SURVIVAL AND RISK FACTORS FOR MORTALITY AMONG INDIVIDUALS WITH CONGENITAL HEART DISEASE

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Abstract

With advances in medical, surgical and intensive care interventions, more individuals with congenital heart disease (CHD) are surviving infancy. However, long-term survival is not well researched. Given that UK paediatric cardiovascular services are undergoing reforms to ensure there are adequate health-care provisions, further information is required on CHD prevalence and survival.

An analysis of data from six British Isles Network of Congenital Anomaly Registers (BINOCARs), showed no overall trend in CHD prevalence between 1991 and 2010. However, there was an increasing trend in the prevalence of tetralogy of Fallot, equating to a yearly excess of 16 cases in England and Wales. There was an increased risk of CHD in twins, particularly monochorionic (MC) twins. The prevalence of CHD in MC twins increased over time, equating to a yearly excess of seven cases in England and Wales.

Using a systematic review and meta-analysis, pooled five and 10-year survival was 85.4% and 81.4%, respectively. Year of delivery, preterm delivery, extra-cardiac anomalies (ECAs) and birth weight were associated with mortality.

In an analysis of data from one BINOCAR linked to death registrations, one-year survival was 89.1%, decreasing to 85.2% at 20 years. Less recent year of delivery, lower gestational age, low birth weight, prenatal diagnosis and the presence of ECAs increased the risk of mortality.

The predicted 20-year survival of individuals born with isolated CHD in 2015 was 98.7%. The predicted prevalence of CHD was 74.0 and 68.8 per 10,000 live births in 2015 and 2020, respectively. Using ONS data to extrapolate, this equates to approximately 296,000 cases of CHD being born between 2012-2017 in the UK.

Given that infants with CHD require complex surgeries, the predicted prevalence and survival estimates described in this thesis are important for health service planning and for providing accurate information to parents when a CHD is diagnosed prenatally.

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Contents

List of Figures

List of Tables

Chapter 1. Background

Congenital anomalies

1.1.1 Definition and prevalence

Congenital anomalies are structural, chromosomal or genetic abnormalities that develop before birth. The consequences of congenital anomalies to the individual vary according to the type of abnormality. However, many of those affected are burdened with lifelong physical or mental disability.

In the UK, congenital anomalies affect approximately 2% of children [1, 2]. Despite the increased availability of prenatal screening and therefore the opportunity for pregnancy termination, the live birth prevalence of congenital anomalies has not declined over the last 20 years. This is partly due to the increased proportion of women entering pregnancy at "advanced" maternal age, the increased uptake of assisted reproductive technologies (ART), the increased prevalence of maternal obesity (and diabetes), all of which are risk factors for congenital anomalies [3-6].

1.1.2 Public health

Congenital anomalies are a significant public health concern for a variety of reasons. Firstly, the static prevalence means that congenital anomalies continue to be a leading cause of fetal and infant death, both in the UK and internationally [7, 8]. Secondly, congenital anomalies are a major cause of morbidity and disability with some requiring surgery in childhood [9]. Therefore, those affected will require considerable medical and health care provision, including specialist surgeries, procedures and medications, which (in the UK) come at a significant cost to the National Health Service (NHS) [9]. Similarly, educational and social care provisions are sometimes required to support the affected individuals and their families [9]. The accuracy and uptake of prenatal screening is also a public health concern. The Fetal Anomaly Screening Programme (FASP) was instigated in England with the aim of setting national prenatal screening standards and overseeing their implementation [10]. Specifically, the FASP states that all women should be offered two prenatal ultrasound scans, a dating scan at eight weeks and an anomaly scan at 18^{+0} to 20^{+6} weeks gestation [11]. Additionally, FASP set targets for 11 congenital anomalies that should be screened for prenatally, including:

anencephaly, spina bifida, cleft lip and/or palate, diaphragmatic hernia, gastroschisis, omphalocele, severe congenital heart disease (CHD), bilateral agenesis, lethal skeletal dysplasias, trisomy 13 (Patau syndrome) and trisomy 18 (Edward's syndrome), with different target detection rates for each [12]. The implementation of FASP requires resources both for the screening process and for the follow-up of affected women.

1.1.3 Classification

Around 76% of cases with a congenital anomaly have only one structural anomaly affecting one organ system [13]. These are known as isolated anomalies, thought to have multifactorial aetiologies involving both environmental and genetic factors. Conversely, around 24% of cases with congenital anomalies have multiple structural anomalies affecting one or more organ system [13]. The majority of these have a recognised pattern of structural anomalies and in most (70% of cases with multiple anomalies) the pattern is caused by a single known chromosomal anomaly or genetic syndrome [13, 14]. Other patterns of congenital anomalies may not have a genetic aetiology and may occur as part of a sequence, association or syndrome. Sequences are a set of anomalies that arise consecutively during fetal development as a consequence of one original anomaly or mechanical issue [15]. Associations are a distinct formation of anomalies, with unknown cause, which arise during blastogenesis [14]. Syndromes encompass all other recognised patterns of anomalies with as yet unknown aetiology, which may or may not be genetic. Finally, cases with several structural anomalies with no distinct pattern are classified as having "multiple structural anomalies". These anomalies may occur together by chance and have separate aetiologies, although this has not been confirmed.

Generally, congenital anomalies are classed as occurring in isolation, occurring with other structural congenital anomalies (excluding cases occurring with chromosomal/ genetic congenital anomalies) or occurring with chromosomal/genetic congenital anomalies. Cases occurring with sequences, associations or non-genetic syndromes are commonly classed as occurring with structural anomalies, but this varies by study. Cases with more than one congenital anomaly may sometimes be classed as isolated if all the anomalies are directly related to a single anomaly, for example congenital diaphragmatic hernia occurring with lung hypoplasia may be classed as isolated diaphragmatic hernia because the hypoplasia is a consequence of the hernia.

1.2 Congenital heart disease

1.2.1 Definition, prevalence and survival

CHD is a diverse group of structural congenital anomalies that affect the cardiovascular system. According to Mitchell's definition, CHD is, "a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance" [16]. CHD is the largest group of congenital anomalies, accounting for a third of congenital anomaly cases [12]. In the UK, the birth prevalence of CHD between 2005-2010 was estimated to be 68 per 10,000 live and stillbirths [17]. However, the prevalence of CHD varies regionally and over time [18, 19]. As a group, CHD is not the most lethal type of congenital anomaly, with survival to age 15 reaching 72% in the UK (for births between 1992-1995) [20]. Despite improvements in surgical interventions, intensive care technologies, anaesthetics and medical therapies, survival for certain CHD subtypes is as low as 21% at age 12 [20].

1.2.2 Public health

Babies born with CHD require highly specialised health care, which may involve multiple, complex and often life-saving surgeries, normally within the first year of life [9, 21]. Adequate paediatric cardiology services are required to treat these children. After reports that post-operative paediatric cardiac mortality at the Bristol Royal Infirmary was higher than in other UK centres between 1984-1995, an independent public inquiry began in 2001, entitled the "Bristol enquiry" [22]. However, the validity of the inquiry was challenged [23] and the outcomes of paediatric cardiology surgeries remained under scrutiny. A subsequent NHS review, "Safe and Sustainable", was undertaken between 2008-2012 to consider the configuration of paediatric cardiology services [24]. The review controversially recommended that paediatric cardiac surgery should be restricted to seven of the original 11 units [24]. The intention was to have fewer, larger units which would have greater expertise due to the increased number of children being treated. However, the reformation has been halted since the Secretary for Health reported that the analysis that formed the basis of the review, was flawed. A new review established by the NHS commenced in 2013, entitled the "New Congenital Heart Disease Review". The aim of this review was to: "agree a model of care and service standards", to "note the analysis of the required service capacity" and to "agree the proposals for commissioning the service" [25].

CHD cases that survive infancy require ongoing medical surveillance, reinvestigation and subsequent operations. UK hospital admission rates have therefore risen as survival has improved [26]. Individuals with CHD are at increased risk of developmental disorders [27]. It is therefore important that adequate services are in place to provide health care for the children and adults affected. However, prevalence and trends in prevalence of individual CHD subtypes in the UK have not been thoroughly researched. Similarly, there is a paucity of research on long-term survival estimates. Therefore, it is difficult to anticipate the expected number of cases in the future and hence the health care provisions required.

Another public health concern is the prenatal diagnosis of CHD, which became possible in the early 1980s. CHD is difficult to diagnose prenatally with only 36% of UK cases being prenatally diagnosed between 2012-2013 [28]. However, the proportion of prenatally diagnosed cases varies by region in the UK, perhaps due to differences in screening programs and uptake [28]. To improve the prenatal diagnosis of CHD, visualisation of the four heart chambers has become a routine part of the second trimester scan. In 2003, the FASP guidelines altered to state that women should expect to be screened for "severe" CHD during pregnancy [11]. The exact definition of severe CHD has altered over time, but in 2015 the FASP defines it as: transposition of the great vessels (TGV, excluding congenitally corrected TGV), atrioventricular septal defect (AVSD), tetralogy of Fallot (ToF) and hypoplastic left heart (HLH). The FASP standards currently state that severe CHD should have a detection rate of $\geq 50\%$ between $18^{+}0$ to $20^{+}6$ weeks gestation, with evidence suggesting that this is being met in most regions [12, 29].

1.2.3 Classification

CHD can occur in isolation, with structural extra-cardiac anomalies (ECAs, excluding those with chromosomal/ genetic ECAs but sometimes including cases with sequences, associations or non-genetic syndromes), or with chromosomal/genetic ECAs.

CHD can be further categorised into CHD subtypes; the most common of which are described in Table 1.1 (and will hereon be referred to as the abbreviations listed). However, there are several coding systems used to code CHD subtypes. Epidemiologists generally use the World Health Organisation's (WHO) International Classification of Disease (ICD) codes [30]. Congenital anomalies of the circulatory system correspond to ICD version nine codes: 745-747, or the ICD version 10 codes: Q20-Q28. The ICD nine codes correspond to anomalies of: the cardiac septal closure (745), the heart (746), and the circulatory system (747) [30]. The ICD 10 codes correspond to anomalies of: the cardiac chambers and connections (Q20), the

cardiac septa (Q21), the pulmonary and tricuspid valves (Q22), the aortic and mitral valves (Q23), the heart (Q24), the great arteries (Q25) and the great veins (Q26), the peripheral vascular system (Q27) and the circulatory system (Q28). In line with Mitchell's definition, congenital anomalies of the peripheral vascular and circulatory system (ICD 10: Q27-28), and minor CHD which are functionless or have little impact on health or wellbeing (such as heart block or patent ductus arteriosus (PDA) in preterm infants) are not generally classed as CHD. This definition of CHD is not universally adopted, but it is used by one of the largest networks of congenital anomalies registers, the European Surveillance of CARs (EUROCAT), which classifies ICD 9: 745, 746, 7470-7474 and ICD 10: Q20-26 as CHD.

Clinicians tend to use a different coding system for CHD, known as the International Cardiology Society (ISC) coding system or more recently, the Association for European Paediatric and Congenital Cardiology (AEPC) coding system [31]. Similar to the ICD coding system, the ISC/AEPC provides separate codes for each CHD subtype. However, the subtypes are further broken down according to the surgeries used to treat the CHD subtype, the exact location of the CHD subtype and the severity of the CHD subtype.

It is common practice to assign cases with multiple CHD subtypes to one subtype. A CHD hierarchy is therefore required, but currently there is little consensus on this. Several hierarchies have been utilised in previous research, which are ordered based on: clinical outcomes ('favouring' subtypes with the lowest survival), physiology (favouring the subtype that first necessitated intervention) and embryology (favouring the subtype that occurs first during fetal development). These hierarchies may cause heterogeneity within subtypes and an under-representation of some subtypes lower down the hierarchy [32]. To address this, Wren et al used a two-dimensional classification system, where cases were categorised by the main CHD subtype (using the clinical hierarchy) and further categorised by the CHD which triggered the diagnosis of CHD [32]. While clinically this is intuitive, the frequency of cases in each sub-group can be unmanageable statistically.

1.2.4 Pathology

1.2.4.1 Fetal heart development

Four weeks into pregnancy, the heart forms as a vascular tube which gradually elongates [33]. As the tube grows longer, primitive chambers called the truncus atreriosus, the bulbus cordis, the primitive ventricle and the primitive atrium form (see Figure 1.1 A) [33]. The chambered

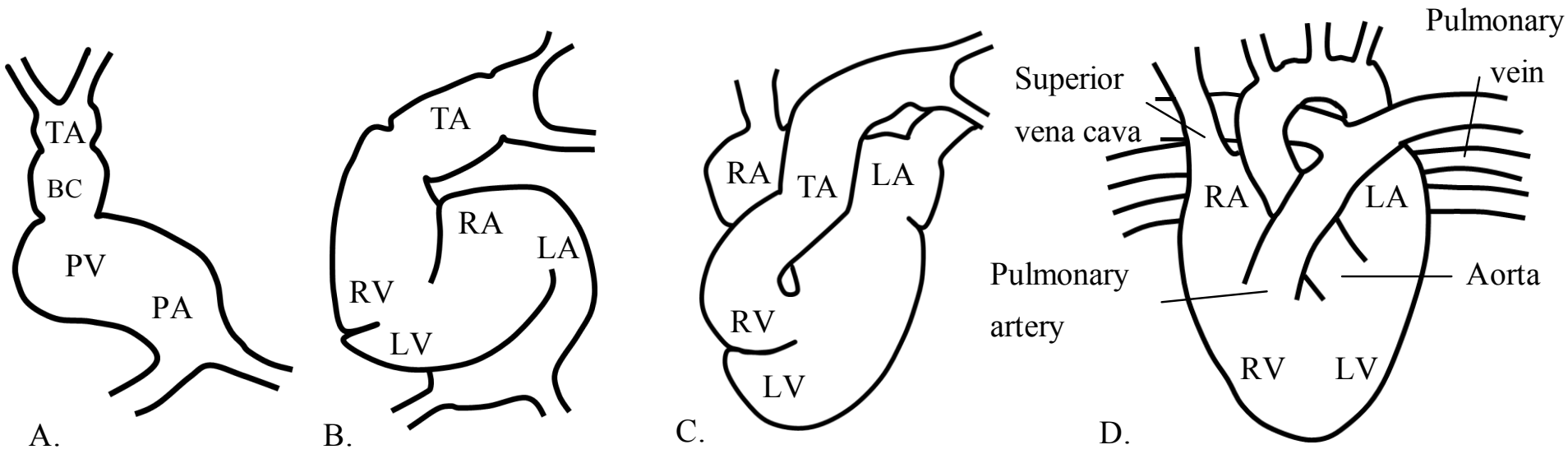
tube loops into an S-shape (see Figure 1.1 B), continuing until the atrium is above and beneath the truncus arteriosus, the ventricle and the bulbus cordis (see Figure 1.1 C) [33, 34].

Septation, the separation of the heart into four chambers, occurs at approximately four weeks gestation [33]. The left and right atria form when a ridge of tissue, called the septum primum, grows downwards to fuse with the endocardial cushions [33, 34]. A small gap called the foramen ovale remains [35]. The septum primum regresses and forms a temporary valve over the foramen ovale [35]. Simultaneously, a septum in the primative ventricle grows upwards to fuse with the endocardial cushion above, to form the left and right ventricles [33] [35].

Cells from the top of the truncus arteriosus and the bottom of the bulbus cordis grow downwards and upwards, respectively [35]. Once these cells meet, they entwine to form a helix structure. The helix divides to form the aorta and the pulmonary artery, which are crossed over each other (Figure 1.1 D). In utero, the pulmonary artery remains connected to the aorta via a small gap called the patent ductus.

At the entrance and exit of each ventricle, one-way valves form [33]. The atrioventricular (tricuspid and mitral) valves form between the atria and the entrance to the ventricles and the semilunar (pulmonic and aortic) valves form between the ventricles and the entrance to the arteries [33, 36].

Figure 1.1 Diagram of fetal heart looping



A. Growth of the fetal heart tube B. S-shaped looping C. Fetal heart looping, D. the developed fetal heart. Abbreviations: TA: Truncus Arteriosus, BC: Bulbus cordis, PV: Primitive ventricle, PA: Primitive atrium, RV: Right ventricle, LV: Left ventricle, RA: Right atrium, LA: Left atrium.

Figure drawn by Kate Best, adapted from "Anatomy of the Human Body" [37]

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1.2.4.2 Fetal circulation

Blood oxygenated by the placenta passes through the fetal liver and the umbilical artery into the right atrium [35]. Most of the oxygenated blood is then shunted through the formaen ovale, into the left atrium and then the aorta (Figure 1.2). The remainder of the oxygenated blood from the umbilical artery mixes with deoxygenated blood coming from the superior vena cava and passes through the right ventricle into the pulmonary artery [35]. By shunting through the patent ductus, the majority of this mixed blood then combines with the oxygenated blood passing through the aorta. The mixed and oxygenated blood is then pumped around the fetus before returning as deoxygenated blood to the right atrium via the superior vena cava, effectively bypassing the lungs [35].

1.2.4.3 Neonatal circulation

After birth, the lungs take in air, causing increased blood flow to the lungs and therefore back to the heart. The pressure in the left atrium increases and thus causes the foramen ovale to close after around five days of life [35]. Similarly, the shift in pressure also causes the patent ductus to shut. As a result, circulation shifts from a shared to a series circuit, the lungs are no longer bypassed and the right side of the heart becomes more dominant than the left [35] (Figure 1.2). This shift explains why babies with CHD remain healthy in utero but become symptomatic after birth or when the ductus closes [38].

When the newborn heart beats, muscles in both ventricle walls contract in unison, causing pressure in the ventricles to increase [36]. When this pressure becomes greater than the pressure in the arteries, the semilunar valves open and the blood is ejected into the arteries. Here, oxygenated blood travels from the left ventricle into the aorta and around the body, while simultaneously, the deoxygenated blood travels from the right ventricle into the superior vena cava and to the lungs to be oxygenated (Figure 1.2). After the blood is released from the ventricles, the ventricle muscles relax and the pressure drops. The semilunar valves close in response to the pressure gradient between the ventricles and arteries [36]. In unison, oxygenated blood flows back from the lungs to the left atrium and deoxygenated blood returns from the body to the right atrium. The blood levels in the atria cause the pressure to increase. When the pressure becomes greater in the atria than the ventricles, the atrioventricular valves open and blood flows into the ventricles. The heart contracts again and the cycle continues.

Figure 1.2 Fetal circulation

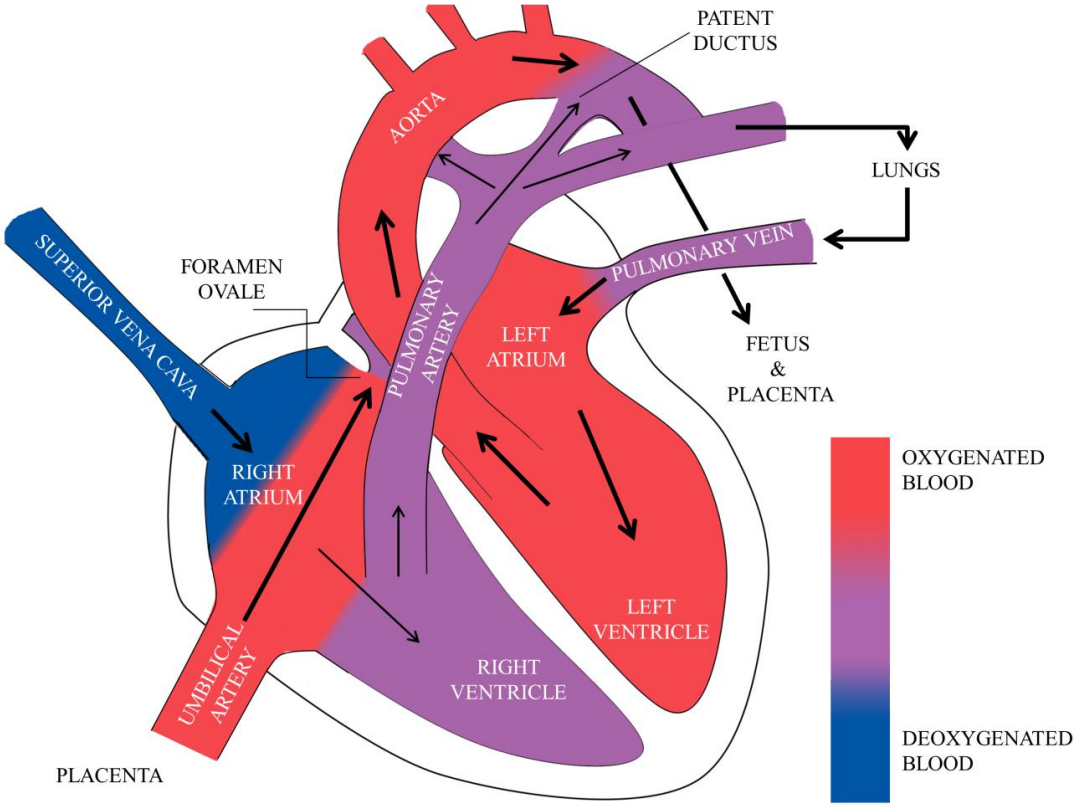


Figure drawn by Kate Best, adapted from [39]

Figure 1.3 Neonatal circulation

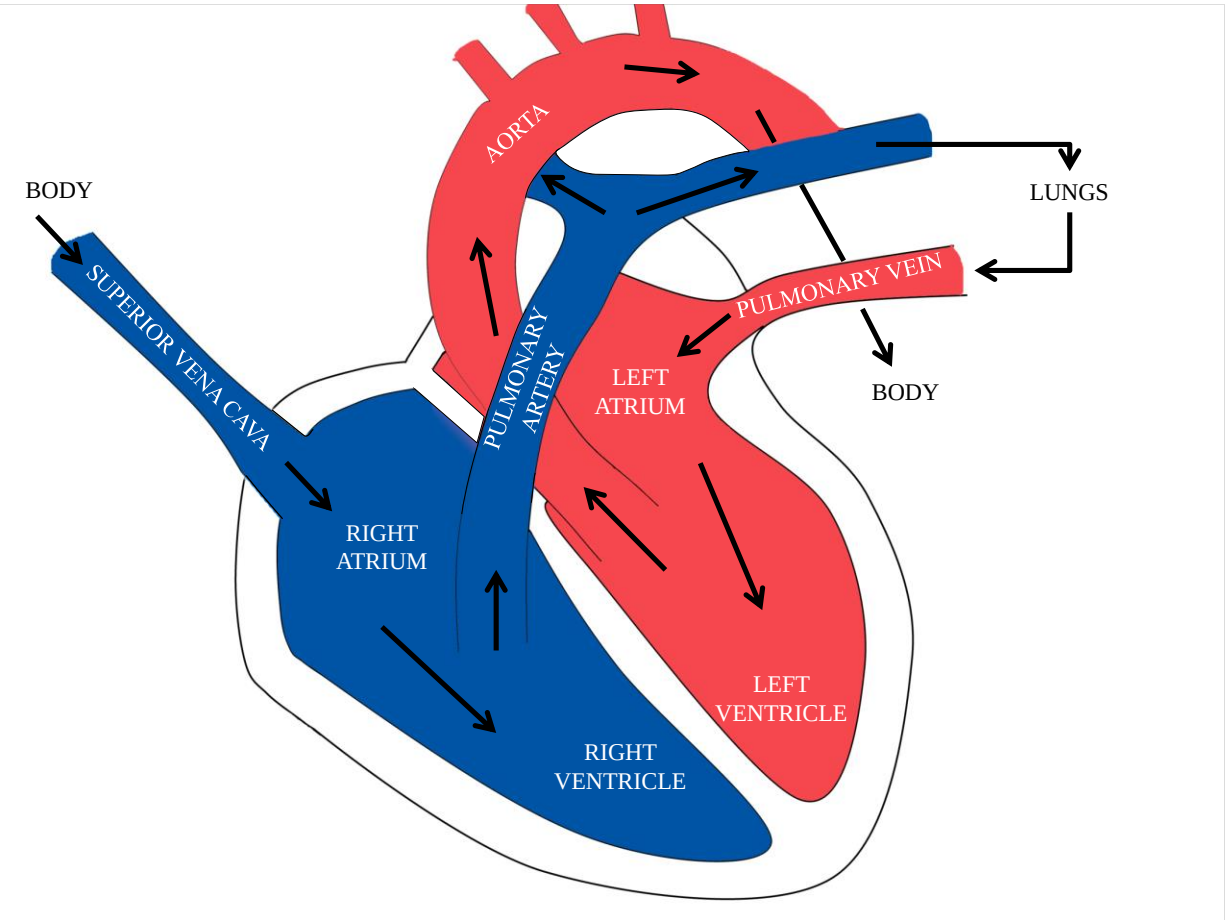


Figure drawn by Kate Best, adapted from [40]

Table 1.1 Descriptions of the most common CHD subtypes

CHD subtype	ICD 9	ICD 10	Description
Common arterial truncus (CAT)	74500	Q200	One large artery leaving the heart instead of two; usually occurs with a VSD [41].
Transposition of the great vessels (TGV)	74510	Q203	A switch over of the pulmonary artery and the aorta, meaning they are connected to opposite ventricles [42]. This causes deoxygenated blood to be sent into the right ventricle and through the aorta without being oxygenated in the lungs [33]. Similarly, oxygenated blood is sent through the pulmonary artery meaning the oxygenated blood is not dispersed around the body [33].
Single Ventricle (SV)	7453	Q204	Only one ventricle, resulting in blood passing from both atria into the same ventricle [41].
Ventricular septal defect (VSD)	7454	Q210	A gap in the ventricular septum [33].
Aortic valve atresia/ stenosis (AVA/S)	7463(no code for atresia)	Q230	Blockage or narrowing of the aortic valve.
Atrial septal defect (ASD)	7455	Q211	A gap between the left and right atrium.
Atrioventricular septal defect (AVSD)	7456	Q212	A common atrioventricular canal and just one atrioventricular valve bridging the canal [41, 42].
Tetralogy of Fallot (ToF)	7452	Q213	A combination of four defects: sub-pulmonary stenosis, VSD, over-riding aorta and thick right ventricle [41].
Tricuspid atresia/ stenosis (TA)	7461	Q224	The lack of an opening between the right atria and ventricle, usually caused by the tricuspid valve failing to form. This means that blood is not able to pass from the atria to the ventricle and into the lungs. The blood must alternatively pass from the right to left atria. Stenosis occurs when the passage exists but is very small. This usually occurs with a VSD.
Ebstein's anomaly (EA)	7462	Q225	EA occurs when the tricuspid valve is located lower than it should be, towards the right ventricle, resulting in an oversized right atrium and an undersized right ventricle [41].
Pulmonary valve stenosis (PVS)	74601	Q221	An obstruction of blood flow through the pulmonary valve [41].
Pulmonary valve atresia (PVA)	74600	Q220	The failure of the pulmonary valve to form.
Hypoplastic left heart (HLH)	7467	Q234	A small or non-existent left ventricle.
Hypoplastic right heart (HRH)	No code	Q226	A small or non-existent right ventricle.
Coarctation of aorta (CoA)	7471	Q251	A narrowing of the aorta.
Total anomalous pulmonary venuous return (TAPVR)	74742	Q262	Incorrect positioning of the pulmonary vein and the superior vena cava, resulting in oxygenated blood entering the right chambers instead of the left. There must be an ASD or patent foramen ovale so that

CHD subtype	ICD 9	ICD 10	Description
			blood can pass to the correct chamber, without these the child will die.
Mitral valve anomalies (MVA)	7465	Q232	Underdevelopment of the mitral valve, usually prolapse, atresia, regurgitation of the mitral valve.
Interrupted aortic arch (IAA)	74711	Q252	An undeveloped aorta usually characterised by a gap or a discontinuation in the aortic arch.
Double outlet right ventricle (DORV)	74511	Q201	The great arteries are both connected to the right ventricle.

1.2.5 Aetiology

The aetiology of CHD is hypothesised to be both environmental and genetic [43-45]. A review of non-inherited risk reported strong evidence that maternal illnesses such as phenylketonuria, diabetes, febrile illnesses, influenza, rubella and epilepsy were associated with CHD [43]. There was also strong evidence that maternal exposure to vitamin A, anticonvulsants, indomethacin, ibuprofen, Sulfasalazine, thalidomide and trimethoprim/ sulfonamides was associated with CHD [43].

Aneuploidies and microdeletions account for approximately 20% of CHDs [45]. For example, 80% of children with Trisomy 13, 40-50% of children with Trisomy 21 (Down syndrome) and 90-100% of children with Trisomy 18 occur with CHD [45]. However, single gene mutations also account for a small proportion of CHDs. Some of these single gene disorders cause a syndrome such as Noonan Syndrome or Holt-Oram syndrome, which are linked with CHD [46]. However other single gene mutations, such as in NKX2.5 or GATA4 are hypothesised to cause CHD directly and do not occur as part of a syndrome [46]. Lastly, Pierpont et al state that a proportion of CHDs are the result of multiple gene mutations, which make the fetus more vulnerable to CHD, particularly upon interaction with environmental exposures [46].

Although the genetic aetiology of CHD is an important area of research, the focus of my thesis is on the birth prevalence and survival of CHD. Therefore, I will not be further investigating the role of genetics in CHD in this thesis.

1.2.6 Care pathway

1.2.6.1 Prenatal diagnosis

For cases of CHD prenatally diagnosed in the UK, there is a structured care pathway outlined by the British Congenital Cardiac Association [47]. Most prenatally diagnosed cases are initially suspected during the 18^{+0} to 20^{+6} routine fetal anomaly scan. These cases are referred to a fetal cardiology service, perhaps after a re-scan at a local hospital, where fetal echocardiography is performed to confirm the diagnosis. At this point, further prenatal tests such as amniocentesis or karyotyping are offered. If the pregnancy continues, local and specialist multidisciplinary teams plan active treatment or palliative care. After birth, there will be a cardiac assessment and treatment. “High-risk” pregnancies (defined as shown in

Figure 1.5), will be referred to fetal cardiology services regardless of whether an anomaly was identified at the routine fetal anomaly scan.

1.2.6.2 Postnatal diagnosis

For babies that were not diagnosed prenatally or at birth, newborn screening checks within 72 hours of birth are in place to diagnose CHD (among other things) before hospital discharge [48]. There is an additional health check at around 6-8 weeks with the baby's GP [48]. These checks involve listening to the heart with a stethoscope with the aim of picking up heart murmurs, which can be indicative of AVA/S, PVS, ToF, PDA, MVA, VSD or ASD. Babies with PDA, VSD, ASD and CAT may present with breathlessness that has developed gradually and with difficulty feeding. Babies with cyanotic CHD (such as ToF, TAPVR, HLH, TGV, TA, IAA and PVA) are sometimes diagnosed before hospital discharge due to their "blue-ish" colouring and difficulty with breathing [49]. While symptoms occur quickly after birth in most babies with PVA, SV, TA and HLH, this is not true for all types of cyanotic CHD. Babies with duct dependent CHD may develop symptoms at around five days of age, when the patent ductus closes [49]. These babies can often go into shock or critical cyanosis, meaning they present as emergencies.

Figure 1.4 Prenatal care pathway for CHD

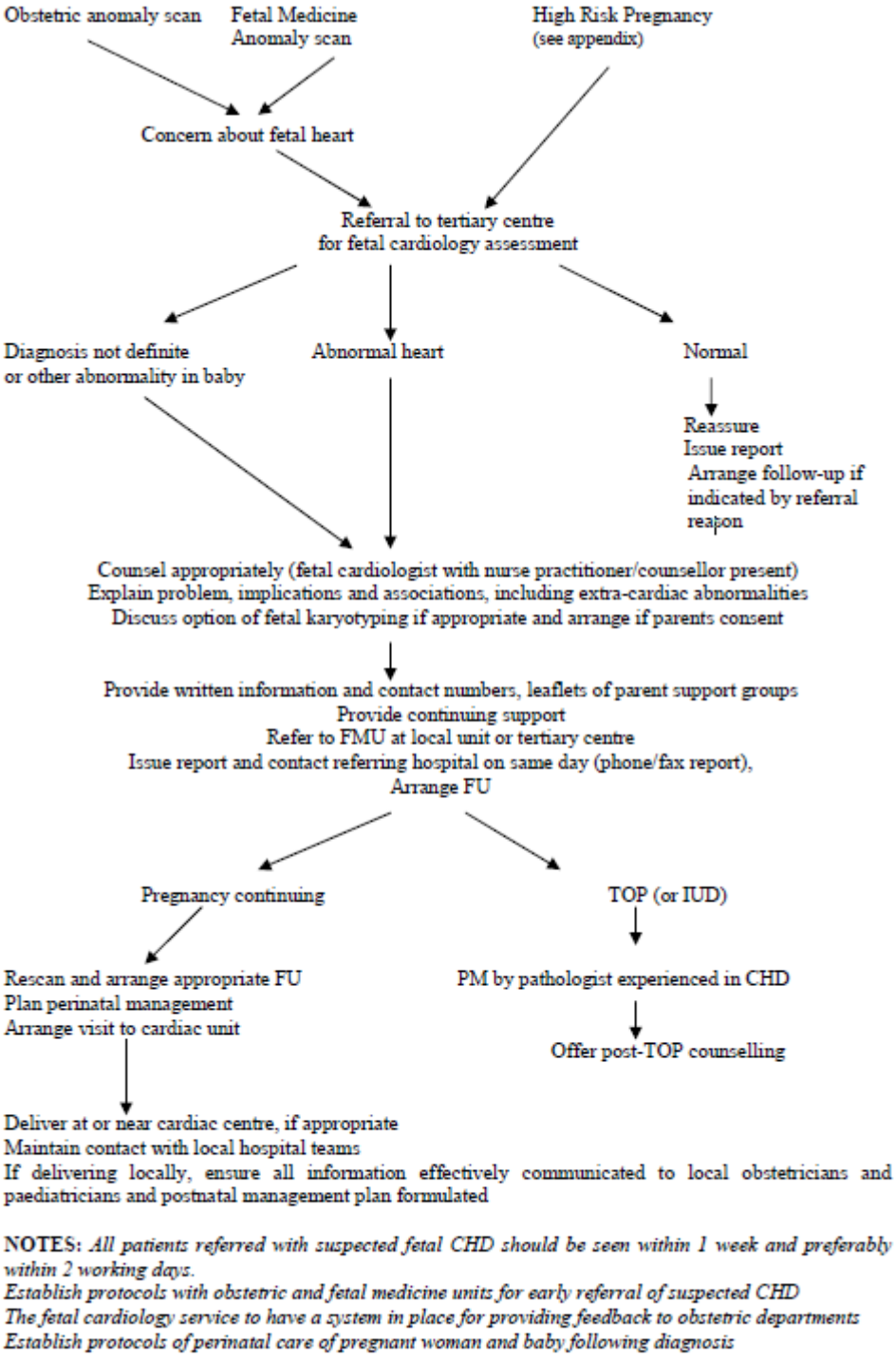


Figure taken from:

http://www.bcs.com/documents/Fetal_Cardiology_Standards_Final_Version_March_2010.pdf

Figure 1.5 Criteria for "high-risk" pregnancy for CHD

Maternal indications

1) Maternal congenital heart disease
2) Maternal metabolic disorders, especially if poor control in early gestation
    i. diabetes mellitus
    ii. phenylketonuria
3) Maternal exposure to cardiac teratogens:
    i. anticonvulsant, retinoic acid, lithium
    ii. viral infection (rubella, CMV, coxsackie, parvovirus) and toxoplasma
4) Maternal collagen disease with anti Ro/SSA and/or anti La/SSB
5) Maternal medication with NSAID drugs after 25-30 gestational weeks

Familial indications

1) Paternal congenital heart disease
2) Previous child or fetus with congenital heart disease or congenital heart block
3) Chromosomal anomalies, gene disorders or syndromes with congenital heart disease or cardiomyopathy

Fetal indications

1) Suspicion of fetal cardiac abnormality during an obstetric scan
2) Fetal hydrops
3) Pericardial effusion
4) Pleural effusion
5) Polyhydramnios
6) Extra-cardiac malformation
7) Chromosomal abnormalities
8) Genetic syndromes
9) Nuchal translucency >99th centile for crown rump length (>3.5mm)
    (A nuchal translucency >95th centile is also associated with an increased risk of CHD but due to the workload involved, local policies will determine whether this group should be offered a detailed cardiac scan)
10) Monochorionic twins
11) Fetal arrhythmias
    i. sustained bradycardia heart rate <120 beats per minute
    ii. tachycardia – heart rate >180 beats per minute

(Irregular heart rhythms can be managed in conjunction with the local obstetric teams. In many cases referral to tertiary centre can be avoided if agreed management protocols are in place locally.)

12) Other states with known risk for fetal heart failure:
    i. tumors with a large vascular supply
    ii. arteriovenous fistulas
    iii. absence of ductus venosus
    iv. acardiac twin
    v. twin-twin transfusion syndrome
    vi. fetal anaemia

Figure taken from:

http://www.bcs.com/documents/Fetal_Cardiology_Standards_Final_Version_March_2010.pdf

1.2.6.3 Treatment

Interventions vary considerably according to CHD subtype. The most common treatments are shown in Table 1.2. To summarise, SV, TA, HLH, ToF, TGV, CAT, AVSD, PVA-VSD cases require open heart surgery to survive. For SV, TA and HLH cases, surgical intervention is required within the first few days of life. For AVSD, PVA-VSD, CAT and TGV, surgical intervention needs to occur within the first few weeks of life. Individuals with AVA/S and CoA generally require catheterisation of the heart, with the timing dependent on severity.

Table 1.2 Treatment for CHD according to NHS Choices

CHD subtype	Treatments	Type of treatment	Timing of treatment
AVA/S	Balloon valvuloplasty *Or (if unsuccessful)* Valve replacement.	Catheter Open heart surgery	Depends on severity, may wait until symptoms present (infancy, childhood or adulthood)
CoA	Inserting a catheter and using a balloon to enlarge the tube or using a metal stent. *Or (for more severe CoA)* Removing the narrow section/ creating a bypass.	Catheter Open heart surgery	First few days of life for severe CoA
EA	Mild EA doesn't require treatment. Severe EA requires valve repair or replacement.	None Open heart surgery	Dependent on severity
PDA	Medicine prescribed to close the duct. *Or (if unsuccessful)* The duct may be sealed with a coil or plug.	Medicine Key hole/ open heart	Dependent on symptoms
PVS	Mild PVS requires no treatment. Severe PVS requires balloon valvuloplasty, valvotomy or valve replacement.	None Catheter	Dependent on symptoms
VSD, ASD	Small septal defects do not require treatment. Larger septal defects can be closed with a catheter. Very large septal defect may require surgery.	None Catheter Key hole surgery or open heart surgery	Dependent on symptoms
SV, TA, HLH	Prostaglandin prescribed after birth to prevent the closure of the ductus. These subtypes are then palliated surgically in three stages *1)* Norwood procedure: A shunt is created between the heart and lungs *2)* Glenn operation: The superior vena cava is connected to the pulmonary artery	Medicine Open heart surgery	Stage 1 performed in first few days of life Stage 2 4-6 months Stage 3 18-36 months

CHD subtype	Treatments	Type of treatment	Timing of treatment
	3) Fonatan operation: the inferior vena cave is connected to the pulmonary artery.		
ToF	Shunt operation sometimes required soon after birth. *Then* The hole in the heart is closed and the pulmonary valve is opened up.	Open heart surgery Open heart surgery	Severe ToF treated soon after birth. Less severe ToF treated at 3-6 months
TAPVR	The abnormally positioned veins are repositioned in the correct position in the left atrium.	Open heart surgery	If the pulmonary vein is obstructed repair is at birth. If not surgery occurs at a few weeks or months
TGV	Prostaglandin prescribed at birth (a catheter may also be used to make a hole in the atrial septum). *Then:* Balloon septostomy *Then:* Later the arterial switch operation is performed to reattach the arteries into the correct positions.	Medicine/ catheter Catheter Open heart surgery	Arterial switch performed in the first month
CAT	The common truncus is split into two and repositioned.	Open heart surgery	A few weeks after birth
AVSD	Holes in the heart will be surgically closed.	Open heart surgery	3-6 months
PVA-VSD	Prostaglandin at birth Arterial shunt then possible major surgery later in life (if the arteries have grown).	Medicine Open heart surgery	First few weeks and then later in life

All information was taken from:

http://www.nhs.uk/Conditions/Congenital-heart-disease/Pages/Treatment.asp

Chapter 2. Aim and objectives

The aim of this PhD is to describe and predict the prevalence and survival of individuals with CHD, overall and by subtype.

The specific objectives are to:

1. Conduct a literature review of CHD birth prevalence, risk factors for CHD and birth characteristics of children with CHD, in population-based studies (Chapter 3).
2. Describe the epidemiology of CHD in singletons including: prevalence, trends in prevalence and CHD risk factors in the UK, using data obtained from the British Isles Network of Congenital Anomaly Registers (BINOCARs) (Chapter 5).
3. Describe the epidemiology of CHD in multiple births, and estimate the relative risk of CHD in twins compared to singletons using data from the Northern Congenital Abnormality Survey (NorCAS) linked to data from the Northern Survey of Twins and Multiple Pregnancies (NorSTAMP) (Chapter 6).
4. Conduct a systematic review on population-based studies that have reported the long-term survival and risk factors for mortality for children born with CHD (Chapter 7).
5. Analyse survival and risk factors for mortality in individuals with CHD in the UK using data obtained from the NorCAS linked to death registrations. Using this data, to estimate the future survival associated with CHD (Chapter 8).
6. Predict the future prevalence of CHD using data from the NorCAS (Chapter 9).

Chapter 3. The birth prevalence of congenital heart disease: a literature review

3.1 Introduction

Worldwide, many studies have been published on the epidemiology of CHD. Recently, two systematic reviews on the global prevalence of CHD have been published, reporting prevalence rates of between 50-70 per 10,000 live births [18, 19]. However, both reviews did not account for cases occurring in terminations of pregnancy for fetal anomaly (TOPFAs) or fetal deaths. Additionally, these reviews consisted of hospital-based studies, meaning cases were included only if they presented in hospital. Population-based studies include cases born in (or to mothers residing in) a pre-defined area, defined by geo-political boundaries [50].

A literature review that solely includes population-based studies will provide more reliable estimates of CHD birth prevalence.

3.1.1 Aim

The primary aim of this literature review is to identify and appraise the relevant international literature on the birth prevalence of CHD.

3.1.1.1 Objectives

1) To identify all population-based studies that have reported the prevalence of CHD, using a systematic search strategy.
2) To critically appraise the studies and identify possible sources of heterogeneity.
3) Using the identified studies, to review CHD risk factors and the characteristics of individuals with CHD.

3.2 Methods

3.2.1 Definitions

Total birth prevalence (per 10,000) was defined as:

$$\frac{\text{No of cases of CHD in live births, stillbirths, late miscarriages, TOPFAs}}{\text{No of live births and stillbirths in the population}} \text{ x } 10{,}000$$

Ideally, total birth prevalence of CHD is calculated using the number of cases occurring in late miscarriages and TOPFAs. However, this is not always possible and so sometimes the numerator consists only of live and stillbirths.

Live birth prevalence (per 10,000) was defined as:

$$\frac{\text{No of cases of CHD in live births}}{\text{No of live births in the population}} \text{ x } 10{,}000$$

3.2.2 Inclusion criteria

Population-based studies that reported the live or total birth prevalence (or frequency of cases and study population) of CHD were included. Studies that reported the prevalence of: a) all cases of CHD; b) cases of CHD excluding cases with CHD and chromosomal/ genetic ECAs; or c) isolated cases of CHD, were included. Only full, original articles available from the British library or internet, written in the English language and reporting on CHDs in humans were eligible for inclusion. There was no restriction based on year of publication.

3.2.3 Exclusion criteria

Case-series, case-control, hospital-based studies and "population-based" studies featuring cases ascertained from a single hospital were excluded. Studies that reported the prevalence of single CHD subtypes, studies requiring parental consent for case inclusion and studies that did not report *birth* prevalence were also excluded. Studies that included the same set or subset of data as a larger or more recent study were excluded.

3.2.4 Search strategy

Medline, Embase and Scopus were searched systematically from their inceptions (1946, 1974 and 1996, respectively) to October 2014 inclusive. MeSH-terms and key word searches were entered systematically into the databases (Table 3.1). After systematic searches of each database, the citations were extracted and titles and abstracts were screened according to the inclusion criteria and full articles were retrieved for all relevant citations. Reference lists of included articles were searched and key journals such as "Congenital Heart Disease", "Birth Defects Research", "Circulation", "Heart" and "Cardiology in the Young" were searched using keywords.

The citations were searched and extracted by one reviewer only, meaning this literature review cannot be considered as a systematic review.

3.2.5 Data extraction

Study characteristics including study period, study region and case definition were extracted. Study quality characteristics including: method of ascertainment, methods of diagnosis, maximum age at diagnosis and case definition were extracted. The frequency of cases and denominators were extracted from all included studies. Where possible, case numbers were extracted separately for: a) all cases of CHD; b) cases of CHD excluding cases with structural ECAs; or c) cases of CHD excluding cases with chromosomal/genetic ECAs. Where possible, case numbers were also extracted for the following CHD subtypes: SV, HLH, HRH, EA, TA, PVA, CAT, AVSD, AVA/S, TGV, ToF, TAPVR, IAA, CoA, DORV, MVA, VSD, ASD, PVS and PDA. This was completed for all cases of CHD only (as opposed isolated cases, as few studies reported subtype specific prevalence for these cases).

Information on trends in CHD prevalence over time was extracted where available. Information on maternal age, maternal ethnicity, infant sex, timing of diagnosis, percentage diagnosed postnatally, birth weight and gestational age at delivery were extracted from the identified studies, where possible.

3.2.6 Statistical analysis

Using the extracted case numbers and denominators, the prevalence of CHD and 95% (binomial) confidence intervals per 10,000 births were calculated. A meta-analysis was not

performed due to the high degree of variation between studies. However, χ^2 tests were applied to test for heterogeneity and Cochrane's Q test was used to quantify heterogeneity between studies, where I^2 >50% was considered as significant heterogeneity [51].

Analyses were performed in Stata version 13 (StataCorp, College Station, Texas) and $p<0.05$ was considered statistically significant.

Table 3.1: Medline, Embase and Scopus search terms

Medline		Embase		Scopus	
1	Heart Defects, Congenital/ or ((cardi$ adj1 anomal$) or (cardi$ adj1 abnormalit$) or (cardi$ adj1 malformation$) or (cardi$ adj1 defect$) or (heart adj1 anomal$) or (heart adj1 abnormalit$) or (heart adj1 malformation$) or (heart adj1 defect$) or (congenital adj1 heart adj1 disease$)).ti,ab.	1	Congenital heart malformation/ or congenital heart disease/ or ((cardi$ adj1 anomal$) or (cardi$ adj1 abnormalit$) or (cardi$ adj1 malformation$) or (cardi$ adj1 defect$) or (heart adj1 anomal$) or (heart adj1 abnormalit$) or (heart adj1 malformation$) or (heart adj1 defect$) or (congenital adj1 heart adj1 disease$)).ti,ab.	1	(TITLE-ABS-KEY((cardi$ anomal$) OR (cardi$ abnormalit$) OR (cardi$ malformation$) OR (cardi$ defect$) OR (heart anomal$) OR (heart abnormalit$) OR (heart malformation$) OR (heart defect$) OR (congenital heart disease$)) AND TITLE-ABS-KEY(survival OR mortality OR incidence OR prevalence OR epidemiology OR (risk factor$) OR (predict$)) AND ALL(epidemiology OR epidemiological) AND NOT ALL(animal$ OR rat OR rats OR cat OR cats OR bovine OR sheep)) AND DOCTYPE(ar OR re) AND (LIMIT-TO(LANGUAGE, "English")) AND (LIMIT-TO(SRCTYPE, "j"))
2	Survival Analysis/ or survival.ti,ab. Or (exp Mortality/ not (Poult Enteritis Mortaliy Syndrome/ or Maternal Mortality/)) or mortality.ti,ab.	2	Survival.ti,ab. or survival/ Or mortality/ or mortality.ti,ab.		
3	Incidence/ or incidence.ti,ab. Or prevalence/ or prevalence.ti,ab. Or predict$.ti,ab. Or exp Risk/ or Epidemiology or epidemiology.ti,ab.	3	Incidence/ or incidence.ti,ab. Or prevalence/ or prevalence.ti,ab. Or Epidemiology/ or epidemiology.ti,ab. Or risk factors/		
4	Exp Epidemiological Studies/	4	Exp epidemiology/ or epidemiology.mp or epidemiological.mp		
5	1 and (2 or 3) and 4	5	1 and (2 or 3) and 4		
6	Limit 5 to (English language and humans)	6	Limit 5 to (english language and humans)		
7	6 not (case study.mp or exp Case Reports/ or exp Clinical Trials as Topic/ or clinical trial.mp)	7	6 not (case study.mp or exp Case Report/ or exp controlled clinical trials or clinical trial.mp)		

3.3 Results

Figure 3.1 shows a PRISMA diagram for the flow of articles through the review. Of 18,280 identified articles, 35 met the inclusion criteria.

3.3.1 Description of studies

Study descriptions are shown in Table 3.2. Of the 35 included articles, two reported data from more than one study. Knoshnood et al presented data from 27 different registers across Europe (data from two registers were excluded due to overlapping data with other included articles) and Pradat et al reported data from a French, a Swedish and an American register [52, 53].

Three articles studied populations in Asia [54-56], 21 in Europe [1, 52, 53, 57-74], eight in North America [53, 75-83], two in Oceania [84, 85] and one in South America [77]. Six articles (10 studies) reported the prevalence of CHD in the UK, three in the North of England, three in Liverpool, one each in Wales, Thames Valley, Wessex and the East Midlands [52, 60, 61, 63, 64, 69].

The oldest study period began in 1960 [64], and the most recent in 2007 [56]. The longest study period spanned 37 years [80] and the shortest spanned one year [56, 66, 68, 71, 85].

The majority of articles (n=19) used ICD versions eight, nine, or 10 to code CHD [1, 52, 54, 55, 57-60, 62, 63, 65, 67, 68, 72, 74, 76, 79-81]. However, seven of these did not state which ICD codes were classed as CHD [55, 58, 59, 62, 68, 79, 81]. Six of the articles using the ICD coding system included cases according to the EUROCAT inclusion criteria [1, 52, 60, 65, 67, 72] and six used a more inclusive set of ICD codes to define CHD [54, 62, 63, 74, 76, 80]. Three articles (five studies) stated that ISC coding was used but provided no further information [53, 70, 82]. One article used the "Anatomical and Clinical Criteria" (ACC) coding [73]. Four articles did not specify codes but defined CHD according to Mitchell's definition (Chapter 1 section 1.2.1) [56, 66, 69, 71]. Two articles used an adapted version of Mitchell's definition ("a structural anomaly of the great vessels") [77, 84]. The six remaining articles provided no definition of CHD [61, 64, 75, 78, 85, 86].

CHD was diagnosed using echocardiography, cardiac catheterisation and post mortem in the majority of articles (n=19) [52, 53, 56, 57, 59-63, 65, 69, 74-77, 80-82, 84]. The method of diagnosis was not stated in nine articles [53-55, 58, 64, 66, 68, 78, 79].

The maximum age at diagnosis ranged from five days to 16 years [57, 60]. There was no maximum age of diagnosis in eight articles, but as none of the eight were register-based studies, cases identified throughout the study periods, regardless of age, were probably included [55, 62-64, 70, 77, 80, 83].

