, binary logistic regression uses the logit (log odds) function, ordinal logistic regression uses the logit transformation of the cumulative odds. In the proportional odds logit model, the slopes that correspond to the model coefficients are parallel to one another and the odds for each cut-off category differ only with regards to the intercept (Box 1). The χ^2 -test for the proportional odds assumption

BOX 1 | Ordinal logistic regression (9, 10).

Cumulative Odds ($Y \leq j$) = $\frac{P(Y \leq j)}{1 - P(Y \leq j)}$, $j = 1, \dots, k$

and in logit form:

$\text{logit}(Y \leq j) = \ln\left(\frac{P(Y \leq j)}{1 - P(Y \leq j)}\right)$, $j = 1, \dots, k$

$\text{logit}(Y \leq j) = \alpha_j + X' \beta$

Where:

$P(Y \leq j) = P_1 + P_2 + \dots + P_j$ is the cumulative probability of the event

α_j : Intercept parameters

$\beta = (\beta_1, \beta_2, \dots, \beta_k)$: a vector of unknown regression coefficients.

suggested that this was a reasonable assumption in the case of our models.

The statistical significance level was set at $\alpha = 0.05$ and all analyses were done using Stata v15.1 software (StataCorp LP, College Station, TX, USA).

Ethics approval was obtained from the CNIL (Commission nationale de l'informatique et des libertés) (6).

RESULTS

Table 1 shows characteristics of the study population. Overall, 1,789 newborns with isolated CHD (not associated with chromosomal or other anomalies) were included in the study population. Of those, 47% were boys and 11% born preterm. Approximately 3% of women reported smoking during pregnancy, 1% had diabetes and 1% reported illicit drug use. Maternal age was 35 years or older for one quarter of women. One half of women were of French origin and 19% of North African origin. Approximately 7% of the study population were born after infertility treatments and 17% had a prenatal diagnosis of the CHD.

Table 2 shows the proportions of SGA and severe SGA for isolated CHD and isolated specific CHD. The prevalence of SGA for isolated CHD was 13% (95%CI 12–15%) and 5% (95%CI 4–6%) for severe SGA. For specific CHD, SGA, ranged from 10% (95% CI 9–12%) for minor non-operated VSD to 26% (95% CI 16–40%) for Tetralogy of Fallot (ToF). Severe SGA proportions for specific CHD ranged from 4% (95% CI 3–5%) for non-operated VSD to 17% (95% CI 9–31%) for the ToF.

Table 3 shows the results of the ordinal logistic regression analysis for the five different types of CHD. There were substantial differences in the odds of both intermediate SGA and severe SGA across the five specific CHD.

In particular, the odds of overall and severe SGA were substantially higher for operated VSD and for ToF as compared with minor non-operated VSD; the adjusted odds ratios from the ordinal logit model were 2.1 (95% CI, 1.1–3.8) and 2.7 (95% CI, 1.3–5.8) for operated VSD and ToF, respectively.

DISCUSSION

Using population-based data from a large prospective cohort of children born with isolated CHD, we found that the overall

TABLE 1 | Characteristics of the study population: EPICARD Study.

	N	%	95% CI
Sex			
Male	847	47	45–50
Preterm birth (< 37 weeks)			
Yes	192	11	9–12
Smoking during pregnancy			
Yes	50	3	2–4
Maternal diabetes			
Yes	25	1	1–2
Maternal illicit drug use			
Yes	10	1	0–1
Maternal age			
< 29	675	38	36–40
30–34	650	37	34–39
35–39	343	19	18–21
> 40	111	6	5–7
Parity			
0	638	36	34–38
1	545	31	29–33
> 2	595	33	31–36
Maternal geographic origin			
France	907	51	49–53
North Africa	330	19	17–20
Sub Saharan Africa	217	12	11–14
Other	329	18	17–20
Maternal high blood pressure			
Yes	22	1	1–2
Prenatal diagnosis of CHD			
Yes	313	17	16–19
Assisted reproductive technologies			
Yes	124	7	6–8
Small for gestational age			
Normal	1,554	87	85–88
< 10th percentile	235	13	12–15
3rd–10th percentile	142	8	7–9
< 3rd percentile	93	5	4–6
Birth weight (gr)	Mean	SD	
	3,175	618.71	3,147–3,204
Total number of patients	1,789		

prevalence of SGA was 13% and that of severe SGA 5%, both of which are higher than the expected proportions in the general population, 10 and 3%, respectively, based on the EPOPé population-based growth curves in France (7, 11).

We also found important differences in the probability of SGA and of severe SGA across the different types of CHD. In particular, VSD, which required surgery and Tetralogy of Fallot were associated with two- to three-folds higher odds of both intermediate and severe SGA, whereas minor VSD that did not require surgery was not associated with any significant increase in the risk of SGA as compared with the expected proportions in the general population. Whereas, newborns with SGA as a whole may include those who are constitutionally small, our findings

TABLE 2 | Proportions of SGA (<10th percentile), Intermediate SGA (\geq 3rd percentile <10th percentile), and severe SGA (<3rd percentile) for all isolated CHD, major isolated CHD, and isolated specific CHD.

	Total	SGA			Intermediate SGA			Severe SGA		
		N	%	95% CI	N	%	95% CI	N	%	95% CI
All Isolated CHD	1,789	235	13	12–15	142	8	7–9	93	5	4–6
All Isolated major CHD	493	78	16	13–19	51	10	8–13	27	6	4–8
Specific Isolated CHD										
ToF	53	14	26	16–40	6	11	5–24	8	15	8–28
TGA	78	9	12	6–21	8	10	5–19	1	1	0–9
CoA	71	12	17	10–28	6	9	4–18	6	9	4–18
FUJH	36	7	19	9–36	3	8	3–24	4	11	4–27
Operated VSD	128	27	21	15–29	16	13	8–20	11	9	5–15
Non-Operated VSD	1,063	113	11	9–13	69	6	5–8	44	4	3–6

CHD, congenital heart defects; CoA, coarctation of the aorta; FUJH, functionally univentricular heart; SGA, small for gestational age; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; VSD, ventricular septal defects.

TABLE 3 | Odds ratios of SGA (severe and Intermediate vs. normal) for different types of Isolated CHD by ordinal logistic regression.

