Infant congenital heart disease prevalence and mortality in French Guiana: a population-based study

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Summary

Background Few studies have assessed the prevalence and mortality of simple or complex congenital heart diseases (CHD) in newborns. In Latin America and Caribbean (LAC), CHD epidemiology seems highly variable, with few population-based assessments and different methodologies between studies. To date, the situation in French Guiana, a French overseas territory located in South America between Brazil and Suriname, has never been described.

Methods We analysed CHD prevalence, characteristics and related infant mortality in French Guiana, with a population-based registry analysis of all fetal and live birth CHD cases in infants under 1 year (January 2012–December 2016).

Findings Overall, 33,796 births (32,975 live births) were registered, with 231 CHD (56 fetuses), including 215 live births. Most frequent CHD categories were anomalies of the ventricular outflow tract and extra-pericardial trunks, and ventricular septal defects. 18.6% (43/231) chromosomal or genetic anomalies, and 6.5% (15/231) terminations of pregnancy were observed. Total CHD prevalence was 68.4 [95% CI: 67.9–68.8] per 10,000, while live birth prevalence was 65.2 [95% CI: 64.7–65.7] per 10,000. Total infant mortality was 9.4/10,000 live births [95% CI 9.1–9.7], with highest rates for functionally univentricular hearts (FUH).

Interpretation A distinct profile for CHD is highlighted in French Guiana with elevated mortality linked to FUH. A potential determinant of the recognized excess mortality risk might be the presence of chromosomal or genetic anomalies in about a fifth of all CHD. This helps us to better understand CHD burden in this part of South America and provides future keys towards reducing CHD-related infant mortality.

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Keywords: Congenital heart disease; Univentricular hearts/single ventricle defects; Latin America and Caribbean; Prevalence; Infant mortality; Chromosomal and genetic anomalies

Introduction

The prevalence of congenital heart diseases (CHD) remains geographically variable, with a global estimate of 80–90/10,000 live births.[1–3] In light of the very heterogeneous worldwide CHD spectrum, the current paucity of large structured population databases might limit the

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Research in context

Evidence before this study

In light of the very heterogeneous worldwide congenital heart diseases (CHD) spectrum, the current paucity of large structured population databases developed on a country-wide scale might limit the precise evaluation of CHD prevalence and related mortality in infants, especially in low-resource settings such as territories of Latin America and Caribbean. The same applies to complex CHD types, such as functionally univentricular hearts (FUH), also known as single ventricle defects, responsible for higher disease morbidity and mortality. In line with the regional context, French Guiana's CHD epidemiological trends have never been reported, with limited health indicators highlighting significant heath disparities. A comprehensive literature search was performed between 1st August 2022 and 17th November 2023 using PubMed, Scopus, EMBASE, Google Scholar, and MedRxiv to identify all relevant articles. Search terms were defined by two senior researchers (HL, RB) and included the following: ("congenital heart diseases" OR "congenital malformations" OR "single ventricle" OR "univentricular hearts" OR "birth defects") AND ("prevalence" OR "cardiac mortality" OR "infant mortality" OR "epidemiology") AND ("Latin America and Caribbean" OR "Latin America" OR "Caribbean" OR "South America" OR "each individual country name of Latin America and Caribbean") AND ("infants" OR "population-based study" OR "registry" OR "socio-demographic index" OR "health disparities" OR "low middle-income countries"). Our search was limited to studies including children without any language limitation. Additional studies were identified from reviewing the reference lists of retrieved studies, as well as with internet searches (Google). After analysis of the 50 studies identified through our search, we observed that the main regional reference for the Latin America and Caribbean region and the rest of South America were the 1990–2017 CHD prevalence projections at birth from the Global Burden of Disease study (GBD). Indeed, rare published studies originating from the Latin America and Caribbean region indicate highly variable prevalence rates between countries such as Brazil, Ecuador and Peru, with differing methodologies between studies. Other reported bias includes divergences in terms of case definition (e.g., inclusion of cerebrovascular malformations), outcome endpoints, selection of study population (e.g., outpatient registration only), as well as the absence of reliable data on complex CHD cases, the use of broad age groups to assess infant mortality, and the lack of data completeness. Thus, CHD prevalence and related infant cardiac mortality in Latin America and Caribbean have yet to be precisely determined especially for complex CHD subtypes, such as functionally univentricular hearts (FUH).

Added value of this study

Located in South America and part of Latin America and Caribbean, French Guiana is a French overseas department with one of the highest fertility rates of the continent. While GBD projections do not include any data from this territory, the latter has a population-based CHD registry which exhaustively records all known cases at country level, with detailed information on CHD types, presence of chromosomal or genetic anomalies, follow-up and infant mortality. The present population-based study analyses French Guianese registry data to describe CHD prevalence, characteristics and related mortality in infants under 1 year in French Guiana over a five-year period. Our study results highlight a different epidemiological and clinical profile for CHD in this part of the world. It underlines a high prevalence of FUH, as well as an important infant mortality related to such defects in the French Guianese population. Another potential determinant of the recognized excess risk of infant mortality might be the presence of chromosomal or genetic anomalies in about a fifth of all CHD.