Twenty-one articles ascertained cases using CARs [1, 52-58, 60, 61, 63-65, 68, 69, 72, 76, 80, 82, 84, 85] and five used CHD registers or databases [53, 59, 62, 66, 73, 81]. Hospital records, admissions/referrals and health systems were used in four articles [55, 70, 77, 79]. The remaining sources were an insurance database [55], patient registry data [67], a birth cohort [71], a birth register [74] and "Crippled children's services" [78].

Figure 3.1: PRISMA diagram showing flow of articles through the review

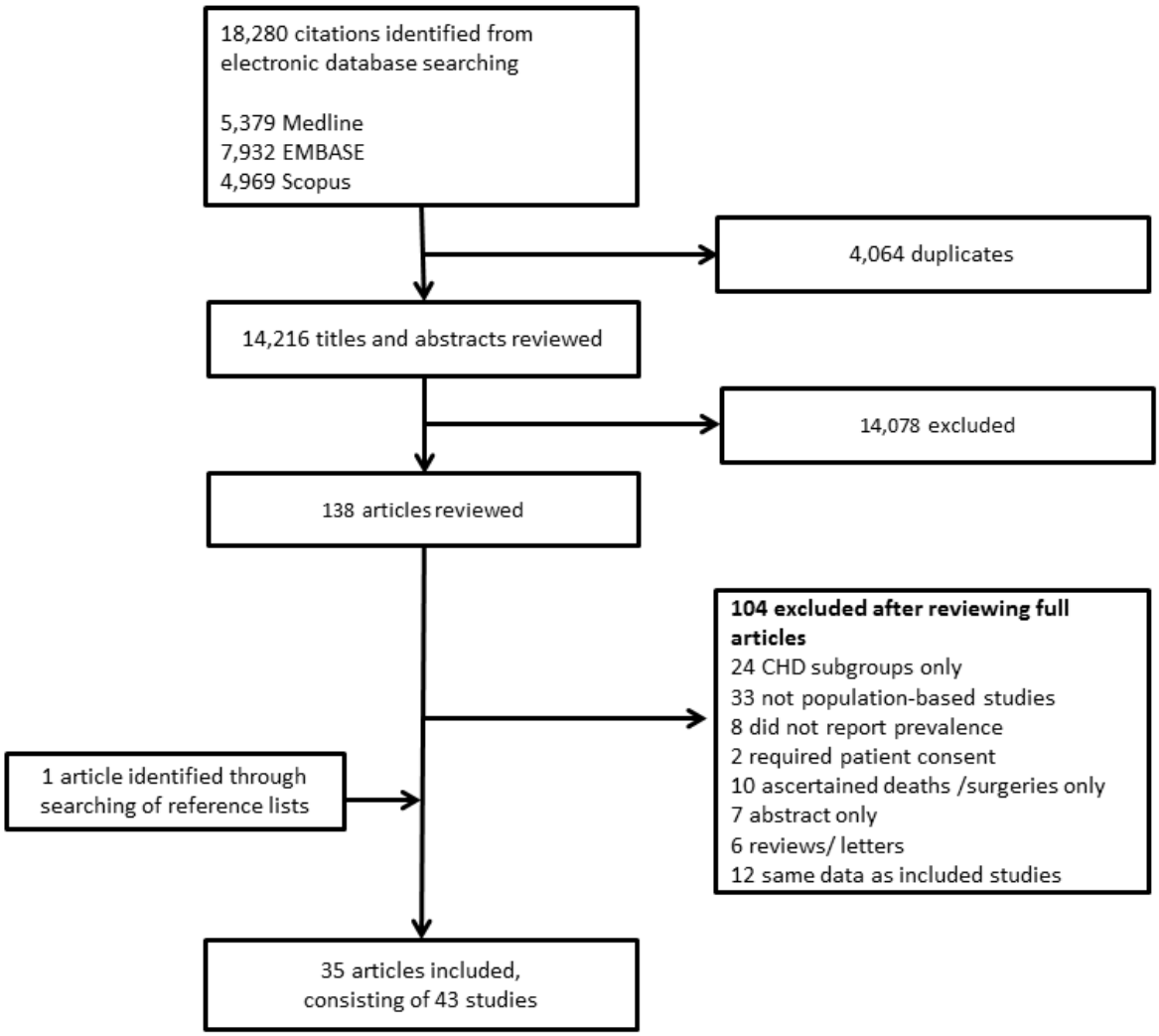


Table 3.2: Description of studies included in the literature review

Article	Study period	Study region, Country, Continent	CHD definition	Methods of Diagnosis	Exclusions	Age limit for diagnosis	Case population, Source of cases	Denominator population, Source of denominator
Anand, et al [75]	1992-1993	Tennessee, USA	None stated	Echocardiography, diagnosed by paediatric cardiologists	None stated	18 months	156 live births None stated	15,949 Live births Live births from all hospitals in the area
Borman, et al [85]	1978	New Zealand, Oceania	None stated	None stated	None stated	1 year	181 live births National CAR	517,77 live births Births notified to the register
Bourdial, et al [1]	2002-2007	La Reunion, France, Europe	ICD 10: Q20-26	Pathology, medical genetics, cardiology units	PDA	1 year	424 live births. 512 total births (live births, fetal deaths, terminations). 448 total births excl. chromosomal cases EUROCAT Reunion register:	88,025 total births (live births and stillbirths), "all births in La Reunion"
Bower and Ramsay [84]	1980-1989	Western Australia, Australia, Oceania	A structural anomaly of the heart or the great vessels, which has a real or potential functional significance	Echocardiography, catheterisation, operation, post mortem, diagnosis from a cardiologist or paediatrician	Disorders of peripheral veins or arteries. PDA if not present after 3 months in term births and after 6 months if preterm	6 years	1,787 live births. 1635 live births excl. chromosomal cases. 1337 isolated live births Western Australia Birth Defects Registry	233,502 total births (no further description given)

Article	Study period	Study region, Country, Continent	CHD definition	Methods of Diagnosis	Exclusions	Age limit for diagnosis	Case population, Source of cases	Denominator population, Source of denominator
Calzolari, et al [57]	1980-1994	Emilia Romagna, Italy, Europe	ICD: specific CHD codes not stated	Echocardiography, surgery, post mortem	PDA< 37 weeks gestational age	≤5 days	1,549 total births (live births and stillbirths. 1397 total births excl. chromosomal cases. 1149 isolated total births Emilia Romagna Congenital Anomaly Malformation Registry	330,017 live births Source not stated
Cambra et al [72]	1999-2008	Basque Country, Spain, Europe	ICD 10: Q20-26	Sonography, genetic test, pathology	None stated	1 year	962 live births, fetal deaths (>22 weeks), termination for fetal anomaly. 873 live births Population registry of Neonatal Screening and Congenital Anomalies	191,171 total births (live and stillbirth) Registry of Newborns of the Basque Country
Caton [58]	1992-2006	New York, USA, North America	ICD 9: specific CHD codes not stated	None stated	CAT	2 years	13,036 live births New York Congenital malformation register	204,4091 live births Birth certificates
Cedergren and Kallen [59]	1992-2001	Sweden, Europe	ICD codes uses, not specific codes for CHD stated	Clinical neonatal diagnosis, echocardiography, catheterisation, operation, post mortem	PDA associated with prematurity and birth weight <2500g. Cases occurring in a multiple pregnancy	1 year	8,947 live births excl. chromosomal cases. 5338 isolated live births Swedish medical birth registries, child	770,355 total births (live births and stillbirths (>28 weeks)) Source not stated

Article	Study period	Study region, Country, Continent	CHD definition	Methods of Diagnosis	Exclusions	Age limit for diagnosis	Case population, Source of cases	Denominator population, Source of denominator
					or in a pregnancy affected by pre-existing diabetes		cardiology register, medical records	
Dadvand, et al. [60]	1985-2003	Northern England, UK, Europe	ICD 10: Q20-26	Echocardiography or cardiac catheterisation, post mortem, surgery	Cardiac murmurs, PDA associated with prematurity, peripheral PVS, heart block	16 years pre-2003, 12 years post-2003	5,715 total births (livebirths, stillbirths (≥28 weeks until 1992, 24 weeks after), late miscarriages and terminations for fetal anomaly (at any gestational age)). 5050 total births excl. chromosomal cases. 4382 isolated total births. 5253 live births Northern Congenital Abnormality Survey	665,377 total births (livebirths, stillbirths *(≥28 weeks until 1992, 24 weeks after)*, terminations). 659234 live births Office for National Statistics
Dickinson, et al [61]	1960-1969	Liverpool, UK, Europe	None stated	Post mortem, surgeries, catheterisation, clinical findings	Endocardial fibroelastosis, congenital heart block, non-obstructive cardiomyopathy	5/6 years	884 live births Liverpool Registry of Congenital Malformations	160,480 live births Office of Population Censuses and Surveys.
Dilber and Malcic [62]	2002-2007	Croatia, Europe	ICD 9: 745-747 ICD 10: Q 20-28	Clinical findings, ECG, X-ray, echocardiography, catheterisation, post mortem	PDA associated with prematurity, PFO with the tiny left-to-right shunt in the first year of life, partial TAPVR, mild PVS	None stated	1,480 total births (live births, still births, late fetal deaths following prenatal diagnoses). 1296 total births excl.	205,051 live births Source not stated

Article	Study period	Study region, Country, Continent	CHD definition	Methods of Diagnosis	Exclusions	Age limit for diagnosis	Case population, Source of cases	Denominator population, Source of denominator
					bicuspid aortic valve, mitral valve prolapse, mitral incompetence, anomalies of coronary arteries, pericardium and AV fistule, aortic arch branch anomaly, and vascular ring. Minor EUROCAT anomalies.		chromosomal cases. 1265 isolated total births Medical records from 14 paediatric cardiology centres	
Forrester and Merz [76]	1986-1999	Hawaii, USA, North America	ICD 9: 745.00-747.99	Echocardiography, catheterisation, surgeries, post mortem, or physician (cardiologist) review	None stated	1 year	5,010 total births (live births, fetal deaths, elective terminations of all gestational ages) Hawaii Birth defects program	282,900 total births (live births and fetal deaths) Department of Health Office of Health Status Monitoring as derived from birth and fetal death certificates
Guitti [77]	1989-1998	Londrina, Brazil, South America	a structural anomaly of the heart or the great vessels, which has a real or potential functional significance	Echocardiography, catheterisation, surgical procedures, post mortem.	PDA only included if present >10 days (normal weight at birth) or >3 months when gestational age was <37 weeks	None stated	441 live births, 390 live births excl. chromosomal cases. 337 isolated live births Hospital records	80,269 live births Official demographic data

Article	Study period	Study region, Country, Continent	CHD definition	Methods of Diagnosis	Exclusions	Age limit for diagnosis	Case population, Source of cases	Denominator population, Source of denominator
Hay [78]	1963	Iowa, USA, North America	"all types"	None stated	Heart murmurs	1 year	233 total births (live births and fetal deaths (>20 weeks)) Iowa hospitals and crippled children's services, hospital data, birth and death certificates.	58,686 total births (live births, terminations and fetal deaths (>20 weeks)) Hospital births in Louisiana
Jackson, et al [63]	1979-1988	Liverpool, UK, Europe	ICD 9: 745.00-747.49	Echocardiography, catheterisation, post mortem	PDA<2500g birth weight	None stated	1,543 live births Liverpool registry of Congenital Malformations	203,880 live births Office of Population censuses and surveys.
Johnson and Rouleau [79]	1979-1993	Canada, North America	ICD 9: specific CHD codes not stated.	None stated	PDA associated with prematurity	1 year	8,012 total births (live births and stillbirths) Hospital admissions and discharges	593,042 total births (live births and stillbirths), The medical research database
Kenna, et al [64]	1960-1969	Liverpool, UK, Europe	None stated	None stated	None stated	Study period (3-12 years)	1,081 total births (No further description). 856 total births Liverpool registry of Congenital Malformations, paediatric cardiology clinic records.	163,692 total births (no further description given) None stated

Article	Study period	Study region, Country, Continent	CHD definition	Methods of Diagnosis	Exclusions	Age limit for diagnosis	Case population, Source of cases	Denominator population, Source of denominator
Khoshnood et al [73]	2005-2008	Paris, France	ACC-CHD coding[87]	Diagnoses are confirmed in specialised paediatric cardiology departments, pathology exam	PDA and PFO	1 year	Live births, fetal deaths and terminations for fetal anomaly. The EPICARD register	Live births and fetal deaths. Not stated
Khoshnood, et al [52]	1990-2007	Europe	ICD 9: 745, 746, 7470-7474 ICD 10: Q20-26	Varies by register	EUROCAT exclusions including: PDA associated with prematurity	varies by register	Total births (live births, fetal deaths (> 20 weeks), and terminations for fetal anomaly) excl. chromosomal cases Hainut 1637, Odense 806, Paris 3954,Tuscany 3229, Dublin 1682, N Netherlands 1956, Emilia Romagna 2434, Strasbourg 1851, Vaud 1573, Zagreb 503, Malta 944, Antwerp 1246, Basque Country 1218, Saxony-Anhalt 2074, Mainz 530, Barcelona 1088, Styria 1747, Cork & Kerry 517, Sicily 1440, Wales 3305, Norway 3774, Ukraine 568, La Reunion 391, Wielkopolska 2776, Thames Valley 493,	Total births (live births and fetal deaths (>20 weeks)), Hainut 225381, Odense 101028, Paris 619098, Tuscany 443981, Dublin 375681, N Netherlands 350223, Emilia Romagna 471367, Strasbourg 191407, Vaud 135154, Zagreb 111048, Malta 81052, Antwerp 256747, Basque Country 293473, Saxony-Anhalt 234610, Mainz 59403, Barcelona 196160, Styria 188454, Cork & Kerry 71625, Sicily 256935, Wales 323462, Norway 406805,

Article	Study period	Study region, Country, Continent	CHD definition	Methods of Diagnosis	Exclusions	Age limit for diagnosis	Case population, Source of cases	Denominator population, Source of denominator
							Wessex 1210, East midlands (UK) 2139, Northern England (UK) 2149, South East Ireland EUROCAT registers	Ukraine 83446, La Reunion 73023, Wielkopolska 278536, Thames Valley (UK) 169919, Wessex (UK) 370122, East midlands (UK) 622064, N England 247091 , SE Ireland 61821, Total 729911629 Source varies by register
Kovacheva, et al [65]	1988-2006	Bulgaria, Europe	ICD 9: 745, 746, 7470-7474 and ICD 10: Q20-26	Echocardiography, catheterisation, surgery or pathological examination	EUROCAT exclusions e.g. cardiac murmurs	1 year	204 isolated total births (live births, stillbirths (≥28 weeks until 1992 and ≥24 weeks after 1992), late miscarriages (≥20 weeks), TOPFA). Pleven, Bulgaria CAR	47,622 total births (live births and stillbirths) Source not stated
Laursen [70]	1963-1973	Denmark, Europe	ISC coding, no specific codes stated	X-ray, ECG, auscultation, catheterisation, post mortem	Bicuspid aortic valves, right aortic arch	During follow-up of children	5,249 Live births excl. chromosomal cases	860,492 live births Source not stated

Article	Study period	Study region, Country, Continent	CHD definition	Methods of Diagnosis	Exclusions	Age limit for diagnosis	Case population, Source of cases	Denominator population, Source of denominator
						aged 0-15 yrs	Hospital records, cardiological department recirds, death certificates.	
Miller, et al [80]	1968-2005	Atlanta, USA, North America	ICD 9: 745.0-747.9	Echocardiography, catheterisation, surgery, post mortem, laboratory tests	PDA, PFO valve insufficiency unrelated to structural valve abnormality in premature or newborn infants less than 6 weeks of age.	None stated	8,277 total births (live births and stillbirths) excl. chromosomal cases. 5289 isolated total births Metropolitan Atlanta Congenital Defects Program	1,301,143 total births (live births (singletons) ≥20) weeks gestation Vital records
Moons, et al [66]	2002	Belgium, Europe	Mitchell's definition	None stated	PFO not requiring closure, rhythm disturbances, mild PVS, PDA not requiring closure, PDA associated with prematurity, hereditary disorders without cardiac consequences and malpositioning of the heart	5 years	922 total births (live births and stillbirths) Cardiology programme database	111,225 total births (live births and stillbirths (≥26 weeks)) National Institute of Statistics

Article	Study period	Study region, Country, Continent	CHD definition	Methods of Diagnosis	Exclusions	Age limit for diagnosis	Case population, Source of cases	Denominator population, Source of denominator
Nuutinen, et al [71]	1966	Oulu and Lapland, Finland, Europe	Mitchell's definition	Catheterisation, operation, post mortem, ECG , X-ray	Arrhythmia, PDA if patent after neonatal period	1 year	50 live births Birth Cohort, hospital admissions, 1 year public health questionnaire filled out by nurses, death certificates.	12,058 live births Source not stated
Olsen, et al [67]	1977-2006	Denmark, Europe	ICD 8: 746-747 ICD 10: Q20-26	Surgeries, catheterisation	PDA <37 weeks gestational age	1 year	6,646 live births. 5191 isolated live births Danish Patient registry data	1,796,216 live births Danish Civil Registration System
Postoev et al [74]	1973-2008	Monchegorsk, North West, Russia, Europe	ICD Q20-28	Echocardiography (from the late 1990s), post mortem	None stated	Not stated	1,029 live births and stillbirths (>28 weeks) The Kola birth register	28,511 total births (live births and stillbirths (>28 weeks)). The Murmansk County Birth Register
Pradat, et al [53]	1983-1992	France, Europe	ISC coding, no specific codes stated	Not stated	Positional anomalies of the heart, cardiomegaly, cardiomyopathy, fibroelastosis, rate or rhythm anomalies, cardiac valve insufficiency and PDA	1 year	2,749 total births (Live births and stillbirths (≥28 weeks)) excl chromosomal cases Central-Eastern France CAR.	951,211 total births (live births and stillbirths) Source not stated

Article	Study period	Study region, Country, Continent	CHD definition	Methods of Diagnosis	Exclusions	Age limit for diagnosis	Case population, Source of cases	Denominator population, Source of denominator
Pradat et al [53]	1981-1992	Sweden, Europe	ISC coding, no specific codes stated	Echocardiography, catheterisation, surgery, post mortem	Positional anomalies of the heart (although ectopia cordis was included), cardiomegaly, cardiomyopathy, fibroelastosis, rate or rhythm anomalies, cardiac valve insufficiency and PDA	1 year	3,171 total births (live births and stillbirths (≥ 28 weeks)) excl chromosomal cases. Cardiology clinics and a CAR	1,268,400 total births (live births and stillbirths) Source not stated
Pradat et al [53]	1985-1992	USA, North America	ISC coding, no specific codes stated	Echocardiography, catheterisation, surgery, post mortem	Positional anomalies of the heart (although ectopia cordis was included), cardiomegaly, cardiomyopathy, fibroelastosis, rate or rhythm anomalies, cardiac valve insufficiency and PDA	1 year	7,012 total births (live births and stillbirths (≥ 20 weeks)) excl chromosomal cases. Californian Birth Defects Research (register)	2,218,987 total births (live births and stillbirths) Source not stated
Samanek, et al [86]	1980-1990	Bohemia, Czech Republic, Europe	All CHD subtypes (no ICD codes specified)	Clinical findings, echocardiography, cardiac catheterisation, angiocardiography, MRI	None stated	None stated	5,030 live births Hospital records	816,569 live births Source not stated

Article	Study period	Study region, Country, Continent	CHD definition	Methods of Diagnosis	Exclusions	Age limit for diagnosis	Case population, Source of cases	Denominator population, Source of denominator
Storch and Mannick [81]	1988-1989	Louisiana, USA, North America	ICD 9: specific CHD codes not stated	Echocardiography or cardiac catheterisation, post mortem.	Cases occurring with trisomy 21 (or unbalanced translocation involving chromosome 21), 13 and 18	1 year	319 live births Hospital records	143,896 live births Office of Public Health Vital Records Database of the State of Louisiana
Tagliabue, et al [68]	1999	Lombardy, Italy, Europe	ICD 9 codes used, no specific codes for CHD stated	None stated	None stated	1 year	109 live births Lombardy Birth Defect Registry	12,008 live births Social Security List
Tan, et al [54]	1994-2000	Singapore, Asia	ICD 9 745-747	None stated	PDA <37 weeks gestational age or birth weight <2500g	Any time in study period	2,977 total births (live births, stillbirths, termination, spontaneous abortion) Singapore National Birth Defects Register	329,093 total births (live births and stillbirths) Birth and death registrations
Wilson, et al [82]	1981-1988	Maryland and District of Columbia , USA, North America	ISC coding, no specific codes stated	Echocardiography or cardiac catheterisation, post mortem, surgery	None stated	1year	2,217 isolated live births Subset of the Baltimore Washington Infant study:	619,367 live births Source not stated
Wren, et al [69]	1987-2006	Northern England, UK Europe	Mitchell's definition	Ultrasound, echocardiography, fetal medicine departments, cytogenic	Cardiac arrhythmia, cardiomyopathy, acquired heart disease,	1 year	4,437 live births Northern Congenital Abnormality Survey	676,927 live births Source not stated

Article	Study period	Study region, Country, Continent	CHD definition	Methods of Diagnosis	Exclusions	Age limit for diagnosis	Case population, Source of cases	Denominator population, Source of denominator
				laboratories, regional cardiology centre, pathology, surgery.	bicuspid aortic valve with no stenosis, mitral valve prolapse without regurgitation, dextrocardia, cardiac tumours, PDA associated with prematurity and ASD			
Wu, et al [55]	2000-2006	Taiwan, Asia	ICD 9: specific CHD codes not stated	None stated	Small VSD, PDA, ASD, and mild PVS, if they didn't have a CHD specific admission or ≤3 outpatient clinic visits	None stated	(Frequencies not stated) live births National health insurance database.	Live births (prevalence: 13.08 per 1000) Source not stated
Yang, et al [56]	2007	Beijing, China, Asia	Mitchell's definition	Echocardiography, case records, post mortem	ASDs <5 mm, PFO, arrhythmias, PDA which was patent throughout the first 14 days of life	28 days	686 total births (live births, stillbirths (>20 weeks), termination of pregnancy (>20 weeks)). 556 live births Beijing Congenital Malformations Registry	84,062 total births (live births and stillbirths). 83929 live births Source not stated

PDA=Patent Ductus Arteriosus, ASD= Atrial septal defect, PFO = Patent Foramen Ovale, PVS= Pulmonary valve stenosis, EUROCAT= European Surveillance of CARs, TAPVR= Total anomalous pulmonary venous return, AV= Atrial ventricular, Excl= Excluding, TOPFA= Termination of pregnancy for fetal anomaly

MRI= Magnetic resonance imaging, ECG= electrocardiogram, STS=Society of Thoracic Surgeons

3.3.2 Prevalence

3.3.2.1 Live birth prevalence

Twenty articles reported the live birth prevalence of CHD, which ranged from 22.1 per 10,000 to 130.7 per 10,000 live births (Table 3.3). The prevalence of individual CHD subtypes was reported by 16 studies, with VSD, ASD and PVS having the greatest prevalence in all of the studies (Table 3.4).

Seven articles reported the live birth prevalence of CHD excluding cases with chromosomal/ genetic ECAs (Table 3.3). The live birth prevalence ranged from 34.9 to 70.2 per 10,000 live births.

Seven articles reported the live birth prevalence of isolated CHD, which ranged from 28.8 to 61.6 per 10,000 total births (Table 3.3).

Table 3.3 Prevalence of CHD per 10,000 live births

	Setting/ Study period	Prevalence per 10,000 live births (95% CI)
All cases	Louisiana, USA 1988-1989 [81]	22.1 (19.8-24.7)
	Monchegorsk, Russia, 1973-2006 [74]	25.4 (19.9-32.1)
	Denmark 1977-2006 [67]	37.0 (36.1-37.8)
	Emilia Romagna, Italy,1980-94 [57]	46.9 (44.6-49.3)
	La Reunion, France, 2002-07 [1]	48.1 (43.7-52.9)
	Oulu & Lapland, Finland, 1966 [71]	41.4 (30.7-54.6)
	Londrina, Brazil, 1989-98 [77]	54.9 (49.9-60.2)
	Liverpool, UK, 1960-69 [61]	55.0 (51.5-58.8)
	Bohemiam Czech Republic, 1980-90 [86]	61.6 (59.9-63.3)
	New York, USA, 1992-2006 [58]	63.7 (62.6-64.8)
	Beijing, China, 2007 [56]	66.2 (60.8-71.9)
	N England, 1987-06 [69]	65.5 (63.6-67.4)
	Croatia, 2002-05 [62]	72.1 (68.5-75.9)
	Paris, France, 2005-09 [73]	74.7 (71.7-77.8)
	Liverpool, UK, 1979-88 [63]	75.6 (71.9-79.5)
	Western Australia, 1980-89 [84]	76.5 (73.0-80.1)
	N England, 1985-2003 [60]	79.6 (77.5-81.8)
	Lombardy, Italy, 1999 [68]	90.7 (74.5-109.)
	Tennessee, USA, 1992-93 [75]	97.8 (83.1-114.3)
	Taiwan, 2000-06 [55]	130.7 (129.0-132.5)
Excluding cases with chromosomal ECAs	New Zealand 1978 [85]	34.9 (30.0-40.4)
	Emilia Romagna, Italy, 1980-94 [57]	42.3 (40.1-44.6)
	Londrina, Brazil, 1989-98 [77]	48.5 (43.8-53.6)
	Denmark 1963-1973 [70]	60.9 (59.3-62.6)
	Croatia, 2002-06 [62]	63.2 (59.8-66.7)
	Western Australia, 1980-1989 [84]	70.0 (66.6-73.4)
	Paris, France, 2005-11 [73]	70.2 (67.3-73.2)
Isolated cases	Denmark 1977-2006 [67]	28.8 (28.1-29.6)
	Emilia Romagna 1980-1994 [57]	34.8 (32.8-36.8)
	Maryland & Columbia, USA 1981-1988 [82]	35.7 (34.3-37.3)
	Londrina, Brazil 1989-1998 [77]	41.9 (37.6-46.7)
	Western Australia 1980-1989 [84]	57.2 (54.2-60.4)
	Paris, France 2005-2013 [73]	60.1 (57.5-62.9)
	Croatia 2002-2007 [62]	61.6 (58.3-65.1)

Table 3.4 Prevalence (95% CI) of individual CHD subtypes per 10,000 live births

Subtype & range	Tennessee 1992-93[75]	NY state 1992-06[58]	Taiwan 2000-06 [55]	Croatia 2000-07[62]	Beijung 2007[56]	Lombardy 1999[68]	Hawaii 1986-99[76]	la Reunion 2002-07[1]	N England 1985-03[60]	Liverpool 1960-69[61]	Londrina 1989-98[77]	Liverpool 1979-88[63]	Denmark 1977-05[67]	Bohemia 1980-90[86]	Louisianna 1988-89[81]	Emilia Romagna 1980-94[57]
SV 0.8-1.5			0.8 (0.7-1.0)				0.8 (0.5-1.2)	0.8 (0.3-1.6)		0.9 (0.5-1.5)	1.5 (0.8-2.6)	1.1 (0.7-1.7)		0.8 (0.6-1)	1.5 (0.9-2.2)	
HLH 0-2.3		1.4 (1.2-1.6)	0.6 (0.5-0.8)	1.7 (1.1-2.3)	0 (0-0.4)	0 (0-6.3)	1.4 (1.0-2.0)	1.1 (0.5-2.1)		1.6 (1-2.3)	1.0 (0.4-2)	1.9 (1.4-2.6)		2.1 (1.8-2.4)		1.7 (1.3-2.2)
HRH 0.2-0.6					0.6 (0.1-1.9)			0.2 (0-0.8)								
EA 0.2-0.9		0.5 (0.4-0.6)	0.5 (0.4-0.6)		0.2 (0-0.9)	1.7 (0.9.5)	0.4 (0.2-0.7)	0.9 (0.4-1.8)						0.3 (0.2-0.4)		0.4 (0.2-0.6)
TA 0.3-1.3		0.7 (0.6-0.8)	0.5 (0.4-0.6)		0.6 (0.2-1.4)		1.4 (1.0-1.9)	0.3 (0.1-1)		0.9 (0.5-1.5)	0.9 (0.4-1.8)				1.3 (0.8-2.1)	0.2 (0.1-0.4)
PVA 0.2-1.3					1.0 (0.4-1.9)			0.2 (0-0.8)		0.4 (0.2-0.9)	0.6 (0.2-1.5)	1.7 (1.2-2.3)		1.3 (1.1-1.6)		1.4 (1-1.9)
CAT 0.2-1.0			0.8 (0.7-0.9)		1.0 (0.4-1.9)		0.7 (0.4-1.1)	0.9 (0.4-1.8)		0.6 (0.3-1.1)	0.2 (0-0.9)	0.6 (0.3-1.1)	0.4 (0.3-0.5)	0.7 (0.5-0.9)	0.5 (0.2-1)	0.6 (0.4-0.9)
AVSD 0.8-4.1		0.8 (0.6-0.9)	2.0 (1.8-2.3)	3.1 (2.4-4)	0.8 (0.3-1.7)	5.1 (1.1-14.9)	2.2 (1.7-2.8)	3.6 (2.5-5.1)		1.3 (0.8-2)	4.5 (3.1-6.2)	3.1 (2.4-4)	2.0 (1.8-2.2)	2.5 (2.1-2.8)	3.5 (2.6-4.6)	2.5 (2-3.2)
AVA/S 0.2-4.8		1.3 (1.2-1.5)		2.4 (1.8-3.2)	1.1 (0.5-2.1)		1.2 (0.9-1.8)	0.2 (0-0.8)		2.8 (2-3.8)	2.4 (1.4-3.7)	3.8 (3-4.7)	2.1 (1.9-2.3)	4.8 (4.3-5.3)		0.5 (0.3-0.7)
TGV 0.2-6.3		1.1 (1-1.3)	6.3 (5.9-6.7)	2.4 (1.8-3.2)	0.2 (0-0.9)	6.8 (1.9-17.4)	3.9 (3.2-4.8)	2.5 (1.6-3.8)		2.7 (2-3.7)	1.4 (0.7-2.5)	3.0 (2.3-3.8)	2.6 (2.3-2.8)	3.3 (2.9-3.7)	2.3 (1.6-3.2)	2.4 (1.9-2.9)

Subtype	Tennessee 1992-93[75]	NY state 1992-06[58]	Taiwan 2000-06 [55]	Croatia 2000-07[62]	Beijung 2007[56]	Lombardy 1999[68]	Hawaii 1986-99[76]	la Reunion 2002-07[1]	N England 1985-03[60]	Liverpool 1960-69[61]	Londrina 1989-98[77]	Liverpool 1979-88[63]	Denmark 1977-05[67]	Bohemia 1980-90[86]	Louisiamna 1988-89[81]	Emilia Romagna 1980-94[57]
ToF 1.9-5.5		1.9 (1.7-2.1)	6.3 (5.9-6.7)	2.4 (1.8-3.2)	3.1 (2-4.6)	3.4 (0.4-12.3)	3.9 (3.2-4.8)	2.4 (1.5-3.6)	5.5 (4.9-6.1)	3.2 (2.4-4.2)	4.1 (2.8-5.8)	3.2 (2.5-4.1)		2.1 (1.8-2.4)	3.5 (2.6-4.7)	2.0 (1.5-2.5)
TAPVR 0.3-1.6			1.1 (0.9-1.2)				1.2 (0.8-1.7)	0.3 (0.1-1)		0.7 (0.4-1.3)	0.7 (0.3-1.6)	1.6 (1.1-2.2)		0.5 (0.3-0.7)	1.5 (0.9-2.2)	0.3 (0.1-0.5)
IAA 0.1-0.8					0.1 (0-0.7)		1.4 (1.0-2.0)					0.8 (0.5-1.3)		0.2 (0.1-0.4)		
CoA 1.8-4.4		3.5 (3.2-3.7)	2.5 (2.3-2.8)		1.2 (0.6-2.2)	5.1 (1.1-14.9)	2.5 (1.9-3.1)	1.8 (1-3)	4.7 (4.3-5.3)	3.5 (2.6-4.5)	2.1 (1.2-3.4)	3.5 (2.8-4.4)	1.9 (1.7-2.1)	3.3 (2.9-3.7)		1.8 (1.4-2.3)
DORV 0.4-2.3			1.5 (1.3-1.7)	2.3 (1.7-3)	0.4 (0.1-1.1)									0.8 (0.7-1.1)	1 (0.5-1.6)	0.1 (0-0.2)
MVA 1.5												1.5 (1-2.1)				
VSD 15.6-71.3	50.8 (40.4-63.1)	24.1 (23.4-24.8)	40.1 (39.2-41.1)	25.0 (22.9-27.3)	22.7 (19.6-26.2)	71.3 (51.4-96.4)	41.7 (39.2-44.2)	24.4 (21.3-27.9)	37.9 (36.4-39.4	17.9 (15.9-20.1)	15.6 (13-18.6)	27.4 (25.1-29.7)	8.7 (8.3-9.1)	25.6 (24.5-26.7)		18.5 (17-20)
ASD 2.0-32.3	10.0 (5.7-16.3)	12.9 (12.5-13.4)	32.3 (31.5-33.2)	11.5 (10-13)	7.2 (5.5-9.3)	6.8 (1.9-17.4)	20.6 (18.9-22.4)	8.6 (6.8-10.8)	11.4 (10.7-12.3)	3.2 (2.4-4.2)	4.2 (2.9-5.9)	3.7 (2.9-4.7)	2 (1.8-2.2)	5.3 (4.9-5.9)		2.5 (2-3.1)
PVS 1.9-13.2	13.2 (8.2-20.1)	6.9 (6.5-7.3)		3.6 (2.8-4.5)				1.9 (1.1-3.1)	9.5 (8.8-10.3)	4.2 (3.2-5.3)	5.1 (3.7-6.9)	7 (5.9-8.2)		3.6 (3.2-4)		2.5 (2-3.1)
PDA 0.9-20.1	2.5 (0.7-6.4)	8.8 (8.4-9.2)	20.1 (19.5-20.8)	7.1 (6-8.3)	15.8 (13.3-18.8)					6.5 (5.4-7.9)	3.2 (2.1-4.7)	6.8 (5.7-8)	1.7 (1.5-1.9)	3.1 (2.8-3.5)		0.9 (0.6-1.3)

In Columbia 1981-88 [82] the prevalence of VSD= 11.6 (10.8-12.5) and PVS= 4.3 (3.8-4.9)

3.3.2.2 Total birth prevalence

Twelve articles reported the total birth prevalence of CHD, with the prevalence ranging between 30.1 to 213.4 per 10,000 total births (Table 3.5). Eight articles (10 studies) reported the prevalence for individual CHD subtypes (Table 3.6).

Seven articles of 33 studies reported the total birth prevalence of CHD excluding cases with chromosomal/ genetic ECAs (Table 3.5). The prevalence ranged between 25.0 to 161.4 per 10,000 live births.

Six articles reported the total birth prevalence of isolated cases of CHD. Which ranged between 42.8 and 69.2 per 10,000 (Table 3.5).

Table 3.5 Prevalence of CHD per 10,000 total births

	Setting/ Study period	Prevalence per 10,000 live births (95% CI)
All cases	Monchegorsk 1973-2005 [74]	30.1 (24.1-37.2)
	Iowa, USA, 1963 [78]	39.7 (34.7-45.1)
	La Reunion, France 2002-07 [1]	58.1 (53.2-63.4)
	Liverpool, UK, 1960-69 [64]	66.0 (62.1-70.0)
	Belgium, 2002 [66]	82.8 (77.6-88.3)
	N England, 1985-2003 [60]	85.8 (83.6-88.1)
	Paris, France, 2005-08 [73]	90.2 (87.0-93.3)
	Singapore, 1994-2000 [54]	90.4 (87.2-93.7)
	Beijing, China, 2007 [56]	81.6 (75.6-87.9)
	Canada 1979-93 [79]	135.1 (132.1-138.0)
	Hawaii, USA, 1986-99 [76]	177.0 (172.2-182.0)
	Basque Country, Spain 1999-2008 [72]	213.4 (207.0-220.1)
Excluding cases with chromosomal ECAs	La Reunion, France, 2002-07 [1]	50.8 (46.3-55.8)
	Basque Country, Spain, 1999-2008 [72]	161.6 (156.0-167.3)
	N England, 1985-2003 [60]	75.8 (73.8-78.0)
	N Netherlands 1990-2007 [52]	55.8 (53.4-58.3)
	Norway, 1990-2005 [52]	92.7 (89.8-95.7)
	East Midlands & South Yorkshire, UK [52]	34.3 (32.9-35.8)
	Saxony Anhalt, 1990-2007 [52]	88.4 (84.6-92.2)
	Sicily, Italy, 1991-2004 [52]	56.0 (53.1-59.0)
	Zagreb, Croatia, 1990-2007 [52]	45.2 (41.4-49.4)
	Dublin, Ireland 1990-2007 [52]	44.7 (42.6-46.9)
	Paris, France, 1990-2006 [52]	63.8 (61.8-65.8)
	Emilia Romagna, Italy, 1990-2006 [52]	51.6 (49.6-53.7)
	Hainut, Belgium, 1990-2007 [52]	72.6 (69.1-76.2)
	Tuscany, Italy, 1990-2007 [52]	72.7 (70.2-75.2)

	Setting/ Study period	Prevalence per 10,000 live births (95% CI)
Excluding cases with chromosomal ECAs	Sweden, 1981-92 [53]	25 (24.1-25.8)
	Central Eastern France, 1983-92 [53]	28.9 (27.8-29.9)
	Thames Valley, UK, 1991-2007 [52]	29.0 (26.5-31.6)
	California, USA 1985-92 [53]	31.6 (30.8-32.3)
	Wessex, UK, 1994-2007 [52]	32.6 (30.8-34.5)
	SE Ireland, 1997-2007 [52]	44.3 (39.2-49.8)
	Antwerp, Belgium, 1990-2007 [52]	48.5 (45.8-51.2)
	La Reunion, France, 2002-06 [52]	53.5 (48.3-59.1)
	Barcelona, Spain, 1992-2006 [52]	55.4 (52.2-58.8)
	Miller, et al. 2011 [80]	63.6 (62.2-64.9)
	Ukraine, 2005-2007 [52]	68.0 (62.6-73.8)
	Cork & Kerry, Ireland, 1996-2004 [52]	72.1 (66.1-78.6)
	Paris, France, 2005-08 [73]	77.8 (74.7-80.9)
	Odense, Denmark, 1990-2007 [52]	79.7 (74.3-85.4)
	N England, 2000-07 [52]	86.9 (83.3-90.7)
	Mainz, Germany, 1990-2006 [52]	89.2 (81.8-97.1)
	Styria, Austria, 1990-2005 [52]	92.7 (88.4-97.1)
	Strasbourg, France, 1990-2004 [52]	96.7 (92.3-101.1)
	Wielkopolska, Poland, 1999-2006 [52]	99.6 (96.0-103.4)
	Wales, UK, 1998-2007 [52]	102.1 (98.7-105.7)
	Vaud, Switzerland, 1990-2007 [52]	116.3 (110.7-122.2)
	Malta, 1990-2007 [52]	116.4 (109.1-124.0)
Isolated cases	Metropolitan Atlanta, USA, 1968-2005 [80]	40.6 (39.5-41.7)
	Pleven region, Bulgaria, 1988-06 [65]	42.8 (37.1-49.1)
	Liverpool, UK, 1960-69 [64]	52.2 (48.8-55.9)
	Paris, France, 2005-08 [73]	64.1 (61.3-66.9)
	N England, 1985-2003 [60]	65.8 (63.9-67.8)
	Sweden, 1992-2001 [59]	69.2 (67.4-71.1)

Table 3.6 Prevalence of individual CHD subtypes per 10,000 total births

Subtype and range	La Reunion 2002-2007[1]	N England 1985-2003[60]	Hawaii 1986-99[76]	Canada 1979-93[79]	Liverpool 1960-69[64]	Belgium 2002[66]	Beijing 2007[56]	California 1985-92[53]	France 1983-92[53]	Sweden 1981-92[53]
SV 0.6-2.6	2.0 (1.2-3.2)		0.8 (0.5-1.2)	2.6 (2.2-3)		0.8 (0.4-1.5)	1.9 (1.1-3.1)	0.7 (0.6-0.8)	0.6 (0.4-0.8)	0.7 (0.6-0.9)
HLH 0.5-3.0	3.0 (1.9-4.3)		1.7 (1.3-2.2)	5.0 (4.4-5.6)		0.9 (0.4-1.7)	0.5 (0.1-1.2)	2.3 (2.1-2.5)	2.4 (2.1-2.7)	2.0 (1.8-2.3)
HRH 0.3	0.3 (0.1-1)									
EA 0.2-1.1	1.1 (0.5-2.1)		0.4 (0.2-0.7)			0.3 (0.1-0.8)	0.2 (0-0.9)	0.5 (0.4-0.6)	0.2 (0.1-0.3)	0.3 (0.2-0.4)
TA 0.4-0.7	0.7 (0.3-1.5)		0.7 (0.5-1.1)			0.6 (0.3-1.3)	0.6 (0.2-1.4)	0.7 (0.6-0.8)	0.7 (0.5-0.9)	0.5 (0.4-0.6)
PVA 0.3-1.1	0.3 (0.1-1)				1.0 (0.6-1.7)	1.1 (0.6-1.9)	1.0 (0.4-1.9)	0.8 (0.7-1)	0.8 (0.6-1)	0.3 (0.2-0.4)
CAT 0.4-2.8	2.5 (1.6-3.8)			2.4 (2-2.8)	0.5 (0.3-1)		1.3 (0.7-2.3)	0.6 (0.5-0.8)	0.4 (0.3-0.6)	0.8 (0.6-1)
AVSD 0.9-6.2	6.2 (4.7-8.1)		2.2 (1.7-2.8)	6.2 (5.6-6.8)	0.9 (0.5-1.5)	3.3 (2.3-4.6)	3.6 (2.4-5.1)	2.6 (2.4-2.9)	2.6 (2.3-3)	3.1 (2.8-3.4)
AVA/S 0.3-3.2	0.3 (0.1-1)		1.2 (0.8-1.7)		3.2 (2.4-4.2)	3.2 (2.3-4.5)	1.2 (0.6-2.2)	1.2 (1.1-1.4)	0.6 (0.5-0.8)	1.2 (1-1.4)
TGV 2.0-8.3	3.7 (2.6-5.3)		3.9 (3.2-4.7)	8.3 (7.6-9.1)	3.6 (2.7-4.6)	2.6 (1.7-3.7)	3.8 (2.6-5.4)	2.8 (2.6-3)	3.3 (2.9-3.6)	3.1 (2.8-3.5)
ToF 2.6-6.5	2.7 (1.7-4.1)	6.5 (5.9-7.1)	3.8 (3.1-4.6)	6.8 (6.2-7.5)	2.6 (1.8-3.5)	4.7 (3.5-6.1)	5.2 (3.8-7.03)	3.4 (3.2-3.7)	2.9 (2.5-3.2)	2.6 (2.4-2.9)

Subtype and range	La Reunion 2002-2007[1]	N England 1985-2003[60]	Hawaii 1986-99[76]	Canada 1979-93[79]	Liverpool 1960-69[64]	Belgium 2002[66]	Beijing 2007[56]	California 1985-92[53]	France 1983-92[53]	Sweden 1981-92[53]
TAPVR **0.2-1.1**	0.5 (0.1-1.2)		1.1 (0.8-1.6)		1.0 (0.6-1.6)			1.1 (0.9-1.2)	0.9 (0.7-1.1)	0.6 (0.4-0.7)
IAA **0.4-0.8**			0.4 (0.2-0.7)				0.4 (0.1-1)	0.7 (0.6-0.8)	0.8 (0.7-1)	0.5 (0.4-0.6)
CoA **1.3-4.9**	1.9 (1.1-3.1)	4.9 (4.4-5.5)	2.4 (1.8-3)		3.3 (2.5-4.3)	4.1 (3-5.5)	1.4 (0.7-2.5)	1.3 (1.2-1.5)	1.5 (1.2-1.7)	1.7 (1.4-1.9)
DORV **0.2-1.8**						1.2 (0.6-2)	1.8 (1-2.9)	0.9 (0.7-1)	0.6 (0.5-0.8)	0.8 (0.7-1)
MVA **1.6**						1.6 (1-2.6)				
VSD **6.6-53.9**	25.8 (22.5-29.4)	39.8 (38.3-41.3)	4.7 (3.9-5.5)	53.9 (52.1-55.8)	19.9 (17.8-22.1)	27.2 (24.3-30.5)	24.7 (21.5-28.3)	6.6 (6.3-6.9)	8.8 (8.2-9.4)	4.1 (3.8-4.5)
ASD **0.1-35.1**	9.7 (7.7-11.9)	11.7 (10.9-12.5)	19.7 (18.1-21.4)	35.1 (33.6-36.6)	4.2 (3.3-5.3)	0.1 (0-0.5)	7.1 (5.4-9.2)	4.3 (4-4.5)	7.0 (6.5-7.5)	1.5 (1.3-1.7)
PVS **0.8-9.7**	1.9 (1.1-3.1)	9.7 (8.9-10.4)			5.1 (4-6.3)		6.5 (4.9-8.5)	1.7 (1.5-1.9)	1.1 0.9-1.3)	0.8 (0.6-1)
PDA **6.5-44.2**				44.2 (42.6-46)	6.5 (5.3-7.8)		15.7 (13.1-18.6)			

3.3.3 Trends in prevalence

Six studies examined trends in CHD live birth prevalence [55, 57, 60, 62, 70, 82]. Wu et al reported a decrease in the live birth prevalence of CHD over time in Taiwan (2000-06). This decrease was apparent for cases of ToF, HLH, AVSD, AVA/S, VSD and ASD, but no other subtypes [55]. However, there was no maximum age of inclusion, suggesting that there was lower case ascertainment in the tail end of the study period. Additionally, decreases in live birth prevalence may be related to increases in TOPFA rates. Dilber et al and Wilson et al reported no evidence of trends in the live birth prevalence of CHD in Croatia (2002-07; 205,051 live births) and Colombia (1981-88; 619,367 live births) [62, 82]. Dilber et al reported an increasing trend in the live birth prevalence of CoA, but suggested this was due to the "continuous improvement of early diagnosis" [62]. Three studies reported increasing trends in the live birth prevalence of CHD [57, 60, 70]. Dadvand et al reported an increase between 1985-2003 in the North of England (659,2344 live births); Calzolari et al reported an increasing trend between 1980-94 in Italy (330,017 live births) and Laursen et al reported an increase between 1963-1973 in Denmark (860,492 live births) [57, 60, 70]. Calzolari et al reported that the increasing trend was restricted to cases of VSD and ASD between 1980-94 in Italy (330,017 live births). Dadvand et al similarly reported that the trends were restricted to cases of VSD, ASD, ToF and AVSD in England between 1985-2003 (665,377 total births). Therefore, it is likely that the trends were mostly related to improvements in ascertain of septal defects over the study period.

Nine studies analysed trends in the total birth prevalence of CHD [52, 53, 60, 64, 72, 74, 76, 79, 80]. Three studies reported no evidence of trends in prevalence rates in Russia (1973-88; 28,511 total births), in Italy (1999-2008; 191,171 total births) and in the UK (1960-69; 163,692 total births), although these were smaller, shorter studies with lower statistical power [64, 72, 74]. Miller et al reported an increasing trend in the total birth prevalence of CHD in the USA (1968-2005; 1,301,143 total births), Johnson et al reported an increasing trend in Canada (1979-93; 593,042 total births), Dadvand et al reported an increasing trend in the North of England (1985-2003; 665,377 total births) and Khoshnood et al reported an increase in Europe until 2000 (7,299,116 total births), and a decrease thereafter [52, 60, 79, 80]. Dadvand et al, Miller et al and Khoshnood et al did not examine trends in individual CHD subtypes [52, 60, 80], but Khoshnood et al did report that their increasing trend was observed amongst moderate (PVA, CAT, AVSD, AVA/S, TGV, ToF, TGV and TAPVR) and mild (VSD, PVS) severity CHD, but not amongst severe CHD (SV, HLH, HRH, EA and TA).

Johnson et al reported increasing trends in the prevalence of ToF, VSD, ASD, PDA, other (unspecified) CHD and HLH, a decreasing trend in AVSD, and no trends in the other CHD subtypes [79]. In Hawaii between 1986-99 (282,900 total births), Forrester et al reported an increasing trend in the total birth prevalence of TGV and EA, a decreasing trend in the prevalence of ToF and no evidence of trends in any other subtypes [76]. In France, California and Sweden, Pradat el al reported an increasing trend in the total birth prevalence of ASD, VSD, ToF and AVSD between 1983-92 (4,438,598 total births).

Increasing trends may be real and perhaps related to the increase in older mothers that has been seen in Europe [88]. Or, as a result of the increasing obese population [89], which is a risk factor for certain CHD subtypes [4]. However, the trends could merely reflect improved ascertainment as data sources have become more established over the study periods. Increasing trends might also reflect improvement in CHD diagnosis due to the development of fetal echocardiography, more accurate ultrasonography and improved prenatal screening programmes [90, 91]. Technological improvements in pulse oximetry and colour Doppler echocardiography may also have increased postnatal diagnosis, although these are not routinely offered to low risk babies [92, 93].

Khoshnood et al suggest that their decreasing trend between 2004-2007 corresponds to increased uptake of folic acid, which has been shown to reduce the risk of a pregnancy associated with a CHD [94, 95]. However, the decreasing trend at the tail end of the study is more likely due to under-ascertainment given that cases born between 2004-2007 had a smaller window for diagnosis.

3.3.4 Heterogeneity in prevalence between studies

As shown in Table 3.7, there was significant heterogeneity in live and total birth prevalence between registers. This heterogenity between studies can be attributed to a number of factors, including: study period, study location, study design and case ascertainment.

Table 3.7 Heterogeneity in prevalence between studies

Case inclusion	Live/total births	Cochrane's Q test and Chi^2 test for heterogeneity
Isolated CHD	Live birth	I^2=99.4%, p<0.001
	Total birth	I^2=96.7%, p<0.001
Isolated CHD and CHD with structural ECAs	Live birth	I^2=99.0%, p<0.001
	Total birth	I^2=99.8%, p<0.001
Isolated CHD with chromosomal/genetic ECAs	Live birth	I^2=99.7%, p<0.001
	Total birth	I^2=99.7%, p<0.001

3.3.4.1 CHD definition

Prevalence rates for each study are dependent on the definition of CHD applied. The studies using the EUROCAT, the ISC and Mitchell's definition had similar inclusion and exclusion criteria. All three criteria excluded anomalies of the circulatory system and minor functionless anomalies. The adapted version of Mitchell's definition includes some minor CHDs (e.g. heart block) that EUROCAT, ISC and Mitchell's full definition would exclude. Therefore, studies using this criterion may have a higher CHD prevalence. Dilber et al and Miller et al defined CHD as ICD 10: Q20-28, which includes anomalies of the peripheral vascular system and the circulatory system as well as cardiovascular anomalies. Circulatory system anomalies are rare and so the impact on prevalence would have been low [62].

3.3.4.2 Study period

Variation in study period may have caused variation in prevalence between articles. While there was no obvious pattern in prevalence with increasingly recent study periods, articles could not be accurately ranked by study period as the years spanned varied between articles. Nevertheless, the more recent articles may have reported greater prevalence rates due to increases over time in the proportion of pregnant women who are obese, have diabetes and who enter pregnancy at advanced maternal age, which are suggested risk factors for certain CHD subtypes [4, 5, 80]. Alternatively, increases in prevalence over time might be related to case ascertainment given that improvements have been made in prenatal diagnosis over time (see section 1.3.3).