	Crude odds ratio	95% CI	Adjusted odds ratio**	95% CI
Minor ventricular septal defect (VSD)	Reference		Reference	
Operated ventricular septal defect (VSD)	2.8	1.6–4.8	2.0	1.1–3.8
Univentricular heart (UVH)	2.2	0.9–5.1	2.0	0.7–5.5
Tetralogy of Fallot (ToF)	3.3	1.7–6.2	2.7	1.3–5.8
Transposition of great arteries (TGA)	1.1	0.5–2.2	1.1	0.5–2.5
Coarctation of the aorta (CoA)	1.8	0.9–3.4	1.4	0.6–3.0

**Adjusted on diabetes, maternal high blood pressure, maternal smoking during pregnancy, maternal geographic origin, parity, prenatal diagnosis, assisted reproductive therapy, gender and prematurity.

were similar when we looked at severe SGA (birthweight <3rd percentile) and the latter is considered, by definition, to represent growth restriction at birth (12).

Our findings on the overall proportion of SGA for isolated CHD are comparable with a previous systematic review (3). However, previous data summarized in this systematic review did not allow estimates for severe SGA or for comparison of proportions of SGA across different types of CHD. Variations in the proportions of SGA and severe SGA for different CHD as reported in our study may provide insights into the pathophysiological mechanisms that link CHD with growth restriction at birth.

Two potential mechanisms may explain the relation between CHD and growth restriction at birth in general and in the case of differences across various types of CHD in particular. These include altered fetal hemodynamics and placental anomalies.

Matthieson et al. studied placental weight z scores in a Danish cohort of 7,569 children with CHD. They found that ToF and major VSD had lower placental weight which was in turn correlated with reduced birth weight and head circumference z scores (13).

Jones et al. found increased placental leptin secretion in children born with hypoplastic left heart syndrome and SGA (14). They argued that placental insufficiency results in SGA through reduced angiogenesis, which in turn reduces the surface area for gaseous exchange.

There may also be common etiological factors that cause both CHD and placental anomalies. Nitric oxide synthase (NOS) deficiency may be the common etiological factor that results in both CHD and fetal growth restriction. Liu et al. found that NOS was important in fetal heart development with deficiencies resulting in CHD (15). Other studies have shown that endothelial NOS may play an important role in fetal growth (16, 17).

Another possible mechanism is that alterations in blood flow circulation, result in differential perfusion and/or oxygen supply in the fetal body, which may in turn cause growth restriction in certain types of CHD but not necessarily others.

Wallenstein et al. found that CHD are associated with growth restriction and based on previous works by Rizzo et al. and Lutin et al., they argued that decreased ventricular output results in SGA but this may only occur in CHD with altered ventricular function (4, 18, 19). Using cardiovascular magnetic resonance, Al Nafsi et al. found that superior vena cava blood flow varied in left sided CHD compared to controls without CHD (20). Story et al. also found differences in the proportion of SGA in specific CHD, notably 13% SGA in TGA, 17% SGA in CoA and 26% SGA in ToF (results similar to those in our study) (5). The authors hypothesized that growth restriction for ToF was due to decreased fetal blood flow and hence reduced oxygenation. This may only be true however, in case of fetal heart failure or when the arterial duct is absent or closed. They also reported that newborns with CoA have decreased overall birthweight and

length but normal head circumference and a greater head volume to birthweight ratio. The latter may be due to decreased caudal blood flow (without a decrease in oxygen saturation).

Donfrio et al. used Doppler ultra sound to demonstrate that decreased blood oxygenation due to abnormal fetal hemodynamics results in enhanced cerebral blood perfusion (brain sparing effect) as an adaptive compensatory mechanism in single ventricle defects (hypoplastic left and right syndromes) (21). However, enhanced cerebral perfusion occurs at the expense of fetal liver, renal, pancreatic and mesenteric circulation, which in turn results in decreased production of insulin growth factor, angiotensin and other endocrine hormones essential for fetal growth (22). These hormones may affect the fetal growth directly as is the case of insulin growth factor or indirectly via placental function (e.g., renin-angiotensin system), inducing an inflammatory response or through other biomolecular pathways (23, 24).

Alternatively, abnormal fetal hemodynamics may affect the placenta resulting in SGA either through elevated fetoplacental vascular resistance due to placental ischemia or by fetoplacental endothelial dysregulation which plays a key role in tempering inflammatory regulators and nutrient exchange (25). Nevertheless, in general, the underlying pathophysiological mechanisms of the associations (or lack thereof) between CHD and the risk of growth restriction are complex and most likely involve multifactorial causal pathways and compensatory mechanisms that are not completely understood. Moreover, in addition to the placental and fetal hemodynamic mechanisms, there are also genetic and epigenetic factors related to the risk of growth restriction with CHD (26–28).

Our study has certain limits. Our study was not designed and cannot disentangle the possible mechanisms that may explain our empirical findings. Indeed, investigation of the possible underlying mechanisms of the relation between CHD and fetal growth were beyond the scope or ambition of our study.

In addition, even if data were from a large, population-based of newborns with CHD, the number of cases for individual specific CHD was relatively small, which resulted in reduced precision in our estimates, particularly for the fortunately less common severe SGA outcomes. However, by using the ordinal logit model, which allowed looking at both severe and intermediate SGA outcomes in the same model, we were able to increase the statistical power of our study, including for severe SGA outcome (9, 10).

Conclusion

Congenital heart defects are associated with a higher risk of growth restriction at birth, including a higher risk of severe growth restriction.

The risk of growth restriction was substantially higher for certain types of CHD, notably operated ventricular septal defects and the Tetralogy of Fallot. The underlying mechanisms of the relation between CHD and growth restriction at birth may be hypoxia and alternations in blood perfusion in the fetus. In addition, placenta is likely to play an important role in the causal links between CHD and fetal growth restriction. Future studies

are needed to disentangle the underlying mechanisms, including genetic and epigenetic factors that may explain the higher risk of growth restriction for newborns with congenital heart defects.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CNIL (French National Committee of information and Liberty). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

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AUTHOR CONTRIBUTIONS

BK conceived the study. AG conducted the statistical analyses and wrote the first draft of the manuscript. DB, FG, and BK contributed to the conceptualization of ideas and

made suggestions about the required analyses. All authors contributed to the interpretation of findings and revisions of the article.