Implications of all the available evidence

The present paper highlights a high prevalence of univentricular hearts in the French Guianese population, as well as an important related infant mortality. Furthermore, our findings raise major questions about the existence of specific ethnic, toxic, environmental, as well as other unidentified risk factors in this part of the world. From a public health perspective, we believe that the observed trends in terms of the complexity of CHD and infant cardiac mortality should be considered as warning signals. This study contributes towards better understanding the burden of such defects in the underserved populations of French Guiana and provides future keys towards reducing infant mortality. It further advocates for the expansion and strengthening of regional standardized CHD data networks for Latin America and Caribbean, with adequate support from regional and international health authorities.

precise evaluation of CHD-related neonatal or infant morbidity and mortality, especially in low-resource settings.[4] Until now, only a few studies have carefully assessed the prevalence and mortality of newborns with either simple or complex CHD,[4–12] while other authors have either limited their focus to the most severe or the most frequent defects, or to premature and very low-weight infants.[1,7,13,14]

In Latin America and Caribbean (LAC), CHD prevalence and distribution seem highly variable between countries, with very different methodologies from one study to another. Thus, CHD prevalence might have yet to be precisely determined, especially for complex CHD types such as functionally univentricular hearts (FUH).[1] To date, the main regional reference remain the 2017 CHD prevalence projections at birth from the Global

Burden of Disease (GBD) study, with reported rates for different parts of Latin America (Central, Tropical, Andean, South) and the Caribbean varying from 62.8 [95% CI 55.4–70.9] to 116.6 [95% CI 102.3–132.9] per 10,000.[15] As for CHD-related infant mortality rates, updated age-period-cohort projections have recently been published for the GBD 2019 study.[16] Part of LAC, French Guiana is a French overseas department, with one of the highest fertility rates in South America.[17–19] In line with the regional context, French Guiana's CHD epidemiological trends have never been reported (even in the GBD study), with limited health indicators highlighting significant heath disparities, difficult healthcare access, variable pregnancy follow-ups and frequent preterm deliveries.[15,20,21]

We hereby describe CHD prevalence, characteristics and related mortality in infants under one year in French Guiana over a five-year period.

Methods

Study setting and health care system in French Guiana

Located between Brazil and Suriname, French Guiana is an extensive territory (84,000 km^2; 315,092 inhabitants according to latest 2023 estimates), with the same legislation as in mainland France.[22] The birth rate is close to 29/1000 inhabitants, with a fertility rate of 3.4 children per woman.[22] Although part of France and Europe, French Guiana presents a high middle socio-demographic index (SDI), which is lower than mainland France (high SDI), but above the average of most LAC countries (Central, Andean, Tropical Latin America; Caribbean) which present with low-middle and middle SDI.[15,23] The French Guianese population is multiethnic (Creole populations, French Europeans, indigenous Amerindians, Maroons and Bushinengue).[24,25]

The health care system is broadly similar to that of mainland France in terms of organization, access to care (including surgical/catheter-based intervention availability) and quality of care, with differences being in terms of lower density of health care infrastructures and human resources in French Guiana. There are three main public hospitals (including the referral hospital in Cayenne, French Guiana's capital city), and numerous small public primary health care centers located in the most remote areas. Private medicine is generally underdeveloped in French Guiana, with limited practice of antenatal screening and diagnosis of CHD in collaboration with the French Guianese perinatal network.

All pregnant women and infants have access to free care. In the event of acute symptoms, free medical evacuations can be rapidly organized to inter-regional pediatric cardiology expert centers (Martinique (French West Indies), mainland France (Paris)). Care procedures for pregnant women include at least one mandatory full morphological fetal ultrasound scan between 20 and 24 weeks of gestation, with the vast majority of women benefiting from regular prenatal check-up visits. In the postnatal phase, several successive and mandatory pediatric examinations are scheduled during the first year of life (at 1, 3, 6, 9 and 12 months).

CHD screening and treatment is carried out under the supervision of the French Guianese perinatal network, created in 2007 and reinforced by pediatric cardiologists from the regional expert pediatric cardiology center at the University Hospital of Martinique island. Since 2012, this successful collaborative medical venture has led to the setting up of a population-based French Guianese CHD registry, which exhaustively records cases originating from all hospitals and primary healthcare centers of the territory.

Study design

This single-center retrospective observational study includes all patients born in French Guiana from January 1st 2012 to December 31st 2016 and diagnosed with CHD during their first year of life. Fetal heart diseases diagnosed during pregnancy were also considered. The last included cases were those in the 2016 birth cohort and diagnosed until December 31st, 2017. Patient follow-up ended on December 31st 2018. Outcome (vital status, presence of chromosomal or genetic anomalies (CGA)) was determined at the study end-point.

Patient eligibility

CHD diagnosis was made on echocardiography by a senior paediatric cardiologist. In some cases, additional investigations (CT scan, cardiac catheterization) were needed. All fetuses diagnosed with CHD during mandatory fetal echocardiography were also evaluated by a senior paediatric cardiologist. Study exclusion criteria were minor cardiac defects such as patent ductus arteriosus (either trivial or requiring elective closure in severely premature babies), patent foramen ovale, mild non-progressive pulmonary valve stenosis resolving spontaneously in small babies, mild muscular ventricular septal defects, isolated cardiomyopathies, acquired lesions, arrhythmias, major extra cardiac non-chromosomal anomalies, and major polymalformation syndromes (>3 organs).[24,26] Parental refusal for study participation immediately entailed patient exclusion from study analysis. All chromosomal or genetic tests performed on patients were also subject to written parental authorization.