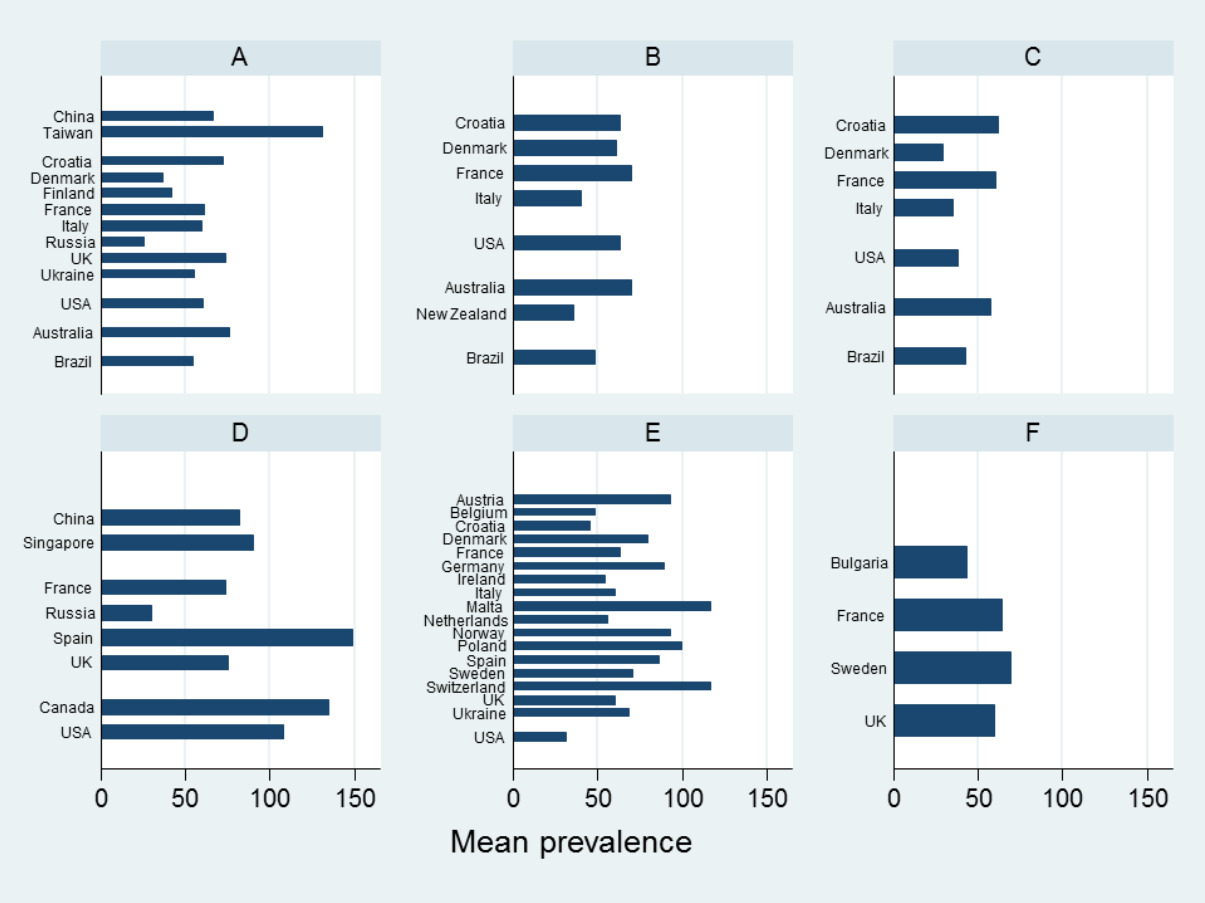
3.3.4.3 Study location

It is possible that geographical location is a source of heterogeneity in prevalence. Figure 3.2 shows that average prevalence varies substantially according to the country the study was performed in. Geographical differences in prevalence could be "real" and related to variation in exposures between countries (such as maternal smoking, maternal age or ethnicity, which may be risk factors for CHD [4, 96, 97] but may also be related to geographical variation in ascetainment perhaps due to differences in health care systems and policies.

TOPFA rates reportedly vary by country, perhaps due to cultural beliefs, difference in TOPFA laws (such as different maximum gestational age at TOPFA) or disparities in prenatal diagnosis rates [98]. This may have contributed to the variation in live birth prevalence between studies. However, even in Brazil where TOPFA is illegal, the live birth prevalence was low compared to the average prevalence of the other countries (Figure 3.2).

Even studies based on data from the same country showed substantial variation in prevalence. This suggests that although some heterogeneity may be attributed to study location, variation is most likely caused by differences between studies caused by other factors, such as case ascertainment, CHD definition and inclusion criteria.

Figure 3.2: Prevalence of CHD per 10,000 live and total births, by country



A= live births, all cases, B= live births, excluding cases with chromosomal/ genetic ECAs, C= live births, isolated cases, D= total births, all cases, E= total births, excluding cases with chromosomal/ genetic ECAs, F= total births, isolated cases.

3.3.4.4 Ascertainment of VSDs

Isolated VSDs are rarely diagnosed prenatally (<1%) and up to 83% are undiagnosed before hospital discharge with 35% still undiagnosed within three months [99]. Indeed, smaller VSDs are often symptomless and can close spontaneously [100]. Given that VSDs are the most common CHD subtype, the prevalence of CHD in each study is likely to be highly influenced by the ascertainment of VSDs.

The proportion of CHD cases that were VSD varied by study, ranging between 11-64%. Articles with a lower proportion of VSDs tended to have earlier study periods [63, 78, 85] and articles with a high proportion of VSDs (>45%) tended to have more recent study periods and the data source was more commonly a CAR [1, 60, 68, 73]. Studies with a higher maximum age at diagnosis also reported a greater proportion of VSD cases [60, 75]. Potentially, under-ascertainment of other difficult to diagnose subtypes (e.g. ASD and PVS) may also be driving some of the heterogeneity.

3.3.4.5 Maximum age at diagnosis

Maximum age at diagnosis may influence ascertainment and therefore cause heterogeneity. The study with the lowest cut-off (five days) yielded the second lowest live birth prevalence [57]. A Chinese study that also used a short cut-off (28 days) reported prevalence only just below average, but compared to the other Asian studies, the prevalence was lower [56]. This suggestion of lower ascertainment complies with existing evidence that just 54% of babies diagnosed with CHD in their first year are diagnosed by six weeks, and 69% are diagnosed by 12 weeks [101]. Studies with higher cut-offs on the other hand, yielded prevalence not too dissimilar to those using a one year cut-off [58, 60, 61, 64, 66, 70, 84, 102, 103]. Approximately 82-97% of CHD cases are diagnosed by age one, so this is not surprising [104].

3.3.4.6 Study design

Koshnood et al reported significant heterogeniety in prevalence between 29 EUROCAT registers [52]. While each EUROCAT register abides by the same inclusion and exclusion criteria, as well as the same coding system, heterogenity still may be caused by variation in ascertainment. For example, some registers have been longer established and are therefore more practiced at ascertaining cases. Other registers may have better links with cardiology departments, which

influences ascertainment. It is possible however, that there is real variation between the regions under surveillance, due to difference in study populations or exposures.

3.3.5 Risk factors and characteristics

3.3.5.1 Associated anomalies

According to eight studies, 9-14% of all cases occurred with chromosomal anomalies, the majority of which were Trisomy 21 (41-89%) [1, 57, 60, 62, 73, 77, 84, 103]. Trisomy 18 and 13 were the second and third most commonly reported chromosomal anomalies, accounting for 4-15% and 4-6% of chromosomal cases, respectively [57, 60, 77, 84]. A further 2-17% of all cases occurred with (non-chromosomal) structural anomalies, according to five studies [57, 60, 62, 73, 77, 84]. Calzolari et al reported that genital/urinary system (combined) and musculoskeletal anomalies were the most commonly associated with CHD, accounting for 23% and 25% of structural anomalies, respectively [57]. However, the types of associated anomalies were dependent on the CHD subtype, for example CNS anomalies were more common in cases of AVSD [57]. Between 71-85% of CHD cases occurred in isolation [57, 60, 62, 73, 77, 84].

Variation in the proportion of associated anomalies may be related to maternal age distributions, which impact the prevalence of congenital anomalies [105]. Additionally, studies that did not use congenital anomaly registers (CARs) as their data source may have under-ascertained co-occurring congenital anomalies, if the main focus was to collect data on CHDs. The classification of multiple CHDs also varied between studies, with some studies excluding these cases, some counting each CHD as opposed to each case and some articles classing them as a specific isolated CHD (with the subtype being dependent on the chosen hierarchy). There was also variation between studies in the anomalies classed as minor congenital anomalies for exclusion.

3.3.5.2 Maternal age

The association between CHD and maternal age was examined in eight articles (nine studies). Pradat et al (USA), Miller et al and Hay, described an increased risk of CHD with ‘advanced’ maternal age (defined by all three articles as ≥35) [53, 78, 80]. Pradat et al (USA), Miller et al and Hay reported that women of advanced maternal age were at 10, 20 and 30% increased risk of a pregnancy associated with any CHD, respectively [53, 78, 80]. Hay’s higher relative risk (RR) likely resulted from the inclusion of cases with chromosomal ECAs, due to the known association between genetic disorders and advanced maternal age [78]. Furthermore, Hay reported the crude

risk whereas Pradat et al (USA) stratified by register, race, year of delivery and parity and Miller et al adjusted for sex, year of birth and ethnicity, which are likely to have reduced the effect size [53, 78, 80].

Miller et al reported that women of advanced maternal age were at significant increased risk of a child with (non-chromosomal) TGV, CoA, VSD and ASD [80]. Pradat et al reported an increased risk of a child with "less severe" CHD (VSD, ASD, corrected TGV, CoA, AVA/S and PVS) but no significant association amongst non-chromosomal cases of severe CHD (HLH, SV, TA, CAT, IAA. PVA, TGV, DORV, AVSD, TAPVR, ToF, EA) [53]. Forrester and Merz reported that the association with advanced maternal age varied by CHD subtype, with increased risks of 25%, 29%, 196%, 221% and 392% for non-chromosomal VSD, ASD, AVSD, HLH and IAA, but for no other CHD subtypes. Miller et al compared the risk of CHD in women of advanced maternal age to women aged 25-29. Pradat et al (USA), Hay and Forrester and Merz controversially used mothers aged <35 as their reference category, meaning the effect could be diluted or biased.

Importantly, none of the risks were adjusted for maternal obesity, which is a risk factor for certain CHD subtypes and is therefore a potential confounder given the correlation between obesity and age [4]. Similarly, none of the studies adjusted for maternal diabetes, which may also have been a confounder since diabetes becomes more prevalent with increasing age [106].

Kenna et al, Cedergren and Kallen, Pradat et al (Sweden) and Posteov et al reported no association between CHD and advanced maternal age [53, 59, 64]. However, Cedergren and Kallen reported a similar distribution of maternal age in case mothers compared to all delivered women, but did not actually calculate RRs [59]. My own calculation of the (unadjusted) RR actually showed a significant 10% increase in the risk of non-chromosomal CHD in women aged ≥35 compared to women aged 25-29. This estimate was slightly lower than Miller et al's, which could perhaps be explained by a different distribution of CHD subtypes [80]. Kenna et al performed the maternal age analysis in a nested case-control study which perhaps led to a lower power to detect an association [64]. Posteov et al did not identify an association but merely compared mean maternal age in cases versus non cases using a t-test [74]. In using a t-test, Posteov et al made the assumption that maternal age was normally distributed, which is not likely to have been the case.

Cedergren and Kallen, Pradet et al, Miller et al and Hay also investigated the association with 'young' maternal age (defined as <20), but none reported significant associations [53, 59, 64, 80].

3.3.5.3 Ethnicity

Four studies examined the association between CHD prevalence and ethnicity. Miller et al reported an 11% significant increased risk of non-chromosomal CHD (amongst total births) in White compared to non-Whites in the USA. Also in the USA, Wilson et al described a 4% increased risk of isolated CHD (amongst live births) in non-Whites compared to Whites, but this did not reach statistical significance. Neither study examined CHD subtypes separately, which may have different associations with ethnicity. For example, previous research from the USA suggests Whites are at increased risk of EA, AVA/S, PVA and AVSD, compared to Blacks, but at decreased risk of PVS [107]. Compared to Whites, Forrester and Merz reported significant increased risks of ToF (amongst total births) in Pacific Islanders and Filipinos, ASD in Pacific Islanders and Filipinos, PVS in Far East Asians, TA in Pacific Islanders, EA in Pacific Islanders, CoA in Far East Asians and Pacific Islanders and TAPVR in Far East Asians, Pacific Islanders and Filipinos. Bower and Ramsay found a 30% significant increased risks of CHD in Aboriginals compared to non-Aboriginals in Australia [80, 84, 96]. All of the studies reported only the crude risk of CHD associated with ethnicity, without adjustment for potential confounders. Potentially, ethnicity may be confounded by socioeconomic status, smoking status, BMI and maternal age, amongst other factors, which are all potential risk factors for CHD [4, 80, 96, 108, 109].

3.3.5.4 Sex distribution

Considering all subtypes of CHD, there was little evidence of a male or female predominance. The proportions of cases in males ranged from 46% to 54% in 18 articles [68, 78, 110, 111]. However, Tennant et al's recent meta-analysis of five population-based studies identified a significant 70% increased risk of CHD in males compared to females [112]. Both Tennant et al and Pradat et al reported that the association with sex varied according to CHD subtype. Tennant et al reported significant increased risks of TGV, HLH, AVA/S, and CoA in males compared to females and a significant decreased risk of AVSs in males compared to females [112]. Pradat et al (USA) reported an increased risk of HLH, PVA, TAPVR, CoA and AVA/S and a decreased risk of AVSD in males compared to females [53]. Bourdial et al also found that the proportion of male cases also decreased with decreasing CHD severity [1].

3.3.5.5 Preterm deliveries

Cederegren and Kallen, and Miller et al reported that 11 and 18% of CHD cases were delivered preterm (<37 weeks), respectively [59, 80]. Variation in rates could be related to the proportion

of induced as opposed to spontaneous preterm births, which may vary by country. With a more pronounced risk of preterm CHD in women of advanced maternal age, the maternal age distributions of the studies may also have impacted on the rates [80]. Cederegren and Kallen uniquely compared the proportion of preterm deliveries in case to the proportion in the general population, identifying a significant increased risk of preterm delivery (RR=2.58), after adjusting for maternal age, parity, smoking, year of delivery and BMI [59]. The risk was slightly lower in isolated cases (RR=2.15) and cases of mild CHD (RR=2.27), and greater in cases of severe CHD (RR=2.58). Cedergren and Kallen's study was also the only one to investigate the risk of post-term delivery (>42 weeks), finding no significant association with CHD. Both articles delivery limited bias by excluding cases from multiple pregnancies, which are more likely to be delivered preterm [113, 114].

3.3.5.6 Birth weight

After adjusting for maternal age, parity, maternal smoking, year of birth and maternal BMI, Cedergren and Kallen reported a significant 96% significant increased risk of small for gestational age (SGA) in children with CHD compared to the general population [59]. Excluding cases with structural ECAs, the risk decreased, but remained significant (RR=1.61). The effect size was greater in severe compared to mild severity CHD (RR=2.46 vs RR=1.47) [59]. No other studies examined SGA but Bower and Ramsay and Kenna et al both report an increased risk of low birth weight (<2500g) in CHD cases [64, 84]. Although these results are somewhat biased by the lack of adjustment for gestational age (among other confounders), the effect sizes are broadly similar and Bower and Ramsay still describe a pattern similar to that of Cedergren and Kallen's in terms of isolated cases having a lower risk [84]. While Cedergren and Kallen describe an increased risk of large for gestation age (LGA) in cases of CHD, Bower and Ramsay did not find an association with higher birth weight [59, 84]. Cedergren and Kallen also showed that when considering severe and mild severity CHD, the effect was confined to those with mild CHD (VSD, ASD, CoA, PVS, corrected TGV, PDA, "other" CHD) [59].

3.3.5.7 Diagnosis

Evidence from four studies showed that prenatal detection of CHD is challenging, with Calzolari et al reporting a detection rate of 5.5%, Yang et al a rate of 22%, Khoshnood et al a rate of 23% and Bourdial et al 33% [1, 56, 57, 73]. However, the studies by Calzolari et al and Yang et al included cases diagnosed in the first 28 and five days of life respectively, meaning they may be

unrealistically high, if postnatally diagnosed cases are under-ascertained [56, 57]. The higher prenatal detection rates described by Yang et al, Bourdial et al and Khoshnood et al may also be attributed to their more recent study periods, with the study populations likely to have had access to more developed fetal diagnostic tools, including fetal echocardiography. Additionally, prenatal diagnosis will be strongly influenced by the frequency of different CHD subtypes. The study by Calzolari et al, for example, had a slightly higher prevalence of VSDs than the study by Yang et al, which may partly explain why their prenatal diagnosis rate was slightly lower.

3.4 Discussion

3.4.1 Summary

In this review of international population-based studies of CHD, the prevalence of CHD ranged between 30-213 cases per 10,000 total births and 22-131 cases per 10,000 live births. There was substantial heterogeneity in prevalence between studies, which may have arisen due to variation in: case definition, case ascertainment, study period, study location and study design.

There were conflicting reports regarding trends in prevalence over time. The larger studies with longer study periods tended to report increasing trends in the prevalence of CHD over time [53, 57, 60, 79, 80]. However, these trends were often driven by increases in the prevalence of septal defects, which have become easier to diagnose and therefore ascertain over time. Several studies reported increasing trends in the prevalence of ToF [53, 60, 79], although one smaller study reported a decreasing trend [76]. There was conflicting evidence on the direction of the trends in AVSD [53, 55, 60, 79, 115] and HLH [55, 79].

Several potential risk factors for CHD were identified including: advanced maternal age [53, 59, 76, 78, 80], White ethnicity [80, 82] and maternal obesity [59]. Compared to the general population, children with CHD were more likely to: have chromosomal anomalies (particularly trisomy 21) [1, 57, 60, 62, 73, 77, 84, 103], be delivered preterm [59, 80] and to be SGA (with a stronger effect size in cases with severe CHD or structural ECAs) [59]. There was also some evidence that post-term delivery was more common in children with CHD compared to the general population [59]. Prenatal detection was shown to be challenging, although appeared to improve over time [1, 56, 57, 73].

3.4.2 Strengths

This review has a number of strengths. Firstly, in order to increase the sensitivity of the search strategy, and thus the number of citations retrieved, three large literature databases were interrogated using a systematic search using keywords and MESH headings. Key journals and reference lists were also searched in order to be as inclusive as possible.

Articles that reported total or live birth prevalence rates were included so that no relevant studies were excluded. Studies that reported the prevalence of isolated CHD or the prevalence of CHD in

the presence of ECAs were analysed separately in order to eliminate this as a source of heterogeneity.

Bias caused by referral was limited by the inclusion of population-based studies only. Hospital-based studies for example, may under-ascertain mild cases that do not require medical or surgical intervention.

Many sources of heterogeneity were examined in order to better distinguish between real differences in prevalence and artificial variation caused by differences in ascertainment. However, with the sample sizes of all studies being large, and therefore the standard errors being relatively small, heterogeneity between studies was inevitable.

Lastly, prevalence estimates were extracted for individual CHD subtypes. In previous systematic reviews of CHD prevalence, only the prevalence of the most common subtypes have been reported [18, 19]. This is problematic from a public health perspective as the rarer subtypes, such as those with HLH or SV, are those that require more complex medical interventions which need to be planned for [116, 117].

3.4.3 Limitations

This review has a number of limitations. While the aim was to be geographically inclusive, few studies reported the prevalence of CHD in less developed countries. European and North American studies dominated the literature and only a few studies from Asia, South America and Oceania were identified. The restriction to articles published in the English language did not contributed to this disparity as I did not identify any articles that were not written in the English language.

The majority of the included articles were comprised of cases diagnosed within the first year of life. CHD subtypes, such as VSD, ASD and PVS, are not always diagnosed infancy [104]. Therefore, the prevalence of CHD may actually be greater than reported. Arguably cases that are not diagnosed during infancy are less functionally significant and from a clinical perspective, should not be included in prevalence estimates.

While I extracted the prevalence of individual CHD subtypes from each study, I restricted my search strategy to studies that reported the prevalence of all CHD subtypes combined. Expanding

the search strategy to include studies of single subtypes would have been more informative, but too time consuming.

Because the primary aim of the review was to establish the international prevalence of CHD, only population-based studies that reported prevalence were included. Therefore, the review of specific risk factors is not inclusive of all relevant published papers regarding risk factors. For example, studies of case-control design were excluded.

3.4.4 Comparison to previous reviews

The range of live birth prevalence rates in my review (22-137 per 10,000 live births) encompasses the pooled prevalence estimate reported in Van der Linde et al's (2011) recent systematic review (68 per 10,000 live births [19]). In Bernier et al's (2010) systematic review, a pooled live birth prevalence is not reported, but most of their studies report a prevalence between 50-70 per 10,000 live births [18]. Neither Van der Linde et al or Bernier et al appear to separate the prevalence of isolated or non-chromosomal CHD, which is important as these cases tend to have different aetiologies and epidemiology. Both reviews include all study designs, including hospital-based studies, which may conversely raise the prevalence.

Chapter 4. Data sources and case classification

In this chapter, the data sources and CHD classification used in chapters 5, 6, 8 and 9 will be described. The study design and statistical analyses are described in the respective chapters.

4.1 Data sources

Data from at least one British Isles Network of Congenital Anomaly Register (BINOCAR) was used in each analysis chapter. In several of the chapters this data was linked to another data source, including: ONS yearly births, the Northern Survey of Twins and Multiple Pregnancy (NorSTAMP), the Northern Perinatal Mortality Survey (PMS) and ONS death registrations. Each of these data sources is described in detail below.

4.1.1 British Isles Network of Congenital Anomaly Registers

The BINOCAR is a collaborative network of regional population-based CARs. Each register prospectively collects data on congenital anomalies occurring in the pregnancies of women residing in their specific region, which is geographically well-defined. Data are recorded on cases occurring in late miscarriages (20-23 weeks gestation), TOPFAs (any gestation), stillbirths (≥24 weeks gestation) or live births.

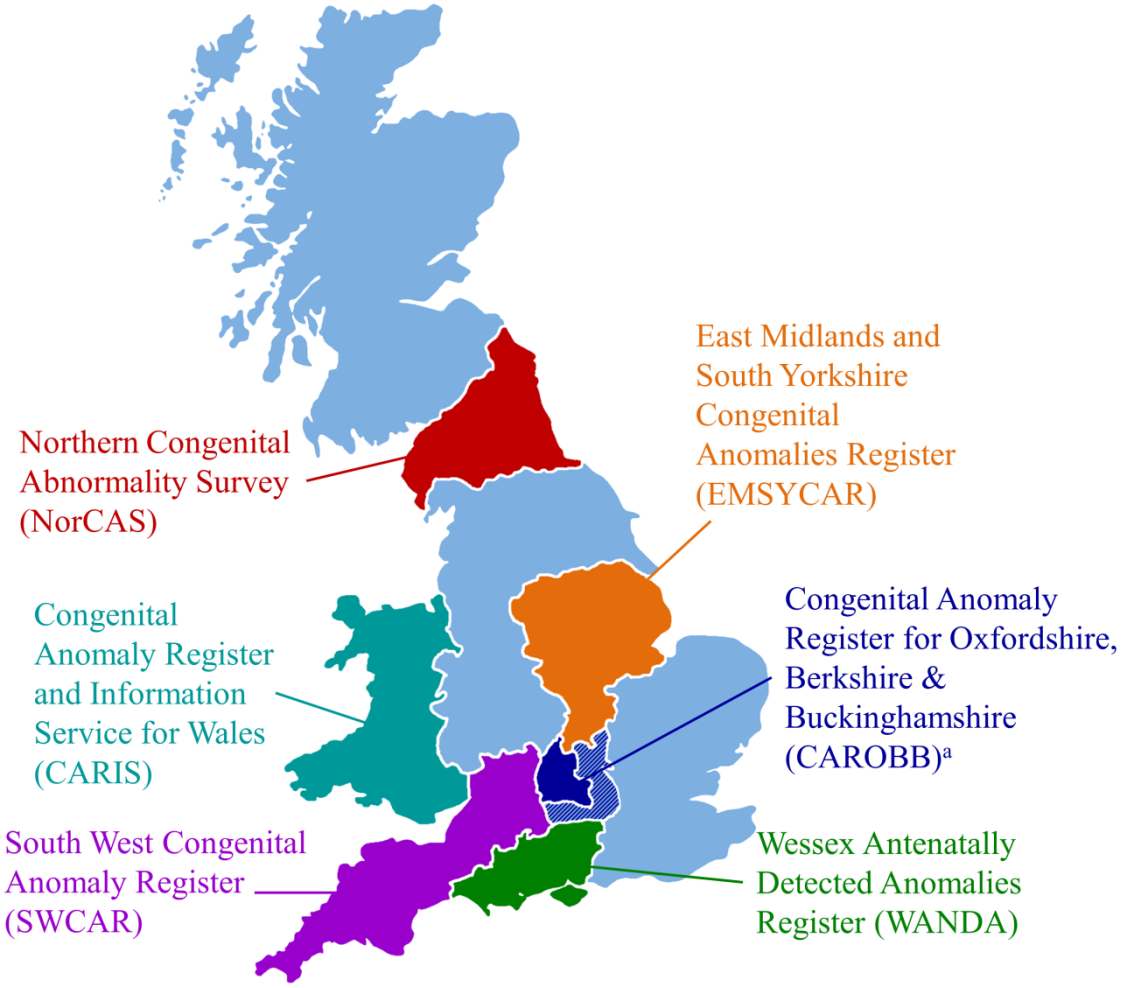
The BINOCAR consists of six full member registers in England and Wales, covering 36% of the birth population in 2014 (Figure 4.1). The Northern Congenital Abnormality Survey (NorCAS), established in 1985, covers the North East of England and North Cumbria; the Wessex Antenatally Detected Anomalies Register (WANDA), established in 1994, covers Wessex (England); the East Midlands and South Yorkshire CAR (EMSYCAR), established in 1997, covers the East Midlands and South Yorkshire; the CAR for Oxford, Berkshire and Buckinghamshire (CAROBB), established in 1991, covered Oxford between 1991-2004 and Oxford, Berkshire and Buckinghamshire from 2005 onwards; the South West CAR (SWCAR), established in 2002, covers South West England; and the CAR and Information Service (CARIS), established in 1998, covers the whole of Wales.

Each BINOCAR allows between six and eight congenital anomalies to be recorded for each case and both prenatal and postnatal diagnoses are recorded (where applicable). Each anomaly is coded using the WHO ICD, consistent with EUROCAT guidelines [118]. The registers originally coded cases using ICD version nine, but began using version ten in the late 1990s.

The change-over was gradual and each register adopted the new coding system at different time points. All cases are now coded according to ICD version 10, with the congenital anomalies originally coded using ICD nine having been translated to ICD 10. To ensure high case ascertainment, congenital anomalies are notified to each register from a variety of sources including prenatal ultrasound departments, fetal medicine records, cytogenetic laboratories, regional cardiology centres, pathology departments and paediatric surgery departments. CHD diagnoses are confirmed by surgery, echocardiography, CT or MRI scans, cardiac catheterisation, or post mortem. For each case, data is recorded on: year of delivery, maternal age at delivery, pregnancy outcome, prenatal diagnosis, sex, birth weight and gestational age at delivery.

Members of the BINOCAR have approval from the National Information Governance Board, subsequently the Confidentiality Advisory Group of the Health Research Authority (PIAG 2-08(e)/2002), to hold data without consent and ethics committee approval (09/H0405/48) to undertake studies involving their data.

Figure 4.1 Map showing the regions covered by the six BINOCARs



[a] CAROBB covered Oxford only (dark blue area) only between 1991- 2005

Map taken from www.BINOCAR.org and subsequently modified

Table 4.1 shows population statistics relating to the populations covered by each register, using data from the ONS, the Census, the General Household Survey (GHS), the General lifestyle survey (GLS) and the English Indices of Deprivation. Smoking data was taken from the GHS, which is completed by a random sample of households in the UK (7,960 in 2010, with a 72% response rate). Given that sampling bias may occur, care should be taken when interpreting these statistics. Calculated from post-codes, the indices of multiple deprivation (IMD) are a comparative measure of area-level socioeconomic deprivation. They are calculated based on seven domains including: income, employment, health, education, access to services, social environment, housing stress, living environment and crime [119, 120]. The IMD data does not correspond completely to the areas covered by the registers and thus should be used as a rough estimation of deprivation.

EMSYCAR and SWCAR cover the largest populations (74,000 and 60,000 births per year, on average). The other four registers cover populations of between 31-35,000 births per year, on average.

Maternal age distribution also varies by region. According to ONS data, the highest proportions of teenage pregnancies are observed in the areas covered by NorCAS, CARIS and EMSYCAR (10.0, 9.4 and 8.4% respectively between 1991-2010). The population covered by CAROBB has the highest proportion of births to mothers aged ≥40 and the largest proportion of births to mothers aged ≥30 (56%) compared to the other registers, followed by SWCAR and WANDA (50.2% and 47.6%, respectively).

While the majority of each population is of White ethnicity, there is some variation by region. In 2011, the regions covered by CAROBB and EMSYCAR have the largest non-White populations (14.9% and 10.4%, respectively) and the highest Asian populations (9.2% and 6.1%).

According to the GLS, the proportion of the population who were current smokers between 1998-2010 varied by region, with the area covered by the NorCAS having the highest proportion of all smokers and female smokers (25.8% and 26.5% respectively). The populations covered by CARIS and NorCAS had the lowest proportion of women claiming to have drunk alcohol in the previous week (64% and 68%, respectively). The area covered by SWCAR had the highest proportion of women who had drunk alcohol on at least five days in the previous week (21%).

Deprivation varied by region, with the area covered by the NorCAS and EMSYCAR having the largest proportions in the top 10% most deprived (9% and 6% respectively).

Table 4.1 Population statistics in the populations covered by the six BINOCARs

Statistics	Area covered by:					
	CARIS	**CAROBB**	**EMSYCAR**	**NorCAS**	**SWCAR**	**WANDA**
Annual births* (n)	35,000	31,000	74,000	33,000	60,000	31,000
Maternal age distribution* (%)						
<20	9.4%	4.3%	8.4%	10.0%	6.3%	6.2%
20-24	22.1%	14.1%	21.0%	23.6%	17.7%	17.7%
25-29	27.6%	25.6%	27.9%	29.9%	25.8%	28.6%
30-34	25.7%	32.8%	26.8%	24.4%	29.3%	29.8%
35-39	12.6%	19.1%	13.3%	10.3%	17.2%	14.8%
≥40	2.5%	4.1%	2.6%	1.8%	3.7%	3.0%
Ethnicity† (%)						
White	95.6%	85.1%	89.6%	95.7%	95.4%	96.6%
Mixed	1.0%	2.4%	1.8%	0.8%	1.4%	1.1%
Asian	2.3%	9.2%	6.1%	2.6%	2.0%	1.8%
Black	0.6%	2.6%	1.8%	0.5%	0.9%	0.4%
Arab	0.3%	0.2%	0.3%	0.2%	0.1%	0.1%
Other	0.2%	0.5%	0.4%	0.2%	0.2%	0.1%
Smoking‡ (%)						

Statistics	Area covered by:					
	CARIS	**CAROBB**	**EMSYCAR**	**NorCAS**	**SWCAR**	**WANDA**
Current smokers (18+)	24.1%	22.0%†	23.1%	25.8%	22.8%	22.0%†
Current smokers (women 18+)	23.7%	20.4%†	22.3%	26.5%	21.8%	20.4%†
Drinking† (%)						
Drank last week (women 16+)	64%	72%†	70%*	68%	74%	72%†
Drank on 5+ days last week (women 16+)	17%	20%†	16%*	16%	21%	20%†
Index of Multiple Deprivation$^{\phi}$ (%)						
1% most deprived	N/A	2%	5%	12%	2%	2%
5% most deprived	N/A	2%	5%	10%	3%	2%
10% most deprived	N/A	3%	6%	9%	4%	3%
20% most deprived	N/A	4%	7%	8%	4%	4%

*Average annual yearly births and maternal age distribution data came from the Office for National Statistics and represents the local areas covered by the registers for the respective years included in the study

†Information on ethnicity, religion and drinking came from the 2011 Census and represents the local areas covered by the registers for the year 2011.

‡Information on smoking came from the General Lifestyle Survey, Office for National Statistics and represents the following Government Office Regions, which do not exactly correspond to the areas covered by the registers: CARIS: Wales; CAROBB: South East; EMSYCAR: East Midlands; NorCAS: North East; SWCAR: South West; WANDA: South East. The General Lifestyle Survey represents 1998-2010 although the survey was not carried out in 1997/98 or 1999/2000.

ϕInformation on the Index of Multiple Deprivation came from the English Indices of Deprivation and represents the following Lower Super Output Areas, which do not exactly correspond to the areas covered by the registers: CAROBB: South East; EMSYCAR: East Midlands; NorCAS: North East; SWCAR: South West; WANDA: South East. The IMD was calculated based on data in 2010 only. The IMD is calculated for England only.

4.1.2 ONS annual births

Denominator data consisting of the number of yearly live and stillbirths in each region was obtained from the ONS. Similarly, yearly denominator data (total births only) grouped by maternal age categories was obtained from the ONS.

4.1.3 The Northern Survey of Twin and Multiple Pregnancies

The Northern Survey of Twin and Multiple Pregnancies (NorSTAMP), established in 1998, collects data on all multiple pregnancies of mothers who reside in the North of England (Figure 4.1) [121]. Multiple pregnancies are ascertained from the prenatal dating scan, the 20 week anomaly scan and at delivery. After gaining parental consent, data on multiple pregnancies are notified to NorSTAMP by midwives and ultra-sonographers. Data recorded includes: year of birth, number of fetuses, maternal age at delivery, and chorionicity (monochorionic (MC) and dichorionic (DC)). The final diagnosis of chorionicity for twins of the same sex is based on placental examination and histology. If there is no pathologic examination of the placenta, the diagnosis is made based on the prenatal ultrasound determination. Information on zygosity is not recorded.

The NorSTAMP is held at the PHE Regional Maternity Survey Office in the North of England, along with the NorCAS and the PMS. NorSTAMP, PMS and NorCAS records are linked using unique maternal ID numbers.

4.1.4 The Northern Perinatal Morbidity and Mortality Survey

The PMS, established in 1981, collects data on all deaths before age one, in infants born to mothers who reside in the North of England (Figure 4.1). Deaths are derived from statutory death registrations.

4.1.5 ONS death registrations

The register of deaths is statutory and death records are derived from this via the ONS. The register holds death records for all individuals who die whilst resident in England. The record holds information on the person's name (forename and surname), last known address, date of birth and sex. These data can be used to link death registrations to other data sources, with appropriate ethical approval.

4.2 Case inclusion

In all chapters, cases with at least one postnatally confirmed CHD (ICD 10: Q20-26) notified to one of the BINOCAR were included; minor anomalies, such as heart murmurs, patent ductus arteriosus (PDA) occurring with a gestational age<37 weeks were excluded according to the EUROCAT guidelines [118, 122]. Cases with an isolated PDA born at an unknown gestational age were excluded.

4.3 Case classification

4.3.1 Subtypes

Cases were categorised into one of the 17 EUROCAT CHD subtypes: SV, HLH, EA, HRH, CAT, AVSD, AVA/S, TGV, ToF, TAPVR, CoA, DORV, IAA, VSD, ASD, PVS, MVA (Figure 4.2).

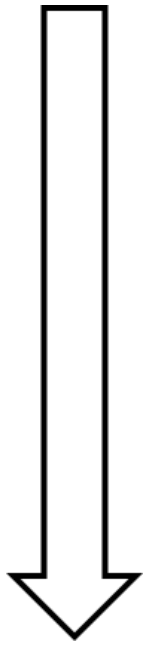
CHD subtypes with ICD 10 codes included in Q20-Q26 but that were not one of the 17 EUROCAT subtypes were included in this study but classified as "Other" CHD. These included: atrial isomerism, corrected TGV, aortopulmonary window, tricuspid regurgitation, aortic regurgitation, dextrocardia, heart block, aortic stenosis, hypoplastic aorta, sinus venosus ASD.

Cases with multiple CHD subtypes were coded as a single CHD subtype according to the subtype of the greatest aetiological severity. As described in Chapter 1 (section 1.1.1), there is no universally accepted CHD hierarchy, but several have been created. Cases were coded using an adapted version of Khoshnood et al's (2012) aetiological hierarchy, used in a similar study of trends in CHD prevalence [52]. However, the groups are altered to include DORV and IAA and MVA, which are placed in the moderate category in line with the more recent EUROCAT guidelines [122]. The hierarchy is depicted in Figure 4.2. A case with CoA and VSD would here be categorised as CoA, for example.

4.3.2 Severity categories

Subtypes were also grouped as *mild*, *moderate* and *severe* severity, according to the functional implications of the CHD. These categories were created based on those used by Khoshnood et al (2012) [52]. Figure 4.2 shows the subtypes according to the three severity categories. Cases categorised as "Other" CHD were not assigned to a severity category.

Figure 4.2 Categorisation of CHD subtypes into severity categories



	Severe	Moderate	Mild
Most Severe	Single Ventricle (SV) Hypoplastic Left Heart (HLH) Ebstein Anomaly (EA) Hypoplastic right heart (HRH)	Common arterial trunk (CAT) Atrioventricular septal defect (AVSD) Aortic valve atresia or stenosis (AVA/S) Transposition of the great vessels (TGV) Tetralogy of Fallot (ToF) Total anomalous pulmonary venuous return (TAPVR) Interrupted aortic arch (IAA) Coarctation of aorta (CoA) Double outlet right ventricle (DORV) Mitral valve anomaly (MVA)	Ventricular septal defect (VSD) Atrial septal defect (ASD) Pulmonary valve stenosis (PVS)
Least Severe			

4.3.3 Extra-cardiac anomalies

Cases were further coded according to the presence of ECAs. Cases were coded as: a) isolated cases i.e. cases with no ECAs; b) cases occurring with structural ECAs (including those occurring with sequences, associations and non-genetic syndromes but excluding those with chromosomal/ genetic ECAs; and c) cases occurring with chromosomal/ genetic ECAs. Cases with multiple CHD subtypes but no ECAs were classed as isolated.

Chapter 5. Epidemiology of congenital heart disease in singletons in the UK

5.1 Introduction

In Chapter 3, a review of the existing literature showed that the global prevalence of CHD ranged between 30-213 per 10,000 total births. Several studies investigated trends in prevalence, but the direction of these were conflicting and varied by CHD subtype, which were rarely examined separately. The review showed that there is a paucity of information regarding the prevalence and trends in prevalence of CHD in the UK. Given that the UK's paediatric cardiology services are currently undergoing reforms (Chapter 1), obtaining accurate information on CHD prevalence will aid health service planning.

Information on prenatal diagnosis, and TOPFA have been previously described for CHD, but trends over time in these pregnancy outcomes have not been reported [1, 21, 56, 57]. This information influences prevalence and is therefore important for the interpretation of temporal trends.

The association between CHD prevalence and maternal age has been researched to some extent, but generally not by CHD subtype (Chapter 3). Recent studies have shown an increased risk of TGV, CoA, VSD and ASD in pregnancies of mothers aged ≥35, despite excluding cases with chromosomal ECAs [76, 80]. It is possible that the changing maternal age distribution over time, due to women postponing childbearing in the UK, may contribute to the increasing trend in prevalence of some CHD subtypes [123]. Therefore, it is important to examine maternal age as a confounder for trends over time.

5.1.1 Aim

The aim of this chapter is to describe the epidemiology of CHD in the UK between 1991-2010.

5.1.1.1 Objectives

To describe for all CHD subtypes combined and by subtype:

- The frequency of ECAs
- Sex distribution

- Average gestational age at delivery
- Average (standardised) birth weight at delivery
- Prenatal diagnosis rates and trends in prenatal diagnosis rates over time
- Pregnancy outcomes and trends in TOPFA over time
- The total birth prevalence of CHD and trends in the total birth prevalence over time
- The live birth prevalence of CHD and trends in the live birth prevalence over time
- The association between total birth prevalence of CHD and maternal age at delivery

5.2 Methods

5.2.1 Case inclusion

All cases with a final diagnosis of CHD notified to six BINOCARs (CARIS and EMSYCAR between 1st January 1998-31st December 2010, NorCAS and CAROBB between 1st January 1991-31st December 2010, SWCAR between 1st January 2003-31st December 2010 or WANDA between 1st January 1994-31st December 2010) were included in this study. Cases occurring in live births, stillbirths, late miscarriages and TOPFAs were included. Cases occurring in multiple pregnancies were excluded in this chapter and were considered separately in Chapter 6, due to the different aetiologies of these cases. Cases with missing data on plurality (n=571, 2.7%) were assumed to be singletons and included in the analysis of this chapter.

5.2.2 Case classification

According to the EUROCAT guidelines, HRH is a secondary CHD which occurs as a result of a primary CHD, namely TA or PVA. While ICD 10 has a specific code for HRH, ICD nine did not. This change in coding system may artificially produce an increasing trend in HRH over time. Ideally all cases with HRH would therefore be coded as the primary anomaly (TA and PVA) in this chapter. However, in some cases of HRH (n=65), the primary CHD was not recorded. Therefore, all cases of PVA, TA and HRH are coded simply as HRH.

5.2.3 Data

Table 5.1 shows the variables included in the analysis. Year of delivery, was considered as a continuous variable; gestational age at delivery, preterm delivery, gestational age at TOPFA, pregnancy outcome, TOPFA, fetal death, sex, maternal age at delivery, prenatal diagnosis and standardised birth weight were all considered as categorical variables. Birth weight at 40 weeks, standardised for gestational age at delivery, sex and plurality, was estimated using Gardosi et al's fetal growth formula with Tin et al's regional birth weight reference [124, 125]. Gardosi et al calculated the fetal growth curves of 38,000 babies born in Nottingham using the adjusted weight centiles [125].

Information on the exact timing of prenatal diagnosis was not available, so prenatal diagnosis was simply categorised as "diagnosed" or "not diagnosed". In this chapter, prenatal diagnosis refers to the diagnosis of *any* congenital anomaly prenatally. Therefore, cases with, for

example, prenatally diagnosed trisomy 21 but an undiagnosed CHD would be coded as 'diagnosed'. Thus, analysis on prenatal diagnosis was restricted to cases of isolated CHD.

Data on the number of live and stillbirths in the population were available from ONS, by year and maternal age category.

Table 5.1 Description of variables used in analysis and frequency of missing data

Variable	Classification
Year of delivery (years)	Continuous variable
Gestational age at delivery (weeks)	Extreme preterm (20-27 weeks) Very preterm (28-31 weeks) Moderately preterm (32-36 weeks) Term (37-41 weeks) Post-term (≥41 weeks) Missing (n= 3,267, 15.9%)
Preterm delivery	Preterm (<37 weeks gestational age) Term (≥37 weeks gestational age) Missing (n= 3,267, 15.9%)
Gestational age at TOPFA (weeks)	≤ 13 weeks 14-18 weeks 19-23 weeks 24-29 weeks ≥30 weeks Missing (n= 788, 33.8%)
Pregnancy outcome	Live birth Late miscarriage (20-23 weeks gestational age at delivery) Stillbirth (≥24 weeks gestational age at delivery) TOPFA (any gestational age at delivery)
Fetal death	Fetal death (late miscarriage or stillbirth) No fetal death
Sex	Male Female Missing (n=289, 1.4%)
Maternal age at delivery (years)	<20 20-24 25-29 (reference category)

Variable	Classification
	30-34 35-39 ≥ 40 Missing (n= 1,382, 6.7%)
CHD Severity	Severe Moderate Mild Unclassified
Extra-cardiac anomalies (ECAs)	Isolated CHD CHD with structural ECAs CHD with chromosomal/ genetic ECAs CHD with teratogenic syndromes
Prenatal diagnosis	Prenatally diagnosed (any anomaly) Not prenatally diagnosed (any anomaly) Missing (n=2,893, 14.0%)
Standardised birth weight (SD from the mean)	Low: SD< -1 Average: -1 ≤ SD ≥1 High: SD> 1 Missing (n= 3,014, 14.6%)

5.2.4 Statistical analysis

Most statistical analyses were performed separately for: a) all cases of CHD; b) isolated cases; c) cases occurring with structural ECAs; and d) cases occurring with chromosomal/genetic ECAs. The analysis was not carried out separately for cases of CHD with teratogenic syndromes because these cases occurred in low frequency and the teratogenic syndromes are likely to be under-ascertained by the registers. Most analyses were also carried out for all CHD subtypes combined and for each individual CHD subtype. Descriptive statistics were calculated for the variables listed in Table 5.1.

5.2.4.1 Birth prevalence

Total and live birth prevalence was defined as outlined in Chapter 3 (section 3.2.1).

5.2.4.2 Modelling birth prevalence

The total birth prevalence of CHD over time were modelled using multilevel Poisson regression models. The number of CHD cases were nested within register, an offset equal to log (yearly total births) and year of birth as a (continuous) explanatory variable. The models were also adjusted for ECAs. Each model estimated RRs representing the risk of CHD per year increase in year of birth. The significance of an interaction between ECAs and year of delivery was tested by incorporating a cross-product term in the models and performing a Wald test. Where the interaction was significant, this implied that trends over time varied according to whether CHD occurred in isolation, with structural ECAs or with chromosomal/ genetic ECAs. Therefore, trends were modelled separately for each of the three ECA groups.

The prevalence models were refitted to include maternal age at delivery (categorised as shown in Table 5.1). Here the offset was equal to log (yearly number of total births, stratified by maternal age categories). All cases notified to WANDA and EMSYCAR, and cases notified to SWCAR in 2010, were excluded from this analysis due to incomplete maternal age data for >10% of cases (Table 5.2). Of the cases notified to the remaining registers, 0.2% of cases were excluded due to missing maternal age data. The adjusted and unadjusted RRs corresponding to year of delivery were then compared to examine whether changes in maternal age distribution confounded trends in CHD prevalence. These models were also used to estimate the association between CHD prevalence and maternal age at delivery, where the significance of the overall association was estimated using a Wald test.

Trends in the live birth prevalence of CHD were similarly modelled with live born cases as the outcome and an offset equal to log (yearly live births). The association between live birth

prevalence and maternal age could not be examined as the maternal age denominator data were available for total births only.

The multilevel models were fitted with random intercepts, to better account for variation between registers. The significance of the random intercept was tested using a likelihood ratio (LR) test, comparing the fixed effects model to the random intercept model. If the intercept improved the fit of the model, this indicated that there was significant heterogeneity in prevalence between registers. Where the intercept improved model fit, LR tests were used to compare random intercept models to random slope models. If the slope was significant, this implied that there was variation in time trends between registers. Additional variance terms were added to models to account for over-dispersion, where necessary.

Table 5.2 Proportion of cases with missing maternal age data

Register	Missing data, N (%)
CARIS	1 (0.0)
CAROBB	46 (4.0)
EMSYCAR	632 (16.6)
NorCAS	148 (2.3)
SWCAR	68 (3.2)
WANDA	485 (25.1)

5.2.4.3 Modelling prenatal diagnosis

This analysis was restricted to isolated cases of CHD. As shown in Table 5.3, prenatal diagnosis data was missing disproportionately by register. The registers with >10% of prenatal diagnosis data missing (i.e. CAROBB, EMSYCAR and SWCAR) were excluded from all analysis of this variable. Of the remaining three registers, 0.8% of cases had missing prenatal diagnosis data and so these cases were excluded from analysis of prenatal diagnosis. Prenatal diagnosis is not possible (or highly unlikely) for cases of ASD, VSD, PVS and PDA [126] and these cases were therefore excluded from this analysis. RRs representing the "risk" of prenatal diagnosis per year increase in year of birth were estimated using multilevel Poisson regression models (as described in section 5.2.4.2). The number of diagnosed cases was used as the outcome and log (number of cases) as the offset. Models were also refitted, adjusting for maternal age at delivery.

Table 5.3 Proportion of cases with missing prenatal diagnosis data by register

Register	Missing data, N (%)
CARIS	36 (0.7)
CAROBB	278 (27.4)
EMSYCAR	1,835 (55.9)
NorCAS	79 (1.0)
SWCAR	665 (29.6)
WANDA	0 (0.0)

5.2.4.4 Modelling TOPFA rates over time

RRs representing the risk of TOPFA per years increase in year of delivery were estimated using multilevel Poisson models, with TOPFA cases nested within registers and modelled with an offset equal to log (number of cases), year of birth as a continuous predictor and ECAs as an explanatory variable. These models were refitted to cases that were prenatally diagnosed only in order to investigate whether trends in TOPFA were caused by improvement in prenatal diagnosis rates. These adjusted models were carried out on isolated cases only, with the same exclusions described in section 5.2.4.3.

All statistical analyses were performed in Stata 13 (Stata Corp, Texas). As all analyses was conducted for each of the 20 subtypes, a Bonferroni adjustment to the nominal significance level was carried out. Therefore $p<0.003$ (i.e. 0.05/20) was considered statistically significant for all analyses. As this is arguably over-conservative, associations significant at the $p<0.05$ level are also discussed and described as having "some evidence of an association".

5.3 Results

There were 19,754 singleton cases notified to the six BINOCARs, among 3,040,952 total births.

5.3.1 CHD severity categories

The frequency and percentage of each CHD severity category is presented in Table 5.4. Severe CHD was rarest, followed by moderate CHD and mild CHD. There was a greater proportion of mild cases among live births.

Table 5.4 Frequency and percentages of CHD severity categories

Severity category*	Total births N (% of 19,754)	Live births N (% of 16,923)
Severe	1,601 (8.1)	919 (5.4)
Moderate	5,431 (27.5)	4,543 (26.9)
Mild	9,911 (50.2)	9,251 (54.7)
Unclassified	2,811 (14.2)	2,210 (13.1)
All subtypes	**19,754 (100)**	**16,923 (100)**

5.3.2 CHD subtypes

The frequency and percentage of each CHD subtype is shown in Table 5.5. Septal defects occurred most frequently, and the subtypes with single ventricle physiology (SV, HLH, HRH) occurred less frequently.

Table 5.5 Frequency and percentage of CHD subtypes

CHD subtype	Total births N (% of 19,754)	Live births N (% of 16,923)
SV	147 (0.7)	93 (0.6)
HLH	882 (4.5)	422 (2.5)
EA	155 (0.8)	118 (0.7)
HRH	573 (2.9)	405 (2.4)
CAT	220 (1.1)	142 (0.8)
AVSD	1,227 (6.2)	861 (5.1)
AVA/S	495 (2.5)	461 (2.7)
TGV	904 (4.6)	833 (4.9)
ToF	1,027 (5.2)	871 (5.2)
TAPVR	191 (1)	189 (1.1)
IAA	108 (0.6)	87 (0.5)
CoA	1,015 (5.1)	936 (5.5)
DORV	244 (1.2)	163 (1.0)
MVA	182 (0.9)	173 (1.0)
VSD	6,741 (34.1)	6,251 (36.9)
ASD	2,225 (11.3)	2,066 (12.2)
PVS	944 (4.8)	933 (5.5)
PDA	533 (2.7)	531 (3.1)
Other	1,941 (9.8)	1,388 (8.2)
All subtypes	**19,754 (100)**	**16,923 (99.9)**

5.3.3 ECAs occurring with total birth cases of CHD

Of 19,754 cases, 53 (0.3%) occurred with a teratogenic syndrome, 3,795 (19.2%) with chromosomal/ genetic ECAs, 2,390 (12.1%) with structural ECAs and 13,516 (68.4%) were isolated CHD. Of the isolated CHD, 3,751 (27.8%) had multiple CHD subtypes and 9,765 (72.2%) occurred with a single subtype. The distribution of ECAs varied by CHD subtype (Table 5.6). For example, 28.4% of AVSD cases were isolated, whereas 88.9% of TGV cases were isolated.