FUNDING

This project financed by APHP DRCI and Association pour la Recherche en Cardiologie du Foetus à l'Adulte (ARCFA).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Paper 3: Early mortality in infants born with neonatally-operated congenital heart defects and low or very-low birthweight: Systematic review and meta-analysis

Objectives

Our first systematic review and meta-analysis on the prevalence of growth restriction in newborns with CHD (presented at the beginning of this chapter), found in addition to a number of knowledge gaps about this subject in the literature, a number of studies reporting adverse outcomes of these children. However because adverse outcomes were not part of the study's objectives or inclusion criteria no definitive conclusions about this could be made. Consequently, we conducted another systematic review and meta-analysis of the literature to provide a comprehensive synthesis on this subject with regards to the morbidity and mortality in low or very low birthweight (LBW and VLBW respectively) and SGA infants with isolated CHD. **This study has been submitted for publication in a peer review journal and is currently under review.**

Methods

The research protocol was registered on the PROSPERO international prospective register of systematic reviews :(32)

(https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=170289 , appendix 2)

and the initial objectives of this study were to answer the following two research questions:

- i) What is the effect of GRN on the risk of adverse outcome in infants born with CHD?
- ii) To what extent do risks of adverse outcomes vary according to the severity of GRN and type of CHD?

The search was carried out on Pubmed and Embase databases using MeSH and key words by two independent blinded reviewers from inception until 13th October 2021. No language restrictions were applied.

Isolated CHD was defined as CHD not associated with chromosomal anomalies, malformations from other systems or syndromes (6,7). While specific CHD subgroups associated with a very low proportions of chromosomal anomalies were also included. Due to data availability, we used SGA as an imperfect measure of growth restriction at birth. Using the consensual definition of SGA, this was defined as birthweight <10th percentile according to gestational age and compared to a standard population (26).

We also used the World Health Organization's (WHO) definition of LBW (i.e. birthweight < 2500g) and VLBW (i.e. birthweight < 1500g).

A number of different adverse outcomes during infancy were selected and included long and short term morbidity and mortality. We made no distinction between different types of mortality i.e. infant (death before 1 year of age) versus childhood (death before 5 years of age) mortality. However proportionate mortality was defined as the proportion of deaths in a specific population over a specified time period. Morbidity was defined as a state of ill health resulting from a disease or condition (symptomatic or sequela) (60). This included a variety of hospital and clinical morbidity indicators including composite outcomes based on the availability of data and was by no means exhaustive.

Selection of included studies

The database search identified 2053 potentially relevant publications of which 104 articles were assessed for eligibility. In total, 23 articles were included in this review of which 11 citations contained sufficient data for a meta-analysis on LBW and VLBW mortality (figure 12). For this reason, this study deviated from the initial search protocol and excluded the results of SGA from the final analysis.

Results

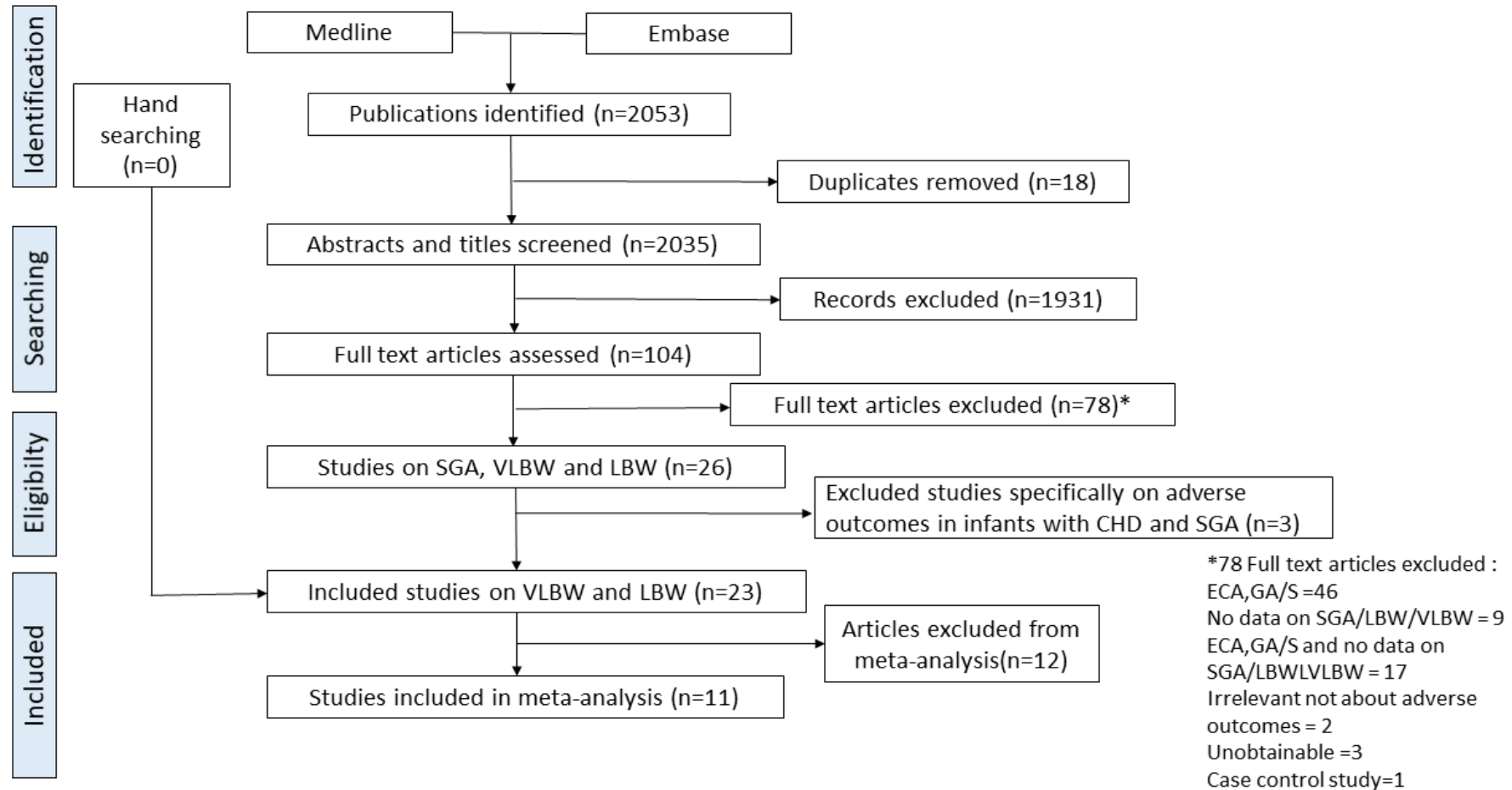
Study characteristics of included studies specifically on SGA

Table 6 shows study characteristics of the 7 (27%) included studies specifically about the adverse outcomes in newborns with SGA and CHD. All these seven studies (100%) were published after the year 2011 with just over half based in the USA (57%). The duration of studies ranged between 3 years and 13 years. The total number of infants born with CHD included in studies ranged between 25 and 6903. Four (57%) of included publications were population based studies.