Fetal studies

For all fetal cases, the frequencies of live births, terminations of pregnancy due to fetal anomaly (TOPFA), and fetal deaths were characterized. Fetal diagnosis was confirmed by necropsy for some TOPFA cases and for one fetal death. For those instances in which a necropsy could not be achieved, diagnosis was confirmed by

consensus between a senior pediatric cardiologist and a fetal echography specialist, based on the analysis of all available records. In case of in utero or neonatal air transfer to expert pediatric cardiac centers (Martinique (1500 km away) or Paris (7216 km away), all relevant data were secondarily obtained, including delivery conditions, cardiac diagnosis, operative notes, catheterization records and outcomes. As some degree of discordance could exist between pre and post-natal diagnosis, all postnatal data were based on live births.

Fetal and pediatric records

In addition to the fetal records mentioned above, patient files from multiple sources (all French Guianese hospitals and primary health care centers and collaborating pediatric cardiology inter-regional expert centers in Martinique and Paris (mainland France) were carefully crossed-matched to input clinical data to the French Guianese CHD registry's centralized database. This included medical reports originating from fetal and neonatology departments, maternity units, neonatal and pediatric intensive care units, as well as outpatient pediatric and cardiac clinics. Relevant data was then extracted from the registry's database for study purposes.

CHD classification

All CHD were classified according to the Anatomical and Clinical Classification of Congenital Heart Defects.[4–6,8] All types of ventricular hypoplasia, such as hypoplastic left heart syndrome, single ventricle of either left or right morphology, severe forms of pulmonary atresia with intact ventricular septum, and tricuspid atresia, were incorporated into the large "Group 6 of FUH", because of a fairly similar surgical palliative management strategy.

Ethical considerations

The study was approved by an independent institutional review board (University Hospital of Martinique; reference: 2022/160). Part of our data analysis used anonymous and aggregated data, which is publicly available and thus did not require formal ethical clearance.[4,5,8,20,21,24] We also obtained legally authorized access to the French Guianese CHD registry's database. Furthermore, in accordance with French legislation for observational studies at the time of study recruitment, all parents of participating infants received individual informative letters translated in four languages (French, French Guianese Creole and 2 West Guyanese dialects), informing them of the use of their infants' personal data for study purposes. In case of non-consent, they were also informed of their right to express a written or verbal refusal with immediate effect (i.e., non-inclusion of their infant's data for study analysis). In the most remote areas, oral parental consent was requested and obtained through primary care doctors and nurses operating in small rural primary health care centers. Any refusal expressed orally induced a written notification to the CHD registry coordinator of the primary health center covering the living area of the patient's parents or legal representatives. Following this written notification, the concerned infant's data was excluded from study analysis.

Statistical analysis

Continuous variables were summarized with means and standard deviations, while categorical variables were summarized with frequency counts and percentages.

Prevalence was presented as the number of overall CHD cases per 10,000 total births or live births, with a 95% confidence interval (CI). Population denominator data was obtained from yearly population census estimates and the French Guianese perinatal network.[27,28] Confidence intervals were generated by assuming a Poisson distribution for all case counts.

All statistical analyses were performed using SAS software 9.4 for Windows (SAS Institute, Cary North Carolina, USA).

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Results

CHD characteristics

The total number of births in French Guiana during the study period was 33,796 births, with 32,975 live births. The total number of CHD fulfilling study inclusion criteria was 236. Five cases were ultimately not included due to insufficient data quality or parents' refusal. Final data analysis thus concerned 231 CHD cases, including 215/231 (93.1%) live births, 15/231 (6.5%) TOPFA, and 1/231 (0.4%) fetal death at more than 20 weeks of gestation (Table 1).

The most frequent CHD categories were ventricular outflow tract anomalies, anomalies of the extrapericardial trunks and ventricular septal defects. The latter were predominantly diagnosed after birth. CGA were diagnosed in 43/231 (18.6%) of CHD cases. Overall fetal CHD detection rate was 56/231 (24.4%). Heterotaxy (including cardiac isomerism) and FUH had the highest probability of prenatal diagnosis (respectively 2/2 (100%) and 26/27 (96.3%), Table 1).

There were 27 diagnoses of FUH including fourteen hypoplastic left heart syndromes, seven single right ventricles, three pulmonary atresia with intact interventricular septum, two double inlet right ventricles with common valve, and one tricuspid atresia. Global TOPFA rates for CHD (Table 2) with and without CGA were respectively 15/231 (6.5%) and 13/188 (6.9%).