Of the 53 cases of CHD with teratogenic syndromes, 19 (35.9%) were fetal alcohol syndrome (35.9%), 10 (18.9%) were cytomegalic virus, seven (13.2%) were valproate syndrome and 16 (30.2%) were other teratogens. Cases with teratogenic syndromes were most commonly VSD or ASD (Table 5.6).

Excluding cases with teratogenic syndromes, chromosomal anomalies occurred in 14.7% of cases of CHD. Chromosomal anomalies occurred in 20% of cases with moderate CHD compared to 13.0% with mild severity CHD and 8.2% with severe severity CHD. The

majority (52.8%) of chromosomal ECAs were Trisomy 21. Trisomy 21 occurred in 12.6% of cases with moderate severity CHD, compared to 7.2% of cases with mild severity CHD and 1.4% of severe severity CHD (Table 5.7). Trisomy 13, Trisomy 18, Turner syndrome, Cri-du-chat syndrome and Wolff Hirschorn syndrome occurred in small numbers amongst cases of CHD, with little variation in whether they occurred with severe, moderate or mild severity CHD (Table 5.7).

Genetic syndromes occurred in 4.6% of cases with CHD, occurring most commonly in cases of moderate severity CHD (6.7%), compared to cases of severe (5.6%) and mild CHD (2.8%). The most commonly occurring genetic syndromes were DiGeorge syndrome (1.3%), Isomerism (0.9%), Noonan syndrome (0.3%) and Williams syndrome (0.2%) (Table 5.7). DiGeorge syndrome occurred most commonly in cases with mild severity CHD whereas Isomerism occurred more commonly in cases with severe severity CHD (Table 5.7).

Table 5.8 and Table 5.9 show the frequency of structural ECAs that occurred with cases of CHD. Discounting those cases with chromosomal/ genetic ECAs, CHD most commonly occurred with anomalies of the digestive system (3.9%), the urinary system (2.8%), the limbs (2.6%) and the nervous system (2.3%). There was little variation in the frequency of ECAs across the CHD severity categories. However, digestive system anomalies were more prevalent amongst cases with moderate and mild severity CHD (4.1% and 3.5%, respectively) compared to those of severe severity (2.9%).

5.3.3.1 Summary

While there was variation in the distribution of ECAs according to CHD subtype, the majority of cases occurred in isolation (68.4%).

Table 5.6 Type of ECA in CHD total births according to CHD subtypes

CHD subtype	Isolated CHD	CHD with structural ECAs	CHD with chromosomal/ genetic ECAs	CHD with teratogenic syndromes	All CHD
	N (% of CHD subtype)				
SV	105 (71.4)	22 (15)	20 (13.6)	0 (0)	147 (100.0)
HLH	708 (80.3)	75 (8.5)	99 (11.2)	0 (0)	882 (100.0)
EA	126 (81.3)	15 (9.7)	13 (8.4)	1 (0.6)	155 (100.0)
HRH	396 (69.1)	73 (12.7)	102 (17.8)	2 (0.3)	573 (100.0)
CAT	106 (48.2)	48 (21.8)	66 (30)	0 (0)	220 (100.0)
AVSD	338 (27.5)	111 (9)	774 (63.1)	4 (0.3)	1,227 (100.0)
AVA/S	414 (83.6)	33 (6.7)	47 (9.5)	1 (0.2)	495 (100.0)
TGV	799 (88.4)	54 (6)	49 (5.4)	2 (0.2)	904 (100.0)
ToF	602 (58.6)	182 (17.7)	241 (23.5)	2 (0.2)	1,027 (100.0)
TAPVR	156 (81.7)	25 (13.1)	10 (5.2)	0 (0)	191 (100.0)
IAA	50 (46.3)	10 (9.3)	48 (44.4)	0 (0)	108 (100.0)
CoA	749 (73.8)	114 (11.2)	148 (14.6)	4 (0.4)	1,015 (100.0)
DORV	134 (54.9)	44 (18)	65 (26.6)	1 (0.4)	244 (100.0)
MVA	150 (82.4)	14 (7.7)	18 (9.9)	0 (0)	182 (100.0)
VSD	5,067 (75.2)	611 (9.1)	1046 (15.5)	17 (0.3)	6,741 (100.0)
ASD	1,361 (61.2)	407 (18.3)	447 (20.1)	10 (0.4)	2,225 (100.0)
PVS	817 (86.5)	55 (5.8)	68 (7.2)	4 (0.4)	944 (100.0)
PDA	370 (69.4)	95 (17.8)	67 (12.6)	1 (0.2)	533 (100.0)
Other	1,068 (55)	402 (20.7)	467 (24.1)	4 (0.2)	1,941 (100.0)
All subtypes	**13,516 (68.4)**	**2,390 (12.1)**	**3,795 (19.2)**	**53 (0.3)**	**19,754 (100.0)**

Table 5.7 Chromosomal/ genetic ECAs in total births, by CHD severity

ECA Group, Subtype	Severe N (% of 1,599*)	Moderate N (% of 5,417*)	Mild N (% of 9,880*)	All CHD N(% of 19,701*)
Chromosomal Anomalies	**131 (8.2)**	**1,083 (20.0)**	**1,284 (13)**	**2,893 (14.7)**
Trisomy 21	23 (1.4)	681 (12.6)	713 (7.2)	1528 (7.8)
Patau sydrome	22 (1.4)	64 (1.2)	75 (0.8)	209 (1.1)
Trisomy 18	31 (1.9)	114 (2.1)	237 (2.4)	446 (2.3)
Turner syndrome	22 (1.4)	67 (1.2)	25 (0.3)	202 (1.0)
Klinefelter syndrome	0 (0)	8 (0.1)	8 (0.1)	17 (0.1)
Cri-du-chat syndrome	0 (0)	0 (0)	10 (0.1)	11 (0.1)
Wolff Hirschorn syndrome	0 (0)	1 (0)	17 (0.2)	20 (0.1)
Other	33 (2.2)	151 (3.4)	218 (2.5)	485 (32.8)
Genetic Syndromes	**90 (5.6)**	**365 (6.7)**	**277 (2.8)**	**902 (4.6)**
Aarskog syndrome	1 (0.1)	1 (0)	13 (0.1)	17 (0.1)
Alagille syndrome	0 (0)	2 (0)	5 (0.1)	10 (0.1)
Angelman syndrome	0 (0)	1 (0)	0 (0)	2 (0)
Apert syndrome	0 (0)	1 (0)	1 (0)	3 (0)
Beckwith-Wiedemann	1 (0.1)	1 (0)	6 (0.1)	10 (0.1)
CHARGE	1 (0.1)	9 (0.2)	1 (0)	11 (0.1)
Chrondrodysplasia	0 (0)	0 (0)	2 (0)	2 (0)
Cornelia de Lange syndrome	1 (0.1)	2 (0)	3 (0)	8 (0)
Crouzon syndrome	0 (0)	0 (0)	2 (0)	2 (0)
DiGeorge syndrome	16 (1)	156 (2.9)	64 (0.6)	253 (1.3)
Ehlers-Danlos syndrome	0 (0)	1 (0)	1 (0)	2 (0)
Ellis van Creveld	0 (0)	3 (0.1)	0 (0)	3 (0)
Holt-Oram syndrome	2 (0.1)	3 (0.1)	7 (0.1)	16 (0.1)
Incontinentia pigmenti	0 (0)	0 (0)	1 (0)	1 (0)
Isomerism/ Ivemark Syndrome	42 (2.6)	86 (1.6)	17 (0.2)	180 (0.9)
Jeune syndrome	0 (0)	1 (0)	1 (0)	5 (0)
Klipped-Feil syndrome	0 (0)	0 (0)	1 (0)	1 (0)
Marfan syndrome	1 (0.1)	0 (0)	3 (0)	16 (0.1)
Moebius syndrome	0 (0)	0 (0)	1 (0)	2 (0)
Exostosis	0 (0)	0 (0)	0 (0)	2 (0)
Nail Patella syndrome	0 (0)	0 (0)	0 (0)	2 (0)
Noonan syndrome	2 (0.1)	9 (0.2)	40 (0.4)	62 (0.3)
Pena Shokeir syndrome	1 (0.1)	1 (0)	1 (0)	6 (0)
Poland syndrome	0 (0)	0 (0)	0 (0)	2 (0)
Prader Willi syndrome	0 (0)	0 (0)	1 (0)	1 (0)
Rubinstein Taybi	0 (0)	4 (0.1)	2 (0)	8 (0)
Seckel syndrome	0 (0)	0 (0)	1 (0)	1 (0)
Silver	0 (0)	0 (0)	2 (0)	2 (0)
Smith-Lemli-Opitz syndrome	1 (0.1)	3 (0.1)	3 (0)	9 (0)
Sotos syndrome	0 (0)	0 (0)	3 (0)	4 (0)
Treacher Collins syndrome	0 (0)	0 (0)	1 (0)	1 (0)

ECA Group, Subtype	Severe N (% of 1,599*)	Moderate N (% of 5,417*)	Mild N (% of 9,880*)	All CHD N(% of 19,701*)
Tricho-rhino phalangeal syndrome	0 (0)	0 (0)	2 (0)	2 (0)
Van der Woude syndrome	1 (0.1)	4 (0.1)	5 (0.1)	14 (0.1)
Williams syndrome	0 (0)	13 (0.2)	14 (0.1)	43 (0.2)
Zellweger syndrome	0 (0)	0 (0)	3 (0)	3 (0)

*Cases with teratogenic syndromes were excluded

Table 5.8 Associations, sequences and syndromes in total births, by CHD severity

Group Subtype	Severe N (% of 1,378)*	Moderate N (% of 3,969)*	Mild N (% of 8,319)*	All CHD N (% of 15,906)*
Association	7 (0.5)	31 (0.8)	35 (0.4)	89 (0.6)
VATER	5 (0.4)	27 (0.7)	30 (0.4)	74 (0.5)
Goldenhar Syndrome	1 (0.1)	4 (0.1)	6 (0.1)	15 (0.1)
MURCS	1 (0.1)	0 (0)	0 (0)	1 (0)
Sequences	6 (0.4)	18 (0.5)	38 (0.5)	87 (0.6)
Pierre Robin	2 (0.2)	2 (0.1)	18 (0.2)	25 (0.2)
Body Stalk	1 (0.1)	4 (0.1)	2 (0)	18 (0.1)
Prune Belly	1 (0.1)	0 (0)	3 (0)	5 (0)
Sirenomelia	1 (0.1)	1 (0)	3 (0)	7 (0)
Partial Urorectal Septum Malformation Sequence	0 (0.0)	3(0.1)	6 (0.1)	13 (0.1)
Amniotic band sequence	1 (0.1)	5 (0.1)	3 (0)	18 (0.1)
Caudal dysplasia	0 (0)	3 (0.1)	0 (0)	3 (0)
Skeletal dysplasia	0 (0)	5 (0.1)	8 (0.1)	20 (0.1)
Syndrome (Non-genetic) Blepharophimosis-ptosis Syndrome	2 (0.2)	2 (0.1)	6 (0.1)	12 (0.1)

*Cases with teratogenic syndromes and chromosomal/ genetic ECAs were excluded

†Cases with teratogenic syndromes, chromosomal/ genetic ECAs, associations, sequences, skeletal dysplasia and non-genetic syndromes were excluded

VATER=co-occurrence of Vertebral anomalies, Anal atresia, CHD, tracheoesophageal fistula/ atresia, renal and radial anomalies and limb anomalies

MURCS=co-occurrence of Mullerian agenesis, renal agenesis and cervicothoracic somite anomalies

Table 5.9 Structural ECAs in total birth cases of CHD, by CHD severity

Group Subtype	Severe N (% of 1,363)†	Moderate N (% of 3,913) †	Mild N (% of 8,232) †	All CHD N (% of 15,698) †
Nervous system anomalies	32 (2.3)	87 (2.2)	159 (1.9)	358 (2.3)
Neural tube defect	7 (0.5)	17 (0.4)	32 (0.4)	75 (0.5)
Anencephaly	2 (0.1)	8 (0.2)	6 (0.1)	21 (0.1)
Encephalocele	3 (0.2)	3 (0.1)	13 (0.2)	26 (0.2)
Spina bifida	2 (0.1)	8 (0.2)	15 (0.2)	36 (0.2)
Spina bifida & hydrocephalus	2 (0.1)	3 (0.1)	12 (0.1)	22 (0.1)
Hydrocephalus	15 (1.1)	36 (0.9)	52 (0.6)	135 (0.9)
Microcephaly	1 (0.1)	18 (0.5)	24 (0.3)	54 (0.3)
Holoprosencephaly	4 (0.3)	3 (0.1)	10 (0.1)	19 (0.1)
Eye anomalies	8 (0.6)	31 (0.8)	46 (0.6)	112 (0.7)
Micophalamos	1 (0.1)	7 (0.2)	9 (0.1)	20 (0.1)
Phalmos	0 (0)	1 (0)	0 (0)	2 (0)
Cateract	2 (0.1)	4 (0.1)	3 (0)	11 (0.1)
Glaucoma	0 (0)	2 (0.1)	3 (0)	5 (0)
Ear, face or neck anomalies	1 (0.1)	21 (0.5)	32 (0.4)	72 (0.5)
Anotia	0 (0)	0 (0)	3 (0)	3 (0)
Respiratory system anomalies	29 (2.1)	91 (2.3)	112 (1.4)	321 (2.0)
Choanal atresia	5 (0.4)	18 (0.5)	19 (0.2)	51 (0.3)
Cystic lung	2 (0.1)	10 (0.3)	8 (0.1)	32 (0.2)
Orofacial anomalies	22 (1.6)	70 (1.8)	141 (1.7)	274 (1.7)
Cleft lip	2 (0.1)	10 (0.3)	21 (0.3)	47 (0.3)
Cleft lip & palate	13 (1)	29 (0.7)	48 (0.6)	102 (0.6)
Cleft palate	7 (0.5)	28 (0.7)	70 (0.9)	119 (0.8)
Digestive system anomalies	39 (2.9)	161 (4.1)	287 (3.5)	614 (3.9)
Oesophageal atresia	10 (0.7)	35 (0.9)	55 (0.7)	119 (0.8)
Duodenal atresia/ stenosis	3 (0.2)	14 (0.4)	23 (0.3)	45 (0.3)
Small intestinal atresia/ stenosis	0 (0)	2 (0.1)	11 (0.1)	15 (0.1)
Anorectal atresia/ stenosis	9 (0.7)	27 (0.7)	50 (0.6)	112 (0.7)
Hirschsprung’s disease	0 (0)	5 (0.1)	5 (0.1)	15 (0.1)
Bile atresia	0 (0)	2 (0.1)	6 (0.1)	8 (0.1)
Diaphragmatic hernia	7 (0.5)	22 (0.6)	54 (0.7)	113 (0.7)
Diaphragmatic event	1 (0.1)	2 (0.1)	3 (0)	8 (0.1)
Abdominal anomalies	5 (0.4)	26 (0.7)	71 (0.9)	136 (0.9)
Gastroschisis	1 (0.1)	3 (0.1)	18 (0.2)	30 (0.2)
Omphalocele	4 (0.3)	23 (0.6)	54 (0.7)	107 (0.7)
Urinary anomalies	38 (2.8)	120 (3.1)	179 (2.2)	445 (2.8)
Renal agenesis	3 (0.2)	12 (0.3)	10 (0.1)	39 (0.2)
Renal dysplasia	8 (0.6)	13 (0.3)	31 (0.4)	67 (0.4)
Cystic kidney	0 (0)	4 (0.1)	5 (0.1)	19 (0.1)
Hydronephrosis	7 (0.5)	28 (0.7)	51 (0.6)	108 (0.7)

Group Subtype	Severe N (% of 1,363)†	Moderate N (% of 3,913) †	Mild N (% of 8,232) †	All CHD N (% of 15,698) †
Bladder extrophy	0 (0)	0 (0)	5 (0.1)	8 (0.1)
Genital anomalies	14 (1)	79 (2)	110 (1.3)	250 (1.6)
Hypospadias	6 (0.4)	48 (1.2)	71 (0.9)	152 (1)
Sex indeterminate	1 (0.1)	5 (0.1)	7 (0.1)	22 (0.1)
Limb anomalies	34 (2.5)	100 (2.6)	190 (2.3)	404 (2.6)
Limb reduction	12 (0.9)	38 (1)	39 (0.5)	106 (0.7)
Upper limb reduction	11 (0.8)	36 (0.9)	29 (0.4)	87 (0.6)
Lower limb reduction	2 (0.1)	6 (0.2)	15 (0.2)	31 (0.2)
Polydactyly	7 (0.5)	18 (0.5)	25 (0.3)	63 (0.4)
Syndactyly	0 (0)	4 (0.1)	3 (0)	12 (0.1)
Arthrogryposis	0 (0)	0 (0)	0 (0)	12 (0.1)
Musculo-skelatal anomalies	23 (1.7)	61 (1.6)	81 (1)	214 (1.4)
Thanatophoric dwarfism	0 (0)	0 (0)	0 (0)	214 (1.4)
Craniosynostosis	0 (0)	4 (0.1)	9 (0.1)	16 (0.1)

*Cases with teratogenic syndromes and chromosomal/ genetic ECAs were excluded

†Cases with teratogenic syndromes, chromosomal/ genetic ECAs, associations, sequences, skeletal dysplasia and non-genetic syndromes were excluded

5.3.4 ECAs occurring with live birth cases of CHD

Of 16,923 live born cases, 42 (0.3%) occurred with a teratogenic syndrome, 2,488 (14.7%) with chromosomal/ genetic ECAs, 1,768 (10.5%) with structural ECAs and 12,625 (74.6%) were isolated CHD. Of the cases with isolated CHD, 9,160 (72.5%) had multiple CHD subtypes and 3,465 (27.4%) occurred with a single CHD subtype. The distribution of ECAs varied by CHD subtype (Table 5.10). For example, 57.8% of AVSD cases compared to 3.4% of TGV cases occurred with chromosomal/ genetic ECAs.

Of the 42 live born cases with a teratogenic syndrome, 18 (42.9%) were fetal alcohol syndrome, 6 (14.3%) were cytomegalic virus, three (7.1%) were valproate syndrome and 15 (35.7%) were other teratogenic syndromes. Cases with teratogenic syndromes were most commonly VSD or ASD.

Excluding cases with teratogenic syndromes, chromosomal anomalies occurred in 10.4% of cases of CHD. Chromosomal anomalies occurred in 14.1% of cases with moderate severity CHD, compared to 9.9% of cases with mild severity CHD and just 4.6% of cases with severe severity CHD. The majority (66.9%) of chromosomal anomalies were Trisomy 21. Cases with moderate severity CHD occurred with Trisomy 21 in 10.3% of cases, compared to 6.6% of mild and 1.3% of severe severity cases (Table 5.11). Trisomy 13, Trisomy 18, Turner syndrome, Cri-du-chat syndrome and Wolff Hirschorn syndrome occurred in small numbers amongst cases of CHD, with little variation in whether they occurred with severe, moderate or mild CHD (Table 5.11).

Genetic syndromes occurred in 4.4% of cases with CHD, with cases of moderate and severe severity CHD occurring with a genetic syndrome more commonly than cases of mild CHD (6.5%, 6.2% and 2.8%, respectively). The most commonly occurring genetic syndromes were DiGeorge syndrome, Isomerism, Noonan syndrome and William syndrome, which occurred in 1.3%, 0.6%, 0.4% and 0.3% of cases, respectively (Table 5.11).

Table 5.12 and Table 5.13 show the frequency of structural ECAs that occurred with live born cases of CHD. Discounting those cases with chromosomal/ genetic ECAs, CHD in live borns most commonly occurred with anomalies of the digestive system (3.2%), the urinary system (1.9%), the limbs (2.0%) and the respiratory system (1.6%). There was little variation in the frequency of ECAs across the CHD severity categories. However, digestive system anomalies were slightly more prevalent amongst cases with moderate and mild severity CHD (3.4% and 2.9%, respectively) compared to severe CHD (2.0%).

Table 5.10 Type of ECA in CHD live births according to CHD subtypes

CHD Subtype*	Isolated CHD	CHD with structural ECAs	CHD with chromosomal/ genetic ECAs	CHD with teratogenic syndromes	All CHD
	N (% of CHD subtype)				
SV	71 (76.3)	12 (12.9)	10 (10.8)	0 (0)	93 (100.0)
HLH	367 (87)	28 (6.6)	27 (6.4)	0 (0)	422 (100.0)
Eb	96 (81.4)	9 (7.6)	12 (10.2)	1 (0.8)	118 (100.0)
HRH	308 (76)	33 (8.1)	62 (15.3)	2 (0.5)	405 (100.0)
CAT	86 (60.6)	24 (16.9)	32 (22.5)	0 (0)	142 (100.0)
AVSD	295 (34.3)	66 (7.7)	498 (57.8)	2 (0.2)	861 (100.0)
AVA/S	400 (86.8)	26 (5.6)	35 (7.6)	0 (0)	461 (100.0)
TGV	759 (91.1)	44 (5.3)	28 (3.4)	2 (0.2)	833 (100.0)
ToF	562 (64.5)	135 (15.5)	172 (19.7)	2 (0.2)	871 (100.0)
TAPVR	155 (82)	24 (12.7)	10 (5.3)	0 (0)	189 (100.0)
IAA	46 (52.9)	9 (10.3)	32 (36.8)	0 (0)	87 (100.0)
CoA	739 (79)	95 (10.1)	99 (10.6)	3 (0.3)	936 (100.0)
DORV	106 (65)	28 (17.2)	28 (17.2)	1 (0.6)	163 (100.0)
MVA	146 (84.4)	14 (8.1)	13 (7.5)	0 (0)	173 (100.0)
VSD	5,020 (80.3)	504 (8.1)	712 (11.4)	15 (0.2)	6,251 (100.0)
ASD	1,334 (64.6)	336 (16.3)	388 (18.8)	8 (0.4)	2,066 (100.0)
PVS	811 (86.9)	51 (5.5)	68 (7.3)	3 (0.3)	933 (100.0)
PDA	370 (69.7)	93 (17.5)	67 (12.6)	1 (0.2)	531 (100.0)
Other	954 (68.7)	237 (17.1)	195 (14.0)	2 (0.1)	1,388 (100.0)
All subtypes	**12,652 (74.6)**	**1,768 (10.5)**	**2,488 (14.7)**	**42 (0.3)**	**16,923 (100.0)**

Table 5.11 Chromosomal\ genetic ECA in live births, by CHD severity

ECA	Severe N (% of 917*)	Moderate N (% of 4,533*)	Mild N (% of 9,225*)	All CHD N (% of 16,881*)
Chromosomal Anomalies	**42 (4.6)**	**641 (14.1)**	**914 (9.9)**	**1753 (10.4)**
Trisomy 21	12 (1.3)	468 (10.3)	610 (6.6)	1172 (6.9)
Patau sydrome	4 (0.4)	14 (0.3)	23 (0.2)	50 (0.3)
Trisomy 18	9 (1)	36 (0.8)	90 (1)	145 (0.9)
Turner syndrome	6 (0.7)	25 (0.6)	16 (0.2)	56 (0.3)
Klinefelter syndrome	0 (0)	6 (0.1)	6 (0.1)	12 (0.1)
Cri-du-chat syndrome	0 (0)	0 (0)	10 (0.1)	11 (0.1)
WolffHirschorn	0 (0)	1 (0)	17 (0.2)	19 (0.1)
Genetic Syndromes	**57 (6.2)**	**293 (6.5)**	**254 (2.8)**	**735 (4.4)**
Aarskog syndrome	0 (0)	1 (0)	13 (0.1)	16 (0.1)
Alagille syndrome	0 (0)	2 (0)	5 (0.1)	10 (0.1)
Angelman syndrome	0 (0)	1 (0)	0 (0)	2 (0)
Apert syndrome	0 (0)	1 (0)	1 (0)	3 (0)
Beckwith-Wiedemann	1 (0.1)	1 (0)	6 (0.1)	10 (0.1)
CHARGE	1 (0.1)	9 (0.2)	1 (0)	11 (0.1)
Chrondrodysplasia	0 (0)	0 (0)	2 (0)	2 (0)
Cornelia de Lange syndrome	1 (0.1)	1 (0)	3 (0)	7 (0)
Crouzon syndrome	0 (0)	0 (0)	2 (0)	2 (0)
DiGeorge syndrome	14 (1.5)	140 (3.1)	58 (0.6)	227 (1.3)
Ehlers-Danlos syndrome	0 (0)	1 (0)	1 (0)	2 (0)
EllisvanCreveld	0 (0)	0 (0)	0 (0)	2 (0)
Holt-Oram syndrome	2 (0.2)	2 (0)	6 (0.1)	12 (0.1)
Incontinentia pigmenti	0 (0)	0 (0)	1 (0)	1 (0)
Isomerism/ Ivemark Syndrome	22 (2.4)	51 (1.1)	11 (0.1)	99 (0.6)
Jeune syndrome	0 (0)	1 (0)	0 (0)	2 (0)
Klipped-Feil syndrome	0 (0)	0 (0)	1 (0)	1 (0)
Marfan syndrome	1 (0.1)	0 (0)	2 (0)	15 (0.1)
Moebius syndrome	0 (0)	0 (0)	1 (0)	2 (0)
Exostosis	0 (0)	0 (0)	0 (0)	2 (0)
Nail Patella syndtrome	0 (0)	0 (0)	0 (0)	2 (0)
Noonan syndrome	1 (0.1)	9 (0.2)	40 (0.4)	61 (0.4)
Pena Shokeir syndrome	0 (0)	0 (0)	1 (0)	3 (0)
Poland syndrome	0 (0)	0 (0)	0 (0)	2 (0)
Prader Willi syndrome	0 (0)	0 (0)	1 (0)	1 (0)
Rubinstein Taybi	0 (0)	4 (0.1)	2 (0)	8 (0)
Silver	0 (0)	0 (0)	2 (0)	2 (0)

ECA	Severe N (% of 917*)	Moderate N (% of 4,533*)	Mild N (% of 9,225*)	All CHD N (% of 16,881*)
Smith-Lemli-Opitz syndrome	1 (0.1)	2 (0)	3 (0)	8 (0)
Sotos syndrome	0 (0)	0 (0)	3 (0)	4 (0)
Treacher Collins syndrome	0 (0)	0 (0)	1 (0)	1 (0)
Tricho-rhino phalangeal syndrome	0 (0)	0 (0)	2 (0)	2 (0)
Van der Woude syndrome	0 (0)	3 (0.1)	3 (0)	9 (0.1)
Williams syndrome	0 (0)	13 (0.3)	14 (0.2)	43 (0.3)
Zellweger syndrome	0 (0)	0 (0)	3 (0)	3 (0)

*Cases with teratogenic syndromes were excluded

Table 5.12 Associations, sequences and syndromes in live births, by CHD severity

Group Subtype	Severe N (% of 1,378*)	Moderate N (% of 3,969*)	Mild N (% of 8,319*)	All CHD N (% of 15,906*)
Association	3 (0.2)	21 (0.5)	25 (0.3)	60 (0.4)
VATER	2 (0.1)	18 (0.5)	19 (0.2)	48 (0.3)
Goldenhar Syndrome	1 (0.1)	3 (0.1)	6 (0.1)	12 (0.1)
Sequences	1 (0.1)	7 (0.2)	29 (0.3)	46 (0.3)
Pierre Robin	1 (0.1)	1 (0)	18 (0.2)	23 (0.1)
Body Stalk	0 (0)	1 (0)	0 (0)	2 (0)
Prune Belly	0 (0)	0 (0)	3 (0)	4 (0)
Partial Urorectal Septum Malformation Sequence	0 (0)	2 (0.1)	4 (0)	10 (0.1)
Amniotic band sequence	(0)	(0)	1 (0)	(0)
Caudal dysplasia	0 (0)	2 (0.1)	0 (0)	2 (0)
Skeletal dysplasia	0 (0)	1 (0)	4 (0)	8 (0.1)
Syndrome (Non-genetic) Blepharophimosis-ptosis Syndrome	2 (0.1)	2 (0.1)	6 (0.1)	12 (0.1)

*Cases with teratogenic syndromes and chromosomal/ genetic ECAs were excluded

† Cases with teratogenic syndromes, chromosomal/ genetic ECAs, associations, sequences, skeletal dysplasia and non-genetic syndromes were excluded

VATER=co-occurrence of Vertebral anomalies, Anal atresia, CHD, tracheoesophageal fistula/ atresia, renal and radial anomalies and limb anomalies

MURCS=co-occurrence of Mullerian agenesis, renal agenesis and cervicothoracic somite anomalies

Table 5.13 Structural ECAs in live births, by CHD severity

Group Subtype	Severe N (% of 812†)	Moderate N (% of 3,568†)	Mild N (% of 7,993†)	All CHD N (% of 14,267†)
Nervous system anomalies	8 (1)	51 (1.4)	96 (1.2)	190 (1.3)
Neural tube defect	0 (0)	3 (0.1)	5 (0.1)	11 (0.1)
Anencephaly	0 (0)	0 (0)	0 (0)	11 (0.1)
Encephalocele	0 (0)	0 (0)	4 (0.1)	6 (0)
Spina bifida	0 (0)	3 (0.1)	1 (0)	6 (0)
Spina bifida & hydrocephalus	0 (0)	1 (0)	1 (0)	4 (0)
Hydrocephalus	3 (0.4)	23 (0.6)	27 (0.3)	68 (0.5)
Microcephaly	1 (0.1)	14 (0.4)	23 (0.3)	48 (0.3)
Holoprosencephaly	2 (0.2)	1 (0)	3 (0)	6 (0)
Eye anomalies	6 (0.7)	30 (0.8)	44 (0.6)	100 (0.7)
Micophalamos	1 (0.1)	7 (0.2)	9 (0.1)	19 (0.1)
Phalmos	0 (0)	1 (0)	0 (0)	1 (0)
Cateract	2 (0.2)	4 (0.1)	3 (0)	11 (0.1)
Glaucoma	0 (0)	2 (0.1)	3 (0)	5 (0)
Ear, face or neck anomalies	0 (0)	18 (0.5)	27 (0.3)	58 (0.4)
Anotia	0 (0)	0 (0)	3 (0)	3 (0)
Respiratory system anomalies	14 (1.7)	61 (1.7)	90 (1.1)	224 (1.6)
Choanal atresia	5 (0.6)	16 (0.4)	18 (0.2)	47 (0.3)
Cystic lung	0 (0)	4 (0.1)	7 (0.1)	23 (0.2)
Orofacial anomalies	10 (1.2)	47 (1.3)	119 (1.5)	202 (1.4)
Cleft lip	0 (0)	9 (0.3)	18 (0.2)	34 (0.2)
Cleft lip & palate	6 (0.7)	20 (0.6)	39 (0.5)	73 (0.5)
Cleft palate	4 (0.5)	16 (0.4)	60 (0.8)	90 (0.6)
Digestive system anomalies	16 (2)	120 (3.4)	234 (2.9)	461 (3.2)
Oesophageal atresia	4 (0.5)	30 (0.8)	53 (0.7)	103 (0.7)
Duodenal atresia/ stenosis	3 (0.4)	11 (0.3)	19 (0.2)	38 (0.3)
Small intestinal atresia/ stenosis	0 (0)	2 (0.1)	11 (0.1)	15 (0.1)
Anorectal atresia/ stenosis	5 (0.6)	17 (0.5)	39 (0.5)	77 (0.5)
Hirschsprung’s disease	0 (0)	5 (0.1)	5 (0.1)	15 (0.1)
Bile atresia	0 (0)	2 (0.1)	6 (0.1)	8 (0.1)
Diaphragmatic hernia	4 (0.5)	16 (0.4)	39 (0.5)	81 (0.6)
Diaphragmatic event	0 (0)	2 (0.1)	3 (0)	6 (0)
Abdominal anomalies	2 (0.2)	17 (0.5)	57 (0.7)	97 (0.7)
Gastroschisis	0 (0)	2 (0.1)	18 (0.2)	26 (0.2)
Omphalocele	2 (0.2)	15 (0.4)	40 (0.5)	72 (0.5)
Urinary anomalies	13 (1.6)	75 (2.1)	130 (1.6)	273 (1.9)
Renal agenesis	1 (0.1)	0 (0)	0 (0)	1 (0)
Renal dysplasia	1 (0.1)	11 (0.3)	20 (0.3)	38 (0.3)
Cystic kidney	0 (0)	4 (0.1)	3 (0)	13 (0.1)

Group Subtype	Severe N (% of 812†)	Moderate N (% of 3,568†)	Mild N (% of 7,993†)	All CHD N (% of 14,267†)
Hydronephrosis	4 (0.5)	23 (0.6)	45 (0.6)	87 (0.6)
Bladder extrophy	0 (0)	0 (0)	4 (0.1)	6 (0)
Genital anomalies	6 (0.7)	65 (1.8)	99 (1.2)	207 (1.5)
Hypospadias	4 (0.5)	47 (1.3)	67 (0.8)	144 (1)
Sex indeterminate	1 (0.1)	2 (0.1)	6 (0.1)	15 (0.1)
Limb anomalies	10 (1.2)	69 (1.9)	142 (1.8)	280 (2.0)
Limb reduction	2 (0.2)	25 (0.7)	22 (0.3)	63 (0.4)
Upper limb reduction	1 (0.1)	24 (0.7)	19 (0.2)	53 (0.4)
Lower limb reduction	1 (0.1)	2 (0.1)	5 (0.1)	14 (0.1)
Polydactyly	2 (0.2)	14 (0.4)	22 (0.3)	49 (0.3)
Syndactyly	0 (0)	4 (0.1)	2 (0)	10 (0.1)
Arthrogryposis	0 (0)	0 (0)	0 (0)	0 (0)
Musculo-skelatal anomalies	5 (0.6)	35 (1)	60 (0.8)	134 (0.9)
Thanatophoric dwarfism	0 (0)	0 (0)	0 (0)	0 (0)
Craniosynostosis	0 (0)	4 (0.1)	9 (0.1)	16 (0.1)

*Cases with teratogenic syndromes and chromosomal/ genetic ECAs were excluded

† Cases with teratogenic syndromes, chromosomal/ genetic ECAs, associations, sequences, skeletal dysplasia and non-genetic syndromes were excluded

5.3.5 Sex distribution in total birth cases of CHD

5.3.5.1 All CHD

Among total birth cases, 51.4% of cases were male. However, sex distribution varied by CHD subtype (Figure 5.1 A). There was a male preponderance of SV, HLH, HRH, AVA/S, TGV, ToF, TAPVR, CoA and DORV and a female preponderance of AVSD, MVA, ASD, PVS and PDA. There was a significant difference in the sex distribution according to the presence of ECAs (χ^2 test on all CHD subtypes combined: $p<0.001$). Specifically, cases with CHD and structural ECAs occurred most frequently in males, whereas cases with CHD and chromosomal/ genetic ECAs and CHD with teratogenic syndromes occurred more frequently in females.

5.3.5.2 Isolated CHD

Of the isolated cases of CHD, 52.1% were male. Amongst isolated cases there was a male preponderance of SV, HLH, HRH, AVA/S, TGV, ToF, TAPVR, IAA, CoA, DORV and "other" CHD subtypes (Figure 5.1 B). Cases of isolated AVSD, MVA, ASD, PVS and PDA were more common in females.

5.3.5.3 CHD with structural ECAs

Of the cases with structural ECAs, 56.8% of cases were male. There was a male preponderance of SV, HLH, HRH, AVA/S, TGV, ToF, CoA, DORV, MVA, VSD, PVS, PDA and "other" CHD subtypes (Figure 5.1 C). Cases with structural ECAs and EA, AVSD and IAA were more common in females.

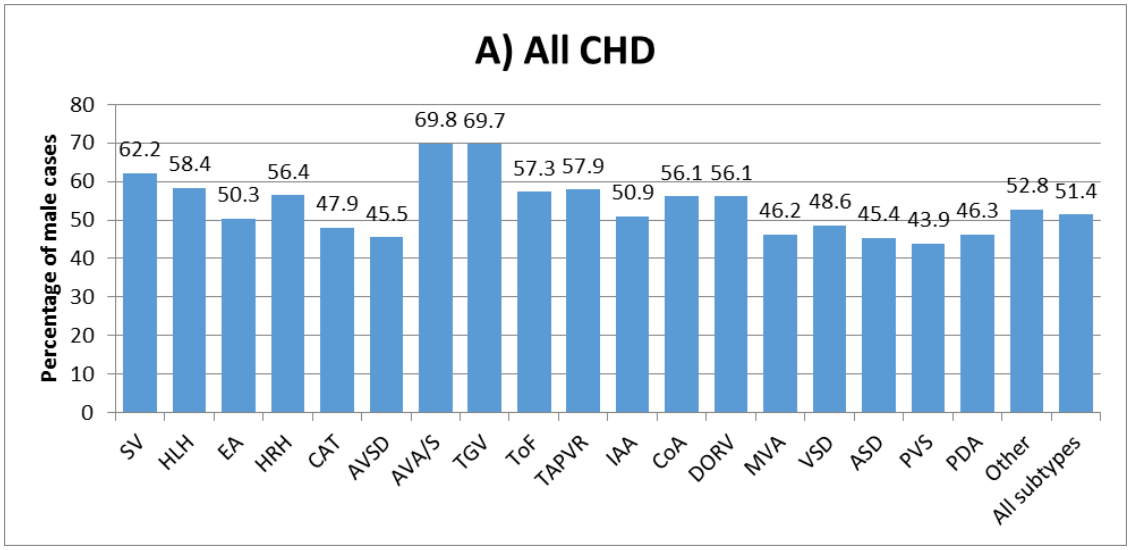
5.3.5.4 CHD with chromosomal/ genetic ECAs

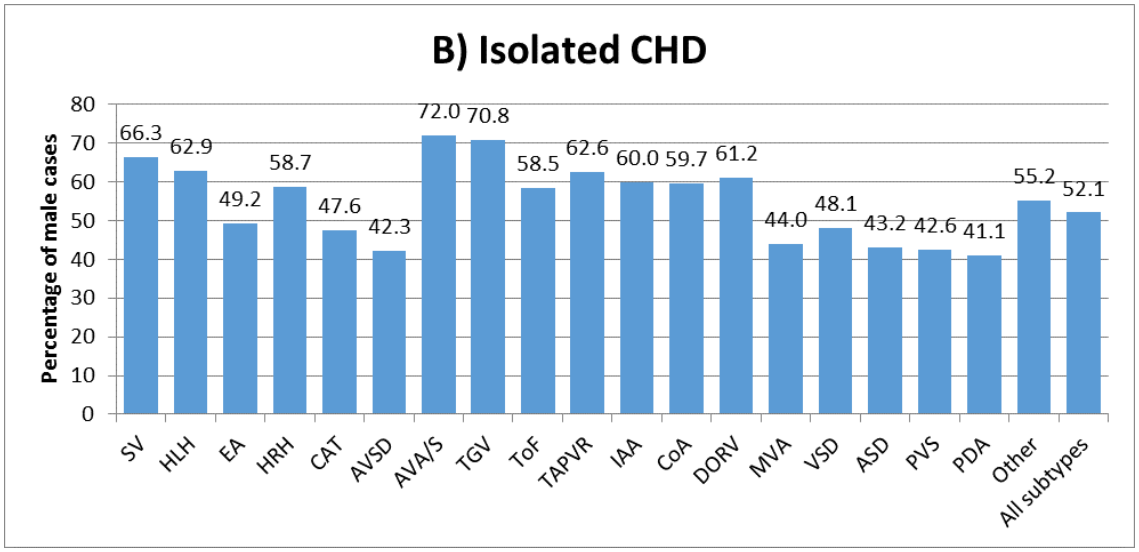
Of the cases with chromosomal/ genetic ECAs, 45.6% were male. As shown in Figure 5.1, there was a male preponderance of EA and TGV. Cases with chromosomal/ genetic ECAS and SV, HLH, HRH, CAT, AVSD, IAA, CoA, DORV, MVA, ASD and other CHD subtypes were more common in females (Figure 5.1 D).

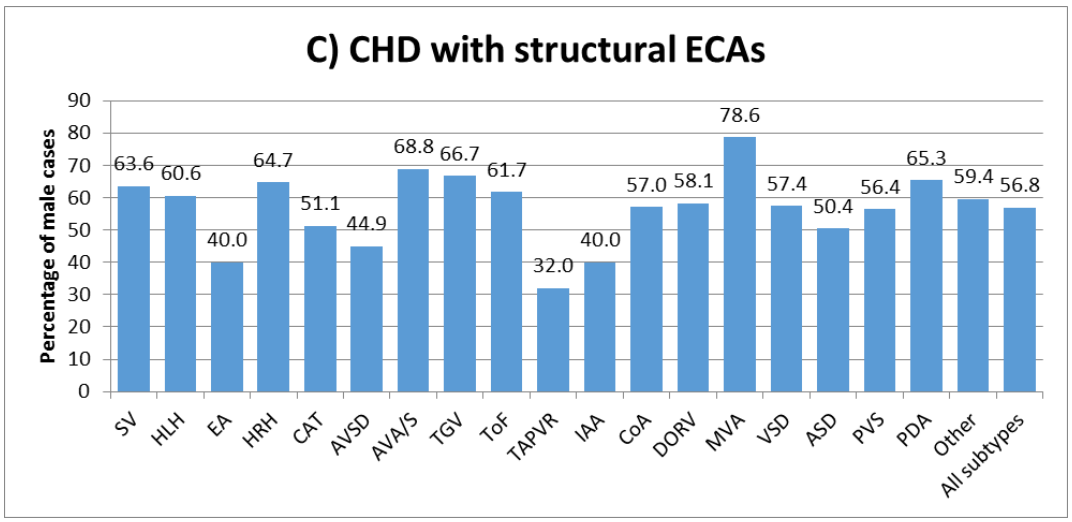
5.3.5.5 Summary

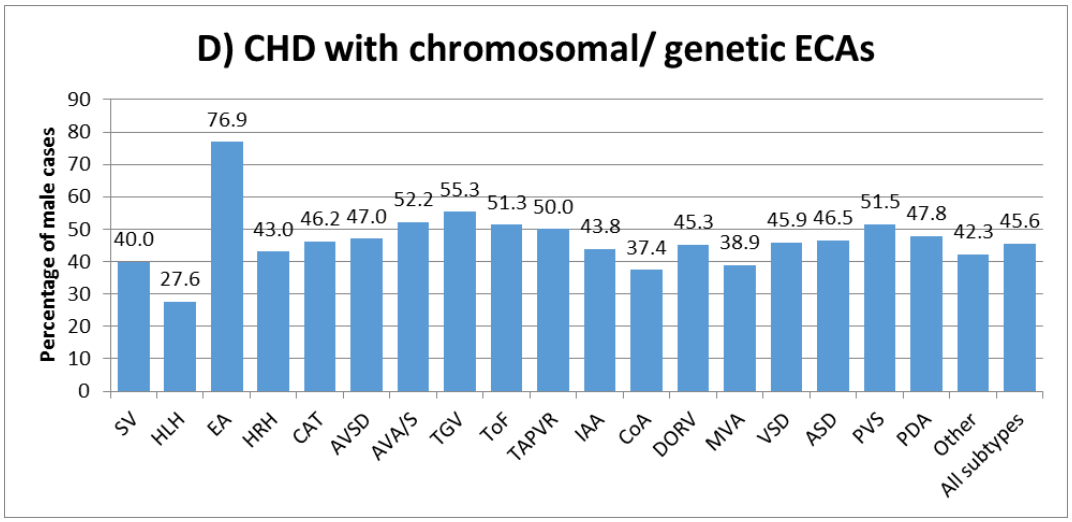
Although sex distribution varied substantially by CHD subtype, there was a male preponderance of cases with CHD and structural ECAs and a female preponderance of cases with CHD and chromosomal/ genetic ECAs.

Figure 5.1 Percentage of male (total birth) cases of CHD, by CHD subtype and ECAs









Infant sex was missing in 185 (1.4%) isolated cases, 49 (2.1%) cases with structural ECAs, 42 (1.1%) with chromosomal/ genetic ECAs.

5.3.6 Gestational age at delivery in live born cases of CHD

5.3.6.1 All CHD

There were 14,553 live born cases of CHD with complete data for gestational age at delivery. Of these, 159 (1.1%) were extremely preterm, 421 (2.9%) were very preterm, 1,902 (13.1%) were moderately preterm, 11,563 were term (79.5%) and 508 (3.5%) were post-term deliveries. As shown in Figure 5.2 A, these proportions varied according to CHD subtype. Cases of TAPVR (87.1%), IAA (88.6%), CoA (85.0%) and MVA (84.9%) were the most likely CHD subtypes to be term deliveries. TAPVR (5.7%) and CAT (4.7%) were the most likely subtypes to be delivered post-term. ASD and HLH was the most likely subtype to be born extremely preterm (2.6% and 2.0%). The distribution of gestational age at delivery varied significantly according to the presence of ECAs (Kruskal-Wallis test: $p<0.001$). Specifically, isolated cases were more likely to be born at term compared to cases with CHD and structural ECAs or chromosomal/ genetic ECAs or teratogenic syndromes. Below, gestational age at delivery is described in more detail according to the presence of ECAs.

5.3.6.2 Isolated CHD

There were 10,634 live born cases of isolated CHD with complete data for gestational age at delivery. Of these, 112 (1.1%) were delivered extremely preterm, 266 (2.5%) were very preterm, 1,134 (10.7%) were moderately preterm, 8,774 (82.1%) were term and 388 (3.6%) were post-term. As shown in Figure 5.2 B, these proportions varied by CHD subtype. For example, cases of HLH and ASD were most likely to be born extremely preterm (2.0% and 3.6%, respectively); cases of ASD, PVS and IAA were most likely to be born very preterm (4.6%, 4.2% and 4.8%, respectively); cases with TAPVR, PDA and MVA were more likely to be born term (91.7%, 95.4% and 87.5% respectively); cases of TAPVR and CAT were most likely to be born post-term (5.5% and 6.8%, respectively).

5.3.6.3 CHD with structural ECAs

There were 1,636 live born cases of CHD with structural ECAs and complete data for gestation age at delivery. Of these 29 (1.8%) were extremely preterm, 104 (6.4%) were very preterm, 336 (20.5%) were moderately preterm, 1,114 (68.1%) were term and 53 (3.2%) were post-term. Again these proportions varied by CHD subtype (Figure 5.2 C). For example, cases of PVS and MVA were most likely to be extremely preterm (11.4% and 7.7%, respectively); cases of MVA were most likely to be very preterm (15.4%); cases with “Other” CHD subtypes were most likely to be born moderately preterm (28.8%), cases of MVA were most likely to be born post-term (7.7%).

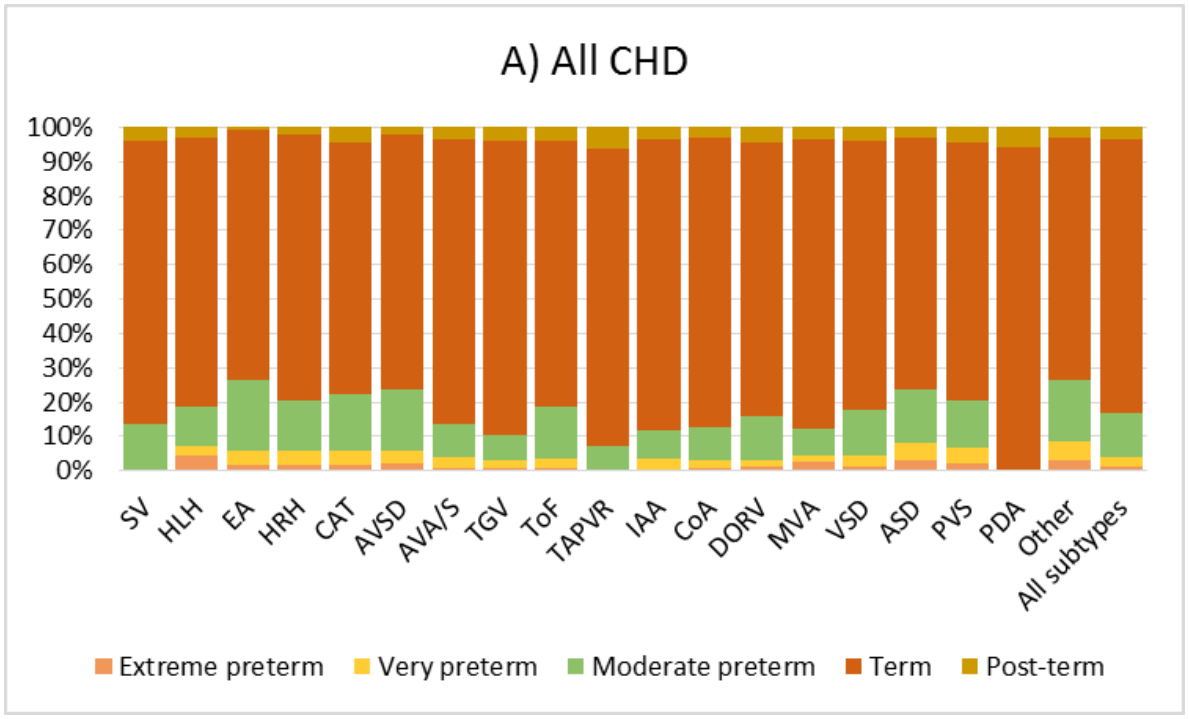
5.3.6.4 CHD with chromosomal/ genetic ECAs

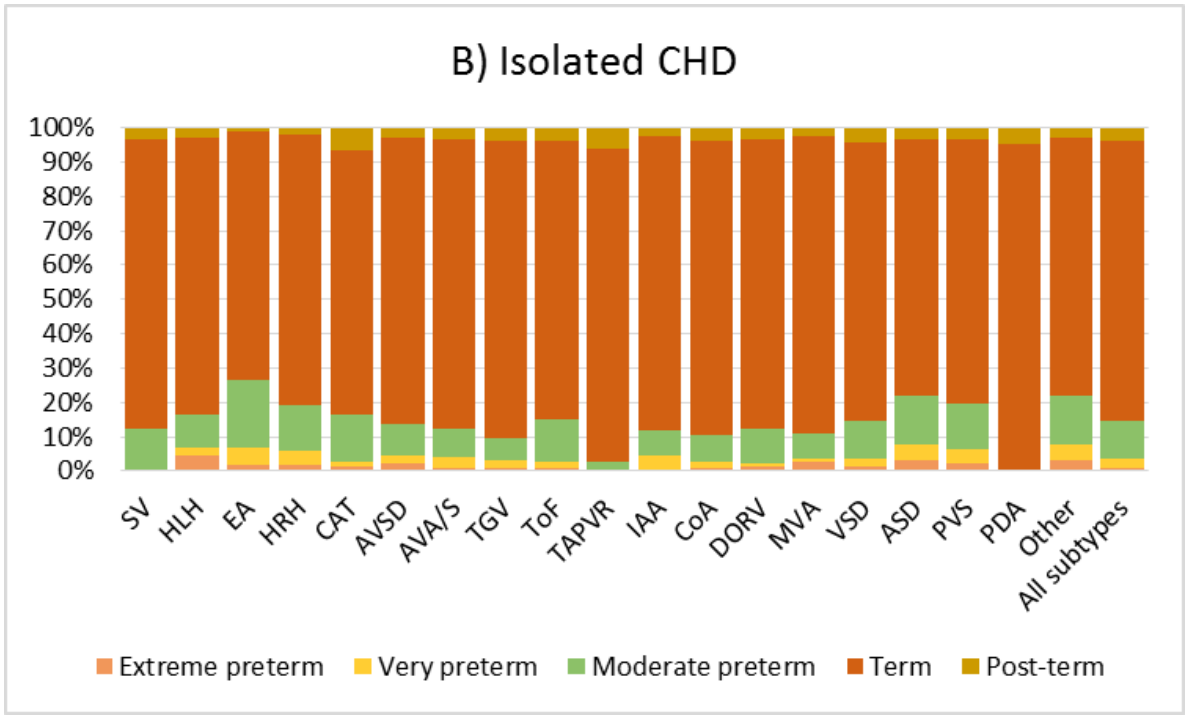
There were 2,243 live or stillborn cases of CHD with chromosomal/ genetic ECAs with complete data for gestational age at delivery. Of these, 18 (0.8%) were extremely preterm, 50 (2.2%) were very preterm, 421 (18.8%) were moderately preterm, 1,689 (75.3%) were term and 65 (2.9%) were post-term. Again these proportions varied by CHD subtype (Figure 5.2 D). Cases with "Other" CHD subtypes were most likely to be born extremely preterm (2.9%); cases of CAT were most likely to be born very preterm (6.7%); cases of EA were most likely to be born moderately preterm (27.3%) and cases of PVS were most the most likely to be born post-term (14.1%).