CHD and subgroups

The type of CHD associated with SGA varied in the included studies. There were 2 publications (29%) that used all isolated CHD. It was found that five studies (71%) were on specific CHD with the majority of these studies on hypoplastic left heart syndrome (HLHS, 43%).

Figure 12: Flow chart to indicate the selection of studies



Legend : ECA, GA/S extra cardiac anomaly, genetic anomaly and/or syndrome; LBW, low birthweight; SGA, small for gestational age; VLBW, very low birthweight

Reported adverse outcomes, comparison groups and measures of association

Although multiple outcomes were studied simultaneously, it was found that infant mortality was the main reported outcome (6 studies, 86%).

Various measures of mortality were used by different authors. Morbidity indicators included a range of heterogeneous measurements for example duration of respiratory support, seizures, sepsis, hypoglycemia etc. Comparison groups varied between studies and consequently this produced outcome results expressed as different measures of association that included proportions, hazards ratios and odds ratios. Table 7 shows the results from studies with similar adverse outcome.

Evaluation of bias

Studies were evaluated for bias using a modified CASP checklist summarized in table 8. All studies addressed a clearly focused issue and had sufficient follow up of cohorts, however the quality of studies regarding other criteria in the checklist varied greatly. In particular, most studies were to some extent subject to selection and measurement bias, especially with regards to diagnosis of CHD using a validated diagnostic method. Notwithstanding differences in geographic locations, external validity criterion was met for over half of studies (57%) as they were population-based and had large sample sizes.

Meta-analysis

Due to incomparable outcomes, effect sizes and type of CHD, a meta-analysis was not possible for adverse outcomes in SGA although we were able to carry out a random effects meta-analysis for LBW and VLBW mortality (37%, 95% CI 27%-47%, I^2 96%)

Conclusion

This study found seven studies whose objectives were to determine adverse effects in newborns born with SGA and CHD in the literature. The most frequent outcome studied was mortality. However due to insufficient number of studies and available data, it was unable to determine the risks of mortality and morbidity in newborns using a meta-analysis. It appears from these studies that newborns with CHD and SGA are more prone to increased mortality, necrotizing enterocolitis and neurological impairment however further studies are required on this subject.

Table 6: summary of individual study characteristics of 7 included studies specifically about adverse outcomes in infants with SGA and CHD

Author	Year	Duration	Location	N CHD	All iCHD	Other Specific CHD	Object	Outcome (s)	Comparison
Calderon [§] (61)	2017	2005-2008	France	419	Yes	No	SGA	cognitive outcomes	non operated CHD
El Hassan [§] (62)	2018	2004-2013	USA	5720	No	HLHS	SGA & LBW	Hospitalisation mortality & NEC	HLHS who did not have NEC
Gelehrter ⁺ (63)	2011	1998-2007	USA	47	No	HLHS	SGA & LBW	Transplant free survival through Fontan palliation	N/A
Miller [§] (64)	2019	2005-2008	USA	509	No	HLHS	SGA & LBW	6 year mortality , neurodevelopment , hospital length of stay, unplanned re-intervention and Quality of life	N/A
Roussin ⁺ (65)	2007	1990-2003	France	25	No	TGA	LBW, SGA & VLBW	Discharge mortality & early morbidity (prolonged inotropic support, cardiac ischemia, pulmonary hypertension, prolonged ventilation, neurologic disease)	N/A
Steurer [§] (66)	2018	2007-2012	USA	6903	No	CCHD	SGA	1 year mortality	normal birth weight
Story (57)	2015	2006-2011	UK	303	Yes	No	SGA	Neonatal mortality, discharge survival & neonatal morbidity (sepsis, seizure, ventilation, hypoglycemia, Jaundice and NEC)	CHD>10P°

Legend: ; § population based study; + preterm births only; i.CHD isolated CHD; CCHD critical CHD; LBW low birthweight; N CHD total number of congenital heart defects; NEC necrotizing enterocolitis; SGA small for gestational age; VLBW very low birthweight; HLHS hypoplastic left heart syndrome; a; TGA transposition of the great arteries

Table 7: Results of studies on SGA and CHD with similar adverse outcomes (1/2)

Outcome	Author	Year	Term (weeks)	CHD	Result	95% CI	measurement
mortality							
During hospitalisation	El Hassan (62)	2018	all	HLHS	27.6%		Proportion
6 year mortality after Norwood procedure	Miller (64)	2019	all	HLHS	0.93	0.86-1.02	Hazards ratio
Hospital mortality after surgery	Roussin (65)	2007	PT	TGA	30.7%		Proportion
1 year	Steurer (66)	2018	PT (<32)	CCHD	1.6	0.8-3.4	adjusted Odds Ratio
			PT (32-33)		2.3	0.9-6.2	
			PT (34)		0.9	0.3-3.0	
			PT (35)		1.8	0.8-4.4	
			PT (36)		1.7	0.9-3.3	
			term (37)		2.8	1.7-4.5	
			term (38)		1.6	1.1-2.6	
			term (39)		1.9	1.3-2.8	
			term (40)		2.6	1.5-4.4	
			term (41)		1.3	0.4-4.4	
Survival							
transplant free survival from birth through Fontan palliation	Gelehrter (63)	2011	PT	HLHS	18%	not stated	proportion
Live at discharge	Story (57)	2015	all	all i.CHD	82%	not stated	proportion
Necrotizing enterocolitis							
	El Hassan (62)	2018	all	HLHS	10.6%	Not stated	proportion
	Story (57)	2015	all	all i.CHD	6%	not stated	Proportion