ACC-CHD main categories	Total birth CHD (N = 231)				Live birth CHD (N = 215)		Total per ACC-CHD category
	Fetal detection (%)	Chromosomal and/or genetic disorder (%)	TOPFA (%)	Stillbirths (%)	Live birth CHD (%)	Chromosomal and/or genetic disorders (%)	
1. Heterotaxy, including isomerism and mirror-imagery	2 (100.0)	0 (0.0)	0 (0)	0 (0.0)	2 (100.0)	0 (0.0)	**2**
2. Anomalies of the venous return	2 (28.6)	2 (28.6)	1 (14.3)	0 (0.0)	6 (85.7)	1 (14.3)	**7**
3. Anomalies of the atria and interatrial communications	0 (0.0)	3 (17.6)	0 (0.0)	0 (0.0)	17 (100.0)	3 (17.6)	**17**
4. Anomalies of the atrio-ventricular junctions and valves	5 (29.4)	12 (70.6)	0 (0.0)	0 (0.0)	17 (100.0)	12 (70.6)	**17**
5. Complex anomalies of atrioventricular connections	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	**1**
6. Functionally univentricular hearts	26 (96.3)	4 (14.8)	13 (48.1)	1 (3.8)	13 (48.1)	3 (11.1)	**27**
7. Ventricular septal defects	4 (7.3)	7 (12.7)	0 (0.0)	0 (0.0)	55 (100.0)	7 (12.7)	**55**
8. Anomalies of the ventricular outflow tracts	16 (28.1)	9 (15.8)	1 (1.8)	0 (0.0)	56 (98.2)	9 (15.8)	**57**
9. Anomalies of the extrapericardial arterial trunks	1 (2.3)	6 (13.6)	0 (0.0)	0 (0.0)	44 (100.0)	6 (13.6)	**44**
10. Congenital anomalies of the coronary arteries	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (100.0)	0 (0.0)	**4**
Overall	**56 (24.4)**	**43 (18.6)**	**15 (6.5)**	**1 (0.4)**	**215 (93.1)**	**41 (17.7)**	**231 (100.0)**

[a]ACC-CHD: Anatomical and clinical classification of congenital heart defects[4]; CHD: congenital heart diseases; TOPFA: terminations of pregnancy due to fetal anomaly. Table frequencies are row frequencies e.g., % of fetal detection for functionally univentricular hearts: 26/27 = 96.3%.

Table 1: **Fetal detection and post natal distribution of all CHD diagnosed in French Guiana using 10 main categories (ACC-CHD[a]).**

ACC-CHD[a] main categories	Total births per ACC-CHD category (N)	LB (%)	TOPFA (%)	SB (%)	Prevalence per 10,000 births	
					Total [95% CI][b]	LB [95% CI][c]
1. Heterotaxy, including isomerism and mirror-imagery	**2**	2 (100.0)	0 (0.0)	0 (0.0)	0.6 [0.5–0.7]	0.6 [0.5–0.7]
2. Anomalies of the venous return	**7**	6 (85.7)	1 (14.3)	0 (0.0)	2.1 [1.9–2.2]	1.8 [1.7–2.0]
3. Anomalies of the atria and interatrial communications	**17**	17 (100.0)	0 (0.0)	0 (0.0)	5.0 [4.8–5.3]	5.2 [4.9–5.4]
4. Anomalies of the atrio-ventricular junctions and valves	**17**	17 (100.0)	0 (0.0)	0 (0.0)	5.0 [4.8–5.3]	5.2 [4.9–5.4]
5. Complex anomalies of atrioventricular connections	**1**	1 (100.0)	0 (0.0)	0 (0.0)	0.3 [0.2–0.4]	0.0 [-]
6. Functionally univentricular hearts	**27**	13 (48.2)	13 (48.1)	1 (3.7)	8.0 [7.7–8.3]	3.9 [3.7–4.2]
7. Ventricular septal defects	**55**	55 (100.0)	0 (0.0)	0 (0.0)	16.3 [15.9–16.7]	15.5 [15.1–15.9]
8. Anomalies of the ventricular outflow tracts	**57**	56 (98.2)	1 (1.7)	0 (0.0)	16.9 [16.4–17.3]	17.0 [16.6–17.4]
9. Anomalies of the extrapericardial arterial trunks	**44**	44 (100.0)	0 (0.0)	0 (0.0)	13.0 [12.7–13.4]	13.3 [13.0–13.7]
10. Congenital anomalies of the coronary arteries	**4**	4 (100.0)	0 (0.0)	0 (0.0)	1.2 [1.1–1.3]	1.2 [1.1–1.3]
All CHD	**231**	**215 (93.1)**	**15 (6.5)**	**1 (0.4)**	**68.4[67.9–68.8]**	**65.2 [64.7–65.7]**
All CHD, excluding chromosomal + genetic anomalies[d]	**188**	**174 (92.5)**	**13 (6.9)**	**1 (0.5)**	**55.6 [55.1–56.2]**	**52.8 [52.2–53.3]**
All CHD, excluding isolated VSD and chromosomal + genetic anomalies[d]	**140**	**126 (90.0)**	**14 (10.2)**	**0 (0.0)**	**41.4 [40.9–42.0]**	**38.2 [37.7–38.7]**

Table frequencies are row frequencies e.g., % of TOPFA for functionally univentricular hearts: 13/27 = 48.1%. [a]ACC-CHD: Anatomical and clinical classification of congenital heart defects[4]; CHD: congenital heart diseases; CI: Confidence Interval; LB: live births; SB: stillbirths; TOPFA: terminations of pregnancy due to fetal anomaly; VSD: ventricular septal defect. (%): percentage per ACC-CHD categories. [b]Total number of births in French Guiana (denominator), 2012–2016: 33,796. [c]Total number of live births (denominator), 2012–2016: 32,975. [d]Some patients may have simultaneously VSD and CGA.

Table 2: **Total and live birth estimated prevalence of all CHD diagnosed in the French Guianese cohort (2012–2016).**

TOPFA was observed mostly in FUH (13/27 (48.1%), Table 2).