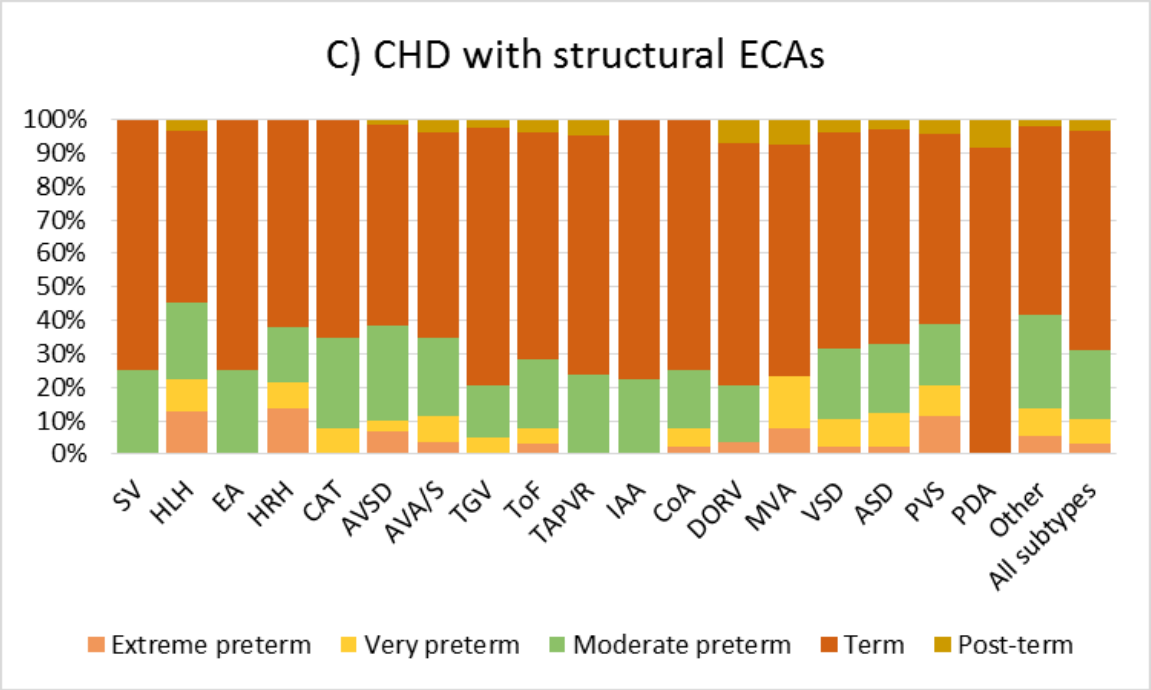
5.3.6.5 Summary

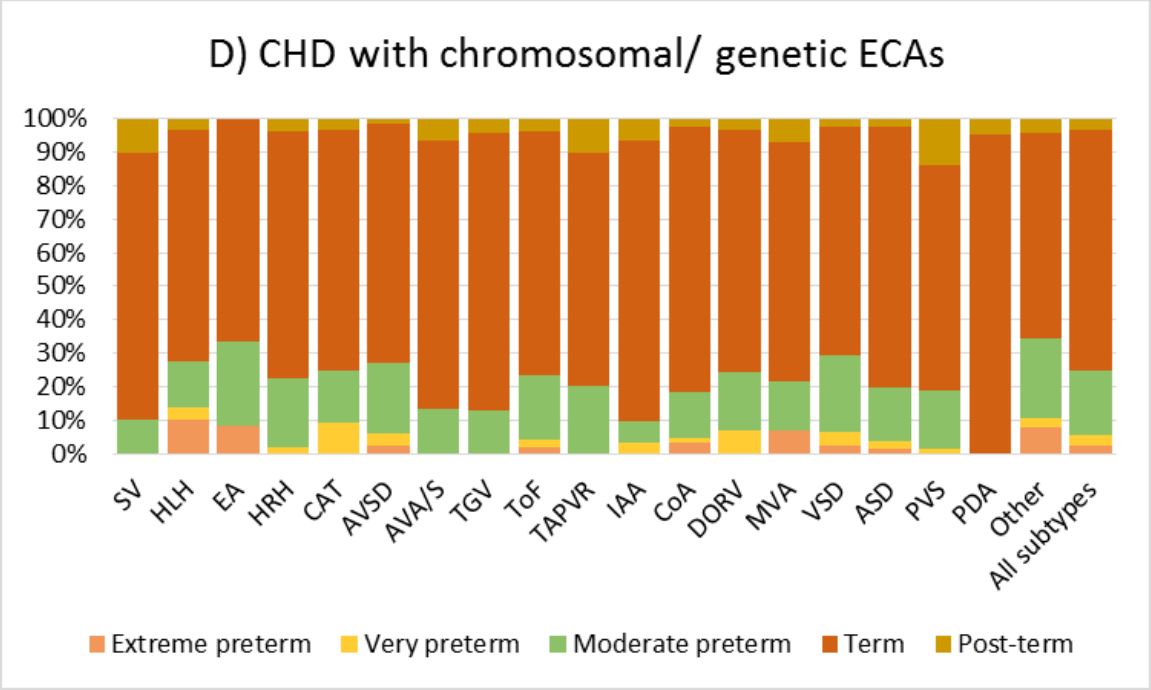
Overall 1.1% of cases were extremely preterm, 2.9% were very preterm and 13.1% were moderately preterm. Cases of HLH, IAA, ASD and PVS were most likely to be born extremely or very preterm. Isolated cases of CHD were more likely to be born at term compared to cases with CHD and structural ECAs or chromosomal/ genetic ECAs.

Figure 5.2 Gestational age at delivery in live births, by CHD subtype and ECAs









Gestational age at delivery was missing in 1,991 (15.8%) isolated cases, 132 (7.5%) cases with structural ECAs and 245 (9.9%) cases with chromosomal/ genetic ECAs.

5.3.7 Gestational age at delivery according to prenatal diagnosis

5.3.7.1 Isolated CHD

Considering all isolated CHD subtypes, 21.4% of prenatally diagnosed cases were delivered preterm compared to 14.5% of non-prenatally diagnosed cases. Prenatally diagnosed cases were significantly more likely to be delivered preterm (test of proportions: p=0.001). With the exception of ToF, all subtypes that were prenatally diagnosed were more likely to be delivered preterm, although this only reached statistical significance in cases with EA, AVA/S, VSD and "Other" CHD subtypes (Table 5.14).

Table 5.14 Preterm birth according to prenatal diagnosis among isolated cases of CHD, by CHD subtype*

Subtype	Preterm births/ Prenatally un-diagnosed cases n/N, %	Preterm births/ Prenatally diagnosed cases n/N, %	P-value (test of proportions)
SV	0/ 17, 0	6/ 34, 17.6	0.065
HLH	17/ 116, 14.7	38/ 230, 16.5	0.654
EA	4/ 38, 10.5	16/ 40, 40	0.003
HRH	15/ 91, 16.5	27/ 137, 19.7	0.539
CAT	3/ 37, 8.1	8/ 23, 34.8	0.009
AVSD	11/ 115, 9.6	18/ 86, 20.9	0.023
AVA/S	27/ 228, 11.8	10/ 31, 32.3	0.002
TGV	30/ 372, 8.1	17/ 132, 12.9	0.102
ToF	34/ 251, 13.5	11/ 83, 13.3	0.946
TAPVR	2/ 73, 2.7	0/ 8, 0	0.636
IAA	3/ 26, 11.5	1/ 6, 16.7	0.732
CoA	38/ 354, 10.7	11/ 96, 11.5	0.840
DORV	6/ 38, 15.8	5/ 40, 12.5	0.677
MVA	5/ 77, 6.5	2/ 10, 20	0.140
VSD	418/ 2,751, 15.2	48/ 197, 24.4	0.001
ASD	184/ 813, 22.6	17/ 57, 29.8	0.213
PVS	90/ 487, 18.5	5/ 17, 29.4	0.257
PDA	0/ 269, 0	0/ 14, 0	-
Other	64/ 419, 15.3	58/ 151, 38.4	0.001
All subtypes	**951/ 6,572, 14.5**	**298/ 1,392, 21.4**	**0.001**

*Cases notified to CAROBB, EMSYCAR and SWCAR were excluded due to incomplete data on prenatal diagnosis. 1,895 (15.7%) cases were excluded due to either missing gestational age or missing prenatal diagnosis data.

5.3.8 Standardised birth weight in live births

5.3.8.1 All CHD

Standardised birth weight was calculated for 13,226 (78.2%) live born cases of CHD. Overall, 3,434 (26.0%) were low birth weight, 7659 (57.9%) were average birth weight and 2,133 (16.1%) were high birth weight. There was variation in standardised birth weight according to CHD subtype (Figure 5.3 A) and standardised birth weight varied significantly according to the presence of ECAs (Kruskal-Wallis test: $p<0.001$).

5.3.8.2 Isolated CHD

Standardised birth weight was calculated for 9,651 (76.4%) live born cases with isolated CHD. There were 2,021 (20.9%) cases with low birth weight, 5,902 (61.2%) with average birth weight and 1,728 (17.9%) with high birth weight, although this varied by CHD subtype (Figure 5.3 B).

5.3.8.3 CHD with structural ECAs

Standardised birth weight was calculated for 1,536 (86.9%) live born cases with CHD and structural ECAs. There were 543 (35.4%) cases with low birth weight, 799 (52.0%) with average birth weight and 194 (12.6%) with high birth weight, although this varied by CHD subtype (Figure 5.3 C).

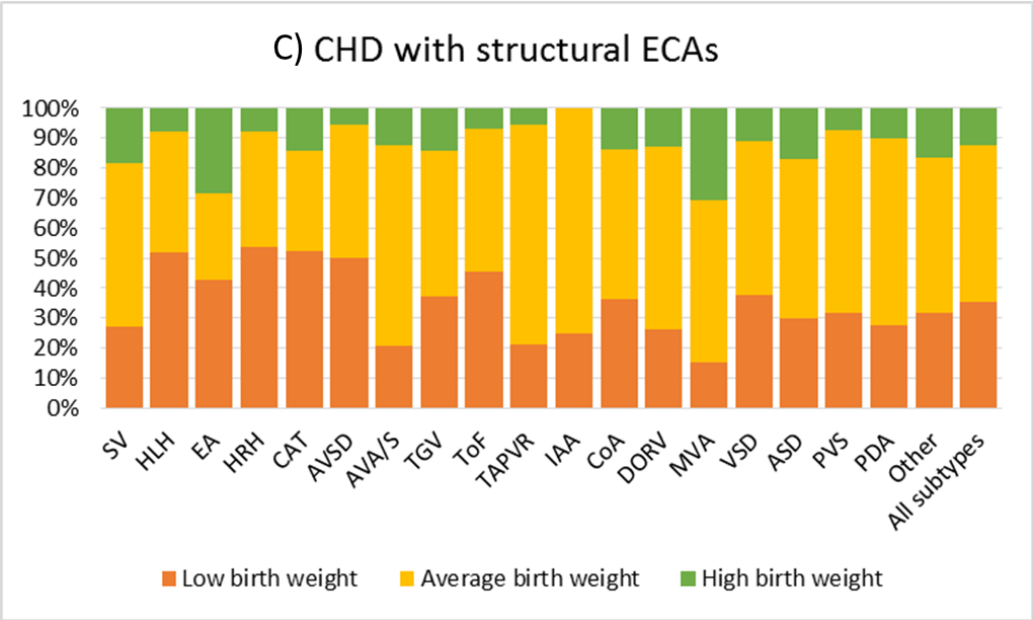
5.3.8.4 CHD with chromosomal/ genetic ECAs

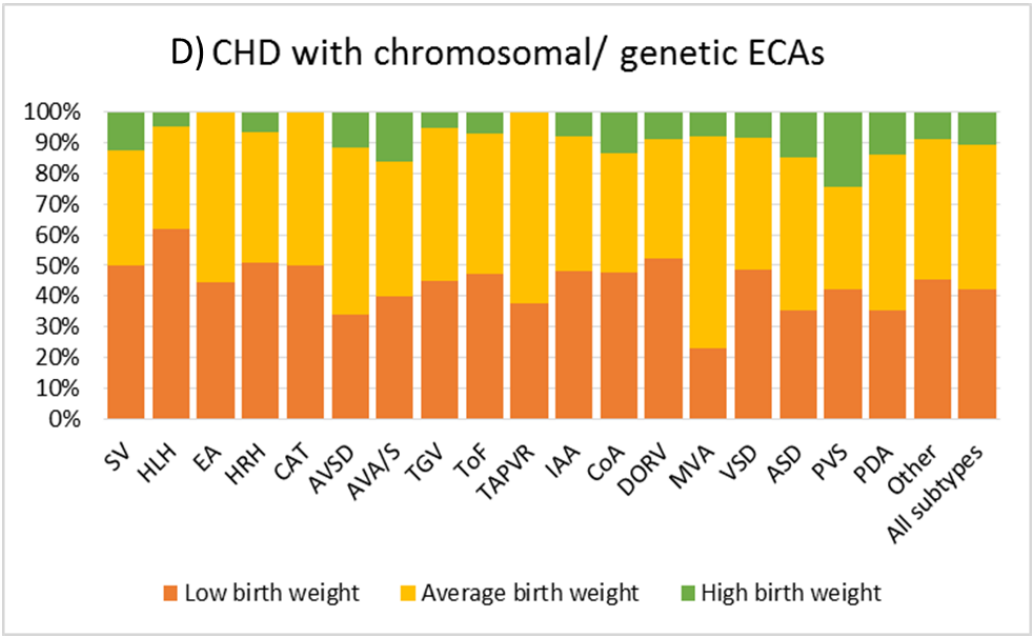
Standardised birth weight was calculated for 2,002 (80.5%) live born cases with CHD and chromosomal/ genetic ECAs. There were 848 (42.4%) cases with low birth weight, 944 (47.2%) with average birth weight and 210 (10.5%) with high birth weight, although this varied by CHD subtype (Figure 5.3 D).

5.3.8.5 Summary

In total, 26% of cases were of low birth weight, although this varied by CHD subtype and the presence of ECAs. In general, cases with ECAs were more likely to have a low birth weight than isolated cases of CHD.

Figure 5.3 Standardised birth weight in live births, by CHD subtype and ECAs





Standardised birth weight was missing in 1,678 (13.3%) isolated cases, 143 (8.1%) cases with structural ECAs and 343 (13.8%) cases with chromosomal/ genetic ECAs.

5.3.9 Total birth prevalence

The total birth prevalence of CHD was 65.0 (95% CI: 64.1-65.9) per 10,000 total births. Table 5.15 shows the total birth prevalence of each CHD subtype according to the presence of ECAs.

Table 5.15 Total birth prevalence (95% CI) of CHD, by CHD subtype and ECAs

CHD subtype	Prevalence per 10,000 total births (95% CI)			
	Isolated CHD	**CHD with structural ECAs**	**CHD with chromosomal/ genetic ECAs**	**All CHD**
SV	0.3 (0.3-0.4)	0.1 (0-0.1)	0.1 (0-0.1)	0.5 (0.4-0.6)
HLH	2.3 (2.2-2.5)	0.2 (0.2-0.3)	0.3 (0.3-0.4)	2.9 (2.7-3.1)
EA	0.4 (0.3-0.5)	0 (0-0.1)	0 (0-0.1)	0.5 (0.4-0.6)
HRH	1.3 (1.2-1.4)	0.2 (0.2-0.3)	0.3 (0.3-0.4)	1.9 (1.7-2)
CAT	0.3 (0.3-0.4)	0.2 (0.1-0.2)	0.2 (0.2-0.3)	0.7 (0.6-0.8)
AVSD	1.1 (1-1.2)	0.4 (0.3-0.4)	2.5 (2.4-2.7)	4.0 (3.8-4.3)
AVA/S	1.4 (1.2-1.5)	0.1 (0.1-0.2)	0.2 (0.1-0.2)	1.6 (1.5-1.8)
TGV	2.6 (2.4-2.8)	0.2 (0.1-0.2)	0.2 (0.1-0.2)	3 (2.8-3.2)
ToF	2 (1.8-2.1)	0.6 (0.5-0.7)	0.8 (0.7-0.9)	3.4 (3.2-3.6)
TAPVR	0.5 (0.4-0.6)	0.1 (0.1-0.1)	0 (0-0.1)	0.6 (0.5-0.7)
IAA	0.2 (0.1-0.2)	0 (0-0.1)	0.2 (0.1-0.2)	0.4 (0.3-0.4)
CoA	2.5 (2.3-2.6)	0.4 (0.3-0.5)	0.5 (0.4-0.6)	3.3 (3.1-3.5)
DORV	0.4 (0.4-0.5)	0.1 (0.1-0.2)	0.2 (0.2-0.3)	0.8 (0.7-0.9)
MVA	0.5 (0.4-0.6)	0 (0-0.1)	0.1 (0-0.1)	0.6 (0.5-0.7)
VSD	16.7 (16.2-17.1)	2 (1.9-2.2)	3.4 (3.2-3.7)	22.2 (21.6-22.7)
ASD	4.5 (4.2-4.7)	1.3 (1.2-1.5)	1.5 (1.3-1.6)	7.3 (7-7.6)
PVS	2.7 (2.5-2.9)	0.2 (0.1-0.2)	0.2 (0.2-0.3)	3.1 (2.9-3.3)
PDA	1.2 (1.1-1.3)	0.3 (0.3-0.4)	0.2 (0.2-0.3)	1.8 (1.6-1.9)
Other	3.5 (3.3-3.7)	1.3 (1.2-1.5)	1.5 (1.4-1.7)	6.4 (6.1-6.7)
All subtypes	**44.4 (43.7-45.2)**	**7.9 (7.5-8.2)**	**12.5 (12.1-12.9)**	**65.0 (64.1-65.9)**

5.3.10 Trends in total birth prevalence

5.3.10.1 All CHD adjusted for the presence of ECAs

Overall, there was no evidence of a trend in total birth prevalence over time (p=0.529) (Table 5.16). However, the total birth prevalence of AVA/S decreased significantly by 3% per year (RR=0.97, 95% CI: 0.95-0.99; p=0.002), the total birth prevalence of CoA decreased significantly by 2% per year (RR=0.98, 95% CI: 0.96-0.99; p<0.001) and the total birth prevalence of ToF increased significantly by 3% per year (RR=1.03, 95% CI: 1.01-1.04; p=0.001). Adjusting for maternal age at delivery had little impact on the trends in CHD over time (Table 5.16).

Table 5.16 Trends in the total birth prevalence of CHD over time, by CHD subtype

Subtype	RR of CHD per year* (95% CI)	P-value	Adjusted RR of CHD per year (95% CI)‡	P-value
SV	0.97 (0.94-1.00)	0.082	0.95 (0.91-0.99)	0.028
HLH	1.01 (1-1.02)	0.191	1.00 (0.98-1.02)	0.706
EA	1.00 (0.97-1.03)	0.979	1.00 (0.96-1.04)	0.914
HRH	0.99 (0.98-1.01)	0.540	0.98 (0.95-1.00)	0.026
CAT	1.02 (0.99-1.05)	0.180	1.02 (0.99-1.06)	0.172
AVSD	1.01 (0.99-1.02)	0.396	1.00 (0.98-1.01)	0.749
AVA/S¥	0.97 (0.95-0.99)	0.002	0.96 (0.94-0.98)	<0.001
TGV	1.00 (0.99-1.02)	0.902	1.01 (0.99-1.03)	0.296
ToF	1.03 (1.01-1.04)	<0.001	1.03 (1.01-1.05)	<0.001
TAPVR	0.99 (0.96-1.02)	0.515	1.00 (0.96-1.03)	0.946
IAA	1.01 (0.97-1.05)	0.667	1.00 (0.96-1.05)	0.962
CoA	0.98 (0.96-0.99)	0.001	0.98 (0.96-0.99)	0.006
DORV	1.01 (0.98-1.04)	0.561	1.02 (0.99-1.06)	0.170
MVA	0.98 (0.95-1.01)	0.202	0.96 (0.93-1.00)	0.034
VSD†	1.02 (0.99-1.06)	0.186	1.04 (0.99-1.10)	0.147
ASD†	1.00 (0.96-1.05)	0.925	0.99 (0.93-1.07)	0.857
PVS†	1.00 (0.99-1.02)	0.585	1.01 (0.99-1.02)	0.221
PDA†	1.08 (1.01-1.14)	0.014	1.09 (0.99-1.19)	0.080
Other†	0.98 (0.96-1.01)	0.146	0.99 (0.97-1.02)	0.636
All subtypes	**1.00 (1.00-1.00)**	**0.529**	**1.02 (0.98-1.06)**	**0.402**

*Relative risks (RRs) were estimated using multilevel Poisson regression models with a random intercept (for register), adjusted for presence of structural and chromosomal extra-cardiac anomalies.

†The RRs for these subtypes were estimated using Poisson regression with a random slope and random intercept

¥ The RR for this subtype was estimated using Poisson regression with a random intercept and an overdispersion term

‡ Adjusted for maternal age at delivery. This analysis excluded cases notified to CAROBB (all years), EMSYCAR (all years) and SWCAR for 2010.

5.3.10.2 Interaction between year of delivery and the presence of ECAs

Overall, there was a significant interaction between year of delivery and the presence of ECAs ($p<0.001$). Therefore, the prevalence models were fitted separately to isolated cases of CHD, CHD with structural ECAs and CHD with chromosomal/ genetic ECAs. The trends over time were slightly steeper among cases with structural ECAs and cases with chromosomal/ genetic ECAs compared to cases with CHD isolated CHD (Table 5.17). As shown in Table 5.17, trends over time were not significant.

Of the individual subtypes, trends in total birth prevalence varied significantly according to the presence of ECAs for VSDs only ($p=0.001$). Trends over time in the total birth prevalence of VSD with chromosomal/ genetic ECAs were steeper than trends over time in isolated VSD, but none of the trends were statistically significant (Table 5.17).

Table 5.17 Unadjusted trends in total birth prevalence according to presence of ECAs

Subtype	**Isolated CHD**		**CHD with structural ECAs**		**CHD with chromosomal/ genetic CHDs**	
	RR (95% CI)	**P-value**	**RR (95% CI)**	**P-value**	**RR (95% CI)**	**P-value**
VSD	1.00 (0.98-1.01)	0.498	1.00 (0.98-1.02)	0.713	1.02 (1.00-1.03)	0.035
All subtypes	0.99 (0.98-1.00)	0.118	1.00 (0.99-1.01)	0.658	1.01 (1.00-1.02)	0.200

5.3.11 Heterogeneity in total birth prevalence between registers

5.3.11.1 All CHD adjusted for the presence of ECAs

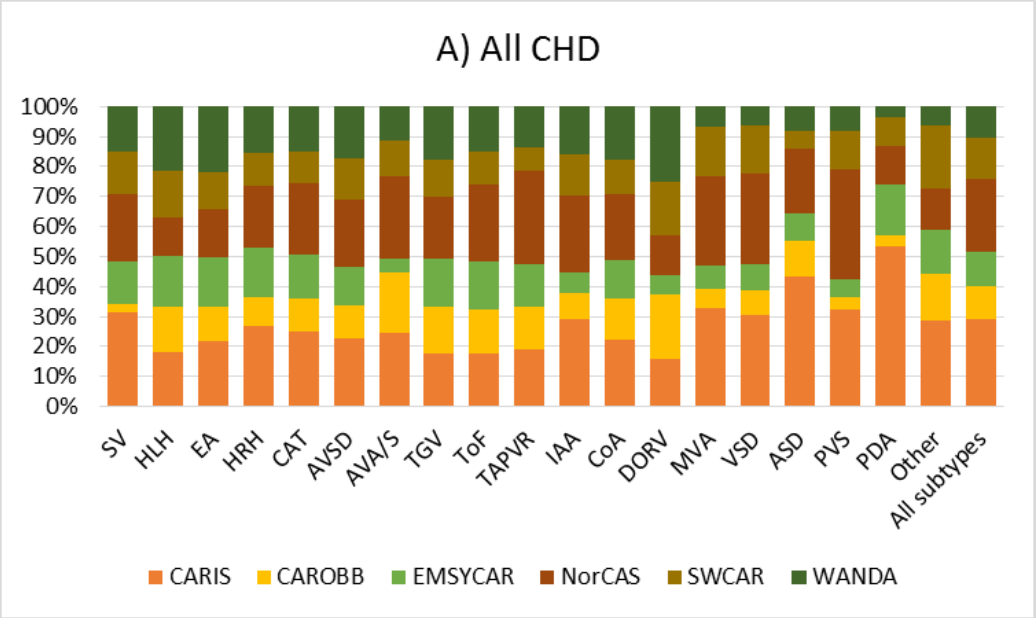
Overall, there was significant heterogeneity in total birth prevalence between registers (LR test for random intercept: $p<0.001$), the total birth prevalence of CHD was greatest in CARIS, followed by NorCAS. CAROBB, EMSYCAR, SWCAR and WANDA had broadly similar total birth prevalence rates. There appeared to be slightly less variation in prevalence among cases with ECAs compared to those with isolated CHD.

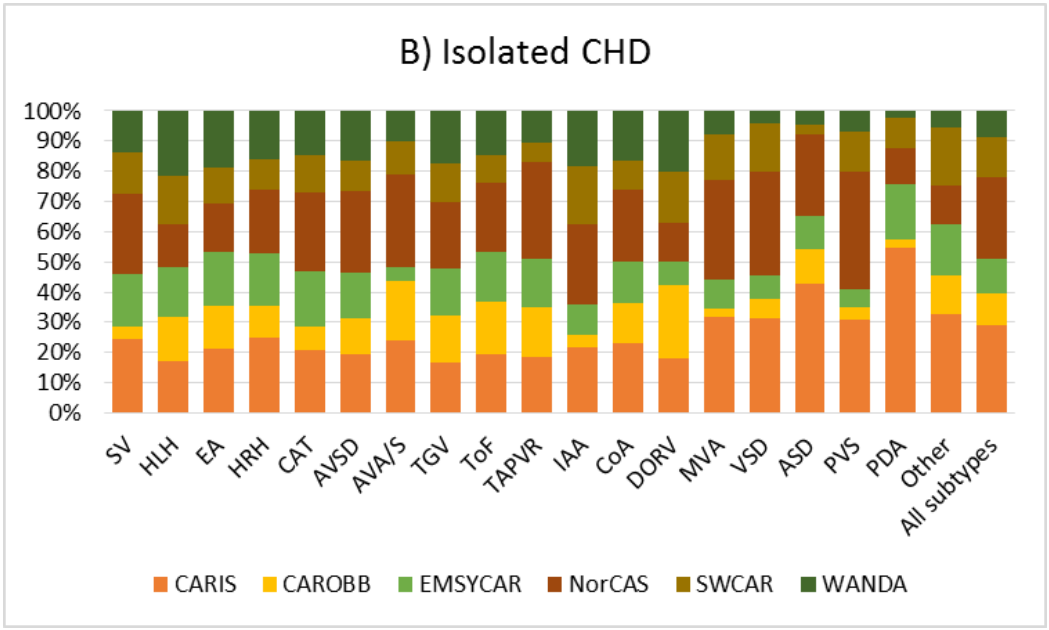
There was also significant heterogeneity in total birth prevalence between registers for every CHD subtype (LR tests: $p<0.001$ for all CHD subtypes). Figure 5.4 shows the percentage of the prevalence contributed by each register. Here, it appears that there is a greater degree of variation among the milder CHD subtypes than the more severe ones, particularly among isolated cases of CHD. For many subtypes, CARIS and NorCAS account for the largest proportions of cases.

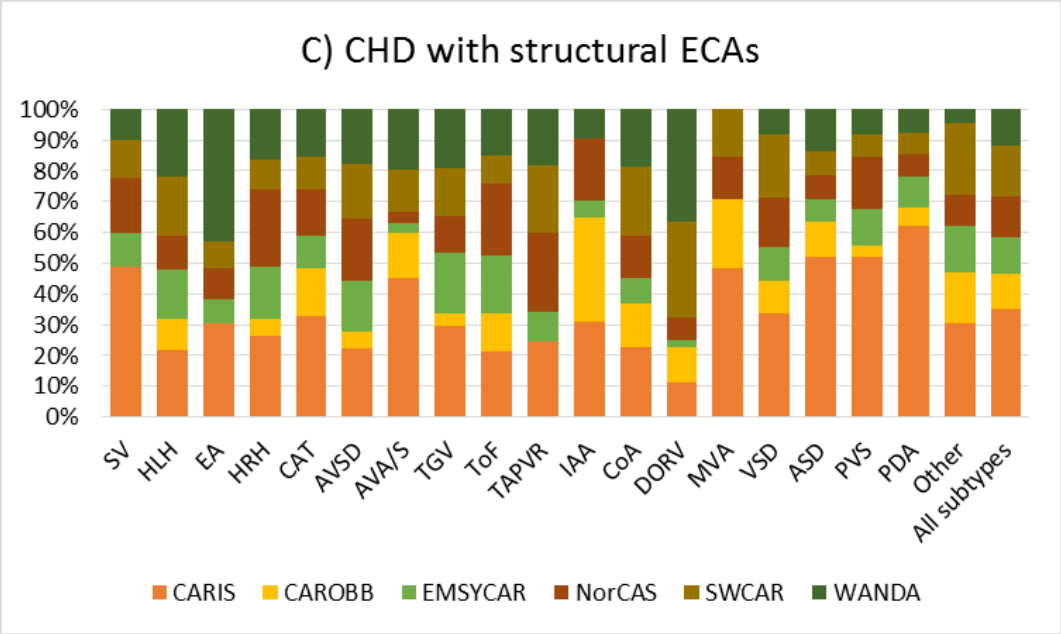
Table 5.18 Total birth prevalence by register

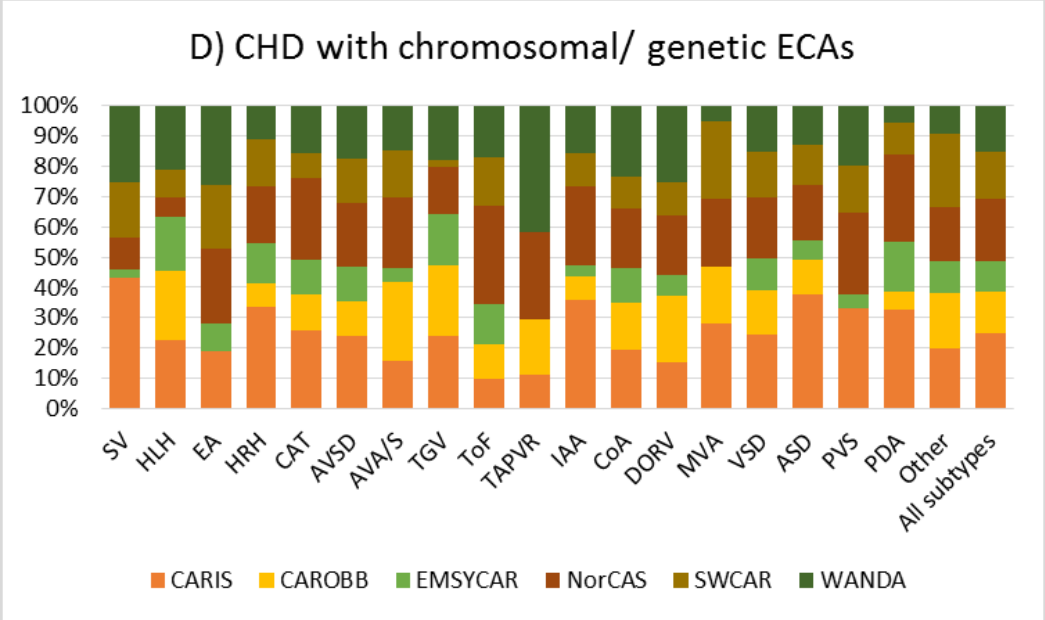
Register	Prevalence per 10,000 total births (95% CI)			
	Isolated CHD	**CHD with structural ECAs**	**CHD with chromosomal/ genetic ECAs**	**All CHD**
CARIS	75.9 (73.3-78.5)	17.4 (16.1-18.6)	18.9 (17.7-20.3)	112.6 (109.5-115.8)
CAROBB	26.3 (24.4-28.4)	5.7 (4.8-6.6)	10.5 (9.3-11.8)	42.8 (40.3-45.4)
EMSYCAR	29.8 (28.6-30.9)	5.7 (5.2-6.2)	8.0 (7.4-8.6)	43.6 (42.2-45)
NorCAS	71.1 (69-73.1)	6.6 (6-7.2)	15.8 (14.8-16.8)	93.5 (91.2-95.9)
SWCAR	33.7 (31.9-35.6)	8.1 (7.2-9)	11.7 (10.6-12.8)	53.7 (51.4-56)
WANDA	22.9 (21.5-24.3)	5.8 (5.2-6.6)	11.7 (10.7-12.7)	40.6 (38.7-42.4)

Figure 5.4 Percentage of total birth prevalence accounted for by each register






C) CHD with structural ECAs
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
SV
HLH
EA
HRH
CAT
AVSD
AVA/S
TGV
ToF
TAPVR
IAA
CoA
DORV
MVA
VSD
ASD
PVS
PDA
Other
All subtypes
CARIS
CAROBB
EMSYCAR
NorCAS
SWCAR
WANDA

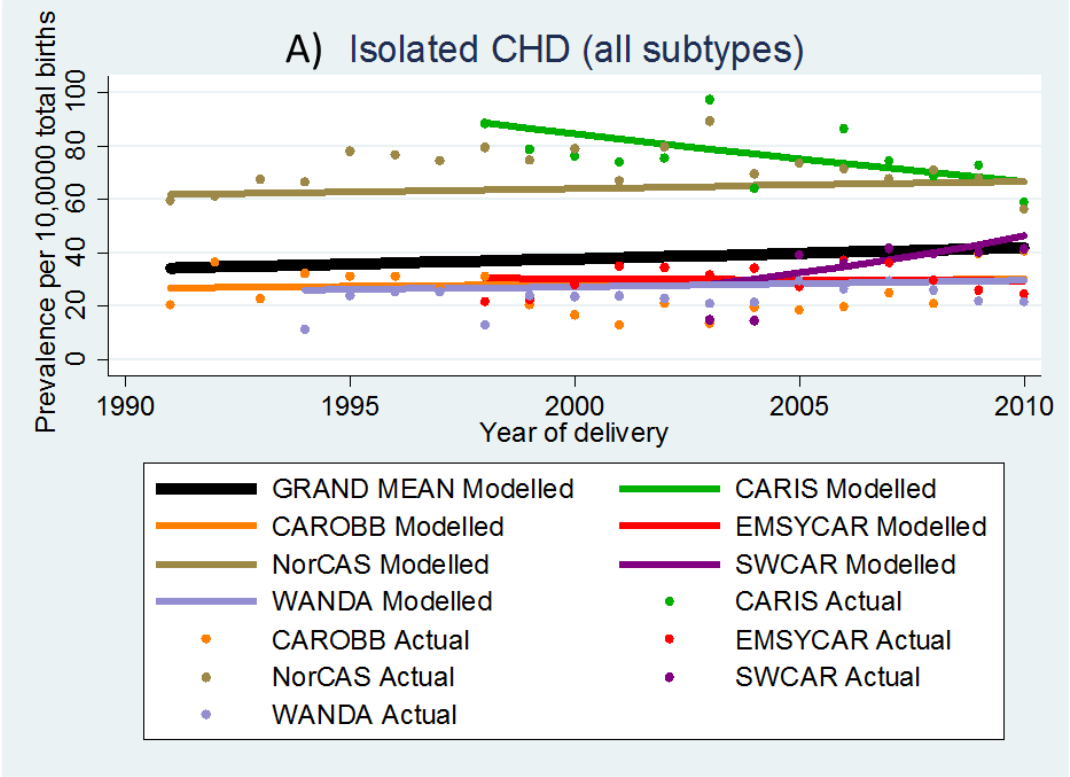

D) CHD with chromosomal/ genetic ECAs
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
SV
HLH
EA
HRH
CAT
AVSD
AVA/S
TGV
ToF
TAPVR
IAA
CoA
DORV
MVA
VSD
ASD
PVS
PDA
Other
All subtypes
CARIS
CAROBB
EMSYCAR
NorCAS
SWCAR
WANDA

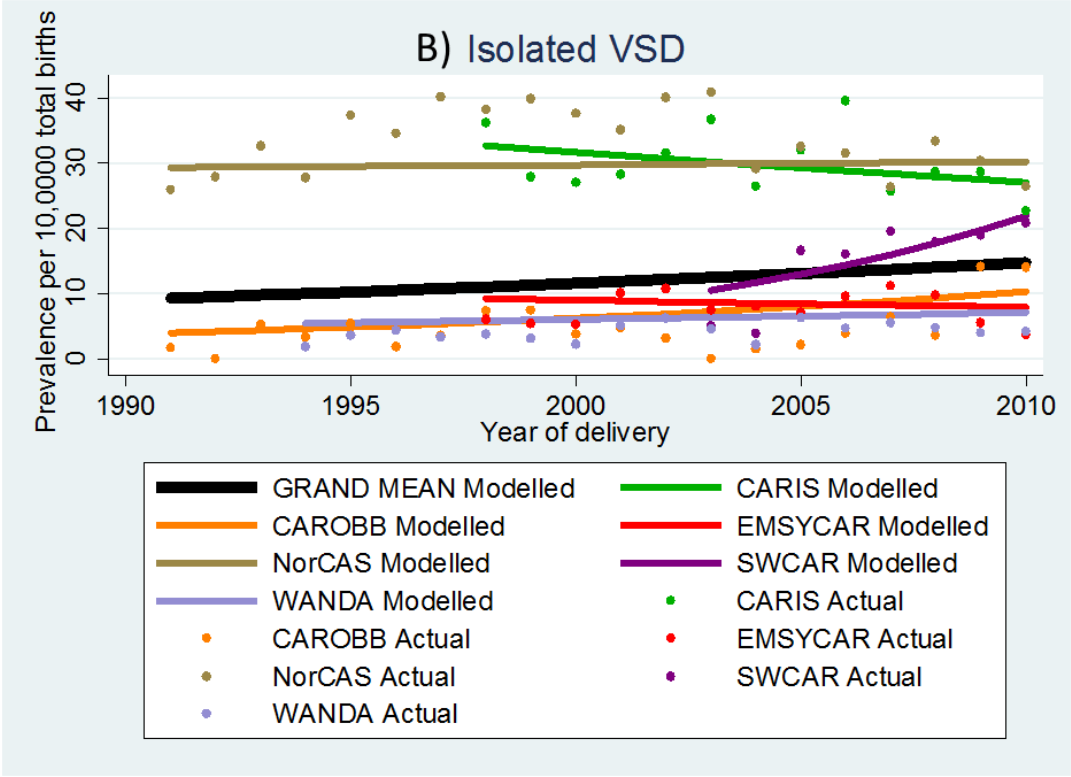
5.3.12 Heterogeneity in trends in total birth prevalence

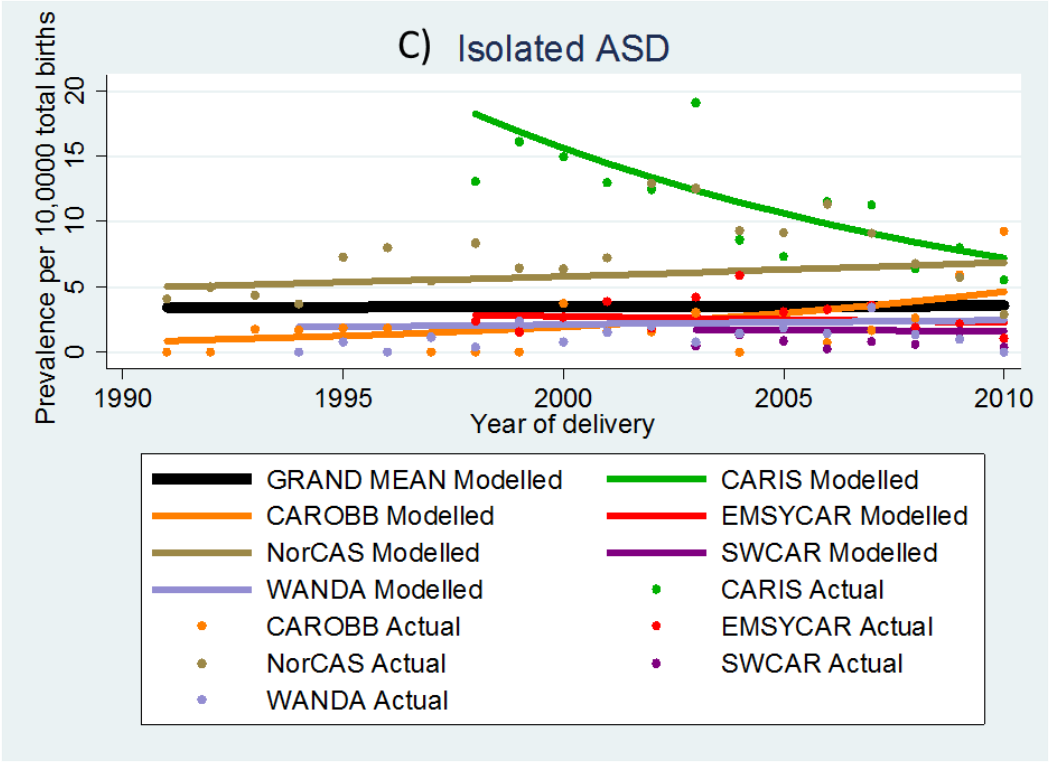
5.3.12.1 All CHD adjusted for the presence of ECAs

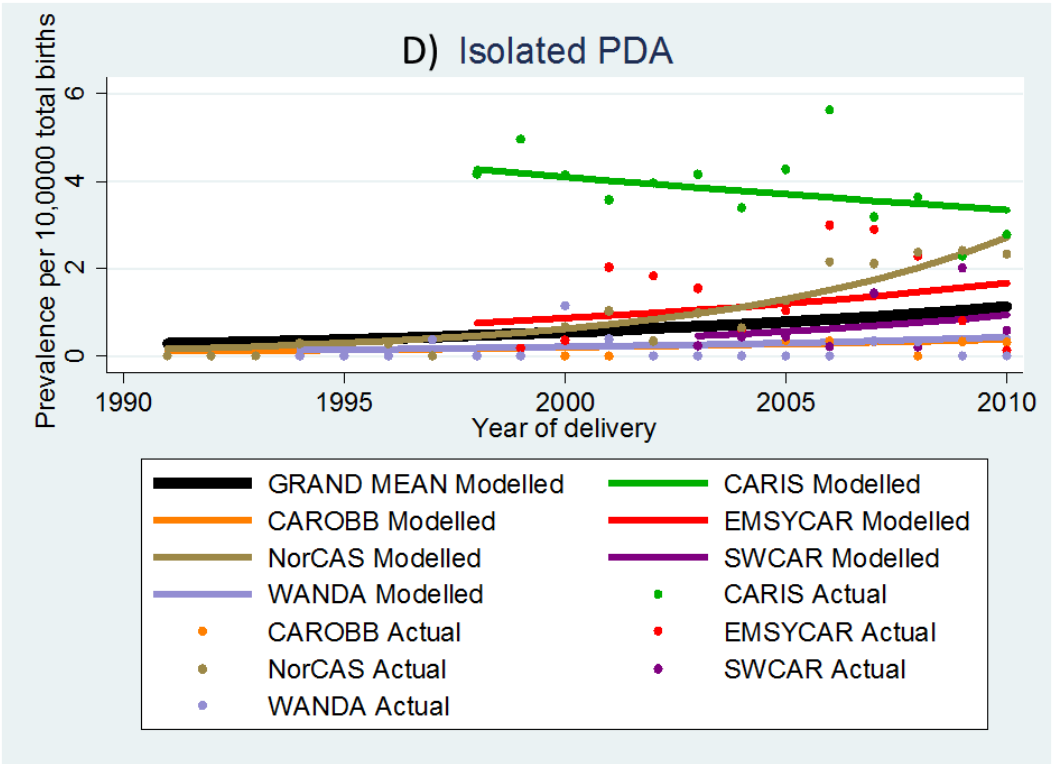
Overall, there was variation in trends in prevalence between registers ($p<0.001$). However, variation in trends over time between registers was observed in only the milder CHD subtypes: VSD, ASD, PDA and "other" CHD subtypes (all at $p<0.001$). As shown in Figure 5.5 A, trends over time were similar in the areas covered by NorCAS, EMSYCAR, CAROBB and WANDA, all showing a slight increase in prevalence over time. Trends in CHD prevalence in the area covered by SWCAR also increased slightly over time, but with a steeper gradient. Alternatively, trends in total birth prevalence over time in the area covered by CARIS appeared to decrease. For cases of VSD, the trends in the registers mirrored those of trends in all CHD subtypes combined. For cases of ASD and PDA, all registers had similar (slightly increasing) trends in total birth prevalence over time, with the exception of CARIS, which showed a decreasing trend in total birth prevalence (Figure 5.5 C and D). For cases with "Other" CHD subtypes, the prevalence decreased slightly for all registers except SWCAR, where the prevalence appeared to increase slightly over time (Figure 5.5 E).

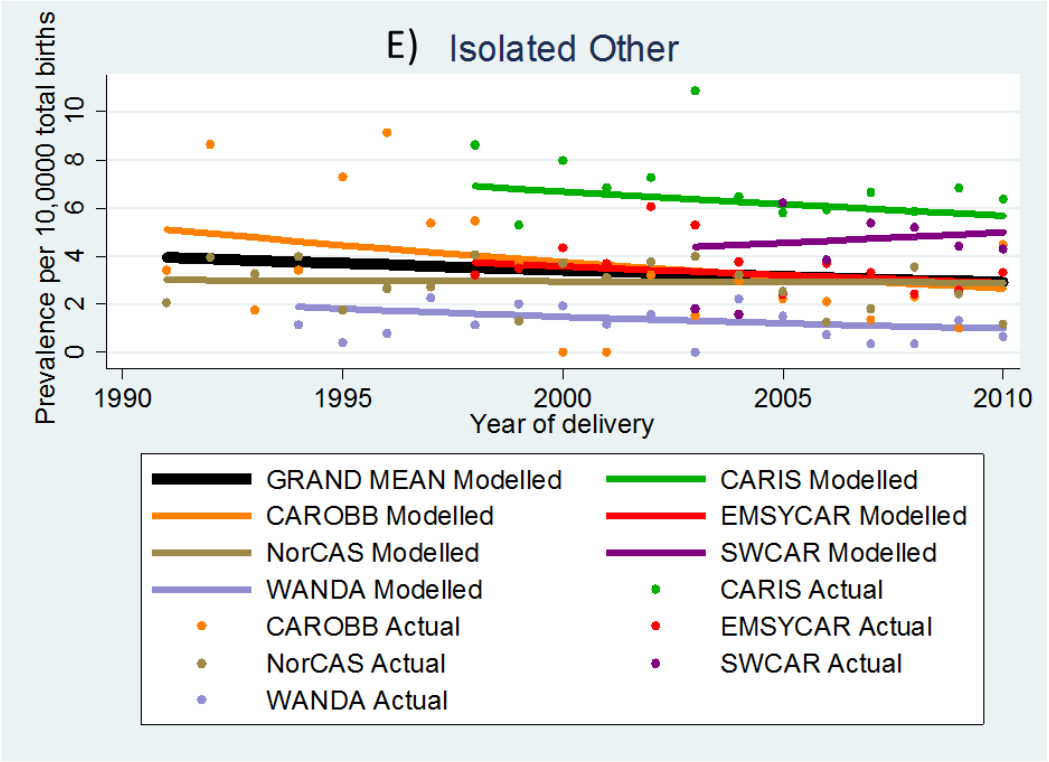
Figure 5.5 Total birth prevalence of CHD over time, by register and subtype






C) Isolated ASD
Prevalence per 10,0000 total births
0
5
10
15
20
1990
1995
2000
2005
2010
Year of delivery
GRAND MEAN Modelled
CAROBB Modelled
NorCAS Modelled
WANDA Modelled
CAROBB Actual
NorCAS Actual
WANDA Actual
CARIS Modelled
EMSYCAR Modelled
SWCAR Modelled
CARIS Actual
EMSYCAR Actual
SWCAR Actual


D) Isolated PDA
Prevalence per 10,0000 total births
0
2
4
6
1990
1995
2000
2005
2010
Year of delivery
GRAND MEAN Modelled
CAROBB Modelled
NorCAS Modelled
WANDA Modelled
CAROBB Actual
NorCAS Actual
WANDA Actual
CARIS Modelled
EMSYCAR Modelled
SWCAR Modelled
CARIS Actual
EMSYCAR Actual
SWCAR Actual


E) Isolated Other
Prevalence per 10,0000 total births
0
2
4
6
8
10
1990
1995
2000
2005
2010
Year of delivery
GRAND MEAN Modelled
CAROBB Modelled
NorCAS Modelled
WANDA Modelled
CAROBB Actual
NorCAS Actual
WANDA Actual
CARIS Modelled
EMSYCAR Modelled
SWCAR Modelled
CARIS Actual
EMSYCAR Actual
SWCAR Actual

5.3.13 Live birth prevalence

The live birth prevalence was 55.9 (95% CI: 55.1-56.7) per 10,000 live births. Table 5.19 shows the live birth prevalence of each CHD subtype according to the presence of ECAs.