Table 7 continued: Results of studies on SGA with similar outcomes (2/2)

Outcome	Author	Year	Term	CHD	Result	95% CI	Measurement
Neurodevelopment							
cognitive impairment: KABC global score \geq 1 SD below normative value evaluated at 3 years	Calderon (61)	2017	all	all i.CHD	no surgery group : 1.3 cardiac surgery group:5.9	0.5-3.6 1.7-20.1	adjusted Odds Ratio
Neurodevelopment evaluated at 6 years using BASC adaptive skill composite score	Miller (64)	2019	all	HLHS	female and male 45	38-58	mean standard deviation
Neurodevelopment evaluated at 6 years Vineland scores					adaptive behaviour composite: 90	80-120	
					communication: 100	82-122	
					daily living skills: 90	80-120	
					motor skills: 85	75-100	
					socialization: 100	80-125	

Table 8: Summary of CASP cohort checklist to evaluate bias of included studies on SGA

Author	CASP criteria							Total Score/9	Bias Risk
	focused issue	selection bias	measurment bias	confounding	follow-up	results	external validity		
Calderon (61)	+	-	+	+	+	-	+	5	moderate
El hassan (62)	+	-	-	-	+	+	+	4	moderate
Gelehrter (63)	+	-	-	+	+	+	-	4	moderate
Miller (64)	+	-	-	+	+	++	+	6	low
Roussin (65)	+	-	+	-	+	-	-	3	high
Steurer (66)	+	-	-	+	+	++	+	6	low
Story (57)	+	-	+	+	+	+	-	5	moderate

Legend : ++ strongly fulfilled criteria ; + fulfilled criteria ; - weakly fulfilled criteria; low bias if score \geq 6

Chapter 4: Discussion and perspectives for future research

In summary, we found that:

- i) The overall prevalence of growth restriction at birth in newborns with CHD, based on its imperfect proxy Small for Gestational Age (SGA), was almost two-fold higher than that in the general population.
- ii) There are substantial variations in the proportion of newborns with different types of CHD who are SGA. For some, minor CHD, the proportion of SGA was comparable to that of the general population whereas for others, notably Tetralogy of Fallot, the SGA was three-fold higher than the expected value.
- iii) Newborns with CHD who are SGA had an increased risk of mortality and morbidity, including necrotizing enterocolitis and neurological impairment.

Pathophysiological considerations

There are at least two possible, not mutually exclusive, explanations of the relation between CHD and growth restriction:

- i) CHD causes growth restriction in the newborn.
- ii) A common risk factor causes both CHD and growth restriction in the newborn simultaneously.

As noted below, the literature suggests that one or both of these mechanisms may underlie the association between CHD and growth restriction. It is also likely that the underlying mechanisms of the association between CHD and growth restriction can vary as a function of the pathophysiology of the specific types of CHD.

1. CHD causes growth restriction in the newborn

Alterations in blood flow circulation associated with CHD may result in differential perfusion and/or oxygen supply in the fetal body. This may in turn cause growth restriction in certain types of CHD but not necessarily others.

Our first two studies provide some evidence in favor of this hypothesis as there were important differences in the proportions of SGA across the spectrum of CHD. Indeed SGA varied from 30% for ToF to 12% in isolated ASD.

Based on previous ultrasound studies by Rizzo *et al.* and Lutin *et al.*, Wallenstein *et al.* hypothesized that reduced ventricular function decreases cardiac output resulting in stunted fetal growth (54,67,68). Using cardiovascular magnetic resonance imaging, Al Nafsi *et al.* found that superior vena cava blood flow varied in left sided CHD compared to controls without CHD (69). The findings from our systematic review of an increased risk of SGA in HLHS (21%) and the proportion of SGA for functionally univentricular heart (FUH) in the EPICARD cohort are consistent with this mechanism.

Story *et al.* also found differences in the proportion of SGA in specific CHD, notably 13% SGA in TGA, 17% SGA in CoA and 26% SGA in ToF (results consistent with those in our study using the EPICARD cohort) (57). The authors hypothesized that growth restriction for ToF was due to decreased fetal blood flow and hence reduced oxygenation (57). This may only be true however, in case of fetal heart failure or when the arterial duct is absent or closed. Story *et al.* also reported that newborns with CoA have decreased birthweight and length but normal head circumference and a greater head volume to birthweight ratio (57). The latter may be due to decreased caudal blood flow (without a decrease in oxygen saturation). Sun *et al.* also found that decreased oxygen consumption is associated with smaller brain sizes in children with CHD(70).

Donfrio *et al.* used Doppler ultra sound to demonstrate that decreased blood oxygenation due to abnormal fetal hemodynamics results in enhanced cerebral blood perfusion (brain sparing effect) as an adaptive compensatory mechanism in single ventricle defects (hypoplastic left and right syndromes) (71). However, enhanced cerebral perfusion occurs at the expense of fetal liver, renal, pancreatic and mesenteric circulation, which in turn results in decreased production of insulin growth factor, angiotensin and other endocrine hormones essential for fetal growth. These hormones may affect the fetal growth directly as is the case of insulin growth factor or indirectly via placental function (e.g., renin-angiotensin system), inducing an inflammatory response or through other biomolecular pathways (72). Alternatively, abnormal fetal hemodynamics may affect the placenta resulting in SGA either through elevated fetoplacental vascular resistance due to placental ischemia or by fetoplacental endothelial dysregulation which plays a key role in tempering inflammatory regulators and nutrient exchange(73).

The redistribution of fetal circulation as an adaptive mechanism to maintain homeostasis and to protect brain from hypoxia (the brain sparing effect) to the detriment of the mesenteric circulation may also provide an explanation for the increased risk of necrotizing enterocolitis (74). However, the brain sparing effect does not completely prevent brain injury, which may explain the increased risk of neurodevelopmental impairment in newborns with CHD and GRN (75) .