CHD prevalence and mortality

Total and non-CGA CHD prevalence were respectively 68.4 (95% CI: 67.9–68.8) and 55.6 (95% CI: 55.1–56.2) per 10,000 births (Table 2). Live birth total and non-CGA CHD prevalence were 65.2 (95% CI: 64.7–65.7) and 52.8 (95% CI: 52.2–53.3) per 10,000 live births respectively. Infant mortality was 9.4/10,000 live births [95% CI: 9.1–9.7], with the highest rates, even after exclusion of CGA, observed in children with FUH (Table 3 and Supplementary Table S1). As such, FUH were the first cause of CHD-related infant mortality.

Discussion

We report the results of the first descriptive population-based analysis of congenital heart diseases (CHD) in French Guiana. Our main findings, in comparison to previously published data, are: 1) total and live birth prevalence of FUH are high while overall CHD prevalence appears low; 2) CHD-related infant mortality is high; 3) one of the potential determinants of the excess infant mortality risk might be the notable frequency of CGA, associated with about a fifth of all CHD cases; 4) cardiac mortality risk is variable in children under one year, but is predominantly related to univentricular hearts.

French Guiana is an integral part of the Latin America and Caribbean (LAC) region.[17–19] As per its

ACC-CHD main categories[a]	Total live births per ACC-CHD category (N)	Number of deaths					Infant mortality per 10,000 live births	
		≤7 days N (%)	8–28 days N (%)	29 days-1 year N (%)	Total deaths N (%)	Total deaths excluding chromosomal and genetic anomalies N = 17 (%)	Total Infant mortality [95% CI][b]	Infant mortality excluding chromosomal and genetic anomalies [95% CI][b]
1. Heterotaxy, including isomerism and mirror-imagery	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 [-]	0.0 [-]
2. Anomalies of the venous return	6	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 [-]	0.0 [-]
3. Anomalies of the atria and interatrial communications	17	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 [-]	0.0 [-]
4. Anomalies of the atrio-ventricular junctions and valves	17	0 (0.0)	1 (5.9)	6 (35.3)	7 (41.2)	1 (5.9)	2.1 [2.0–2.3]	0.3 [0.2–0.4]
5. Complex anomalies of atrioventricular connections	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 [-]	0.0 [-]
6. Functionally univentricular hearts	13	7 (53.8)	4 (30.8)	0 (0.0)	11 (84.6)	8 (61.5)	3.3 [3.1–3.5]	2.4 [2.3–2.6]
7. Ventricular septal defects	55	0 (0.0)	0 (0.0)	3 (5.5)	3 (5.5)	2 (3.6)	0.9 [0.8–1.0]	0.6 [0.5–0.7]
8. Anomalies of the ventricular outflow tracts	56	1 (1.8)	0 (0.0)	6 (10.7)	7 (12.5)	5 (8.9)	2.1 [2.0–2.3]	1.5 [1.4–1.6]
9. Anomalies of the extrapericardial arterial trunks	44	0 (0.0)	0 (0.0)	2 (4.5)	2 (4.5)	2 (4.5)	0.6 [0.5–0.7]	0.6 [0.5–0.7]
10. Congenital anomalies of the coronary arteries	4	0 (0.0)	0 (0.0)	1 (25.0)	1 (25.0)	1 (25.0)	0.3 [0.2–0.4]	0.3 [0.2–0.4]
All CHD	**215**	**8 (3.7)**	**5 (2.3)**	**18 (8.4)**	**31 (14.4)**	**–**	**9.4 [9.1–9.7]**	**–**
All CHD, excluding chromosomal + genetic anomalies[c]	**174**	**6 (3.5)**	**2 (1.1)**	**11 (6.3)**	**19 (10.9)**	**19 (10.9)**	**5.8 [5.5–6.0]**	**5.8 [5.5–6.0]**
All CHD, excluding isolated VSD and chromosomal + genetic anomalies[c]	**126**	**6 (4.8)**	**2 (1.6)**	**9 (7.1)**	**17 (13.5)**	**17 (13.5)**	**5.2 [4.9–5.4]**	**5.2 [4.9–5.4]**

Table frequencies are row frequencies e.g., % of deaths occurring in ≤7 days for functionally univentricular hearts: 7/13 = 53.8%. [a]ACC-CHD: anatomical and clinical classification of congenital heart defects[4]; CHD; congenital heart diseases; CI: confidence Interval; LB; live births; SB; stillbirths; TOPFA: terminations of pregnancy due to fetal anomaly; VSD: ventricular septal defect. (%): percentage per category. [b]Total number of live births in French Guiana (denominator), 2012–2016: 32,975. [c]Some patients may have simultaneously VSD and chromosomal or genetic anomalies.