Table 5.19 Live birth prevalence of CHD, by CHD subtype and ECAs

CHD subtype	Prevalence per 10,000 live births (95% CI)			
	Isolated CHD	**CHD with structural ECAs**	**CHD with chromosomal/ genetic ECAs**	**All CHD**
SV	0.2 (0.2-0.3)	0 (0-0.1)	0 (0-0.1)	0.3 (0.2-0.4)
HLH	1.2 (1.1-1.3)	0.1 (0.1-0.1)	0.1 (0.1-0.1)	1.4 (1.3-1.5)
EA	0.3 (0.3-0.4)	0 (0-0.1)	0 (0-0.1)	0.4 (0.3-0.5)
HRH	1.0 (0.9-1.1)	0.1 (0.1-0.2)	0.2 (0.2-0.3)	1.3 (1.2-1.5)
CAT	0.3 (0.2-0.4)	0.1 (0.1-0.1)	0.1 (0.1-0.1)	0.5 (0.4-0.6)
AVSD	1 (0.9-1.1)	0.2 (0.2-0.3)	1.6 (1.5-1.8)	2.8 (2.7-3)
AVA/S	1.3 (1.2-1.5)	0.1 (0.1-0.1)	0.1 (0.1-0.2)	1.5 (1.4-1.7)
TGV	2.5 (2.3-2.7)	0.1 (0.1-0.2)	0.1 (0.1-0.1)	2.8 (2.6-2.9)
ToF	1.9 (1.7-2)	0.4 (0.4-0.5)	0.6 (0.5-0.7)	2.9 (2.7-3.1)
TAPVR	0.5 (0.4-0.6)	0.1 (0.1-0.1)	0 (0-0.1)	0.6 (0.5-0.7)
IAA	0.2 (0.1-0.2)	0 (0-0.1)	0.1 (0.1-0.1)	0.3 (0.2-0.4)
CoA	2.4 (2.3-2.6)	0.3 (0.3-0.4)	0.3 (0.3-0.4)	3.1 (2.9-3.3)
DORV	0.4 (0.3-0.4)	0.1 (0.1-0.1)	0.1 (0.1-0.1)	0.5 (0.5-0.6)
MVA	0.5 (0.4-0.6)	0 (0-0.1)	0 (0-0.1)	0.6 (0.5-0.7)
VSD	16.6 (16.1-17)	1.7 (1.5-1.8)	2.4 (2.2-2.5)	20.6 (20.1-21.2)
ASD	4.4 (4.2-4.6)	1.1 (1-1.2)	1.3 (1.2-1.4)	6.8 (6.5-7.1)
PVS	2.7 (2.5-2.9)	0.2 (0.1-0.2)	0.2 (0.2-0.3)	3.1 (2.9-3.3)
PDA	1.2 (1.1-1.4)	0.3 (0.2-0.4)	0.2 (0.2-0.3)	1.8 (1.6-1.9)
Other	3.2 (3-3.4)	0.8 (0.7-0.9)	0.6 (0.6-0.7)	4.6 (4.3-4.8)
All subtypes	**41.7 (41-42.4)**	**5.8 (5.6-6.1)**	**8.2 (7.9-8.5)**	**55.9 (55.1-56.7)**

5.3.14 Trends in live birth prevalence

5.3.14.1 All CHD adjusted for the presence of ECAs

Overall, there was no evidence of a trend in live birth prevalence over time (adjusted for the presence of ECAs) (p=0.986) (Table 5.16 and Table 5.20). However, the live birth prevalence of AVA/S decreased significantly by 3% per year (RR=0.97, 95% CI: 0.95-0.99), the live birth prevalence of CoA decreased significantly by 2% per year (RR=0.98, 95% CI: 0.97-0.99) and the live birth prevalence of ToF increased significantly by 3% per year (RR=1.03, 95% CI: 1.01-1.04).

Table 5.20 Trends in the live birth prevalence of CHD over time, by CHD subtype

Subtype	RR (95% CI)	P-value
SV	0.96 (0.92-1.01)	0.083
HLH	1.00 (0.98-1.02)	0.795
EA	0.99 (0.95-1.02)	0.412
HRH	0.99 (0.97-1.01)	0.353
CAT	1.00 (0.97-1.04)	0.889
AVSD	1.01 (0.99-1.02)	0.366
AVA/S¥	0.97 (0.95-0.99)	<0.001
TGV	1.00 (0.98-1.01)	0.915
ToF	1.03 (1.01-1.04)	0.001
TAPVR	0.99 (0.96-1.02)	0.371
IAA	1.00 (0.96-1.05)	0.885
CoA	0.98 (0.97-0.99)	0.002
DORV	1.01 (0.97-1.04)	0.736
MVA	0.98 (0.95-1.01)	0.160
VSD†	1.03 (0.99-1.08)	0.113
ASD†	1.01 (0.96-1.07)	0.640
PVS†	1.00 (0.99-1.02)	0.707
PDA†	1.08 (1.02-1.14)	0.013
Other†	0.97 (0.95-0.99)	0.008
All subtypes	**1.00 (1.00-1.00)**	**0.986**

*Relative risks (RRs) were estimated using multilevel Poisson regression models with a random intercept (for register), adjusted for presence of structural and chromosomal extra-cardiac anomalies.

†The RRs for these subtypes were estimated using Poisson regression with a random slope and random intercept

¥ The RR for this subtype was estimated using Poisson regression with a random intercept and an over-dispersion term.

5.3.14.2 Interaction between year of delivery and the presence of ECAs

Overall, there was an interaction between year of delivery and the presence of ECAs ($p<0.001$). The trends were therefore modelled separately for isolated cases, cases with structural ECAs and cases with chromosomal/ genetic ECAs. The trend over time in CHD with chromosomal ECAs decreased very slightly over time, whereas the prevalence of isolated CHD and CHD with structural ECAs remained stable (Table 5.21). There were no significant trends over time in the prevalence of isolated CHD ($p=0.505$), CHD with structural ECAs ($p=0.729$) and CHD with chromosomal/ genetic ECAs ($p=0.239$).

There was an interaction between year of delivery and the presence of ECAs in cases of VSD ($p<0.001$). The trends in VSD were therefore modelled separately for cases with isolated VSD, VSD with structural ECAs and VSD with chromosomal/ genetic ECAs. The live birth prevalence of isolated VSD increased by 2% per year, whereas the live birth prevalence of VSD with structural ECAs and the live birth prevalence of VSD with chromosomal/ genetic VSD, increased by 1% per year. However, none of these trends reached statistical significance (Table 5.21).

Table 5.21 Trends in live birth prevalence according to the presence of ECAs

Subtype	Isolated CHD		CHD with structural ECAs		CHD with chromosomal/ genetic ECAs	
	RR (95% CI)	**P-value**	**RR (95% CI)**	**P-value**	**RR (95% CI)**	**P-value**
VSD	1.02 (1.00-1.04)	0.027	1.01 (0.99-1.04)	0.524	1.01 (0.99-1.03)	0.406
All subtypes	1.00 (0.99-1.01)	0.505	1.00 (0.99-1.02)	0.729	0.99 (0.98-1.00)	0.239

5.3.15 Heterogeneity in live birth prevalence between registers

5.3.15.1 All CHD adjusted for the presence of ECAs

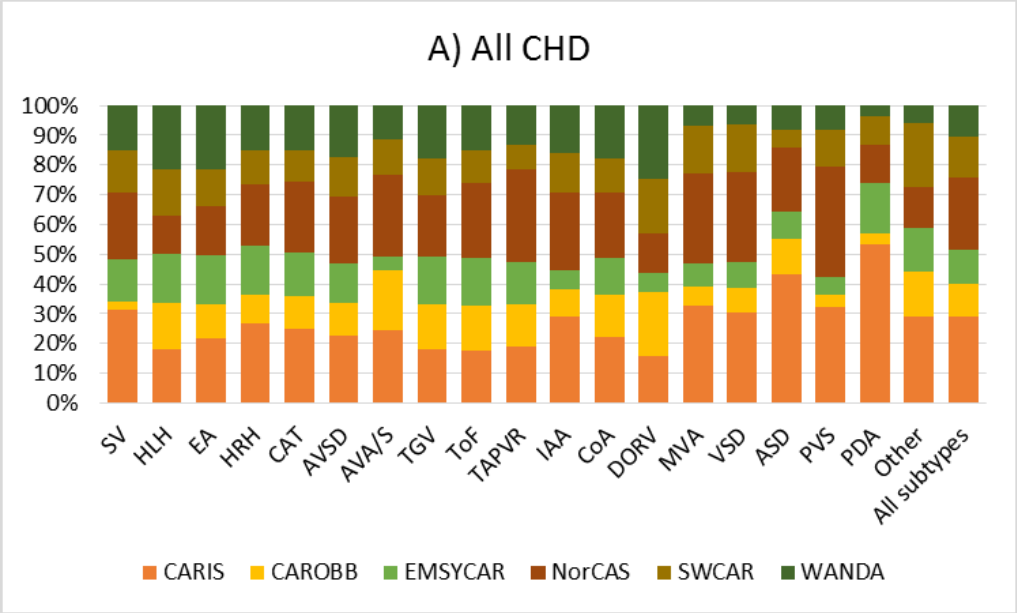
Overall, there was significant heterogeneity in live birth prevalence between registers (LR test for random intercept: $p<0.001$). As shown in Table 5.22, the live birth prevalence of all CHD was greatest in the CARIS, followed by NorCAS. CAROBB, EMSYCAR, SWCAR and WANDA had broadly similar live birth prevalence rates.

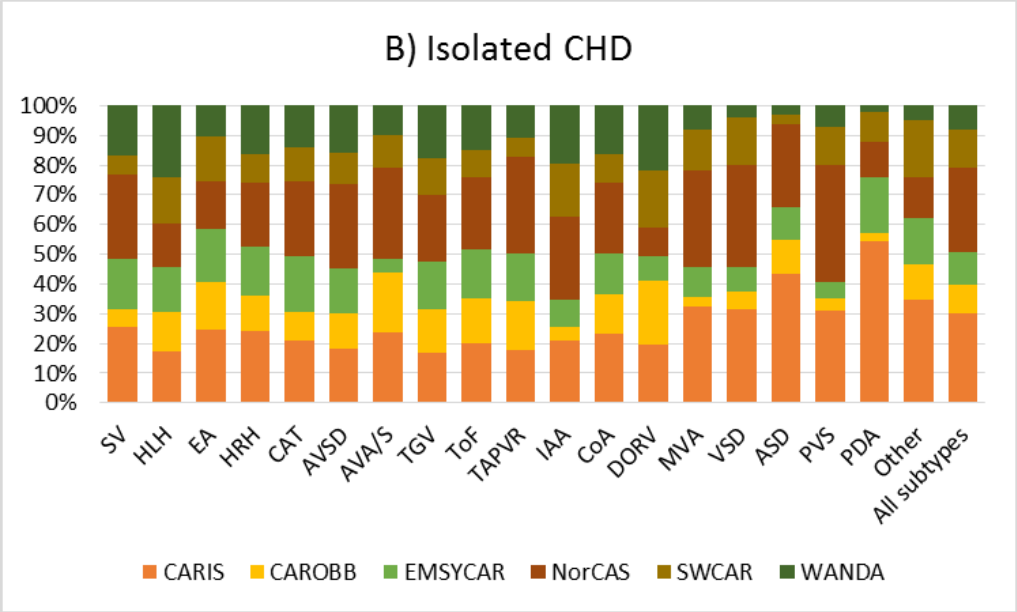
There was also significant heterogeneity in live birth prevalence between registers for every CHD subtype (LR test: $p<0.001$ for each CHD subtype). Figure 5.6 shows the percentage of the prevalence contributed by each register. Here, it appears that there is a greater degree of variation among the milder CHD subtypes than the more severe ones, particularly among isolated cases of CHD. For many subtypes, CARIS and NorCAS account for the largest proportions of cases.

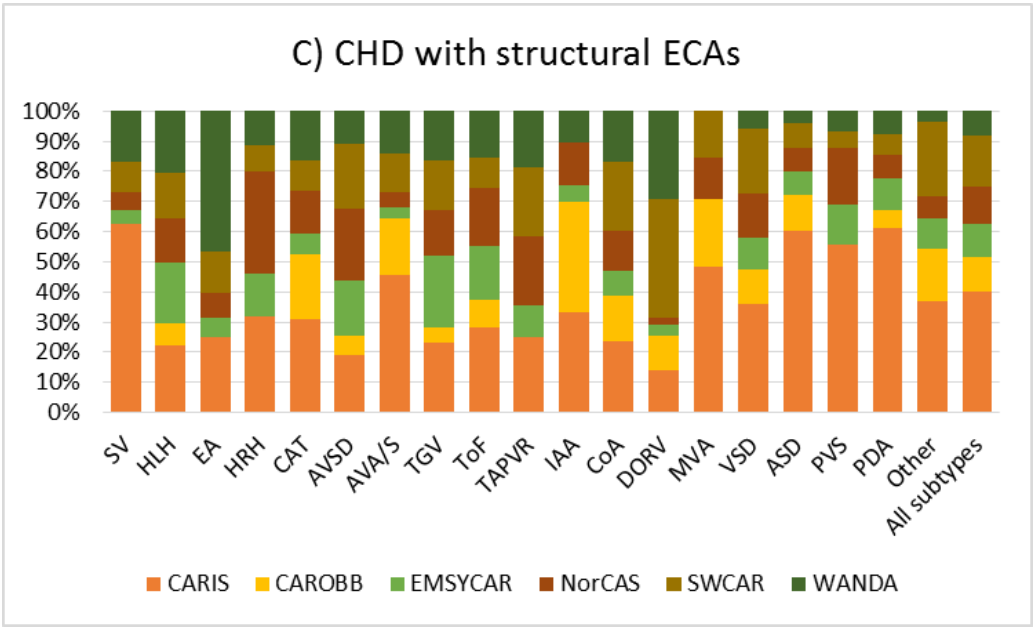
Table 5.22 Live birth prevalence by register

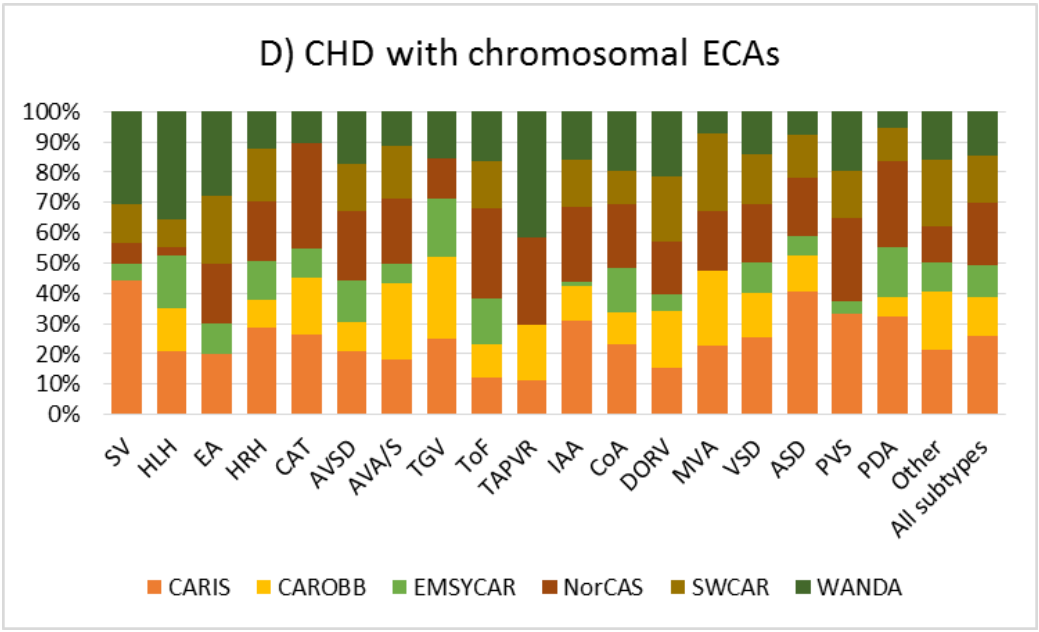
Register	Prevalence per 10,000 live births (95% CI)			
	Isolated CHD	**CHD with structural ECAs**	**CHD with chromosomal/ genetic ECAs**	**All CHD**
CARIS	73.2 (70.6-75.8)	14.9 (13.8-16.1)	13.1 (12-14.2)	113.2 (110-116.4)
CAROBB	23.5 (21.7-25.4)	4.3 (3.5-5.2)	6.4 (5.5-7.5)	43.0 (40.5-45.6)
EMSYCAR	26.8 (25.7-27.9)	3.9 (3.5-4.4)	5.3 (4.8-5.8)	43.8 (42.4-45.2)
NorCAS	68.8 (66.9-70.9)	4.7 (4.2-5.2)	10.3 (9.6-11.1)	94.1 (91.7-96.4)
SWCAR	31.3 (29.6-33.2)	6.2 (5.5-7.1)	7.9 (7-8.9)	53.9 (51.6-56.3)
WANDA	19.6 (18.4-20.9)	3.1 (2.6-3.6)	7.3 (6.5-8.1)	40.6 (38.8-42.5)

Figure 5.6 Percentage of prevalence contributed by each register, by CHD subtype






C) CHD with structural ECAs
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
SV
HLH
EA
HRH
CAT
AVSD
AVA/S
TGV
ToF
TAPVR
IAA
CoA
DORV
MVA
VSD
ASD
PVS
PDA
Other
All subtypes
CARIS
CAROBB
EMSYCAR
NorCAS
SWCAR
WANDA

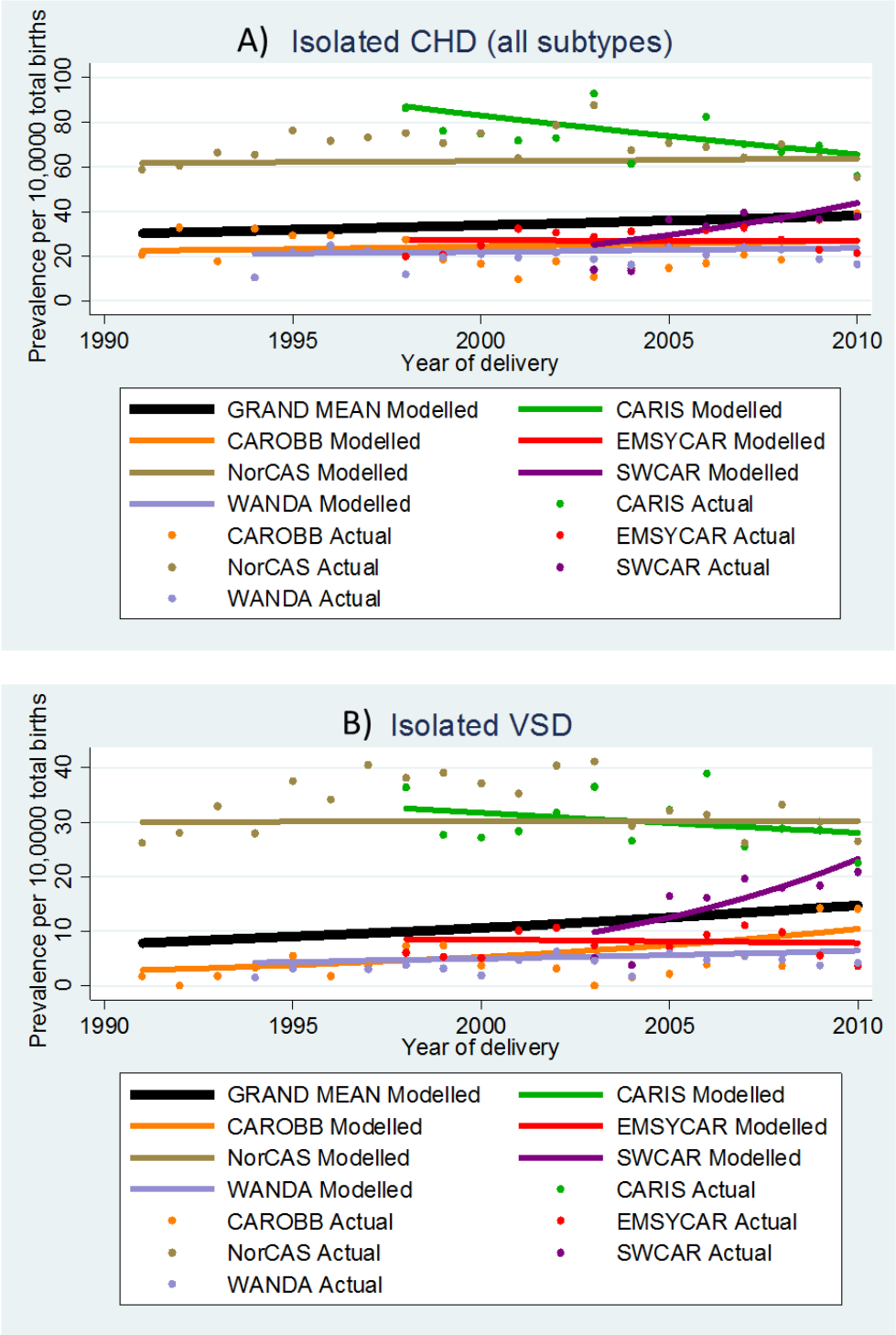

D) CHD with chromosomal ECAs
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
SV
HLH
EA
HRH
CAT
AVSD
AVA/S
TGV
ToF
TAPVR
IAA
CoA
DORV
MVA
VSD
ASD
PVS
PDA
Other
All subtypes
CARIS
CAROBB
EMSYCAR
NorCAS
SWCAR
WANDA

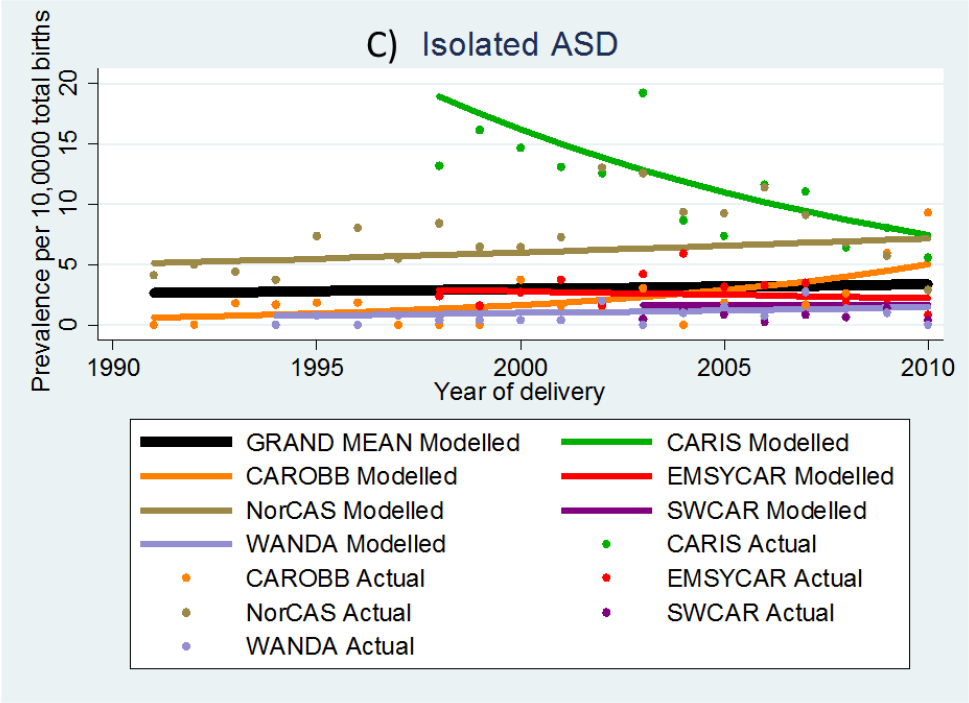
5.3.16 Heterogeneity in trends in live birth prevalence between registers

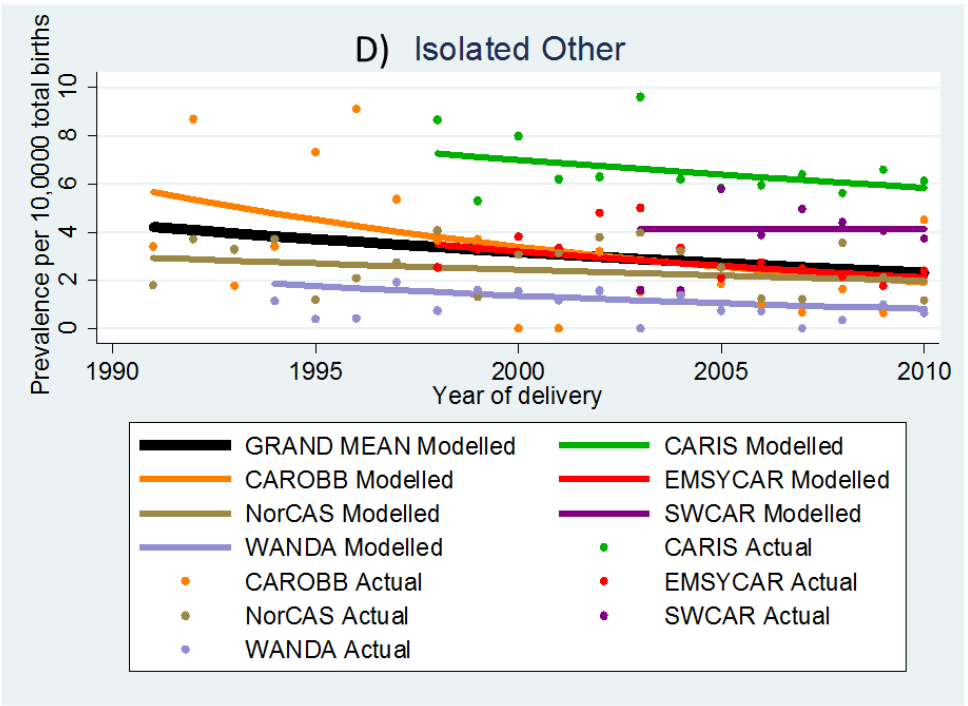
5.3.16.1 All CHD adjusted for the presence of ECAs

Overall, there was variation in trends in live birth prevalence between registers ($p<0.001$). However, variation in trends over time between registers was observed in only the milder CHD subtypes: VSD, ASD, PDA and "other" CHD subtypes (all $p<0.001$). As shown in Figure 5.7 A, trends in live birth prevalence over time in all CHD subtypes combined were similar in the areas covered by NorCAS, EMSYCAR, CAROBB and WANDA, with a slight increase in prevalence over time. Trends in CHD prevalence in the area covered by SWCAR also increased slightly over time, but with a steeper gradient. Alternatively, trends in live birth prevalence over time in the area covered by CARIS appeared to decrease. For cases of VSD, the trends in the registers mirrored those of trends in all CHD subtypes combined. For cases of ASD and PDA, all registers had very similar (slightly increasing) trends in total birth prevalence over time, with the exception of CARIS, which showed a decreasing trend in total birth prevalence (Figure 5.7 C and D). For cases with "Other" CHD subtypes, the prevalence decreased slightly for all registers except SWCAR, where the prevalence appeared to increase slightly over time (Figure 5.7).

Figure 5.7 Live birth prevalence of CHD over time, by register and subtype




C) Isolated ASD
Prevalence per 10,0000 total births
0
5
10
15
20
1990
1995
2000
2005
2010
Year of delivery
GRAND MEAN Modelled
CAROBB Modelled
NorCAS Modelled
WANDA Modelled
CAROBB Actual
NorCAS Actual
WANDA Actual
CARIS Modelled
EMSYCAR Modelled
SWCAR Modelled
CARIS Actual
EMSYCAR Actual
SWCAR Actual


D) Isolated Other
Prevalence per 10,0000 total births
0
2
4
6
8
10
1990
1995
2000
2005
2010
Year of delivery
GRAND MEAN Modelled
CAROBB Modelled
NorCAS Modelled
WANDA Modelled
CAROBB Actual
NorCAS Actual
WANDA Actual
CARIS Modelled
EMSYCAR Modelled
SWCAR Modelled
CARIS Actual
EMSYCAR Actual
SWCAR Actual

5.3.17 Prenatal diagnosis

5.3.17.1 Isolated CHD

Excluding cases notified to CAROBB, EMSYCAR and SWCAR (see section 5.2.3.4), there were 8,956 (98.2%) cases of isolated CHD with data on prenatal diagnosis. Of these, 3,225 were CHD subtypes that are possible to prenatally diagnose. Overall, 935 (30.0%) cases had a prenatal diagnosis (of any congenital anomaly). There was substantial variation in prenatal diagnosis by subtype (Table 5.23). For example, 72.4% of cases with HLH had a prenatal diagnosis compared to just 5.9% of cases with IAA.

Table 5.23 Prenatal diagnosis of (all birth) isolated cases of CHD, by CHD subtype

Subtype	Prenatal Diagnosis N (%)	RR of prenatal diagnosis (95% CI); p-value
SV	42 (64.6)	1.06 (1.00-1.12); p=0.035
HLH	270 (72.4)	1.05 (1.02-1.07); p<0.001
EA	33 (47.8)	1.06 (0.99-1.14); p=0.087
HRH	124 (52.8)	1.08 (1.04-1.12); p<0.001
CAT	26 (41.3)	1.07 (0.99-1.15); p=0.104
AVSD	71 (33.3)	1.07 (1.02-1.12); p=0.006
AVA/S	26 (8.8)	1.05 (0.97-1.13); p=0.220
TGV	82 (18.1)	1.15 (1.10-1.21); p<0.001
ToF	51 (14.6)	1.21 (1.12-1.30); p<0.001
IAA	2 (5.9)	0.95 (0.74-1.21); p=0.665
CoA	67 (14.1)	1.09 (1.04-1.15); p<0.001
DORV	37 (48.7)	1.05 (0.99-1.12); p=0.130
Other	104 (19.8)	1.03 (0.98-1.07); p=0.237
All subtypes	**935 (30.0%)**	**1.07 (1.06-1.09); p<0.001**

TAPVR, MVA, VSD, ASD, and PVS were not included as they are very difficult to diagnose prenatally. PDA was excluded because the ductus arteriosus is always open prenatally.

5.3.18 Trends in prenatal diagnosis

5.3.18.1 Isolated CHD

Overall, there was a significant 7% increase in prenatal diagnosis rates per year (RR=1.07, 95% CI: 1.06-1.09; p<0.001). As shown in Table 5.23, there was a significant increase in the prenatal diagnosis rate of HLH (5% per year, p<0.001), HRH (8% per year, p<0.001), TGV (15% per year, p<0.001), ToF (21% per year, p<0.001) and CoA (9% per year, p<0.001).

5.3.19 Heterogeneity in prenatal diagnosis between registers

5.3.19.1 Isolated CHD

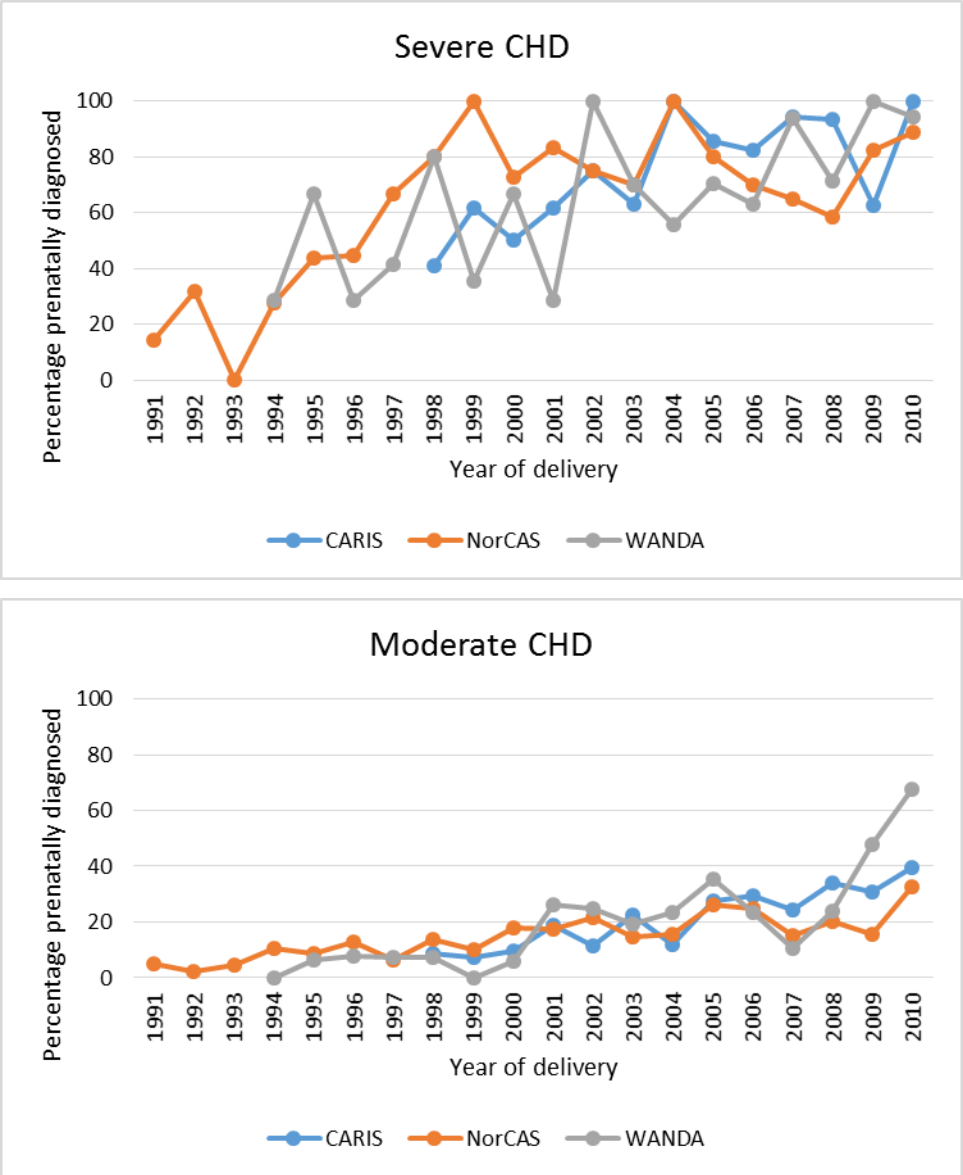
Overall, there was significant variation in prenatal diagnosis rates between registers (LR test for random intercept: p<0.001). However, variation in prenatal diagnosis rates between registers was only evident in the "Other" CHD subtype (p<0.001). Indeed, prenatal diagnosis rates for CHD of severe and moderate severity are comparable between registers (Figure 5.8).

5.3.20 Heterogeneity in trends in prenatal diagnosis between registers

5.3.20.1 Isolated CHD

The trends in prenatal diagnosis rates over time, shown in Figure 5.8, do not vary substantially by register for severe, moderate or mild CHD. Indeed, the addition of a random slope into the regression models did not improve model fit for any of the CHD subtypes.

Figure 5.8 Graph showing percentage of prenatally diagnosed cases of isolated CHD over time, by register and CHD severity



Trends in prenatal diagnosis rates are not presented for cases with mild CHD as these cases are very difficult to diagnose prenatally.

5.3.21 Association between prenatal diagnosis and maternal age

5.3.21.1 Isolated CHD

Considering all CHD subtypes combined, there was no association between prenatal diagnosis rates and maternal age at delivery (p=0.493) (Table 5.24). It was not possible to examine the association between prenatal diagnosis rates and maternal age in individual subtypes, due to low sample size. However, it was possible to examine this association in the severity categories. Here, there were no significant associations between maternal age and prenatal diagnosis rates in cases with CHD of severe and moderate severity (p=0.789 and p=0.502, respectively) (Table 5.24).

Table 5.24 Association between maternal age category and prenatal diagnosis of CHD, by CHD severity†

Severity category	Maternal age	RR of prenatal diagnosis (95% CI)ϕ	P-value
Severe	<20	1.28 (0.92-1.78)	0.789
	20-24	1.07 (0.82-1.41)	
	25-29	1 (Reference category)	
	30-34	1.10 (0.84-1.44)	
	35-40	1.03 (0.76-1.40)	
	≥40	0.96 (0.54-1.71)	
Moderate	<20	1.09 (0.76-1.56)	0.502
	20-24	0.78 (0.58-1.06)	
	25-29	1 (Reference category)	
	30-34	0.88 (0.66-1.16)	
	35-40	0.95 (0.68-1.33)	
	≥40	0.77 (0.41-1.43)	
All subtypes	**<20**	**1.19 (0.95-1.50)**	**0.493**
	20-24	**0.97 (0.81-1.17)**	
	25-29	**1 (reference category)**	
	30-34	**0.95 (0.79-1.14)**	
	35-40	**1.08 (0.87-1.32)**	
	≥40	**0.96 (0.65-1.40)**	

† CAROBB, EMSYCAR and SWCAR were excluded due to missing prenatal diagnosis data

Φ Adjusted for year of birth and estimated using a multilevel Poisson model with a random intercept.

‡Isolated cases included only.

5.3.22 Pregnancy outcomes

5.3.22.1 All CHD

Overall, 0.8% of cases occurred in late miscarriages, 1.9% in stillbirths, 11.6% in TOPFAs and 85.7% in live births. As shown in Figure 5.9, there was variation in pregnancy outcomes between CHD subtypes. There was significant variation in pregnancy outcomes according to the presence of ECAs (Chi-square test: $p<0.001$). Specifically, cases of isolated CHD tended to occur more frequently in live births than cases of CHD with structural ECAs, chromosomal/ genetic ECAs and teratogenic syndromes. Pregnancy outcomes are discussed below in more detail, according to the presence of ECAs.

5.3.22.2 Isolated CHD

Altogether, 58 (0.4%) isolated cases occurred in late miscarriages, 144 (1.1%) in stillbirths, 687 (5.2%) in TOPFAs and 12,625 (96.0%) in live births. These proportions varied according to subtype, with just 51.8% of cases with HLH occurring in live births compared to 99.1% of cases with VSD.

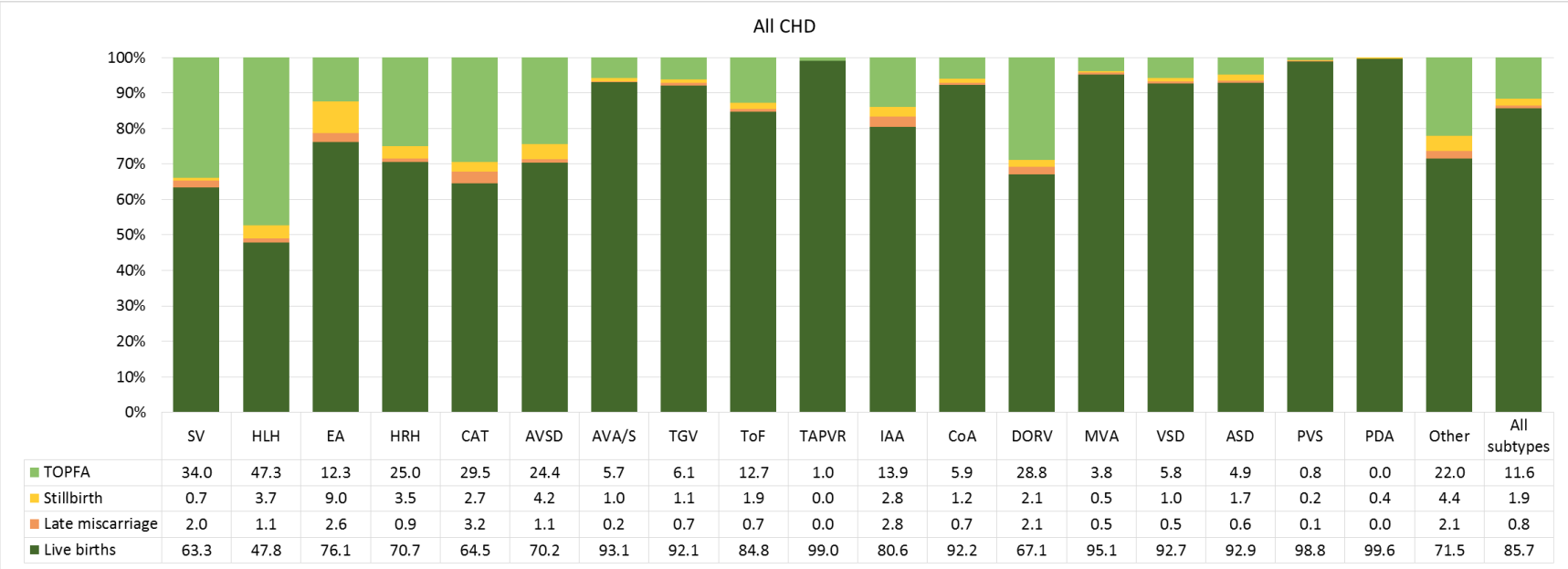
5.3.22.3 CHD with structural ECAs

Of the cases with CHD and structural ECAs, 38 (1.6%) were late miscarriages, 87 (3.6%) were stillbirths, 497 (20.8%) were TOPFAs and 1,768 (74.0%) were live born. Again there was variation in pregnancy outcomes according to CHD subtype (Table 5.25). For example, just 28 (37.3%) cases of HLH were live born whereas 97.9% of cases with PDA were live born.

5.3.22.4 CHD with chromosomal/ genetic ECAs

Of the cases of CHD with chromosomal/ genetic ECAs, 66 (1.7%) were late miscarriages, 140 (3.7%) were stillbirths, 1,100 (29.0%) were TOPFAs and 2,488 (65.6%) were live born. Pregnancy outcomes differed according to CHD subtype (Table 5.25). For example, 27 (27.3%) HLH cases were live born compared to 68 (100%) cases with PVS.

Figure 5.9 Pregnancy outcome for All CHD, by CHD subtype



	SV	HLH	EA	HRH	CAT	AVSD	AVA/S	TGV	ToF	TAPVR	IAA	CoA	DORV	MVA	VSD	ASD	PVS	PDA	Other	All subtypes
TOPFA	34.0	47.3	12.3	25.0	29.5	24.4	5.7	6.1	12.7	1.0	13.9	5.9	28.8	3.8	5.8	4.9	0.8	0.0	22.0	11.6
Stillbirth	0.7	3.7	9.0	3.5	2.7	4.2	1.0	1.1	1.9	0.0	2.8	1.2	2.1	0.5	1.0	1.7	0.2	0.4	4.4	1.9
Late miscarriage	2.0	1.1	2.6	0.9	3.2	1.1	0.2	0.7	0.7	0.0	2.8	0.7	2.1	0.5	0.5	0.6	0.1	0.0	2.1	0.8
Live births	63.3	47.8	76.1	70.7	64.5	70.2	93.1	92.1	84.8	99.0	80.6	92.2	67.1	95.1	92.7	92.9	98.8	99.6	71.5	85.7

Table 5.25 Pregnancy outcomes for CHD cases, by CHD subtype and ECAs

CHD subtype	Isolated CHD				CHD with Structural ECAs				CHD with Chromosomal/ Genetic ECAs			
	LB	LM	SB	TOPFA	LB	LM	SB	TOPFA	LB	LM	SB	TOPFA
SV	71 (67.6)	0 (0)	1 (1.0)	33 (31.4)	12 (54.5)	1 (4.5)	0 (0)	9 (40.9)	10 (50)	2 (10)	0 (0)	8 (40)
HLH	367 (51.8)	7 (1.0)	25 (3.5)	309 (43.6)	28 (37.3)	0 (0)	4 (5.3)	43 (57.3)	27 (27.3)	3 (3)	4 (4)	65 (65.7)
EA	96 (76.2)	3 (2.4)	12 (9.5)	15 (11.9)	9 (60)	1 (6.7)	1 (6.7)	4 (26.7)	12 (92.3)	0 (0)	1 (7.7)	0 (0)
HRH	308 (77.8)	1 (0.3)	10 (2.5)	77 (19.4)	33 (45.2)	3 (4.1)	8 (11)	29 (39.7)	62 (60.8)	1 (1)	2 (2)	37 (36.3)
CAT	86 (81.1)	2 (1.9)	1 (0.9)	17 (16)	24 (50)	2 (4.2)	3 (6.3)	19 (39.6)	32 (48.5)	3 (4.5)	2 (3)	29 (43.9)
AVSD	295 (87.3)	5 (1.5)	6 (1.8)	32 (9.5)	66 (59.5)	2 (1.8)	4 (3.6)	39 (35.1)	498 (64.3)	7 (0.9)	42 (5.4)	227 (29.3)
AVA/S	400 (96.6)	0 (0)	3 (0.7)	11 (2.7)	26 (78.8)	1 (3)	1 (3)	5 (15.2)	35 (74.5)	0 (0)	0 (0)	12 (25.5)
TGV	759 (95)	2 (0.3)	9 (1.1)	29 (3.6)	44 (81.5)	2 (3.7)	0 (0)	8 (14.8)	28 (57.1)	2 (4.1)	1 (2)	18 (36.7)
ToF	562 (93.4)	0 (0)	7 (1.2)	33 (5.5)	135 (74.2)	3 (1.6)	6 (3.3)	38 (20.9)	172 (71.4)	4 (1.7)	6 (2.5)	59 (24.5)
TAPVR	155 (99.4)	0 (0)	0 (0)	1 (0.6)	24 (96)	0 (0)	0 (0)	1 (4)	10 (100)	0 (0)	0 (0)	0 (0)
CoA	46 (92)	1 (2.0)	1 (2)	2 (4)	9 (90)	0 (0)	0 (0)	1 (10)	32 (66.7)	2 (4.2)	2 (4.2)	12 (25)
IAA	739 (98.7)	1 (0.1)	3 (0.4)	6 (0.8)	95 (83.3)	0 (0)	5 (4.4)	14 (12.3)	99 (66.9)	6 (4.1)	3 (2)	40 (27)
DORV	106 (79.7)	3 (2.3)	1 (0.8)	23 (17.3)	28 (63.6)	2 (4.5)	1 (2.3)	13 (29.5)	28 (43.1)	0 (0)	3 (4.6)	34 (52.3)
MVA	146 (97.3)	1 (0.7)	0 (0)	3 (2)	14 (100)	0 (0)	0 (0)	0 (0)	13 (72.2)	0 (0)	1 (5.6)	4 (22.2)
VSD	5020 (99.1)	11 (0.2)	16 (0.3)	20 (0.4)	504 (82.5)	8 (1.3)	14 (2.3)	85 (13.9)	712 (68.1)	15 (1.4)	37 (3.5)	281 (26.9)
ASD	1334 (98)	9 (0.7)	15 (1.1)	3 (0.2)	336 (82.6)	3 (0.7)	11 (2.7)	57 (14)	388 (86.8)	2 (0.4)	11 (2.5)	46 (10.3)
PVS	811 (99.3)	1 (0.1)	1 (0.1)	4 (0.5)	51 (92.7)	0 (0)	0 (0)	4 (7.3)	68 (100)	0 (0)	0 (0)	0 (0)
PDA	370 (100)	0 (0)	0 (0)	0 (0)	93 (97.9)	0 (0)	2 (2.1)	0 (0)	67 (100)	0 (0)	0 (0)	0 (0)
Other	954 (89.4)	11 (1.0)	33 (3.1)	69 (6.5)	237 (59)	10 (2.5)	27 (6.7)	128 (31.8)	195 (41.8)	19 (4.1)	25 (5.4)	228 (48.8)
All subtypes	**12625 (96)**	**58 (0.4)**	**144 (1.1)**	**687 (5.2)**	**1768 (74)**	**38 (1.6)**	**87 (3.6)**	**497 (20.8)**	**2488 (65.6)**	**66 (1.7)**	**140 (3.7)**	**1100 (29)**

ECA=ECAs, LB= Live birth, LM= Late miscarriage, SB= Stillbirth, TOPFA= Termination of pregnancy for fetal anomalies

5.3.23 Termination of pregnancy for fetal anomaly

5.3.23.1 All CHD

Overall, 2,292 (11.6%) cases of CHD occurred in TOPFA, of which 93 (4.3%) occurred <13 weeks gestational age, 392 (18.2%) between 14-18 weeks, 1,461 (68.0%) between 19-23 weeks, 181 (8.4%) between 24-29 weeks and 22 (1.0%) occurred ≥30 weeks (Table 5.25). As shown in Figure 5.10 A, these proportions varied by CHD subtype. Additionally, TOPFA rates varied according to the presence of ECAs (Chi-square test: $p<0.001$); cases of CHD with structural ECAs or chromosomal/ genetic ECAs tended to be terminated earlier than isolated cases. TOPFA rates according to the presence of ECAs are described in more detail below.

5.3.23.2 Isolated CHD

As shown in Table 5.25, 687 (5.1%) cases of isolated CHD occurred in TOPFA. Among isolated cases of CHD that resulted in TOPFA, 10 (1.5%) occurred at <13 weeks gestational age, 35 (5.4%) occurred between 14-18 weeks, 545 (83.5%) occurred between 19-23 weeks, 56 (8.6%) between 24-29 weeks and seven (1.1%) occurred at ≥30 weeks. These proportions varied by CHD subtype (Figure 5.10 B).

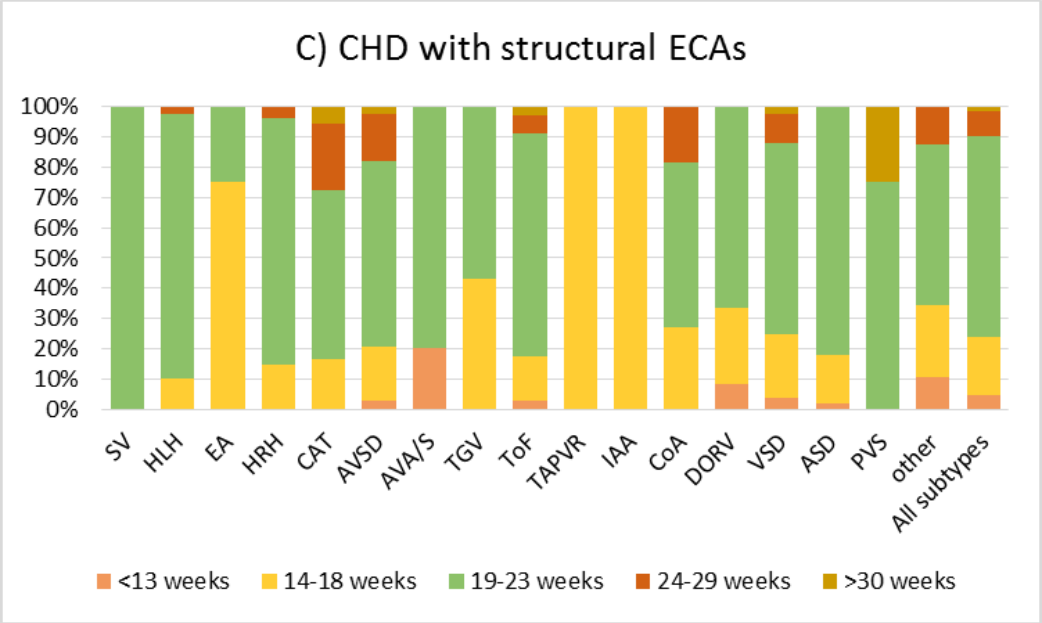
5.3.23.3 CHD with structural ECAs

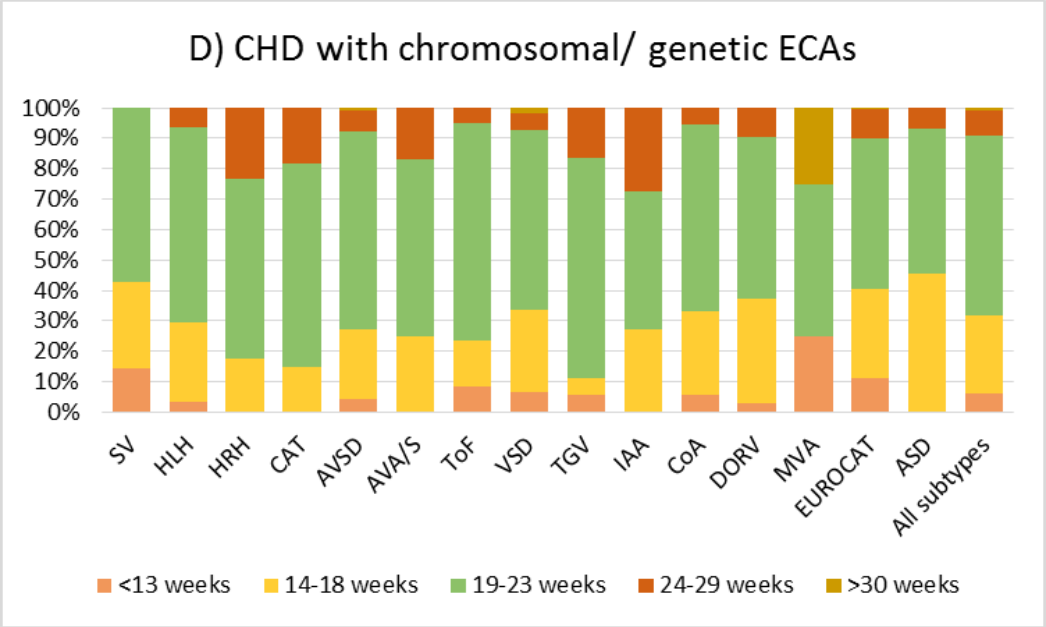
As shown in Table 5.25, 497 (20.8%) cases of CHD with structural ECAs occurred in TOPFA. Of these, 21 (4.5%) occurred <13 weeks gestational age, 91 (19.6%) between 14-18 weeks, 309 (66.5%) between 19-23 weeks, 38 (8.2%) between 24-29 weeks and six (1.3%) occurred ≥30 weeks. These proportions varied by CHD subtype (Figure 5.10 C).