2. A common risk factor causes both CHD and growth restriction in the newborn simultaneously

An alternative etiological mechanism is that a common risk factor causes both CHD and GRN. Several authors have hypothesized that such common etiological factors may be from maternal, placental, fetal, and/or environmental sources. Malik *et al.* proposed that smoking may contribute to a common etiological pathway for CHD and GRN, while Cedergren and Kallen theorized that abnormal trophoblastic growth in early pregnancy results in both growth restriction and CHD (56,76). Jones *et al.* argued that placental insufficiency may be the common causal pathway for HLHS and growth restriction (77). The authors of this study asserted that placental insufficiency reduces angiogenesis and villous tree maturation of the placenta, thereby reducing the surface area for gaseous and nutritional exchanges. As a result, growth restriction is induced directly and indirectly by nutritional deficiency. Their observation of increased placental leptin secretion led them to speculate that a predisposition for HLHS is the result of a compensatory mechanism. Nevertheless, the effect of leptin in myocardial hypertrophy remains uncertain (78).

Matthieson *et al.* studied placental weight z scores in a Danish cohort of 7,569 children with CHD (79). They found that ToF and major VSD had lower placental weight which was in turn correlated with reduced birth weight and head circumference z scores (79). There may also be other common etiological factors that cause CHD, placental anomalies and growth restriction. For example, Nitric Oxide Synthase deficiency may be the common etiological factor that results in both CHD and fetal growth restriction. Liu *et al.* found that this enzyme was important in fetal heart development with deficiencies resulting in CHD, while other studies have shown that endothelial nitric oxide synthase may play an important role in fetal growth (80–82).

The underlying pathophysiological mechanisms of the associations (or lack thereof) between CHD and the risk of growth restriction are complex and most likely involve multifactorial causal pathways and compensatory mechanisms that are not completely understood. Moreover, in addition to the placental and fetal hemodynamic mechanisms, there are also the contribution of genetic and epigenetics factors related to the risk of growth restriction with CHD.

Clinical implications

The clinical implications of our findings and those in the literature are that fetuses with CHD have an almost two-fold increased risk of being growth restricted at birth but that this association seems relatively limited to certain types of CHD and not others. Moreover, newborns with both CHD and GRN have an increased risk of early mortality and morbidity and long-term adverse outcomes. This implies that newborns with CHD and GRN are a high risk group of newborns with CHD and require close surveillance and possible early delivery in case of suboptimal fetal growth. To date, interventions that may alleviate the problem of growth restriction in newborns with CHD are not available whereas in the case of pre-eclampsia such an intervention is available using low dose aspirin. Finally, increased awareness about the long-term adverse outcomes of newborns with CHD and GRN, including neurodevelopmental outcomes can provide useful information for professionals involved in the care of children with CHD.

Strengths

Our systematic reviews used robust and replicable methodology by a multi-disciplinary team with specializations in pediatric cardiology, obstetrics, epidemiology, and library science. Following good research practice, the study protocols for both systematic reviews were registered on the PROSPERO database. Abstracts and articles were reviewed by two independent reviewers and data extraction followed standardized procedures. The risk of bias was evaluated using a validated standardized checklist.

The set of studies included in the systematic reviews and particularly in the meta-analysis for our first publication included many large population-based studies, which strengthened the external validity of the study in high resource countries.

The results of our first two studies also highlighted differences in the risk of SGA across different CHD subgroups. This provides additional information for health care providers, patients and parents and may be beneficial for generating hypotheses about the relation between CHD and growth restriction. Furthermore, as our population-based study was concerned only with isolated CHD, we were able to analyze the effect of CHD *per se* on growth restriction, and avoid the problem of attributing growth restriction to CHD vs. any associated, including genetic anomalies and syndromes.

We found that there is confusion over the definitions of SGA, FGR and GRN in the literature with certain authors using the terms interchangeably. A strength of this thesis is that by analyzing severe (< 3rd percentile) SGA separately in our population-based study, we were able to look at the relation between CHD and growth restriction while avoiding inclusion of newborns who may be constitutionally small and included in the overall (< 10th percentile) SGA category. Finally, through the use of an ordinal logit model which allowed us to look at both severe and intermediate SGA outcomes in the same model, we were able to increase the statistical power of our population-based prospective cohort study and compare the relations between severe and moderate (3-10th percentile) SGA outcomes.

Limitations

This thesis has certain limitations and caveats. The first being that as it is only concerned with live births and growth restriction of the newborns, we were not able to look at fetal growth restriction in its entirety. Moreover, differences in practices and policies for prenatal diagnosis and TOPFA across populations and over time can and do result in changes in the proportion of growth restriction at birth among newborns with CHD. As TOPFA concerns more severe CHD, increases in TOPFA is likely to decrease the proportion of SGA among newborns with CHD. This is more likely to have been the case for our first systematic review which included CHD associated with genetic or other severe anomalies and is one of the reasons why the study on the EPICARD cohort and final systematic review both focused on isolated CHD.

The fact that we were only concerned with liveborns may also explain the limited number of studies found in the literature on adverse outcomes in growth restricted newborns with CHD in our second systematic review. Fetuses with either severe CHD (e.g. HLHS) or severe growth restriction with CHD are less likely to be live born in countries with an active prenatal diagnosis policy and widely available access to TOPFA, which is the case in France and many other European countries.

Studies found in our systematic reviews were from high resource countries, while our population-based study concerned a cohort of newborns in Greater Paris area. Hence, our results may not be generalizable to middle and low resource countries or countries where restrictions exist in access to high quality prenatal diagnosis services and TOPFA.

Some of the articles included in the systematic reviews were based on data from administrative databases, where errors in coding and data entry are likely to occur. The thesis was not designed and cannot disentangle the possible mechanisms that may explain our empirical findings. Indeed, investigation of the possible underlying mechanisms of the relation between CHD and fetal growth were beyond the scope or ambition of our analyses. This was in part due to the limitations of the data available from the EPICARD cohort (e.g. absence of ultrasound Doppler measurements or placental weight or biopsy) In addition, even if EPICARD was a large, population-based cohort of newborns with CHD, the number of cases for individual CHD was relatively small, which resulted in reduced precision in our estimates, particularly for the less common outcome of severe SGA.

Perspectives for future research

Future epidemiological investigations of the relation between CHD and GRN include assessments of the impact of GRN on postnatal growth of newborns with CHD and the extent to which such an impact may vary for different CHD. Another line of research would be to look at the extent to which consequences of GRN on short- and long-term adverse outcomes including mortality, morbidity and neuro-developmental outcomes may depend on the type of CHD.

An interesting approach to these questions involves the use of path analyses and more generally structural equation modelling that may help elucidate the mediators and moderators of the complex relations between CHD, GRN and outcomes.