Table 3: **Description of CHD-related infant mortality in the French Guianese live birth cohort (2012–2016).**

geographical, ethnic and environmental characteristics, as well as population emigrational movements, French Guiana shares similarities with the neighboring countries of Brazil, Suriname and Guyana. Conversely, differences are to be noted between French Guiana (dependency territory, part of France and Europe) and its South American neighbors, notably in terms of health care system and socio-demographic index, with French Guiana presenting with a higher socio-demographic index (SDI) than its direct South American neighbors (predominantly middle SDI). In contrast, French Guiana's SDI is lower than mainland France and other European nations.[15,23]

In light of French Guiana's affiliation to mainland France, we analyzed French Guianese CHD epidemiological trends in infants in light of previously published data for French infants. For mainland France, the 2005–2008 EPICARD (Etude EPIdémiologique sur le devenir des enfants porteurs de CARDiopathies congénitales) study is the only well-designed population-based neonatal and perinatal prospective CHD cohort available to date, based in the Greater Paris area (Paris and its surrounding suburbs), and integrating long-term follow-up of all CHD cases (live births, pregnancy terminations, fetal deaths) diagnosed in the prenatal period or up to one year of age in birth cohorts between May 2005 and April 2008.[3–6] Due to methodological differences in eligibility criteria between our study cohort and EPICARD (notably non-inclusion of minor CHD types for the French Guianese analysis), overall live birth CHD prevalence could not be directly compared between French Guiana (65.2 [95% CI: 64.7–65.7]/10,000) and mainland France (74.8 [95% CI: 87.0–93.6]/10,000). The same goes for overall CHD-related infant mortality (French Guiana: 9.4 [95% CI: 9.1–9.7]/10,000 vs. EPICARD: 4.8 [95% CI: 4.7–5.0]/10,000). However, prevalence and mortality comparison according to CHD subtype was possible between our study population and EPICARD because of the standardized use of the Anatomical and Clinical Classification of Congenital Heart Defects in both cohorts. When compared to mainland France, total FUH prevalence for French Guiana appeared higher (5.0 [95% CI: 4.2–5.8]/10,000 vs. 8.0 [95% CI: 7.7–8.3]/10,000), as were live birth FUH prevalence and FUH-related infant mortality, respectively two to three-fold higher. Total and live birth prevalence for extra-pericardial trunk anomalies (Group 9) and congenital anomalies of the coronary arteries (Group 10) appeared also higher in French Guiana in comparison to mainland France without significant impact on infant mortality. In contrast, no difference in epidemiological trends was observed for atrial septal defects (Group 3), atrioventricular septal defects (Group 4), as well as complex abnormalities of the right ventricular outflow tract

(Group 8) between French Guiana and the EPICARD cohort.

Moving forward, we further analyzed infant CHD trends for French Guiana in its regional context by contrasting French Guianese CHD indicators with reported trends in the LAC region and the rest of the South American continent. Rare published studies originating from the LAC region indicate highly variable prevalence rates between countries such as Brazil, Ecuador and Peru, with differing methodologies between studies in terms of information sources, data exhaustiveness, case and outcome definitions, study population selection criteria, as well as the absence of reliable data pertaining to infants under 1 year or complex CHD subtypes.[13,14,29–33] To date, the main regional reference for the LAC region and the rest of South America remains the CHD prevalence projections at birth from the Global Burden of Disease (GBD) study with estimates for prevalence and mortality for overall CHD and different CHD sub-types in infants under 1 year available only in the GBD 1990–2017 study.[12,13] As with EPICARD, due to divergent eligibility criteria for CHD cases, overall live birth CHD prevalence and related infant mortality could not be directly compared between GBD and French Guiana. Only FUH prevalence could be contrasted between both studies due to homogenous Group 6 definitions (according to the Anatomical and Clinical Classification of Congenital Heart Defects). FUH mortality could however not be contrasted between French Guiana and GBD due to a lack of FUH-related mortality projections in GBD.[15] Similar trends were observed for FUH prevalence at birth between French Guiana (39 (95% CI: 37–42)/100,000) and GBD projections for neighboring countries such as Brazil and Paraguay, presenting with a lower SDI than French Guiana and regrouped in the GBD subzone "Tropical Latin America" (35 (95% CI: 28–44)/100,000). The same was observed in comparison to GBD subzones "Andean Latin America" and "Central Latin America", with respective prevalence rates of 31 (95% CI: 24–39) and 30 (95% CI: 24–37) per 100,000. In contrast, the GBD subzone "Caribbean" region, comprising Suriname and Guyana but excluding French Guiana (no existing GBD estimates), presented with a lower FUH prevalence rate (19 (95% CI: 15–24)/100,000) in comparison to French Guiana.[15]

Using original projection models, the GBD study recently adjusted both CHD prevalence and mortality according to geographic, socio-demographic, anatomical and clinical features.[15,16] Current CHD detection in many South American countries is hypothesized to be low and correlated to regional human development index, with a potential high mortality rate among neonates suffering from complex cardiac defects.[34] This is particularly true for FUH, the real prevalence of which remains to be better assessed for the LAC region. Single ventricles are known to be associated with worst prognosis, and to generate significant health costs and infantile mortality.[5,11,15] When taking into account socio-demographic index according to GBD, French Guiana (high middle SDI territory, 39 (95% CI: 37–42)/100,000) presented rather similar FUH prevalence rates to middle SDI countries (32 (95% CI: 25–40)/100,000), but higher rates than other high middle SDI regions (21 (95% CI: 17–25)/100,000), such as GBD subzone "Southern Latin America" region.[15,23]

As reported recently by an African hospital-based registry, observed low total CHD prevalence rates in low and middle income settings might potentially be explained by lower detection rates of mild to moderate CHD cases (ventricular and atrial septal defects, patent ductus arteriosus).[35] In the present study, while we did not observe any under-diagnosis of CHD of intermediate severity, we reported fewer ventricular septal defects (Group 7) compared to mainland France, which might be at least partially explained by a relative under-detection of such pathologies particularly in infants living in more remote areas of French Guiana, albeit with no clinical repercussions for the latter. Our estimated non-CGA prevalence for CHD, excluding all isolated ventricular septal defects, appears also in the same range as rates previously observed in European countries.[29,36] Thus, our study findings potentially highlight a distinct epidemiological and clinical profile for CHD in French Guiana.