5.3.23.4 CHD with chromosomal/ genetic ECAs

As shown in Table 5.25, 1,100 (29.0%) cases of CHD with chromosomal/ genetic ECAs resulted in TOPFA. Of these, 62 (6.1%) occurred <13 weeks gestational age, 265 (25.9%) between 14-18 weeks, 602 (58.8%) between 19-23 weeks, 85 (8.3%) between 24-29 weeks and nine (0.9%) occurred ≥30 weeks. These proportions varied by CHD subtype (Figure 5.10 D).

Figure 5.10 Gestational age at TOPFA, by CHD subtype and ECAs


C) CHD with structural ECAs
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
SV
HLH
EA
HRH
CAT
AVSD
AVA/S
TGV
ToF
TAPVR
IAA
CoA
DORV
VSD
ASD
PVS
other
All subtypes
<13 weeks
14-18 weeks
19-23 weeks
24-29 weeks
>30 weeks


D) CHD with chromosomal/ genetic ECAs
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
SV
HLH
HRH
CAT
AVSD
AVA/S
ToF
VSD
TGV
IAA
CoA
DORV
MVA
EUROCAT
ASD
All subtypes
<13 weeks
14-18 weeks
19-23 weeks
24-29 weeks
>30 weeks

5.3.24 Trends in termination rates

5.3.24.1 All CHD adjusted for the presence of ECAs

Table 5.26 shows the "risk" for TOPFA per year's increase in year of delivery, adjusted for the presence of ECAs. Overall, the risk of TOPFA increased significantly by 2% per year (p=0.001). While there was a significant increase in TOPFA rates for "Other" CHD subtypes over time (8% per year, p<0.001), there were no significant trends for the other CHD subtypes. However, there was some evidence of an increase in TOPFA rates for EA (17% per year, p=0.023), CAT (8% per year, p=0.023) and TGV (3% per year, p=0.010), although these did not reach statistical significance after applying the Bonferroni adjustment.

Table 5.26 RRs of TOPFA per year's increase in year of delivery, adjusted for ECAs

CHD subtype	RR of TOPFA per year	P-value
SV	1.04 (0.97-1.12)	0.291
HLH	1.03 (1.00-1.06)	0.074
EA	1.17 (1.02-1.34)	0.023
HRH	1.04 (0.99-1.08)	0.099
CAT	1.08 (1.01-1.16)	0.023
AVSD	0.98 (0.95-1.01)	0.231
AVAs	1.04 (0.96-1.13)	0.375
TGV	1.09 (1.02-1.16)	0.010
ToF	1.03 (0.99-1.08)	0.130
IAA	1.09 (0.96-1.24)	0.181
CoA	0.97 (0.91-1.02)	0.248
DORV	1.00 (0.94-1.07)	0.955
PVS	1.18 (0.97-1.43)	0.100
Other	1.08 (1.05-1.11)	<0.001
All subtypes	**1.02 (1.01-1.03)**	**0.001**

VSD, ASD, TAPVR, MVA and PDA are not included as these subtypes are very rarely diagnosed prenatally.

OR=Odds ratio, TOPFA=Termination of pregnancy for fetal anomaly

5.3.24.2 Interaction between trends in TOPFA and the presence of ECAs

Considering all CHD subtypes combined, the interaction between year of delivery and the presence of ECAs was statistically significant ($p<0.001$); in other words trends over time in TOPFA rates varied significantly in cases of isolated CHD, CHD with structural ECAs and CHD with chromosomal/ genetic ECAs. Therefore, TOPFA rates over time were modelled separately in isolated cases of CHD, CHD with structural ECAs and CHD with chromosomal/ genetic ECAs. In cases of isolated CHD, the risk of TOPFA increased by 4% per year (RR=1.04, 95% CI: 1.02-1.06; $p<0.001$), in cases of CHD with structural ECAs, the risk of TOPFA increased by 3% per year (RR=1.03, 95% CI: 1.02-1.06; $p<0.001$) and in cases of CHD with chromosomal/ genetic ECAs, the risk of TOPFA increased by 1% per year (RR=1.01, 95% CI: 1.00-1.02; $p=0.033$).

There were no significant interactions between year of delivery and the presence of ECAs in any of the CHD subtypes. That is, there was no evidence that trends in TOPFA rates over time varied according to the presence of ECAs.

5.3.25 Trends in terminations in prenatally diagnosed cases only

5.3.25.1 Isolated CHD

Among prenatally diagnosed cases of CHD, the risk of TOPFA decreased by 3% per year, although this did not quite reach statistical significance ($p=0.031$). Among prenatally diagnosed cases only, there was some evidence that the risk of TOPFA decreased by 33% per year in cases of DORV ($p=0.011$) (Table 5.27).

Table 5.27 Trends in TOPFA rates over time in isolated cases of CHD, by prenatal diagnosis

CHD subtype	Prenatally diagnosed and prenatally undiagnosed cases		Prenatally diagnosed cases*		
	RR (95% CI)	Variation between registers, p-value	TOPFA/ Prenatally diagnosed (%)	RR (95% CI)	Variation between registers, p-value
SV	1.05 (0.97-1.13); p= 0.217	1.000	16/42 (38.1)	0.95 (0.85-1.07); p= 0.385	1.000
HLH	1.04 (1.01-1.07); p= 0.023	1.000	153/270 (56.7)	0.98 (0.93-1.03); p= 0.357	1.000
EA	1.13 (0.98-1.3); p= 0.094	0.036	10/33 (30.3)	1.15 (0.94-1.4); p= 0.183	0.132
HRH	1.06 (1.01-1.11); p= 0.027	1.000	38/124 (30.6)	0.95 (0.87-1.03); p= 0.231	1.000
CAT	1.03 (0.93-1.15); p= 0.573	1.000	10/26 (38.5)	1.02 (0.86-1.21); p= 0.834	1.000
AVSD	1.00 (0.92-1.09); p= 0.973	1.000	18/71 (25.4)	0.87 (0.76-1); p= 0.053	0.065
AVA/S	1.03 (0.92-1.14); p= 0.624	0.117	9/26 (34.6)	0.98 (0.87-1.12); p= 0.817	1.000
TGV	1.15 (1.04-1.26); p= 0.005	1.000	13/82 (15.9)	1.00 (0.88-1.14); p= 0.985	1.000
ToF	1.09 (1-1.19); p= 0.063	1.000	11/51 (21.6)	1.19 (0.92-1.54); p= 0.188	1.000
IAA	1.13 (0.76-1.67); p= 0.549	0.474	1/2 (50)		
CoA	0.98 (0.84-1.15); p= 0.823	1.000	5/67 (7.5)	0.97 (0.8-1.17); p= 0.746	1.000
DORV	0.99 (0.9-1.08); p= 0.779	1.000	15/37 (40.5)	0.67 (0.5-0.91); p= 0.011	0.053
Other	1.06 (1-1.13); p= 0.043	1.000	20/104 (19.2)	0.96 (0.86-1.06); p= 0.402	1.000
All subtypes	1.04 (1.02-1.06); p<0.001	0.001	334/1165 (28.7)	0.97 (0.95-1.00); p= 0.031	1.000

TAPVR, MVA, VSD, ASD, and PVS were not included as they are very difficult to diagnose prenatally. PDA was excluded because the ductus arteriosus is always open prenatally. There were too few cases of IAA to examine TOPFA rates in prenatally diagnosed cases only.

OR=Odds ratio, TOPFA=Termination of pregnancy for fetal anomaly

*Analysis carried out on cases notified to CARIS, NorCAS and WANDA

5.3.26 Heterogeneity in termination rates between registers

5.3.26.1 All CHD adjusted for the presence of ECAs

There was significant variation in TOPFA rates between registers (significance of random intercept: $p<0.001$). There was no significant difference in TOPFA rates between registers for any of the CHD subtypes. However, in cases of EA and TAPVR, the random intercept almost reached statistical significance (significance of random intercept: $p=0.036$ and $p=0.035$, respectively). EA resulted in TOPFA in 4.6% of cases notified to CARIS, 0% of cases notified to CAROBB, 13.5% of cases notified to EMSYCAR, 7.7% of cases notified to NorCAS, 0% of cases notified to SWCAR and 33.3% of cases notified to WANDA. TAPVR resulted in TOPFA in just one case, which was notified to CARIS.

5.3.27 Association between maternal age and total birth prevalence

5.3.27.1 All CHD adjusted for ECAs

Considering all CHD subtypes, there was a significant association between the total birth prevalence of CHD and maternal age at delivery (adjusted for the presence of ECAs) ($p<0.001$). Specifically, the risk of CHD increased as maternal age increased (Table 5.28). The total birth prevalence was 86.6 per 10,000 total births in mothers aged <20 and 123.1 per 10,000 total births in mothers aged ≥40.

VSD, ASD and AVSD were significantly associated with maternal age at delivery (after adjustment for the presence of ECAs) ($p<0.001$ for each). Specifically, the risk of VSD, ASD and AVSD increased with increasing maternal age, with mothers aged 40 and over at 80%, 126% and 443% significant increased risk compared to mothers aged between 25 and 29, respectively (Table 5.27). There was some evidence that the prevalence of HRH was associated with maternal age at delivery ($p=0.033$), although the association did not quite reach statistical significance. Here there appeared to be a U-shaped association between the total birth prevalence of HRH and maternal age at delivery.

As shown in Table 5.28, adjusting the models for year of delivery had little impact on the association with maternal age at delivery.

Table 5.28 Prevalence and RR of CHD according to maternal age, by CHD subtype

Subtype	Age	N	Prevalence per 10,000 total births (95%CI)	RR (95% CI)*†	P-value	Adjusted RR (95% CI)† ‡	P-value
SV	<20	8	0.6 (0.2-1.1)	0.83 (0.38-1.82)	0.195	0.84 (0.38-1.83)	0.174
	20-24	22	0.6 (0.4-0.9)	0.91 (0.52-1.59)		0.92 (0.53-1.61)	
	25-29	31	0.6 (0.4-0.9)	1 (Ref category)		1 (Ref category)	
	20-34	14	0.3 (0.2-0.5)	0.47 (0.25-0.91)		0.48 (0.25-0.92)	
	35-39	17	0.7 (0.4-1.1)	1.21 (0.66-2.23)		1.27 (0.69-2.35)	
	≥40	3	0.7 (0.1-1.9)	1.17 (0.36-3.84)		1.25 (0.38-4.12)	
HLH	<20	47	3.4 (2.5-4.5)	1.31 (0.93-1.83)	0.363	1.31 (0.93-1.83)	0.357
	20-24	101	2.9 (2.4-3.5)	1.10 (0.85-1.44)		1.10 (0.85-1.43)	
	25-29	125	2.6 (2.2-3.1)	1 (Ref category)		1 (Ref category)	
	20-34	114	2.5 (2-3)	0.93 (0.72-1.2)		0.93 (0.72-1.2)	
	35-39	59	2.4 (1.8-3.2)	0.92 (0.67-1.26)		0.91 (0.66-1.25)	
	≥40	11	2.2 (1-4)	0.83 (0.44-1.58)		0.83 (0.43-1.57)	
EA	<20	9	0.4 (0.2-0.9)	0.68 (0.28-1.63)	0.566	0.68 (0.28-1.63)	0.565
	20-24	15	0.4 (0.2-0.7)	0.68 (0.36-1.26)		0.68 (0.36-1.26)	
	25-29	30	0.6 (0.4-0.9)	1 (Ref category)		1 (Ref category)	
	20-34	17	0.4 (0.2-0.6)	0.58 (0.32-1.06)		0.58 (0.32-1.06)	
	35-39	13	0.6 (0.3-1)	0.89 (0.46-1.7)		0.88 (0.46-1.7)	
	≥40	0	0 (0-0.8)				
HRH	<20	38	2.7 (1.9-3.7)	1.56 (1.06-2.29)	0.033	1.56 (1.06-2.31)	0.028
	20-24	95	2.6 (2.1-3.2)	1.5 (1.1-2.03)		1.51 (1.11-2.05)	
	25-29	82	1.7 (1.3-2.1)	1 (Ref category)		1 (Ref category)	
	20-34	81	1.7 (1.3-2.1)	1.02 (0.74-1.41)		1.03 (0.75-1.42)	
	35-39	50	1.9 (1.4-2.5)	1.22 (0.84-1.78)		1.25 (0.86-1.82)	
	≥40	11	2.4 (1.2-4.3)	1.61 (0.86-3.03)		1.67 (0.89-3.15)	
CAT	<20	15	1.1 (0.6-1.8)	1.23 (0.68-2.24)	0.067	1.23 (0.68-2.23)	0.080
	20-24	21	0.6 (0.4-0.9)	0.67 (0.39-1.16)		0.67 (0.39-1.15)	
	25-29	44	0.8 (0.6-1.1)	1 (Ref category)		1 (Ref category)	
	20-34	31	0.7 (0.5-1)	0.86 (0.54-1.38)		0.85 (0.53-1.37)	
	35-39	28	1.1 (0.7-1.7)	1.49 (0.9-2.45)		1.45 (0.88-2.39)	
	≥40	6	1.3 (0.5-2.9)	1.77 (0.75-4.2)		1.71 (0.72-4.06)	
AVSD	<20	69	4.9 (3.8-6.2)	1.41 (1.06-1.87)	<0.001	1.41 (1.06-1.87)	<0.001
	20-24	142	3.9 (3.3-4.7)	1.14 (0.91-1.44)		1.15 (0.91-1.44)	
	25-29	159	3.3 (2.8-3.9)	1 (Ref category)		1 (Ref category)	
	20-34	180	3.9 (3.3-4.5)	1.22 (0.98-1.52)		1.22 (0.98-1.52)	
	35-39	156	6.4 (5.4-7.5)	2.12 (1.69-2.66)		2.12 (1.69-2.66)	
	≥40	76	16 (12.5-20.1)	5.43 (4.11-7.18)		5.45 (4.12-7.21)	
AVA/S	<20	32	2.3 (1.6-3.2)	0.84 (0.57-1.24)	0.093	0.85 (0.58-1.25)	0.147
	20-24	85	2.4 (1.9-3)	0.88 (0.67-1.16)		0.89 (0.68-1.18)	
	25-29	129	2.7 (2.2-3.2)	1 (Ref category)		1 (Ref category)	
	20-34	103	2.2 (1.8-2.6)	0.84 (0.64-1.09)		0.85 (0.65-1.11)	
	35-39	34	1.4 (0.9-1.9)	0.54 (0.37-0.81)		0.57 (0.38-0.84)	
	≥40	12	2.2 (1-4)	0.91 (0.48-1.73)		0.97 (0.51-1.86)	
TGV	<20	39	2.7 (1.9-3.7)	0.84 (0.59-1.2)	0.828	0.84 (0.59-1.2)	0.822
	20-24	107	3.1 (2.5-3.7)	0.96 (0.75-1.22)		0.95 (0.74-1.22)	

Subtype	Age	N	Prevalence per 10,000 total births (95%CI)	RR (95% CI)*†	P-value	Adjusted RR (95% CI)† ‡	P-value
	25-29	156	3.2 (2.7-3.8)	1 (Ref category)		1 (Ref category)	
	20-34	142	3.0 (2.6-3.6)	0.96 (0.76-1.21)		0.96 (0.76-1.21)	
	35-39	64	2.7 (2-3.4)	0.87 (0.64-1.17)		0.86 (0.64-1.16)	
	≥40	17	3.5 (2-5.7)	1.17 (0.7-1.96)		1.15 (0.69-1.93)	
ToF	<20	51	3.6 (2.7-4.7)	0.99 (0.72-1.36)	0.087	0.98 (0.71-1.35)	0.143
	20-24	142	4.1 (3.4-4.8)	1.16 (0.92-1.45)		1.14 (0.91-1.43)	
	25-29	168	3.5 (2.9-4)	1 (Ref category)		1 (Ref category)	
	20-34	155	3.1 (2.6-3.7)	0.95 (0.75-1.18)		0.94 (0.75-1.17)	
	35-39	99	4 (3.2-4.9)	1.25 (0.97-1.62)		1.22 (0.94-1.57)	
	≥40	23	4.8 (3-7.3)	1.58 (1.01-2.46)		1.51 (0.96-2.36)	
TAPVR	<20	14	1 (0.5-1.7)	1.34 (0.72-2.5)	0.735	1.34 (0.72-2.5)	0.735
	20-24	32	0.9 (0.6-1.3)	1.25 (0.77-2.02)		1.25 (0.77-2.02)	
	25-29	36	0.7 (0.5-1)	1 (Ref category)		1 (Ref category)	
	20-34	29	0.6 (0.4-0.9)	0.89 (0.54-1.47)		0.89 (0.54-1.47)	
	35-39	15	0.6 (0.3-1)	0.92 (0.49-1.73)		0.93 (0.49-1.73)	
	≥40	3	0.7 (0.1-1.9)	1.03 (0.32-3.37)		1.03 (0.32-3.38)	
IAA	<20	7	0.5 (0.2-1)	0.79 (0.34-1.8)	0.645	0.79 (0.34-1.8)	0.645
	20-24	14	0.4 (0.2-0.7)	0.64 (0.34-1.21)		0.64 (0.34-1.21)	
	25-29	29	0.6 (0.4-0.9)	1 (Ref category)		1 (Ref category)	
	20-34	18	0.4 (0.2-0.6)	0.66 (0.37-1.19)		0.66 (0.37-1.19)	
	35-39	10	0.4 (0.2-0.8)	0.75 (0.36-1.54)		0.75 (0.36-1.54)	
	≥40	1	0.2 (0-1.2)	0.38 (0.05-2.82)		0.38 (0.05-2.82)	
CoA	<20	56	4 (3-5.2)	1.13 (0.84-1.54)	0.084	1.14 (0.84-1.55)	0.052
	20-24	125	3.5 (2.9-4.2)	1 (0.79-1.27)		1.01 (0.8-1.28)	
	25-29	167	3.4 (2.9-4)	1 (Ref category)		1 (Ref category)	
	20-34	174	3.5 (3-4.1)	1.07 (0.86-1.34)		1.08 (0.87-1.35)	
	35-39	105	4.1 (3.4-5.1)	1.29 (1-1.67)		1.32 (1.02-1.71)	
	≥40	28	5.2 (3.4-7.8)	1.71 (1.11-2.63)		1.77 (1.15-2.72)	
DORV	<20	18	1.3 (0.8-2)	1.86 (1.04-3.29)	0.209	1.86 (1.05-3.31)	0.227
	20-24	31	0.9 (0.6-1.2)	1.23 (0.75-2.02)		1.23 (0.75-2.01)	
	25-29	34	0.7 (0.5-1)	1 (Ref category)		1 (Ref category)	
	20-34	39	0.8 (0.6-1.1)	1.12 (0.7-1.8)		1.11 (0.69-1.78)	
	35-39	22	0.9 (0.6-1.4)	1.3 (0.75-2.25)		1.26 (0.73-2.18)	
	≥40	7	1.5 (0.6-3.2)	2.21 (0.98-4.99)		2.11 (0.93-4.78)	
MVA	<20	16	1.1 (0.7-1.9)	1.63 (0.89-2.98)	0.469	1.64 (0.9-3)	0.457
	20-24	33	0.9 (0.6-1.3)	1.35 (0.82-2.21)		1.36 (0.83-2.23)	
	25-29	33	0.7 (0.5-0.9)	1 (Ref category)		1 (Ref category)	
	20-34	42	0.9 (0.6-1.2)	1.37 (0.85-2.2)		1.39 (0.86-2.23)	
	35-39	19	0.8 (0.5-1.2)	1.31 (0.73-2.35)		1.36 (0.76-2.45)	
	≥40	1	0.2 (0-1.2)	0.38 (0.05-2.76)		0.4 (0.05-2.92)	
VSD	<20	468	32.2 (29.3-35.3)	1.02 (0.92-1.14)	<0.001	1.02 (0.92-1.14)	<0.001
	20-24	1090	30.5 (28.7-32.4)	0.99 (0.92-1.08)		0.99 (0.92-1.08)	
	25-29	1436	29.4 (27.9-31)	1 (-)		1 (Ref category)	
	20-34	1421	29.8 (28.2-31.4)	1.08 (1-1.17)		1.08 (1-1.17)	
	35-39	779	31.8 (29.5-34.2)	1.21 (1.11-1.32)		1.21 (1.11-1.32)	

Subtype	Age	N	Prevalence per 10,000 total births (95%CI)	RR (95% CI)*†	P-value	Adjusted RR (95% CI)† ‡	P-value
	≥40	229	46.4 (40.3-53)	1.8 (1.55-2.08)		1.79 (1.55-2.08)	
ASD	<20	138	9.6 (8.1-11.4)	0.96 (0.79-1.17)	<0.001	0.96 (0.79-1.17)	<0.001
	20-24	391	10.7 (9.7-11.9)	1.13 (0.99-1.3)		1.13 (0.99-1.3)	
	25-29	446	9.1 (8.3-10)	1 (Ref category)		1 (Ref category)	
	20-34	401	8.3 (7.5-9.2)	0.97 (0.84-1.11)		0.97 (0.84-1.11)	
	35-39	277	11.5 (10.1-13)	1.41 (1.21-1.65)		1.41 (1.21-1.65)	
	≥40	85	17.7 (14.1-22)	2.26 (1.78-2.86)		2.26 (1.78-2.86)	
PVS	<20	67	4.7 (3.6-5.9)	0.94 (0.72-1.25)	0.167	0.94 (0.71-1.25)	0.199
	20-24	160	4.5 (3.8-5.2)	0.94 (0.76-1.16)		0.94 (0.76-1.15)	
	25-29	227	4.5 (3.9-5.2)	1 (Ref category)		1 (Ref category)	
	20-34	205	4.2 (3.6-4.8)	1 (0.82-1.21)		0.99 (0.82-1.21)	
	35-39	116	4.8 (3.9-5.8)	1.24 (0.99-1.57)		1.23 (0.98-1.55)	
	≥40	26	5 (3.2-7.5)	1.37 (0.89-2.11)		1.35 (0.88-2.08)	
PDA	<20	39	2.7 (1.9-3.7)	1.4 (0.95-2.06)	0.248	1.4 (0.95-2.06)	0.248
	20-24	77	2.2 (1.7-2.8)	1.18 (0.86-1.61)		1.18 (0.86-1.61)	
	25-29	83	1.8 (1.4-2.2)	1 (Ref category)		1 (Ref category)	
	20-34	108	2.4 (2-2.9)	1.39 (1.04-1.85)		1.39 (1.04-1.85)	
	35-39	47	2 (1.4-2.6)	1.17 (0.81-1.68)		1.17 (0.81-1.68)	
	≥40	12	2.6 (1.4-4.6)	1.56 (0.85-2.86)		1.56 (0.85-2.85)	
Other	<20	111	7.8 (6.4-9.4)	1.03 (0.83-1.28)	0.153	1.03 (0.83-1.28)	0.151
	20-24	246	6.9 (6-7.8)	0.91 (0.77-1.07)		0.91 (0.77-1.07)	
	25-29	373	7.5 (6.7-8.3)	1 (Ref category)		1 (Ref category)	
	20-34	346	7.4 (6.6-8.2)	0.98 (0.84-1.14)		0.98 (0.84-1.14)	
	35-39	190	7.8 (6.7-9)	1.03 (0.86-1.23)		1.03 (0.86-1.23)	
	≥40	49	10.5 (7.7-13.9)	1.4 (1.04-1.9)		1.4 (1.04-1.9)	
All subtypes	**<20**	**1241**	**86.6 (81.8-91.6)**	**1.06 (0.99-1.13)**	**<0.001**	**1.05 (0.99-1.13)**	**<0.001**
	20-24	**2929**	**81.9 (79-85)**	**1.02 (0.97-1.07)**		**1.02 (0.97-1.07)**	
	25-29	**3788**	**77.5 (75-80.1)**	**1 (Ref category)**		**1 (Ref category)**	
	20-34	**3620**	**75.8 (73.3-78.4)**	**1.03 (0.99-1.08)**		**1.03 (0.98-1.08)**	
	35-39	**2100**	**85.9 (82.1-89.7)**	**1.22 (1.16-1.29)**		**1.21 (1.14-1.28)**	
	≥40	**600**	**123.1 (113.2-133.7)**	**1.81 (1.65-1.98)**		**1.78 (1.63-1.95)**	

*Adjusted for ECAs

‡Adjusted for ECAs and year of delivery

†Cases notified to CAROBB (all years), EMSYCAR (all years), and SWCAR for 2010 were excluded from this analysis due to missing maternal age data.

Maternal age was missing in 187 (1.9%) isolated cases, 10 (0.6%) cases with structural ECAs and 24 (1.0%) cases with chromosomal/ genetic ECAs.

5.3.27.2 Interaction between maternal age and the presence of ECAs

There was a significant interaction between maternal age and the presence of ECAs ($p<0.001$). Therefore, the association with maternal age was modelled separately for isolated CHD, CHD with structural ECAs and CHD with chromosomal/ genetic ECAs. As shown in Table 5.29, there was no association between maternal age and the prevalence of isolated CHD ($p=0.103$). There was a significant association between maternal age and the prevalence of CHD with structural ECAs ($p<0.001$). The association appeared to be U-shaped, with mothers under 20 and aged 35 and over at increased risk (Table 5.27). There was also a significant association between maternal age and the prevalence of CHD with chromosomal/ genetic ECAs ($p<0.001$), where the risk of CHD increased linearly with increasing age (Table 5.27).

There was a significant interaction between maternal age and the presence of ECAs in cases of AVSD ($p<0.001$), VSD ($p<0.001$) and ASD ($p<0.001$). There was some evidence of an association between maternal age and the presence of ECAs in cases of ToF ($p=0.016$), although this did not quite reach statistical significance. Table 5.28 shows the RRs of CHD according to maternal age in cases of AVSD, ToF, ASD, and VSD modelled separately according to the presence of ECAs.

In isolated cases of AVSD, there was no statistically significant association between prevalence and maternal age at delivery ($p=0.103$). However, the risk of AVSD appeared to decrease linearly with increasing maternal age at delivery. For example, compared to cases born to mothers aged 25-29, the risk of AVSD was 74% greater in cases born to mothers aged <20 (RR=1.74, 95% CI: 1.11-2.74). In cases of AVSD with structural ECAs, the association between prevalence and maternal age did not reach statistical significance ($p=0.061$), but a U-shaped association was observed (Table 5.28). There was a significant association between maternal age and prevalence in cases of AVSD with chromosomal/ genetic ECAs ($p<0.001$) (Table 5.28). Mothers of increased maternal age were at increased risk of AVSD, for example, mothers aged 40 and over were eight times significantly more likely to have a pregnancy associated with AVSD (Table 5.29).

In cases with ToF, there was no significant association with maternal age in isolated cases ($p=0.462$) or cases with structural ECAs ($p=0.178$), but there was an association with maternal age in cases with chromosomal/ genetic ECAs ($p<0.001$). Increased maternal age was associated with an increased risk of ToF (Table 5.29).

For cases of VSD and ASD, there were no significant associations with maternal age in isolated cases ($p= 0.485$ and $p=0.025$, respectively) or in cases with structural ECAs ($p=0.085$ and $p=0.028$, respectively), but there was a significant association in cases with chromosomal/ genetic ECAs ($p<0.001$ and $p<0.001$); increasing maternal age was associated with an increased risk of VSD and ASD (Table 5.29).

Table 5.29 RR of CHD according to maternal age, by CHD subtype and presence of ECAs

CHD subtype	Age	Isolated CHD		CHD with structural ECAs		CHD with chromosomal ECAs	
		RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
AVSD	<20	1.74 (1.11-2.74)	0.103	2.99 (1.15-7.80)	0.061	1.08 (0.72-1.62)	<0.001
	20-24	1.18 (0.80-1.73)		2.69 (1.21-6.00)		0.99 (0.72-1.35)	
	25-29	1 (Ref category)		1 (Ref category)		1 (Ref category)	
	20-34	0.98 (0.66-1.44)		1.61 (0.70-3.74)		1.31 (1.00-1.73)	
	35-39	0.83 (0.49-1.38)		2.07 (0.81-5.26)		2.84 (2.16-3.74)	
	≥40	0.86 (0.31-2.37)		4.69 (1.43-15.37)		8.07 (5.86-11.1)	
ToF	<20	0.84 (0.55-1.28)	0.463	2.19 (1.11-4.31)	0.178	0.73 (0.34-1.58)	<0.001
	20-24	1.10 (0.83-1.46)		1.46 (0.81-2.63)		1.17 (0.72-1.89)	
	25-29	1 (Ref category)		1 (Ref category)		1 (Ref category)	
	20-34	0.82 (0.62-1.10)		1.32 (0.74-2.34)		1.07 (0.67-1.72)	
	35-39	0.90 (0.63-1.29)		1.65 (0.86-3.18)		2.07 (1.27-3.37)	
	≥40	0.74 (0.35-1.60)		2.66 (1.00-7.09)		3.52 (1.74-7.12)	
VSD	<20	1.00 (0.88-1.12)	0.485	1.47 (1.05-2.07)	0.085	0.83 (0.58-1.19)	<0.001
	20-24	1.01 (0.92-1.10)		1.10 (0.83-1.46)		0.8 (0.62-1.05)	
	25-29	1 (Ref category)		1 (Ref category)		1.06 (0.84-1.34)	
	20-34	1.08 (0.99-1.17)		1.03 (0.79-1.35)		2.68 (2.15-3.34)	
	35-39	1.01 (0.90-1.12)		1.20 (0.87-1.64)		7.39 (5.7-9.59)	
	≥40	1.03 (0.84-1.27)		1.75 (1.06-2.89)			
ASD	<20	0.86 (0.67-1.09)	0.025	1.47 (0.97-2.23)	0.028	0.84 (0.5-1.41)	<0.001
	20-24	1.13 (0.95-1.34)		1.37 (0.98-1.91)		0.88 (0.6-1.28)	
	25-29	1 (Ref category)		1 (Ref category)		1 (Ref category)	
	20-34	0.90 (0.75-1.06)		0.91 (0.65-1.29)		1.26 (0.91-1.74)	
	35-39	1.13 (0.92-1.38)		1.45 (1.00-2.10)		2.47 (1.77-3.45)	
	≥40	1.34 (0.93-1.93)		1.72 (0.91-3.26)		6.55 (4.39-9.78)	
All Sub-types	**<20**	**0.99 (0.92-1.07)**	**0.976**	**1.52 (1.27-1.82)**	**<0.001**	**1.04 (0.87-1.23)**	**<0.001**
	20-24	**1.00 (0.95-1.06)**		**1.27 (1.1-1.47)**		**0.93 (0.82-1.06)**	
	25-29	**1 (Ref category)**		**1 (Ref category)**		**1 (Ref category)**	
	20-34	**0.99 (0.94-1.05)**		**1.04 (0.9-1.2)**		**1.18 (1.05-1.32)**	
	35-39	**1.00 (0.94-1.07)**		**1.23 (1.04-1.45)**		**2.18 (1.94-2.47)**	
	≥40	**1.04 (0.91-1.19)**		**1.47 (1.1-1.96)**		**5.63 (4.85-6.53)**	

5.4 Discussion

This is the largest and most comprehensive study to examine the epidemiology of CHD in the UK, according to CHD subtype. Using data from six BINOCARs, I found a total birth prevalence of 65 per 10,000 total births and a live birth prevalence of 56 per 10,000 live births. Over time, the total birth prevalence and the live birth prevalence of ToF increased, whereas the prevalence of AVA/S and CoA decreased. Trends were not observed in any other CHD subtype. The prevalence of all CHD subtypes varied between the registers. CHD occurred in isolation in the majority of cases (68% of total birth cases and 75% of live born cases). Isolated cases of CHD were rarely prenatally diagnosed (30%), although the more severe subtypes were diagnosed more frequently than the milder subtypes. Prenatal diagnosis rates for HLH, HRH, TGV, ToF and CoA increased over the study period. This increase in prenatal diagnosis rates appeared to account for an increase in TOPFA rates over the study period. Maternal age at delivery was associated with the prevalence of ToF, AVSD, VSD and ASD but only in cases with chromosomal/ genetic ECAs.

5.4.1 Strengths

The primary strength of this study is the use of population-based data derived from established, high-quality, CARs. Standard methods of identifying and classifying cases across all registers and the use of multiple sources of notifications ensure high case ascertainment. Moreover, all registers use the same ICD coding system, resulting in consistent coding across the registers. Accurate diagnoses are achieved by the review of complex cases by paediatric pathologists and clinical geneticists and, where relevant, diagnoses are confirmed via post mortem.

Using data from six CARs covering a birth population of three million, I was able to examine the epidemiology of CHD according to CHD subtype. I was also able to examine CHD according to the presence of ECAs, which not only have very different aetiologies but are also diverse in terms of outcome, characteristics and interventions. Due to the richness of the data, I was able to investigate characteristics of cases with CHD including: standardised birth weight, gestational age, sex, maternal age, prenatal diagnosis and pregnancy outcomes. I was also able to examine trends in prevalence, TOPFA rates and prenatal diagnosis rates, which are important factors in determining the number of children living with CHD.

A further strength is that I was able to examine all pregnancy outcomes, including late miscarriages, stillbirths and TOPFAs. Therefore, I could report on pregnancy outcomes, which may be useful for parents when a diagnosis is made during the prenatal period.

Additionally, the fact that the study was not restricted to live births meant that my trends in total birth prevalence are not likely to be confounded by changing trends in TOPFA or fetal death.

The multilevel methods utilised to analyse trends in prevalence, TOPFA rates and prenatal diagnosis rates enable more accurate estimates of standard error to be calculated compared to a single level analysis of the nested data. The random effects limit the potential for confounding due to registers contributing data from different time periods [127]. I was also able to examine trends in prevalence adjusted for maternal age, which may have been a confounding factor, given that the proportion of births to mothers of advanced maternal age increased from 12% in 1998 to 19% in 2010.

5.4.2 Limitations

This study also has some limitations. Firstly, LR tests were used to assess the fit of models after the inclusion of a random intercept, a random slope and to test the presence of over-dispersion. However, in random effect models, the LR test is known to be conservative. Therefore the p-values provided for the LR test represent the upper bound of the significance level [128]. This should not have impacted the interpretation of the results given that the p-values for heterogeneity were highly significant.

To account for multiple testing, I applied a Bonferroni adjustment and classified $p<0.003$ as statistically significant, as opposed to the more commonly used nominal significance level of $p<0.05$. This adjustment limited the possibility of type I errors (i.e. false positives), but as a result may have increased the possibility of type II errors (i.e. false negatives). This may have been particularly problematic given that many of the subtypes occurred infrequently, and therefore the power may have been low for some analyses. However, in the results section, I also highlighted the results that were significant at the $p<0.05$ level.

Additionally, there was a high level of maternal age data missing and so analyses on maternal age was restricted to cases notified to four BINOCARs. After adjustment for maternal age, I found that the association between CHD prevalence and year of birth did not alter. Due to the models being fitted to two slightly different data sets, this should perhaps be interpreted with caution. However, refitting the unadjusted models to the subset of the data, showed very similar RRs to the unadjusted models fitted to the full data set. This suggests that the subset of data was representative of the full set of data.

Similarly, data on prenatal diagnosis was used from three registers only. Given the small numbers for certain subtypes combined with the rarity of prenatal diagnosis, it was possible that the study did not have the power to detect trends in diagnosis rates over time for all subtypes. Additionally, I was only able to examine prenatal diagnosis of isolated CHD because the BINOCARs do not specifically record which anomaly was prenatally diagnosed.

Heterogeneity in prevalence estimates between registers will have been caused by differences in ascertainment as opposed to real variation. For example, close relations between paediatric cardiology departments with NorCAS and CARIS, may have caused increased ascertainment of CHD cases by these registers. This is evident in the high level of ascertainment of mild cases specifically. Other registers rely more heavily on cardiac databases which have greater focus on cases that were admitted for catheterization, investigation or surgery. This is likely to have impacted on the ascertainment of CHD of milder severity (in particular on VSDs that close spontaneously), but would have had little impact on CHD of moderate or severe severity, which are more likely to require medical intervention. The ascertainment of the less severe forms of mild CHD by NorCAS and CARIS may explain why I identified a suggestion of a decreasing trend post-2005 in these two registers only, if the milder cases tended to be diagnosed later in life and were, therefore, not captured in the data despite being born during the study period. As discussed by Hoffman et al, it is likely that the under ascertained cases of VSDs are milder forms of the CHD subtype and arguably, these cases are not clinically significant [129]. Differences in ascertainment may also have been caused by the observed variation in prenatal diagnosis rates. Alternatively, heterogeneity in prevalence may be linked to differences in study populations. For example, as discussed in Chapter 4, the populations covered by the six BINOCAR were diverse in terms of maternal ethnicity, smoking status, maternal BMI and maternal diabetes which may be risk factors for certain CHD [4, 5, 80, 96, 97, 108, 130, 131]. All data notified to the BINOCAR are routinely collected in the clinical setting and, therefore, these variables were not complete enough to include in my analysis.

I modelled trends in the prevalence of CHD linearly, as most other studies have done [55, 57, 60, 62]. An alternative approach would have been to model the trends non-linearly using piecewise regression (splines). Piecewise regression can be used to model trends in several sections, which must join at pre-specified time-points called knots. Had I used this approach however, my results for severe and moderate subtypes would have remained unchanged. For CHD overall and for the mild CHD subtypes however, I would not have found similar trends prior to 2004 but significant decreases thereafter. This decrease in prevalence is likely caused by the cases delivered at the end of the study period having a smaller window for diagnosis.

For this reason, modelling this plateau may actually be more misleading than merely modelling the trend linearly. The other disadvantage of using piecewise regression, is that it is heavily influenced by the natural fluctuations in yearly prevalence, which always occur due to CHD being a rare event.

5.4.3 Summary and comparison to other studies

5.4.3.1 Sex distribution

There was an even distribution of male and female cases. This is consistent with 18 studies identified in the literature review detailed in Chapter 3, where 46-54% cases were male. However, Tennant et al's meta-analysis of five studies showed a 70% increased risk of CHD in males compared to females. I found that the more severe subtypes tended to have a male preponderance, so perhaps the studies discussed by Tennant et al had lower ascertainment of the milder CHD subtypes. Lary and Paulozzi hypothesise that sex differences in congenital anomalies that originate within the first eight weeks may be related to variation in susceptibility to teratogens or to X or Y linked genes that influence morphogenesis [132].

5.4.3.2 Prenatal diagnosis

There was a significant increase in the rate of prenatal diagnosis over the study period. While the trend was only significant among cases of HLH, HRH, TGV, ToF and CoA, prenatal diagnosis rates increased in all subtypes with the exception of IAA. Few studies have reported on trends in prenatal diagnosis of CHD, but those that have reported improvements over time in the North of England (1985-2004, using a subset of my data), France (1983-2000) and the USA (1990-1994) [133-135]. This is likely to have resulted from improvements in diagnostic technologies over time (e.g. fetal echocardiography) but in the UK, may also be related to the recent implementation of the FASP guidelines, which state that all pregnant women should have their pregnancies prenatally screened for "severe" CHD [136].

I found a prenatal diagnosis rate of 30% amongst isolated cases of CHD. This exceeds Ailes et al's prenatal diagnosis rate of 15% (among "non-syndromic" cases of CHD) in the USA (1998-2005) [126]. However, Ailes et al included cases of TAPVR, VSD, ASD and PVS, which I excluded as prenatal diagnosis is uncommon in these subtypes. My prenatal diagnosis rate also exceeds Bull et al's rate of 23.4% in the UK (1993-1995), despite Bull et al examining "complex" cases of CHD only (defined as those requiring intervention or resulting in death in the first year of life). Bull et al's lower rate is likely related to the earlier study period [137]. Compared to my study, Khoshnood et al reported a substantially greater prenatal

diagnosis rate of 40%, among isolated cases of CHD (excluding VSDs) born in Paris (2005-2008) [73]. This higher rate is likely due to Khoshnood et al's more recent study period. Indeed, between 2005-2008 my prenatal diagnosis rate increased to 36.7%.

When considering all CHD subtypes combined, I identified significant heterogeneity in prenatal diagnosis rates between registers. However, this variation was restricted to "Other" CHD subtypes. After excluding these cases, there was no longer significant variation in prenatal diagnosis rates. The "Other" CHD subtype is a very heterogeneous group, and therefore variation in the prenatal diagnosis of these anomalies may be related to differences in coding between registers. For example, some registers may not record exactly the same set of anomalies given that there is no specific EUROCAT criteria for this group [138].

In my study, there was no association between prenatal diagnosis and maternal age at delivery. Conversely, in Ailes et al's study, women aged <30 were significantly more likely to have a prenatal diagnosis than women aged ≥30 (RR=1.50). However the effect size decreased after adjustment for CHD complexity, presence of ECAs, year of delivery, family history of CHD, gestational age, plurality, ethnicity, maternal education, BMI, pre-gestational diabetes, hypertension, fertility treatments, previous pregnancy loss, pregnancy intention and trimester of first prenatal visit (aRR=1.13). Given that advanced maternal age is a risk factor for certain congenital anomalies [105, 139, 140], these women tend to be scanned more frequently and perhaps more likely to be offered fetal echocardiography, which may explain the increased prenatal diagnosis rates. Perhaps the difference in my results compared to the study by Ailes et al is related to inclusion criteria. For example, Ailes et al included cases with ECAs whereas these were excluded in my analyses of prenatal diagnosis. Had I included these cases, I would have identified significantly greater prenatal diagnosis rates among mothers aged ≥30 compared to <30.

5.4.3.3 TOPFA rates

There was an increasing trend in the proportion of isolated CHD cases that resulted in TOPFA. Given that the trend was not present amongst prenatally diagnosed cases only, this suggests that the trend in TOPFA rates was driven my improvements in prenatal diagnosis. While the trend did not reach statistical significance in the individual subtypes, TOPFA rates increased over time in all subtypes, with the exceptions of AVSD, CoA and DORV. While there was an increase in prenatal diagnosis rates for AVSD, there was no increase in TOPFA for these cases. Indeed, among prenatally diagnosed cases of AVSD, TOPFA rates actually decreased, although this did not quite reach statistical significance. Potentially, improvements

in the prognosis of children with this CHD subtype resulted in fewer women considering TOPFA.

Khoshnood et al reported that TOPFA rates for CHD increased in Paris between 1983-1994, but stabilised between 1995-2000 [133]. In my study, the trend in TOPFA appeared steeper prior to 2000 but still increased at a lower rate thereafter. Given that the trend in prenatal diagnosis increased steadily over the study period, the stabilisation of the TOPFA rate is perhaps due to other factors that impact upon women's decision to terminate, such as improved prognosis.

5.4.3.4 Total birth prevalence of CHD

I found that the total birth prevalence of CHD in England and Wales was 65 per 10,000 total births. In Chapter 3, 12 studies were identified that had reported the total birth prevalence of all CHD. Here, the prevalence ranged between 30.1 to 213.4 per 10,000 total births, meaning my prevalence rate is at the lower end of the spectrum. However, in my study, the prevalence of CHD varied by register, with the prevalence rates associated with CARIS (112.3 per 10,000 total births) and NorCAS (93.5 per 10,000 total birth), being more comparable to the previous studies. The ascertainment of the milder subtypes, which are difficult to diagnose, is likely to be a large contributing factor to the variation in prevalence. Additionally, in my study, cases are coded according to the EUROCAT guidelines, which has a strict definition of CHD. For example, the EUROCAT does not class cases of PDA< 37 weeks gestational age, heart murmurs and heart block as CHD, which were included in some of the other studies.

As shown in Table 5.30, the prevalence estimates of the individual CHD subtypes in my study are generally comparable to those reported elsewhere. With the exceptions of SV, HRH and PDA, all of my prevalence estimates fall within the range of those reported elsewhere. The prevalence of SV is slightly lower in my study than in eight previous studies. This is likely a result of differences in coding systems. For example, some studies may have coded cases with HRH as SV, given that this subtype was not analysed separately [1, 53, 56, 66, 76, 79]. Indeed, the study with the greatest prevalence of SV (prevalence=2.6 per 10,000), actually defined the condition as "common ventricle" [79]. The variation in the prevalence of PDA is also likely due to coding, given that all studies had different criteria for excluding PDA in preterm infants. For example, Yang et al excluded PDA if it closed during the first 14 days of life (prevalence= 15.7), whereas Johnson et al excluded PDA if it was "associated with prematurity", but provided no definition of prematurity (prevalence=44.2) [56, 79]. In my study, the prevalence of HRH was substantially higher than in previous studies because I

classed TA, PVA and HRH as HRH. Had the other studies combined the subtypes in this manner, then similar prevalence rates would have been observed.

Table 5.30 Total birth prevalence in the current study and previous population-based studies (as discussed in Chapter 3)

Subtype	Range in previous literature (see Chapter 3)	My study
SV	0.6-2.6	0.5 (0.4-0.6)
HLH	0.5-3.0	2.9 (2.7-3.1)
EA	0.2-1.1	0.5 (0.4-0.6)
HRH	0.3	1.9 (1.7-2)
TA	0.4-0.7	
PVA	0.3-1.1	
CAT	0.4-2.8	0.7 (0.6-0.8)
AVSD	0.9-6.2	4.0 (3.8-4.3)
AVA/S	0.3-3.2	1.6 (1.5-1.8)
TGV	2.0-8.3	3.0 (2.8-3.2)
ToF	2.6-6.5	3.4 (3.2-3.6)
TAPVR	0.2-1.1	0.6 (0.5-0.7)
IAA	0.4-0.8	0.4 (0.3-0.4)
CoA	1.3-4.9	3.3 (3.1-3.5)
DORV	0.2-1.8	0.8 (0.7-0.9)
MVA	1.6*	0.6 (0.5-0.7)
VSD	6.6-53.9	22.2 (21.6-22.7)
ASD	0.1-35.1	7.3 (7-7.6)
PVS	0.8-9.7	3.1 (2.9-3.3)
PDA	6.5-44.2	1.8 (1.6-1.9)

*Only one study reported the prevalence of MVA

5.4.3.5 Live birth prevalence

While there is substantial variation in prevalence estimates between studies, my estimates generally fall in the middle of the range for most of the CHD subtypes (Table 5.31). This is likely due to more inclusive definitions of SV; for example, in Wu et al's study, TA is classed as SV (SV prevalence=0.8, TA prevalence =0.5). Similar issues with coding are also likely to have influenced the prevalence of HRH, which is also composite group of subtypes and has a lower prevalence in my study. In my study, the live birth prevalence of VSD was comparable to six studies [1, 56, 58, 61, 62, 86], but around half that reported in a three studies [55, 68, 76]. However, these estimates were more comparable to the prevalence of VSD in the areas covered by CARIS and NorCAS (prevalence = 39.9 and 39.1 per 10,000 live births, respectively). As discussed in Chapter 3, large VSDs tend to be well ascertained, but small VSDs are not because they are very difficult to diagnose. Therefore, heterogeneity in prevalence is related to the maximum age at diagnosis and the method of ascertainment of cases.

Table 5.31 Live birth prevalence in the current study and previous population-based studies (as discussed in Chapter 3)

Subtype	Range in previous literature (see Chapter 3)	My study
SV	0.8-1.5	0.3 (0.2-0.4)
HLH	0-2.3	1.4 (1.3-1.5)
EA	0.2-1.3	0.4 (0.3-0.5)
HRH	0.2-0.6	1.3 (1.2-1.5)
TA	0.2-0.9	-
PVA	0.3-1.3	-
CAT	0.2-1.0	0.5 (0.4-0.6)
AVSD	0.8-4.1	2.8 (2.7-3)
AVA/S	0.2-4.8	1.5 (1.4-1.7)
TGV	0.2-6.3	2.8 (2.6-2.9)
ToF	1.9-5.5	2.9 (2.7-3.1)
TAPVR	0.3-1.6	0.6 (0.5-0.7)
IAA	0.1-0.8	0.3 (0.2-0.4)
CoA	1.8-4.4	3.1 (2.9-3.3)
DORV	0.4-2.3	0.5 (0.5-0.6)
MVA	1.5*	0.6 (0.5-0.7)
VSD	15.6-71.3	20.6 (20.1-21.2)
ASD	2.0-32.3	6.8 (6.5-7.1)
PVS	1.9-13.2	3.1 (2.9-3.3)
PDA	0.9-20.1	1.8 (1.6-1.9)

*MVA prevalence was reported in a single study

5.4.3.6 Trends in the prevalence of CHD

I found no evidence of a trend over time in the total birth prevalence of CHD. While three previous studies reported no evidence of trends in prevalence rates in Russia (1973-88, 28,511 total births), in Italy (1999-2008, 191,171 total births) and in the UK (1960-69, 163,692 total births), these were relatively small studies [64, 72, 74]. Several larger studies have conversely reported increasing trends in the prevalence of CHD in the USA (1968-2005, 1,301,143 total births) and in Canada (1979-93, 593,042 total births) [79, 80]. Additionally, Khoshnood et al reported an increasing trend in Europe up to the year 2000 (7,299,116 total births), and a decrease thereafter [52]. Leirgul et al also reported an increasing trend between 1994-2005 and decreasing trend between 2005-09 in Norway (954,413 total births) [141]. While overall I did not identify an increasing trend however, in five of the six BINOCAR registers the prevalence appeared to increase slightly over the study period. Indeed the trend may not have been apparent due to the slight decreasing trend in cases notified to CARIS, which is one of the larger registers. While all of the registers use the same coding system, methods of ascertainment vary slightly between register. For example, cases notified to CARIS are classed as: confirmed, suspected or probable [142]. Confirmed cases are those based on cytogenetics, post mortem or clinical reports on live births; those classed as suspected cases are those picked up prenatally but not yet confirmed clinically or those with inpatient data but with non-specific codes; probable cases are those with impatient data and specific codes. Only probable and confirmed cases contribute to the prevalence rates for CARIS. Cases with inpatient data but non-specific codes are followed up and verified with paediatric case notes. Possibly these cases take longer to ascertain and therefore cases born towards the end of the study period are less likely to have been confirmed yet, which could contribute towards the decreasing trend. Alternatively, the population in Wales may differ slightly from that of England. Perhaps smoking rates or maternal age distribution have not followed the same patterns as England.