An alternative and hitherto not used empirical approach to the questions related to CHD and fetal and postnatal growth of newborns with CHD is to look at the distribution of the relevant parameters, birth weight, gestational age, weight changes after birth, beyond the commonly used notions of a category or categories of growth restriction such as SGA. Instead, it may be fruitful to look at the entire distribution of birth weight as well as gestational age in newborns with CHD and examine the extent to which different parts of the distribution, particularly on the lower side of the distribution may be affected. This is possible with the use of quantile regression for example, which allows assessment of possibly differential effects of CHD on different percentiles of the birth weight distribution or that of gestational age.

Perspectives for future research also include those aimed at investigating the underlying pathophysiological mechanisms of the relation between CHD and GRN. In this regard, it would be interesting to look at the extent to which growth restriction may be asymmetric by simultaneously analyzing longitudinal data on head circumference, height and weight. Further studies of the underlying mechanisms of the relation between CHD and GRN would also benefit from more extensive studies of the placenta as well as genetic and epigenetic studies.

Our understanding of the clinical and developmental implications and consequences of growth restriction remains incomplete. Future research regarding these issues may, at term, lead to ways of preventing the adverse consequences of fetal and postnatal growth restriction by interventions implemented along the different stages of the causal chains that link CHD with GRN and adverse short and long-term developmental outcomes.

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Live births with CHD

CHD defined as developmental abnormalities involving structures of the heart. These defects are based on (or confirmed by) expert diagnosis made prenatally, at birth or later in life.

Intervention(s), exposure(s)

CHD including different categories and individual types of CHD.

Comparator(s)/control

Comparisons of FGR by type of CHD and in relation to expected population levels of FGR

Context

Studies in all settings and in all countries will be included.

Main outcome(s)

Prevalence and severity of FGR (given as proportions)

Measures of effect

FGR will be assessed at birth.

Additional outcome(s)

None

Measures of effect

Not applicable

Data extraction (selection and coding)**a) Selection**

Selected studies must focus on FGR (either as the main or secondary objective) in children with CHD.

FGR will be studied for all live births regardless of gestational age.

Articles that associate maternal CHD and the risk of FGR in their offspring will be excluded.

From the keywords and MeSH/Emtree terms, first level screening will be carried out by 2 independent reviewers (AG and ND) from the titles and abstracts. Articles will be excluded at this level if the reviewers deem that they do not analyze FGR/SGA rates in newborns with CHD. Articles accepted for full review will be evaluated in detail using the methods detailed in the next section.

Zotero, Excel and Rayyan will be used to manage screening and the review process by the two independent reviewers. Records will be made of the number of publications found using the search criteria, the number of duplicates, the number of studies excluded and the rationale for exclusion using the PRISMA flow chart throughout the review process.

In the event of disagreement at any stage (first level screening or full article review), the reviewers will confer to obtain a consensus. In the event a consensus is not reached two independent, senior reviewers (BK and LS) will make a final decision on whether to include or exclude the article.

b) Extraction

Publications eligible for full review will be assessed using the Critical Appraisal Skills Programme (CASP) method of critical analysis. From each publication, information on the type of study, participant data (number, type of CHD, gestational age, FGR status, gender, geographic location, socioeconomic status and ethnicity), FGR definition and reference population used, year of study and the use of prenatal diagnosis to determine

severity of FGR will be used in the data synthesis

Risk of bias (quality) assessment

Quality assessment will be based on the CASP method to identify major risks of bias (internal and external validity, poor reporting of study design and conduct, choice of outcome measures and conflicts of interest)

Strategy for data synthesis

We will use aggregate data from identified studies to calculate the proportion of FGR in children with CHD. This will be done for overall CHD, to the extent possible limited to isolated CHD, i.e. CHD not associated with chromosomal anomalies or malformations from other systems or syndromes. In addition, when sufficient detail is provided, we will look at data on specific CHD; in particular Transposition of great arteries, Tetralogy of Fallot or Coarctation of the aorta. A meta-analysis of proportions will be done using a random effects model. STATA 12.1 software will be used to carry out the meta-analysis. The I² statistic and Forest plots will be used to assess heterogeneity. We will use Funnel plots, Egger's and Begg's tests to assess publication bias. A narrative synthesis will be carried out for studies not included in the meta-analysis due to insufficient data. The analysis will be carried out by two reviewers (AG and ND) and any discrepancies will be resolved by senior reviewers (BK and LS)

Analysis of subgroups or subsets

Analysis of subgroups: Subgroup analysis (classification system used to categorize the type of CHD, severity of FGR, geographic location/ ethnicity, socioeconomic status, prenatal diagnosis) will be carried out if there are sufficient data.

Contact details for further information

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Type and method of review

Epidemiologic, Meta-analysis, Systematic review

Anticipated or actual start date

05 April 2019

Anticipated completion date

31 December 2019

Funding sources/sponsors

APHP

Conflicts of interest

Language

English

Country

France

Stage of review

Review Completed published

Details of final report/publication(s) or preprints if available

Ghanchi A, Derridj N, Bonnet D, Bertille N, Salomon LJ, Khoshnood B. Children Born with Congenital Heart Defects and Growth Restriction at Birth: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health*. 2020;17(9):3056. Published 2020 Apr 28. doi:10.3390/ijerph17093056

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7246925/>

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Child; Female; Fetal Growth Retardation; Heart Defects, Congenital; Humans; Parturition; Pregnancy; Prevalence

Date of registration in PROSPERO

12 July 2019

Date of first submission

04 April 2019

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

Changes made to authors: email and country missing completed the status of our review: finished and published

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

12 July 2019

30 October 2020

Appendix 2: search protocol for Paper 3 published on the University of York Centre for reviews and dissemination PROSPERO international prospective register of systematic reviews website: (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=170289)