We further hypothesize that our observations might point towards high CHD complexity in this part of Latin America, with increased case distributions in particular subgroups, such as FUH. With similar antenatal diagnostic rates for FUH (90–100%) as mainland France, total and live birth FUH prevalence in French Guiana interestingly remain much higher than EPICARD rates, most probably in link with the territory's specificities.[4] Indeed, in comparison to mainland France, French Guiana presents higher rates for fertility and prematurity. In addition, endogamous habits of French Guianese communities could lead to a greater risk of complex congenital anomalies.[6,24,25,29] Furthermore, the higher FUH rates in French Guiana compared to other high middle SDI regions further consolidate our hypothesis of frequent complex CHD in French Guiana.[15] As such, ethnicity could play a role, with genetic diversity potentially being one of the reasons behind eventual disparities in CHD burden across South America.[10] A high prevalence of hypoplastic left heart syndromes (3.5/10,000 live births) has also been reported in the French Caribbean since the 1990s, suggesting potential ethnic risk factors in a geographical zone subject to significant population migration.[37] Moreover, despite regular access to cardiac surgery or catheter-based interventions through a dedicated Caribbean and European pediatric cardiology network, the risk of infantile death from congenital cardiac malformations is higher in French Guiana (9.4/10,000 live

births) compared to other cohorts, particularly in the event of associated CGA.[4,6,21] Indeed, in spite of a well-resourced health system, French Guiana is a large territory, where timely access to appropriate care remains a challenge. Furthermore, we observed that almost half of recorded deaths occurred during the first weeks of life, which might further underline the seriousness and complexity of CHD in French Guianese neonates. Even after excluding CGA and isolated ventricular septal defects, CHD-related infant mortality remained high (5.2/10,000 live births). This might be partially explained by the low TOPFA rate for FUH in French Guiana (51% vs. 70% in mainland France), despite a fetal detection rate of most complex CHD similar to other studies.[4,6] The low TOPFA rate might be linked to untimely access to care particularly for those patients living in the most remote areas of French Guiana, or cultural and religious barriers.[20,21] This further underlines the limited impact of prenatal diagnosis and compassionate care in the country. Indeed, during local prenatal diagnosis and counseling sessions, women bearing fetuses with severe CHD are offered the choice to terminate pregnancy or to request compassionate care within the neonatal period, especially in the presence of associated CGA.[5,36,38] Prenatal diagnosis potentially optimizes chances of delivery within the most suitable medical structures offering adequate care for these complex cases, including prenatal transfer from French Guiana to expert centers in Martinique island or mainland France.[39] In a surprising way, we observe specific behavior profiles in French Guianese women who often decide to pursue pregnancy even in the case of CGA and complex or inoperable CHD, thus resulting in a higher mortality risk as highlighted by our current patient series.[21] In addition, anatomical specificities also play a role. The majority of severe CHD diagnosed in French Guiana might represent the worst candidates for univentricular palliation surgical programs. Some risk factors are well-identified such as very poor anatomical variants, e.g., morphologically right single ventricle, tricuspid atresia with small ventricular septal defects and transposition of the great arteries, FUH with common atrioventricular valve, FUH with total abnormal pulmonary venous drainage, severely leaking valves, poor ventricular function, or very small pulmonary arteries. Small birth weight for gestational age, as well as moderate prematurity, also have negative effects on surgical or interventional plans.

While it is likely that CHD-related infant mortality in French Guiana is linked to the high prevalence of complex types such as FUH, other parameters are to be considered. Well-known risk factors, such as socioeconomic status or prematurity could play an aggravating role in CHD severity and outcomes.[20,21] Family socioeconomic status has been described as worsening postoperative prognosis of children with complex CHD in low and middle-income countries.[40] Other potential hypotheses for high CHD-related infant cardiac mortality in French Guiana have been recently emphasized, such as infections during pregnancy, alcohol consumption, exposure to toxic metals and other teratogenic agents in women of reproductive age, maternal age–related syndrome, diabetes, nutritional deficiencies, social precariousness, and endogamy.[15,20,21,41] The necessity to transfer abroad patients with complex cases, due to limited French Guianese medical infrastructures and resources, might also potentially cause higher patient morbidity inherent to long-distance air transfer which influences numerous hemodynamic parameters such as oxygenation levels, pulmonary vascular resistance, and balance between pulmonary and systemic cardiac output.

Study strengths and limitations

The present study findings unambiguously highlight a high FUH prevalence, potentially one of the highest in the world for a high middle SDI territory if we refer to the projections from the GBD study which do not include data from French Guiana. GBD projections however include neighboring territories to French Guiana: Brazil, Guyana and Suriname. The reported French Guianese high FUH prevalence contributes to a significant proportion of cardiac infant mortality, with a high probability of a worse situation in those territories neighboring French Guiana (Brazil, Guyana and Suriname) which have a lower SDI.

The present study presents some methodological nuances with previously published studies such as EPICARD and GBD.[4,15] Firstly, we excluded minor CHD as we hypothesized, like others before us, that due to favorable outcome within the first year of life, minor CHD will not significantly affect cardiac related mortality.[26] Secondly, we did not include CHD diagnosis after the first year of life, but this is likely to represent mostly mild-moderate CHD forms and only a small minority of severe CHD. Our figures are notably fairly close to those of the EUROCAT registry, which includes patients whose malformations are detected later in life.[36] On the other hand, it remains possible that some very complex CHD in remote areas of French Guiana could have gone undetected during the study period. If this was to be the case, this would support an even higher prevalence for the most severe CHD types, including FUH, thus painting an even direr picture.

It is also to be noted that potential period and cohort effects could be expected when contrasting our study data (2012–2016 birth cohorts) to previously published data, notably EPICARD data (2005–2008 birth cohorts).[4,6,8] However, these effects are expected to be limited. While annual total and live birth rates have remained stable in French Guiana, total and live birth rates for mainland France (Paris region-Epicard study site) have declined since 2005.[42] As a resultant, it is to be expected that lower birth rates might have resulted in a lower prevalence of CHD in more recent birth cohorts for mainland France. It is also to be noted that health

systems between mainland France and French Guiana are similar, with little variation in CHD access to care, screening, diagnosis, management, treatment and reporting in mainland France since 2005. As such, little to no variation in CHD mortality are to be expected for mainland France since 2005. All in all, the difference in time period between the EPICARD and French Guianese cohorts does not undermine the hypothesized presence of more complex CHD in French Guiana in comparison to mainland France, with elevated prevalence and mortality rates linked to univentricular hearts.

Furthermore, the data in the French Guianese CHD registry is cross–referenced with many sources within a structured network, further reinforced by the compulsory medical consultations imposed by French law for pregnant women and infants under one year of age. These elements, along with prospective registration of cases as well as standardised definition and expert coding of all CHD cases (including TOPFA) by paediatric cardiologists and foetal pathologists, guarantee data exhaustiveness, completeness, reliability and quality, and limit study bias. Moreover, even though a pathological examination was carried out in only 15% of TOPFA cases in our study sample, we mostly observed complete agreement with prenatal cardiac data for all infants born with FUH, with eventual postnatal modifications remaining minor and not altering the diagnosis or management strategy. This thus underlines the quality of prenatal screening for complex CHD in French Guiana.

Finally, we observed an expected lag in data consolidation between the 2012–2016 study period (historical cohort) and the time of data analysis, as is often the case in registry or population-based studies. However, our results remain consistent with the most recent GBD projections for LAC and middle SDI regions.[15,16] Thus, we hypothesize that our observations concerning FUH could be potentially indicative of the situation in other territories of the LAC region with middle SDI.

Conclusion and perspectives

The present study highlights for the first time a high prevalence of univentricular hearts in French Guiana, as well as an important infant mortality significantly related to such defects. About a fifth of all CHD are associated with CGA, another potential contributor to a recognized excess infant mortality risk. Despite free access to a well identified specialized pediatric cardiac care network, low TOPFA rates, complex anatomy, underlying differences of disease as well as social, educational, or cultural considerations are factors potentially linked to excessive infant mortality. Furthermore, our findings raise major questions about the existence of specific ethnic, toxic, environmental, as well as other unidentified risk factors that might predispose infants born in French Guiana to having a higher risk of congenital malformations and death. Observed complex CHD trends and infant cardiac mortality in French Guiana should be considered as warning signals for Latin America and Caribbean, vouching for the necessity to strengthen and sustain the provision, capacity, accessibility, management and follow-up of congenital cardiac care in the region, both in early childhood and across later life. Our report contributes further towards this goal and strongly advocates for the expansion and strengthening of funded regional standardized data networks with appropriate support from national and international health authorities.

Contributors

HL: Methodology, data curation, formal analysis, writing–original draft, writing–review & editing, project administration, supervision. MB, JO: conceptualization, investigation, data curation, supervision, writing-review & editing. LL: project administration, data curation, writing-review & editing. MS, JI, VL, AHG, ST, PA, SZA, RG, FC, NE: investigation, data curation. DB: methodological support, final proofreading of the manuscript and contribution via EPICARD study. RB: Methodology, formal analysis, complete statistical analysis, writing–original draft, writing review & editing, supervision. All authors contributed to subsequent drafts, read, and approved the final version of the manuscript. All authors had full access to the study data. HL, MB and JO verified all study data. The corresponding author was responsible for the final decision to submit for publication and has full access to all study data.

All authors take responsibility for every aspect of the reliability and freedom from bias of the data presented and their discussed interpretation. All authors have validated the final article version.

Data sharing statement

Data used to generate the results reported in this study will be made available following publication to researchers who provide a methodologically sound proposal. Data will only be made available if approval is granted from the Institutional Review Board (University Hospital of Martinique, Martinique, France). Furthermore, all requesters will need to sign a data transfer agreement. Requests should be directed to the corresponding author.

Declaration of interests

The authors declare no conflicts of interest with respect to the present research, authorship and/or publication of this article.

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Appendix A. Supplementary data

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