<p>NIHR National Institute for Health Research</p> <p>PROSPERO International prospective register of systematic reviews</p> <p>To enable PROSPERO to focus on COVID-19 submissions, this registration record has undergone basic automated checks for eligibility and is published exactly as submitted. PROSPERO has never provided peer review, and usual checking by the PROSPERO team does not endorse content. Therefore, automatically published records should be treated as any other PROSPERO registration. Further detail is provided here.</p> <p>Citation</p> <p>Ali GHANCHI, Neil DERRIDJ, Nathalie BERTILLE, Laurent J. SALOMON, Babak KHOSHNOOD. Adverse outcomes in infants born with isolated congenital heart defects and growth restriction in the newborn (GRN): A systematic review and meta-analysis. PROSPERO 2020 CRD42020170289 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020170289</p> <p>Review question</p> <ol style="list-style-type: none">1. What is the effect of GRN on the risk of adverse outcome in infants born with CHD?2. To what extent do risks of adverse outcomes vary according to the severity of GRN and type of CHD? <p>Searches</p> <p>We will search PubMed and Embase databases from inception up until 29/02/2020 cutoff point and there will be no language restrictions</p> <p>Types of study to be included</p> <p>All type of observational study designs in humans are eligible for inclusion</p> <p>Condition or domain being studied</p> <p>Adverse outcomes in infants born with isolated CHD and affected by either Growth Restriction in the Newborn or Low birth weight</p> <p>Participants/population</p> <p>Infants born with isolated CHD, i.e., CHD not associated with any known chromosomal, genetic or other anomalies or syndromes. CHD defined as developmental abnormalities involving the structure of the heart and the great vessels.</p> <p>Intervention(s), exposure(s)</p> <p>GRN is defined by the failure of a fetus to attain expected growth (Fetal Growth Restriction (FGR)) at birth. Empirically, GRN is defined as birthweight <3rd percentile or 3/5 following criteria: birthweight <10th percentile, head circumference <10th percentile, length <10th percentile, prenatal diagnosis of FGR and/or maternal pregnancy information (hypertension or pre-eclampsia) Historically and in practice FGR at birth has been mostly defined and studied by its imperfect proxy Small for Gestational Age (SGA). SGA is defined by birthweight <10th percentile for a given gestational age and reference population. Severe FGR at birth is usually defined as birthweight for gestational age <3rd percentile, or in some cases by <2 SD of the mean birthweight. We will also include newborns with isolated CHD and low birth weight using the WHO definition which is "birth weight <2500g regardless of gestational age".</p> <p>Comparator(s)/control</p> <p>Infants born with CHD or with another congenital anomaly or from the general population</p> <p>Context</p> <hr/> <p style="text-align: right;">Page: 1 / 4</p>
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To be included in the review, the articles must focus on outcomes of infants with isolated CHD and GRN (including small for gestational age and low birth weight).
Studies of newborns with only isolated patent ductus arteriosus and/or patent foramen ovalae will not be eligible for the study.
Articles about the relation between maternal CHD and the risk of growth restriction in the offspring will be excluded.

Main outcome(s)

Based on data availability, the adverse outcomes may include:

- Perinatal death / mortality
- Apgar score
- Hypo-ischemic encephalopathy/ cerebrovascular accident and seizure
- Periventricular leukomalacia
- Intraventricular hemorrhage (IVH)
- Bronchopulmonary dysplasia
- Duration of respiratory support
- Vertically transmitted Infection (mother-to- child transmission)
- Length of Hospital / neonatal unit stay
- Necrotizing enterocolitis
- Retinopathy
- Any other relevant outcome identified during the review

Measures of effect

We will look at odds ratios, risk ratios, hazards ratios and other measures of association for adverse birth outcome

Additional outcome(s)

None

Measures of effect

None

Data extraction (selection and coding)

a) Selection

From the keywords and MeSH/Emtree terms, first level screening will be carried out by 2 independent reviewers (AG and ND) from the titles and abstracts. Articles will be excluded at this level if the reviewers deem that they do not analyze adverse outcomes in infants with either isolated CHD and GRN (FGR/SGA) or isolated CHD and LBW. Articles accepted for full review will be evaluated in detail using the methods detailed in the next section

Zotero, Excel and Rayyan will be used to manage screening and the review process by the two independent reviewers. Records will be made of the number of publications found using the search criteria, the number of duplicates, the number of studies excluded and the rationale for exclusion using the PRISMA flow chart throughout the review process.

In the event of disagreement at any stage (first level screening or full article review), the reviewers will confer to obtain a consensus. In the event a consensus is not reached two independent, senior reviewers (BK and LS) will make a final decision on whether to include or exclude the article.

b) Extraction

Publications eligible for full review will be assessed using the Critical Appraisal Skills Programme (CASP) method of critical analysis. Based on data availability from each publication, information on the type of study, participant data (number, type of CHD, gestational age, GRN or LBW status, gender, geographic location, socioeconomic status and ethnicity), GRN definition and reference population used, year of study, surgical intervention and birth outcome will be used in the data synthesis.

Risk of bias (quality) assessment

Quality assessment will be based on the CASP method to identify major risks of bias (internal and external validity, poor reporting of study design and conduct, choice of outcome measures and conflicts of interest)

Strategy for data synthesis

A narrative synthesis of major findings from each study is planned. If the data permits a meta-analysis may be conducted. We intend to use aggregate data from identified studies to calculate pooled OR (or RR or Hazards ratios) of adverse birth outcome in infants with isolated CHD and GRN and isolated CHD and LBW. In addition, when sufficient detail is provided, we will look at data on specific CHD; in particular Transposition of great arteries, Tetralogy of Fallot or Coarctation of the aorta.

A meta-analysis of ORs will be done using a random effects model.

STATA 12.1 software will be used to carry out the meta-analysis. The I^2 statistic and Forest plots will be used to assess heterogeneity. We will use Funnel plots, Egger's and Begg's tests to assess publication bias. A narrative synthesis will be carried out for studies not included in the meta-analysis due to insufficient data. The analysis will be carried out by two reviewers (AG and ND) and any discrepancies will be resolved by senior reviewers.

Analysis of subgroups or subsets

Subgroup analysis: classification system used to categorize the type of CHD or specific CHD subtypes, severity of GRN, geographic location/ ethnicity, socioeconomic status, prematurity status and year of study will be carried out if there are sufficient data

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Type and method of review

Meta-analysis, Synthesis of qualitative studies, Systematic review

Anticipated or actual start date

01 March 2020

Anticipated completion date

01 October 2020

Funding sources/sponsors

APHP

Grant number(s)

State the funder, grant or award number and the date of award

N/A

Conflicts of interest

Language

English

Country

France

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

MeSH headings have not been applied to this record

Date of registration in PROSPERO

28 April 2020

Date of first submission

28 February 2020

Stage of review at time of this submission

The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

28 April 2020