For the individual subtypes, I identified a small increasing trend in the prevalence of ToF. While the risk of ToF increased by just 3% per year, this equates to an excess of approximately 16 cases per year in England and Wales. As discussed in the literature review in Chapter 3, Pradat et al reported an increasing trend in the total birth prevalence of ToF in Sweden (1981-92) and Johnson et al reported an increasing prevalence of ToF in Canada (1979-1988) [53, 79]. Additional studies that did not meet the inclusion criteria for the literature review have also reported increasing trends in ToF prevalence. For example, Botto et al reported a doubling in the

total birth prevalence of ToF in 1995-1997 compared to 1968-1972 in Metropolitan Atlanta. Grech et al reported an increasing trend in ToF in Malta (1980-94), but did not perform a formal statistical test [143]. Conversely, Francannett et al did not identify any increasing trends in ToF in their study of five registers (Australia, New South Wales 1981-1984; Central Eastern France 1983-1989; Italy (IMER) 1982-1989, Sweden 1981-1986 and France, Strasbourg 1979-1985), although the increasing trend was of borderline statistical significance in the register with the longest period of follow-up (France, Strasbourg) [144]. Although these trends may be related to improved ascertainment over time, there is some evidence that ART is a risk factor for ToF [145]. Therefore, if uptake of ART increased over time, this may explain some of the increase in prevalence.

I also identified a significant decreasing trend in the prevalence of AVA/S and CoA. The trend in AVA/S was also observed by Wu et al, although this was amongst live births and may have been confounded by increasing rates of TOPFA [55]. Conversely, Pradat et al reported an increasing trend in the prevalence of aortic stenosis in Sweden (1981-92), although did not include cases of aortic atresia as I did in my study [53]. No other studies have identified a decreasing trend in the prevalence of CoA. Without further research it is not possible to assess whether these decreases in CoA and AVA/S are "real" or chance findings.

Several population-based studies have reported an increasing trend in the prevalence of VSD and ASD [53, 57, 79, 130, 131, 146]. Additionally, Khoshnood et al reported that the prevalence of mild CHD (classed as VSD, ASD and PVS), increased until 2000 and decreased thereafter [52]. Several authors hypothesise that increasing trends are related to improved ascertainment over the study period as opposed to real increases. Diagnoses of septal defects are likely to have improved due to improved echocardiography equipment, lower waiting times for outpatient clinic appointments, a greater number of paediatricians with expertise performing scans, and lower thresholds for referral. Increasing trends may also have been related to the changing age distribution over time, with older mothers perhaps being more at risk of a pregnancy affected by septal defects [80]. Similarly, research shows that CHD is also more common in the offspring of women with pre-gestational diabetes, which is becoming more prevalent over time [5, 147]. In my study, I did not identify an overall increasing trend in the prevalence of VSD or ASD. However, in five of the six BINOCARs there was some indication of a slight increase over time.

5.4.3.7 Maternal age

I found an association between maternal age at delivery and the prevalence of ToF, AVSD, ASD and VSD. However, the association reached statistical significance in cases that occurred with chromosomal/ genetic ECAs only. This is unsurprising given the known association between advanced maternal age and chromosomal anomalies. Indeed, it is likely that maternal age is a risk factor for a chromosomal anomaly which is directly responsible for the development of the CHD, as opposed to maternal age being a risk factor for ToF, AVSD, ASD and VSD directly. Although the overall association with maternal age was not significant amongst isolated cases of AVSD, the prevalence was significantly greater amongst mothers aged <20 compared to 25-29. There was also some evidence of an association with the prevalence of HRH, although this did not reach statistical significance at the $p<0.002$ level. Here there was a U-shaped association between HRH prevalence and maternal age, which was not restricted to cases with chromosomal/ genetic ECAs.

Other studies have shown that increased maternal age is a risk factor for AVSD (occurring with chromosomal/ genetic ECAs) and (non-chromosomal) VSD, ASD, CoA and TGV. For example, Forrester et al reported a 25 and 29% significant increased risk of (non-chromosomal) VSD and ASD respectively, in cases with mothers aged ≥35 compared to <35, although they did not adjust for year of birth [76]. Miller et al have shown that compared to women aged 25-29, women aged 35 and over are at 20, 36, 54 and 65% significant increased risk of a pregnancy associated with (non-chromosomal) VSD, ASD, CoA or TGV, respectively, after adjustment for year of delivery [80]. Given that these studies examined multiple subtypes it is possible that some of these associations were identified by chance. Indeed, Long et al did not report an association between (non-chromosomal) TGV prevalence and maternal age, although prevalence increased linearly over the maternal age categories [148]. On the other hand, cases born to mothers of advanced maternal age may have been subjected to more screening prenatally and postnatally, meaning the increased risk may be related to ascertainment bias. Additionally, the populations described by Forrester et al, Miller et al and Long et al are more ethnically diverse than the population covered by the BINOCAR, so this may have had an impact if an interaction exists between maternal age and ethnicity. Lastly, Long et al also reported that women aged ≥35 were 45% significantly more likely to have a pregnancy associated with (non-chromosomal) ToF compared to women aged 25-29. While I did not find an overall association with maternal age and ToF prevalence, I did find a significant 58% increased risk in women aged ≥40 compared to those aged 25-29

Chapter 6. Congenital heart disease in twins: what are the risks?

6.1 Introduction

Research consistently suggests that there is an increased risk of congenital anomalies in multiple compared to singleton pregnancies [113, 149-151]. Most of these studies combine twins and higher order births [149, 151], or examine twins only [113]. However, one study has shown that the risk of congenital anomaly increases with increasing number of fetuses within the multiple birth [150]. There is also some evidence that the risk amongst twins that share a placenta, monochorionic (MC) twins, exceeds that of twins that do not share a placenta, dichorionic (DC) twins [113]. The risk of CHD amongst twins and multiples is less well researched. While several case-series have investigated the prevalence of CHD in twins [152-155], few studies have compared the rate to singletons [113, 151, 156]. Of those that have, the risk of CHD was significantly increased by between 47-63% in twins [113, 151, 156]. Even fewer studies have examined the risk of CHD according to chorionicity. In Glinianaia et al's study, there was a 30% and 50% increased risk of CHD in MC and DC twins compared to singletons, but this only reached significance in DC twins [113]. Herskind et al examined the RR in twins compared to singletons according to zygosity, which can act as a proxy for chorionicity given that all DZ twins are DC and approximately two thirds of MZ twins are MC [157]. Herskind et al reported significant increased risks of 35 and 30% in MZ and DZ twins, respectively [156]. No studies have separately examined the risk of CHD in higher order births, likely due to low case numbers.

6.1.1 Aim

The aim of this study was to examine the epidemiology of twins and higher order births born with CHD in the North of England between 1998-2010, using high quality population-based registers (see Appendix A for the publication corresponding to this chapter).

6.1.1.1 Objectives

1. To describe pregnancy outcomes, gestational age at delivery, standardised birth weight, prenatal diagnosis and maternal age distribution in twins versus singletons with CHD.
2. To report the prevalence and trends in prevalence of CHD in singletons, twins and higher order multiples.

3. To estimate the RR of CHD in twins compared to singletons, by CHD severity and chorionicity.

6.2 Methods

6.2.1 Case inclusion

Cases of CHD notified to the NorCAS between 1st January 1998-31st December 2010 were included in this study. Information on chorionicity was obtained from the NorSTAMP (see Chapter 4).

Cases of CHD known to occur with ECAs are likely to have different aetiologies than cases with isolated CHD. For example, CHD occurring with chromosomal or genetic ECAs may be a result of the chromosomal anomaly, perhaps caused by chromosomal aneuploidy [45]. These cases are likely to have different risk factors, such as increased maternal age, which has been associated with an increased risk of chromosomal anomalies [158, 159]. Analysis was carried out on cases of isolated CHD only, to investigate the purest possible association between CHD and plurality.

6.2.2 Case coding

Twins were coded as MC or DC. Due to small case numbers, it was not possible to analyse the association between plurality and CHD according to CHD subtype. However, it was possible to analyse groups of CHD subtypes, which were classified according to CHD severity.

6.2.3 Data

Data on the annual number of live and stillbirths born to mothers residing in the North of England (combined and by maternal age) was provided by the ONS. Data on the annual number of twin and higher order multiple live and stillbirths (combined and by maternal age) were provided by the NorSTAMP. The annual numbers of singleton births (combined and by maternal age) were calculated by subtracting the annual number of multiple births (provided by the NorSTAMP) from the annual number of all births (provided by the ONS). Maternal age data was missing for 248 (2.1%) twin pregnancies and were excluded from the denominator for analysis of maternal age.

Table 6.1 shows the variables included in the analysis. Year of delivery was classed as a continuous variable and all other variables were treated as categorical. By performing a fetal growth formula to calculate birth weight at 40 weeks gestation (according to a regional birth weight reference)[125], birth weight was standardised for gestational age at delivery, sex and

plurality. Due to missing data, it was not possible to calculate birth weight in 50 (1.7%) singletons and one (0.7%) twin, so these cases were excluded from this analysis. Gestational age was missing in 43 (1.5%) singletons and one twin (0.7%), so these cases were excluded form analysis for this variable.

Information on the exact timing of prenatal diagnosis was not available, so prenatal diagnosis was simply categorised as "diagnosed" or "not diagnosed". Prenatal diagnosis refers to the diagnosis of *any* congenital anomaly. Prenatal diagnosis was missing in 1,256 (31.6%) singletons, 62 (33.2%) twins and in three (37.5%) triplets. These cases were therefore excluded from the analysis of prenatal diagnosis.

Table 6.1 Description of variables used in analysis

Variable	Classification
Year of delivery (years)	Continuous variable
Gestational age at delivery (weeks)	Extreme preterm (20-27 weeks) Very preterm (28-31 weeks) Moderately preterm (32-36 weeks) Term (37-41 weeks) Post-term (≥41 weeks)
Sex	Male (reference category) Female
Maternal age at delivery (years)	<20 20-29 30-34 ≥35
Extra-cardiac anomalies (ECAs)	Isolated CHD CHD with structural ECAs CHD with chromosomal/ genetic ECAs
Prenatal diagnosis	Prenatally diagnosed (any congenital anomaly) Not prenatally diagnosed (any congenital anomaly)
Standardised birth weight (SD from the mean)	Low birth weight: SD<-1 Average birth weight: -1 ≤ SD ≥1 High birth weight: SD>1
Plurality	Singleton Twin Higher order multiple

6.2.4 Statistical analysis

Descriptive statistics were produced for gestational age at delivery, standardised birth weight, maternal age at delivery, sex and the presence of ECAs. χ^2 or Fisher's exact tests were performed to assess the association between plurality and pregnancy outcomes, sex and the presence of ECAs. Mann-Whitney tests were used to assess the associations between plurality and gestational age at delivery and standardised birth weight (both categorical variables). Total birth prevalence was calculated as the number of cases (in live births, late miscarriages, stillbirths or TOPFA) per 10,000 live and stillbirths (total births). Analysis was completed separately for twins and higher order multiple births as these cases are not necessarily homogenous in terms of prevalence, gestational age at delivery, birthweight and maternal age at delivery [149]. Additionally, the RR of congenital anomalies in higher order multiples compared to singletons is likely to exceed the RR of CHD in twins compared to singletons. From a counselling point of view and a public health perspective, it was therefore more appropriate to separate the twins and higher order pregnancies.

The unadjusted RR of isolated CHD in twins compared to singletons was estimated using Poisson regression models with log of the total births as the offset and plurality (classed as singleton or twin) as an explanatory variable. Adjusted RRs were estimated by refitting the models to include year of delivery (as a continuous variable) and maternal age (categorised as <20, 20-29, 30-34 and ≥35). The interaction between year of delivery and plurality was investigated by refitting the model with a cross product term. The unadjusted RR of CHD per years increase in year of delivery were also estimated using Poisson regression. The unadjusted RR of CHD associated with maternal age was similarly estimated.

Analyses were completed for all twins, according to chorionicity and CHD severity. The RR of CHD in higher order pregnancies compared to singletons was not estimated due to low case numbers.

All statistical analyses were performed in Stata 13 and $p<0.05$ was considered statistically significant.

6.3 Results

Between 1998-2010, there were 399,414 singleton pregnancies, 6,101 twin pregnancies and 161 higher order multiple pregnancies that resulted in (at least one) live or stillbirth. This equated to 11,871 twin total births, given that only one twin was live born or stillborn in 331 pregnancies, and 497 higher order births. Of the twin births, 4,359 pregnancies (8,605 births) (72.5%) were DC and 1,170 pregnancies (2,317 births) (19.5%) were MC, leaving 542 pregnancies (949 births) (8.0%) with unknown chronicity. The proportion of twin pregnancies increased from 2.6% in 1998 to 2.9% in 2010, although this did not quite reach statistical significance (test for trend: p=0.069). The proportion of higher order pregnancies decreased significantly from 0.03% in 1998 to 0.02% in 2010 (test for trend: p=0.004).

There were 4,160 cases of CHD notified to NorCAS between 1998-2010: 3,965 singletons, 187 twins and eight triplets. Of the 187 twins with CHD, 114 (61.0%) were DC twins, 60 (32.1%) were MC twins and 13 (7.0%) had unknown chorionicity.

6.3.1 Extra-cardiac anomalies

Of the singletons with CHD, 700 (17.7%) occurred with chromosomal/ genetic ECAs and 281 (7.1%) occurred with structural ECAs. Of the twins with a CHD, 15 cases (8.0%) occurred with chromosomal/ genetic ECAs and 18 (9.6%) occurred with structural ECAs. Twins with CHD were at significant decreased risk of chromosomal/ genetic ECAs compared to singletons (RR=0.45, 0.28-0.740; p<0.001). The risk of structural ECAs was not significantly different in twins compared to singletons (RR=1.22, 95% CI: 0.77-1.91; p=0.399).

Of the triplets with CHD, one (12.5%) occurred with chromosomal/ genetic ECAs, one occurred with structural ECAs (12.5%). Cases with ECAs were excluded from further analysis, leaving 2,984 singletons, 154 twins and six triplets with isolated CHD.

6.3.2 CHD severity and concordance

Of the singletons with isolated CHD, 132 (4.4%) had severe CHD, 721 (23.9%) had moderate CHD, 1,967 (65.9%) had mild CHD and 173 (5.8%) were of unclassified severity. Of the twins, seven (4.5%) had severe CHD, 31 (20.1%) had moderate CHD, 106 (68.8%) had mild CHD and 10 (6.5%) were of unclassified severity. Of the triplets, one (16.7%) had moderate CHD, four (66.7%) had mild CHD and one had CHD of unclassified severity. The distribution of the severity categories in twins according to chorionicity is shown in Table 6.2.

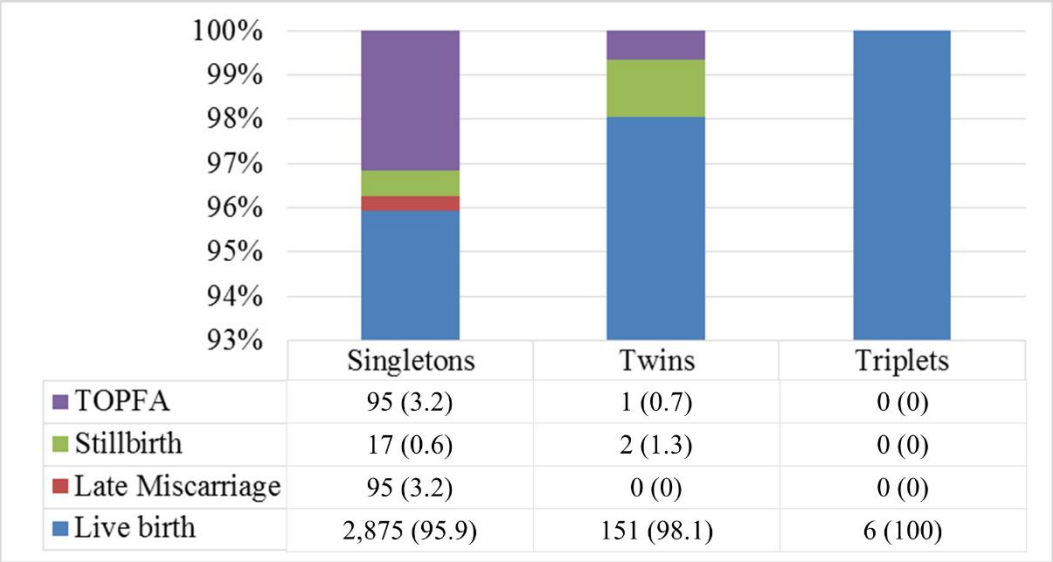
There were eight sets of twins with concordant CHD (four sets with the same subtype), of which six sets were DC and two were MC twins. None of the triplets were concordant.

6.3.3 Pregnancy outcomes

Pregnancy outcomes varied significantly in twins compared to singletons (Fisher's exact test: p=0.255). As shown in Figure 6.1, live births and stillbirths were more common in twins than singletons. TOPFAs and late miscarriages were more common in singletons. All six triplets were live births.

There was no evidence of an association between pregnancy outcomes and chorionicity in twins (Fisher's exact test: p=0.281). Of the DC twins with CHD, 109 (95.6%) were live births, three (2.6%) were stillbirths and two (1.8%) were TOPFAs. Of the MC twins with CHD, 55 (91.7%) were live births, one (1.7%) was a stillbirth and four (6.7%) were TOPFAs.

Figure 6.1 Pregnancy outcomes in cases of CHD, by plurality



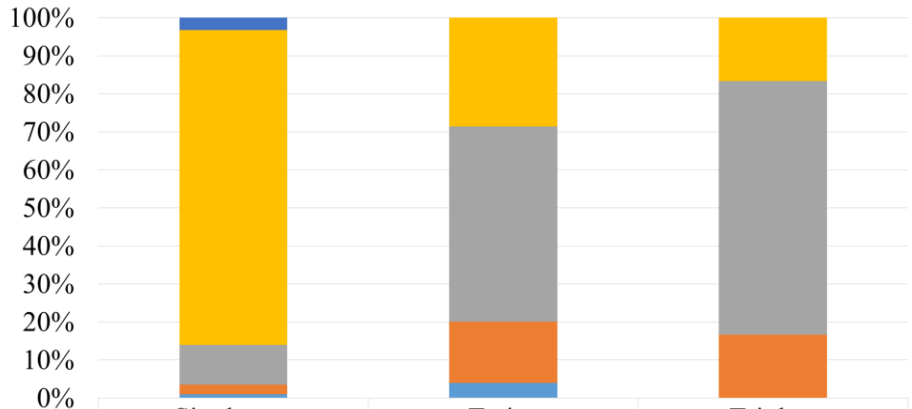
	Singletons	Twins	Triplets
TOPFA	95 (3.2)	1 (0.7)	0 (0)
Stillbirth	17 (0.6)	2 (1.3)	0 (0)
Late Miscarriage	95 (3.2)	0 (0)	0 (0)
Live birth	2,875 (95.9)	151 (98.1)	6 (100)

6.3.4 Gestational age at delivery

Among live born cases, the distribution of gestational age at delivery was significantly different in twins compared to singletons (Mann-Whitney test: p<0.001). A greater proportion of twins were born preterm compared to singletons (Figure 6.2). An even greater proportion of triplets were delivered preterm (Figure 6.2), although no formal statistical test was performed due to low case numbers.

There was a significant difference in the distribution of gestational age at delivery according to chorionicity in twins (Mann-Whitney test: p=0.004). Of the DC twins with CHD, four (4.2%) were extremely preterm, 13 (13.7%) were very preterm, 44 (46.3%) were moderately preterm, and 34 (35.8%) were term. Of the MC twins with CHD, two (4.4%) were extremely preterm, 10 (22.2%) were very preterm, 29 (64.4%) were moderately preterm and 4 (8.9%) were term.

Figure 6.2 Gestational age at delivery in live born cases of CHD, by plurality



	Singletons	Twins	Triplets
Post-term	93 (3.3)	0 (0)	0 (0)
Term	2,343 (82.7)	43 (28.7)	1 (16.7)
Moderately preterm	297 (10.5)	77 (51.3)	4 (66.7)
Very preterm	72 (2.5)	24 (16.0)	1 (16.7)
Extremely preterm	27 (1.0)	6 (4.0)	0 (0)

Gestational age at delivery was missing for 43 (1.5%) of singletons and 1 (0.7%) twin, so these cases were excluded from this analysis.

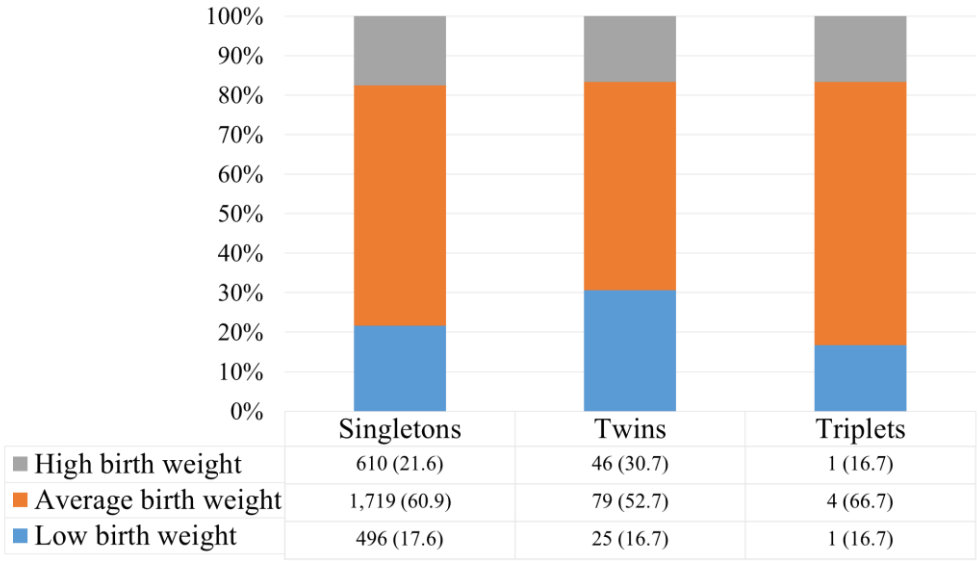
6.3.5 Standardised birthweight

Among live born cases of CHD, there was some evidence that the distribution of standardised birth weight varied between twins and singletons, although this did not quite reach statistical significance (p=0.053). Indeed, twins were more likely to have low standardised birth weight compared to singletons (37.5% vs 29.6%) (Figure 6.3). All three triplets were of average standardised birth weight.

Among twins, there was no significant difference in the distribution of standardised birth weight according to chorionicity (Mann-Whitney test: p=0.104). In DC twins with CHD, 25 (26.3%) cases were low birth weight, 55 (58.9%) were average birth weight and 15 (15.6%)

were high birth weight. Of the MC twins with CHD, 20 (44.4%) were low birth weight, 18 (40.0%) were average birth weight and seven (15.6%) were high birth weight.

Figure 6.3 Standardised birth weight in live born cases of CHD, by plurality



	Singletons	Twins	Triplets
High birth weight	610 (21.6)	46 (30.7)	1 (16.7)
Average birth weight	1,719 (60.9)	79 (52.7)	4 (66.7)
Low birth weight	496 (17.6)	25 (16.7)	1 (16.7)

Standardised birthweight was missing for 50 (1.7%) singletons and one (0.7%) twins and was excluded from this analysis

6.3.6 Prenatal diagnosis

There were 1,256 (31.6%) singletons, 62 (33.2%) twins and three (50.0%) triplets with missing prenatal diagnosis data. Excluding these cases, 880 (32.4%) singleton cases, 38 (30.4%) twin cases and one (20.0%) triplet case had a prenatal diagnosis (of any congenital anomaly). There was no significant difference in the proportion of singleton compared to twin cases that were prenatally diagnosed (χ^2 test: p=0.642).

There was no significant difference in the prenatal diagnosis rates between DC and MC twins (Fisher's exact test=1.00). There was a prenatal diagnosis (of any congenital anomaly) in 23 (31.5%) DC twins with CHD and in 14 (31.1%) MC twins with CHD.

6.3.7 Birth prevalence and pregnancy risk

There were 2,984 cases of isolated CHD amongst singletons, giving a prevalence of 74.7 per 10,000 total births (Table 6.2); 0.7% of singleton pregnancies were associated with CHD. There were 154 twins with CHD, giving a prevalence of 129.7 per 10,000 total births; in 2.5% of twin pregnancies, at least one twin was affected by isolated CHD. There were six higher order multiples with CHD, giving a prevalence of 120.7 (95% CI: 44.4-260.9) per 10,000

total births; in 3.7% of higher order pregnancies, at least one fetus was affected by isolated CHD.

Of the 154 twins with CHD, 96 (62.4%) occurred in DC pregnancies and 47 (30.5%) occurred in MC pregnancies, giving prevalence rates of 111.6 and 202.8 per 10,000 total births, respectively (Table 6.2). Specifically, at least one twin was affected by isolated CHD in 2.2% of DC twin pregnancies and 4.0% of MC twin pregnancies. The prevalence of severe, moderate and mild CHD are shown in Table 6.2 according to chorionicity. At least one twin was affected by severe, moderate and mild CHD in twin pregnancies 0.1%, 0.5% and 1.7% of twin pregnancies, respectively.

Table 6.2 Prevalence of CHD in twins and singletons, according to CHD severity and chorionicity

CHD severity	Twins			Singletons
	Twins (any chorionicity) N (% of 154), prevalence per 10,000 total births (95% CI)	Dichorionic Twins N (% of 96), prevalence per 10,000 total births (95% CI)	Monochorionic Twins N (% of 47), prevalence per 10,000 total births (95% CI)	N (% of 2,984), prevalence per 10,000 total births (95% CI)
All CHD severities	154 (100%) 129.7 (110.2-151.7)	96 (100%) 111.6 (90.5-136.1)	47(100%) 202.8 (149.4-268.8)	2,984(100%) 74.7 (72.1-77.4)
Severe CHD	7 (4.5%) 5.9 (2.4-12.2)	4 (4.2%) 4.6 (1.3-11.9)	3 (6.4%) 12.9 (2.7-37.8)	132 (4.4%) 3.3 (2.8-3.9)
Moderate CHD	31 (20.1%) 26.1 (17.8-37.0)	25 (26.0%) 29.1 (18.8-42.9)	5 (10.6%) 21.6 (7.0-50.3)	712 (23.9%) 17.8 (16.5-19.2)
Mild CHD	106 (68.8%) 89.3 (73.2-107.9)	63 (65.6%) 73.2 (56.3-93.6)	35 (74.4%) 151.1 (105.4-209.5)	1967 (65.9%) 49.2 (47.1-51.5)

6.3.8 Maternal age

Amongst singletons, the risk of CHD was not associated with maternal age (p=0.528). Amongst twins, the association between CHD and maternal age was of borderline statistical significance (p=0.070), with mothers aged <20 having a 93% increased risk of a pregnancy associated with CHD than mothers aged 20-29 (Table 6.3). Of the triplets with CHD, three (37.5%) were born to mothers aged 20-29, two (25.0%) to mothers aged 34-35 and three (37.5%) to mothers aged ≥35. Due to low case numbers, it was not possible to test the association with maternal age in higher order multiple births

Amongst DC twins, there was no significant association between maternal age and CHD (p=0.412) (Table 6.3). Amongst MC twins, there was a significant association between maternal age and CHD (p=0.012), with mothers aged<20 being at 237% increased risk of a pregnancy associated with CHD compared to mothers aged 20-29 (Table 6.3).

Table 6.3 Relative risk of CHD according to maternal age and year of delivery

	N, Unadjusted RR (95% confidence intervals)			
Maternal age at delivery*	**Twins (Any chorionicity)**	**Dichorionic Twins**	**Monochorionic Twins**	**Singletons***
<20	N=14 RR=1.93 (0.96-3.88)	N=5 RR=1.06 (0.33-3.43)	N=8 RR=3.37 (1.27-8.95)	N=290 RR=0.94 (0.83-1.06)
20-29	N=66 RR=1 (reference)	N=40 RR=1 (reference)	N=21 RR=1 (reference)	N=1491 RR=1 (reference)
30-34	N=40 RR=0.74 (0.50-1.10)	N=25 RR= 0.76 (0.46-1.26)	N=11 RR=0.64 (0.31-1.33)	N=754 RR= 1.04 (0.95-1.13)
≥35	N=34 RR=0.97 (0.64-1.47)	N=26 RR=1.22 (0.75-2.01)	N=7 RR=0.63 (0.0.27-1.48)	N=422 RR=1.03 (0.93-1.15)
Year of delivery	RR=1.00 (0.96-1.04)	RR=0.96 (0.91-1.02)	RR=1.08 (1.01, 1.18)	RR=0.98 (0.97-0.99)

*29 (0.7%) singletons had missing maternal age data and were excluded. Maternal age data was missing in 2.1% of twins without CHD so these were excluded from the denominator.

RR=Relative Risk

6.3.9 Temporal trends

The risk of CHD amongst singletons decreased significantly by 2% per year (p<0.001) (Table 6.3). There was no evidence of a trend in CHD prevalence over time in twins (any chorionicity) (p=0.954) or in DC twins (p=0.091). In MC twins, the risk of CHD increased significantly by 8% per year (p=0.036) (Table 6.3). Due to low case numbers, it was not possible to analyse temporal trends in the prevalence of CHD in higher order multiple births.

6.3.10 Relative risk of CHD in twins compared to singletons

Twins were at 73% significant increased risk of CHD compared to singletons (p<0.001) (Table 6.4). There was an 78%, 46% and 81% increased risk of severe, moderate and mild CHD in twins (any chorionicity) compared to singletons (p=0.135, p=0.037 and p<0.001 respectively) (Table 6.4), although this only reached statistical significance in cases of moderate and mild CHD.

MC twins were at 82% significant increased risk of CHD compared to DC twins (RR=1.82, 95% CI, 1.29-2.57; p<0.001). Compared to singletons, DC twins were at 49% significant

increased risk of CHD (p<0.001) and MC twins were at 172% significant increased risk of CHD (p<0.001) (Table 6.4). DC twins were at 41%, 63% and 49% increased risk of severe, moderate and mild CHD respectively (Table 6.4), although this did not reach statistical significance for severe CHD (p=0.501, p=0.016 and p=0.002, respectively). MC twins were at 292% significant increased risk of severe CHD (p=0.020) and 207% significant increased risk of mild CHD (p<0.001). There was no significant effect amongst cases of moderate CHD (p=0.637) (Table 6.4).

The adjustment for year of delivery and maternal age at delivery had little impact on the RR of CHD in twins compared to singletons (Table 6.4).

When considering all twins (any chorionicity), the interaction between year of delivery and plurality was non-significant (p=0.446), meaning there was no evidence that the RR in twins compared to singletons altered over the study period. Similarly, the interaction between year of delivery and plurality was not statistically significant amongst DC twins (p=0.521). Amongst MC twins there was a significant interaction between year of delivery and plurality (p=0.012), with the RR of CHD in MC twins compared to singletons increasing over the study period (interaction term: RR=1.11, 95% CI:1.02-1.20).

Table 6.4 Relative risk of CHD in twins versus singletons, according to CHD severity and chorionicity

CHD Severity	Twins (any chorionicity) RR (95% CI); p-value		Dichorionic Twins RR (95% CI); p-value		Monochorionic Twins RR (95% CI); p-value	
	Unadjusted	**Adjusted***	**Unadjusted**	**Adjusted***	**Unadjusted**	**Adjusted***
All CHD severities	1.73 (1.48-2.04); p<0.001	1.75 (1.48-2.06); p<0.001	1.49 (1.22-1.83); P<0.001	1.51 (1.24-1.86); P<0.001	2.72 (2.04-3.62); p<0.001	2.76 (2.07-3.69); p<0.001
Severe CHD	1.78 (0.83-3.82); p=0.135	1.82 (0.85-3.90); p=0.124	1.41 (0.52-3.80); p=0.501	1.39 (0.51-3.76); p=0.521	3.92 (1.25-12.30); p=0.019	3.90 (1.24-12.27); p=0.020
Moderate CHD	1.46 (1.02-2.10); p=0.037	1.54 (1.07-2.20); p=0.020	1.63 (1.09-2.43); p=0.016	1.67 (1.12-2.49); p=0.012	1.21 (0.50-2.92); p=0.670	1.24 (0.51-2.98); p=0.637
Mild CHD	1.81 (1.49-2.20); p<0.001	1.80 (1.47-2.20); p<0.001	1.49 (1.16-1.91); p=0.002	1.50 (1.17-1.13); p=0.001	3.07 (2.20-4.28); p<0.001	3.12 (2.23-4.36); p<0.001

*Adjusted for year of delivery and maternal age. Maternal age was missing in 29 (0.7%) singleton cases and so these cases were excluded. Maternal age data was missing in 2.1% of twins without CHD so these were excluded from the denominator.

6.4 Discussion

In this population-based study, there was a 73% increased risk of CHD in twins compared to singletons. MC twins were at 172% and DC twins were at 49% increased risk of CHD compared to singletons. The risk did not vary substantially by severity, except for MC twins, where the risk of severe CHD had the largest effect size. I did not examine the RR of CHD in triplets, but the prevalence exceeded that of singletons and twins.

This is one of few studies to examine the RR of CHD in twins compared to singletons. The primary strength of this study is the use of population-based data derived from an established, high-quality, CAR. Multiple sources notify the register of cases which ensures high case ascertainment. Accurate diagnoses are achieved by the review of complex cases by paediatric pathologists and clinical geneticists and, where relevant, diagnoses are confirmed via post mortem. Additionally, by linking to a population-based register of multiple pregnancies, I was able to estimate the RR of CHD according to chorionicity, which very few studies have been able to do [113, 156]. Data on chorionicity is unlikely to be misclassified, given that the final diagnosis of like-sex twins is based on placental examination and histology.

A further strength is that cases of CHD occurring in TOPFAs, late miscarriages and stillbirths were included. TOPFA are less frequent in twin compared to singleton pregnancies, so had they been excluded, the RR of CHD associated with twins may have been overestimated [160]. Stillbirth is more common in twin compared to singleton pregnancies; the exclusion of stillbirths could have had the opposite effect and diluted the RR of CHD [160].

I also examined the RR of CHD in twins versus singletons adjusted for some confounding factors. I adjusted for year of delivery, which is a potential confounder given that the twinning rate has increased slightly over the study period. Maternal age may have been a confounding factor due to the known association between increased maternal age and multiple pregnancy [161] and the increased risk of CHD with increased maternal age, which is reported in some, but not all studies of singletons [53, 59, 76, 80].

This study has some limitations. Firstly, the sample size was small meaning non-significant results should be interpreted with caution as they could have resulted from type II errors. Additionally, I was only able to examine severity categories as opposed to subtypes, which may

have different RRs. As NorSTAMP requires parental consent, chorionicity data was not available for all twins. However, choronicity data was missing for just 7% of cases and 8% of the denominator. Moreover, eight sets of twins with CHD were from the same pregnancy. This violates one of the assumptions of Poisson regression, which specifies that all observations should be independent. However, after excluding eight cases (one out of each twin pair), the RR reduced only slightly (unadjusted RR=1.63, 95% CI: 1.38-1.93; p<0.001, RR=1.40, 95% CI: 1.14-1.73; p=0.002 and RR=2.60, 95% CI: 1.94-3.49; p<0.001 for all twins (any chorionicty), DC twins and MC twins, respectively). I did not have data on zygosity as this is not recorded on the NorSTAMP. However, chorionicity can be used to make inference on zygosity given that all MC twins are monozygotic and the majority (~90%) of DC twins are dizygotic [155]. Lastly I was not able to investigate the risk associated with ART as the NorCAS and NorSTAMP and did not record this information at the time of the study.

My 73% significant increased risk of CHD in twins compared to singletons is slightly greater than that reported elsewhere [113, 151, 156]. Mastroiacovo et al reported an increased risk of 51% in Europe and Latin America (1978-1995), Glinianaia et al reported an increased risk of 47% in the North of England (using a subset of the present data, 1998-2002) and Herskind et al reported an increased risk of 63% in Denmark (1977-2001)[113, 151, 156]. In my study, the RR of CHD in MC twins increased significantly over the study period, so I may have found a greater RR than other studies due to my more recent study period. The increase in risk may be a result of increased screening of MC twins, given that the increased risk of congenital anomaly in MC twins has become more widely known over time. In the UK, the National Institute for Health and Care Excellence (NICE) guidelines were updated in 2011 to recommend at least nine antenatal scans for MC twin pregnancy[162]. However, in my analysis of prenatal diagnosis, there was no significant difference in the prenatal diagnosis of MC compared to DC cases of CHD. However, the data on prenatal diagnosis was incomplete and was likely not to be missing completely at random, which may have introduced some bias. While MC twin births account for just 0.6% of all births, on a population level (England and Wales) this amounts to an excess of approximately seven cases per year.

I identified a greater risk of CHD in MC twins compared to DC twins. Conversely, in the study by Glinianaia et al, there was no significant difference in the RR by chorionicity, but just nine cases in MC twins were examined [113]. Herskind et al estimated the RR of CHD according to

zygosity, finding no significant difference in risk [156]. However, bias may have been incurred due to missing zygosity information. Indeed, in their cases with missing zygosity, the RR of CHD was greater than that of all twins (RR=2.41, 95% CI: 2.07-2.80). Had a higher proportion of MZ twins had missing zygosisty, this could partly explain why monozygotic twins were not at increased risk. Alternatively, given that one third of MZ twins are DC, it is likely the effect size is deflated due to mixing of chorionicity types [156]. Lastly, Herskind et al included only live births, which may have impacted on their results given that TOPFAs are more common in singleton pregnancies [156, 160].

I found a significant increased risk of moderate and mild CHD in twins (any chorionicity) compared to singletons. While the risk of severe CHD was increased, it did not reach statistical significance, likely due to low sample size. The RR was statistically significant amongst MC twins, due to the larger effect size. Several studies have examined the RR of CHD in multiples compared to singletons by CHD subtype [150, 151, 163]. Significant increased risks have been reported for VSD, ASD, SV, ToF, AVSD and CoA, although the effect sizes vary by study. Herskind et al uniquely examined subtypes separately according to zygosity, but could only examine VSD in MZ twins due to low sample size, finding a 73% increased risk compared to singletons.

The aetiology of the increased risk of CHD in multiple births is unresolved. Twin to twin transfusion in MC twins was identified as an important risk factor for CHD [155, 164]. However, this doesn't explain why there would be an increased risk in DC twins. Others hypothesise that placental vascular anastomoses between the MZ co-twins' circulations may lead to fluctuations in blood flow during fetal heart development, causing CHD [165, 166]. Potentially, this anastomoses is even more severe in triplets, which would explain the even greater prevalence. Alternatively, MZ twinning itself is hypothesized to be part of a morphogenic anomaly which leads to a congenital anomaly [167]. Given that all MC twins are MZ and around 10% of DC twins are MZ, this might explain why there was an increased risk in both MC and DC twins and why the effect size was greater in MC twins. However, previous research also found an increased risk amongst DZ twins [163]. Perhaps the increased risk in DC twins could be related to the use of ART, which can result in twin pregnancy and has been linked to an increased CHD prevalence [168]. However, a systematic review of four studies that compared twins conceived by ART compared to naturally conceived twins found that there was no increased risk of congenital

anomaly [169]. Additionally, NICE guidelines have recently changed to state that just one embryo, as opposed to three, should be implanted in the first round of IVF (in women aged <40) [170].

Chapter 7. Long-term survival and risk factors for mortality among individuals with congenital heart disease: A systematic review and meta-analysis

7.1 Introduction

As discussed in Chapter 1, during the first year of life, babies with severe CHD require complex surgeries to enable survival. With advances in medical, surgical and intensive care interventions, an estimated 83% of babies with CHD now survive infancy [171]. Whilst one year survival estimates have been described [1, 20, 60, 62, 172-174], long-term survival estimates are not as well researched.

A systematic review on the long-term prognosis of CHD was published in 2008 [175]. However, this revolved around hospital-based studies that ascertained cases post-surgically or in adulthood, so estimates were not representative of all individuals with CHD [175].

7.1.1 Aim

To conduct a systematic review and meta-analysis of population-based studies that reported long-term survival of children born with CHD. The aim was to accurately assess and quantify long-term survival and risk factors for mortality in order to aid health service planning and decision making.

7.2 Methods

7.2.1 Inclusion criteria

Population-based, original studies were included if they: 1) ascertained all individuals born with CHD within a pre-defined geo-political area; 2) reported survival estimates (or the number of cases born and the number/proportion alive) at age ≥5 years; 3) reported survival estimates for all CHD (in humans) combined or a single CHD subtype including: VSD, PVS, ASD, AVA/S, AVSD, CoA, CAT, PVA (with VSD or with intact ventricular septum (IVS)), ToF, TAPVR, TGV, TA, SV, HLH and EA; 4) were available from the British library or internet, written in the English language.

7.2.2 Exclusion criteria

Articles were excluded if: cases were not followed from birth (e.g. follow-up began in adulthood or after surgical correction); cases were not born in well-defined regions (i.e. hospital-based studies); survival was not estimated as a proportion of those born with CHD (e.g. age-specific population mortality rates); survival was only reported for certain subtype groups (e.g. "severe" CHD). Where multiple articles reported on the same dataset, the most recent (in terms of birth years included) or the largest study was included. Both articles were included if they reported survival for different CHD subtypes or ages.

7.2.3 Search strategy

I conducted comprehensive literature searches of MEDLINE, EMBASE and Scopus from their inception (1946, 1974 and 1996, respectively) to June 2015 inclusive. MeSH-terms and key word searches were entered systematically into the databases (Table 7.1).

After systematic searches of each database, the citations were extracted and titles and abstracts were screened according to the inclusion criteria and full articles were retrieved for all relevant citations. Reference lists of included articles were searched and key journals such as "Congenital Heart Disease", "Birth Defects Research", "Circulation", "Heart" and "Cardiology in the Young" were searched using keywords.

Table 7.1 Medline, Embase and Scopus search terms

	Medline	Embase	Scopus
1	exp Heart Defects, Congenital/ep, mo or (((congenital) and (heart or cardiac or cardiovascular)).ti,ab)	exp congenital heart disease/ep or exp congenital heart malformation/ep or (((congenital) and (heart or cardiac or cardiovascular)).ti,ab)	TITLE-ABS-KEY ((congenital) and (heart or cardiac or cardiovascular))
2	survival analysis/ or kaplan-meier estimate/ or proportional hazards models/or mortality/ or child mortality/ or fatal outcome/ or infant mortality/ or mortality, premature/ or survival rate/ or ((surviv$ or death$ or mortalit$ or fatalit$ or die$).ti,ab)	survival/ or life expectancy/ or long term survival/ or overall survival/ or short term survival/ or survival prediction/ or survival rate/ or survival time/ or Mortality/ or childhood mortality/ or premature mortality/or ((surviv$ or death$ or mortalit$ or fatalit$ or die$).ti,ab)	TITLE-ABS-KEY (surviv$ or death$ or mortalit$ or fatalit$ or die$)
3	Epidemiologic studies/ or Exp cohort studies/ or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or population-based.tw.	Epidemiology/ or Longitudinal study/ or Retrospective study/ or Prospective study/ or Cohort analysis/ or (Cohort adj (study or studies)).mp. or (follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or (epidemiologic$ adj (study or studies)).tw. or population-based.tw.	TITLE-ABS-KEY (Epidemiology or “Longitudinal stud$” or “Retrospective stud$” or “Prospective stud$” or “Cohort analys$” or “Cohort stud$” or “follow up stud$” or “follow-up stud$” “observational stud$” or “epidemiologic$ stud$” or “population-based”)
4	1 and 2 and 3	1 and 2 and 3	(LIMIT-TO(EXACTKEYWORD, **"Human"**)
5	4 not (case study.mp or exp Case Reports/ or exp Clinical Trials as Topic or clinical trial.mp)	4 not (case study.mp or exp Case Report/ or exp controlled clinical trial/ or clinical trial.mp.)	(LIMIT-TO(LANGUAGE, **"English"**)
6	Limit 5 to humans	Limit 5 to humans	
7	Limit 6 to English language	Limit 6 to English language	

7.2.4 Data extraction

I performed the literature searches, citation screening and reviewed the full papers. One of my supervisors, Prof Judith Rankin, screened 10% of the titles and all abstracts to confirm decisions on inclusion, and extracted data on all included papers. There were no discrepancies in terms of article inclusion between reviewers.

Study characteristics including study design, quality, sources of data, risk factors for mortality (log-rank tests, crude hazard ratios (HRs) and adjusted hazard ratios (aHRs)) were extracted from each article (using the data extraction form in Appendix C).

Kaplan-Meier survival estimates and corresponding 95% confidence intervals (CIs) were obtained from each included study at age one, five, 10 etc. Where 95% CIs were not reported, the number of cases born, and the proportion survived, were used to estimate 95% binomial CIs, assuming no cases were censored. Survival estimates for all CHD subtypes combined, and for each CHD subtype, were extracted. Where survival estimates were presented only graphically, these were extracted using Plot Digitizer software [176, 177].

Authors were contacted and asked to provide further survival estimates or confidence intervals where they were not reported in the manuscript. Additionally, authors were contacted when it was not clear whether cases with ECAs were included or excluded.

7.2.5 Statistical analysis

Where there were at least three studies reporting survival, pooled estimates of survival were calculated using a meta-analysis with random effects. Weighting to each articles was allocated using the inverse of the variance. To stabilise the variance and adjust the study weights, a simplified double arcsine transformation was performed on the survival estimates and 95% CIs [178]. This approach also restricts the estimates to be ≤ 100%. Cochrane's Q test and the I^2 statistic was used to test for heterogeneity in survival estimates between articles, with I^2> 50% indicating substantial heterogeneity [51]. Random effects meta-regression was performed for all CHD subtypes combined in order to assess year of delivery as a source of heterogeneity. Here the year the study commenced in was used as an explanatory variable. The adjusted R-squared value was used to estimate the proportion of between article variation accounted for by the year of study commencement. A "bubble plot" was used to present the fitted meta-regression model. Here bubbles represent each article, with sizes dependent on the precision of the survival estimates. Publication bias was assessed via Egger's test [179].

Analysis was performed in Stata 13 and $p<0.05$ was considered statistically significant.

7.2.6 Quality assessment

Quality appraisal was based on four of Hayden et al's six domains, developed to assess potential bias in systematic reviews of prognostic studies [180]. The domains used included: study ascertainment, study attrition, outcome ascertainment and analysis. The domains relating to confounding and prognostic factors were not relevant to this review because the primary aim was to investigate unadjusted survival estimates.

Table 7.2 Study descriptions

Study	Included birth years	Study location	Included CHD Subtypes (ICD codes)	Inclusion of extra-cardiac anomalies (ECAs)	Age limit for diagnosis	Source of cases	Source of death information	% of traced cases	Prevalence per 1000 live births
Dastgiri et al [181]	1980-97	Glasgow, Scotland	All CHD subtypes (ICD 10: Q20-26)	Author's response: excluded (unless CHD was primary diagnosis)	No age limit	Glasgow register of Congenital Anomalies	Registrar General for Scotland	97% (all congenital anomalies)	Not stated
Fixler et al [182]	1996-2003	Texas, USA	Single ventricle: HLHS (ICD 9: 746.7), PVA-IVS (746.0), SV (745.3), TA (746.1), d-TGV (745.1)	Cases with trisomy 13 or 18 were excluded. 14.1% of HLH, 21.0% of SV, 15.3% of PVA-IVS, 17.9% of TA, 9.3% of d-TGV had ECAs	1 year	Texas Birth Defects Registry	Medical records, death-certificates, National death index	N/A, non-traced cases considered alive	Not stated
Frid et al [183]	1973-97	Sweden	AVSD (ICD 9: 745G, ICD 10: 21.2)	Cases with trisomy 13 or 18 were excluded. 68.9% had trisomy 21.	None stated	The Register of Congenital Malformations, the Register of Congenital Heart malformations, and the Medical Birth Register. Local registries at four paediatric cardiology centres were also searched	National Population database and medical records	98.7% of all cases with AVSD	0.3

Study	Included birth years	Study location	Included CHD Subtypes (ICD codes)	Inclusion of extra-cardiac anomalies (ECAs)	Age limit for diagnosis	Source of cases	Source of death information	% of traced cases	Prevalence per 1000 live births
						for the beginning of the study period.			
Garne [184]	1986-1998	Funen County, Denmark	All CHD subtypes (EUROCAT criteria i.e. ICD 10:Q20-26)	Cases with ECAs were included, 21% of cases	5 years and diagnosed before 2002	EUROCAT Registry of Congenital Malformations for Funen County	National registration system	99.6%	7.9
Idorn et al [185]	1977-2009	Denmark, Europe	HLH (ICD 10: Q234), PVA-IVS (Q220), TA (Q224)	Cases with ECAs were included, 10% of cases.	All ages	Danish register of congenital heart disease, local surgical registries, medical records, local fetal ultrasound registries.	Civil registration system	Not stated	0.4
Jackson et al [186]	1979-1988	Merseyside, England	All CHD subtypes (ICD 9: 745.00-747.49)	Cases with ECAs were included, percentage not stated.	No restrictions	Liverpool registry of Congenital Malformations	Liverpool registry of Congenital Malformations and hospital records	Not stated	7.6
Meberg et al [187]	1982-1996	Vestfold, Norway, Europe	All CHD subtypes (no ICD codes stated)	Cases with ECAs were included, 20% of cases.	None stated	Vestfold County Central Hospital, regional cardiology services, Child	Hospital records	100%	10.2

Study	Included birth years	Study location	Included CHD Subtypes (ICD codes)	Inclusion of extra-cardiac anomalies (ECAs)	Age limit for diagnosis	Source of cases	Source of death information	% of traced cases	Prevalence per 1000 live births
						Health Centres and paediatric departments of the hospital in neighbouring counties			
Miller et al [188]	1979-03	Metropolitan Atlanta, USA	AVSD (ICD 9: 745.000-747.999 were screened for AVSD)	Cases with trisomy 13 or 18 were excluded, 52.4% had trisomy 21.	None stated	Metropolitan Atlanta Congenital Defects Program	Hospital records and vital records from the state of Georgia, National Death Index	Not stated, but number of untraced "assumed to be small"	Not stated
Moons et al [189]	2002	Belgium	All CHD subtypes (no ICD codes specified)	Author response: cases with ECAs were included, percentage not stated	5 years	Paediatric cardiology database covering seven tertiary care centres in Belgium.	Medical records	Not stated	8.3
Nembhard et al [190]	1996-2003	Texas, USA	ICD 9 (746 to 747)	Cases with trisomy 13 or 18 were excluded, 20.7% of cases had ECAs.	1 year	Texas birth defects register	Death certificates linked to the Texas birth defects register	Not stated	8.7
Olsen et al [67]	1977-06	Denmark	All CHD subtypes: ICD 8: 746 to 747 (except 746.7 and 747.5-	Cases with ECAs were included, 20.0% of cases	1 year	Danish National Registry of Patients	Civil registration system	100%	3.7

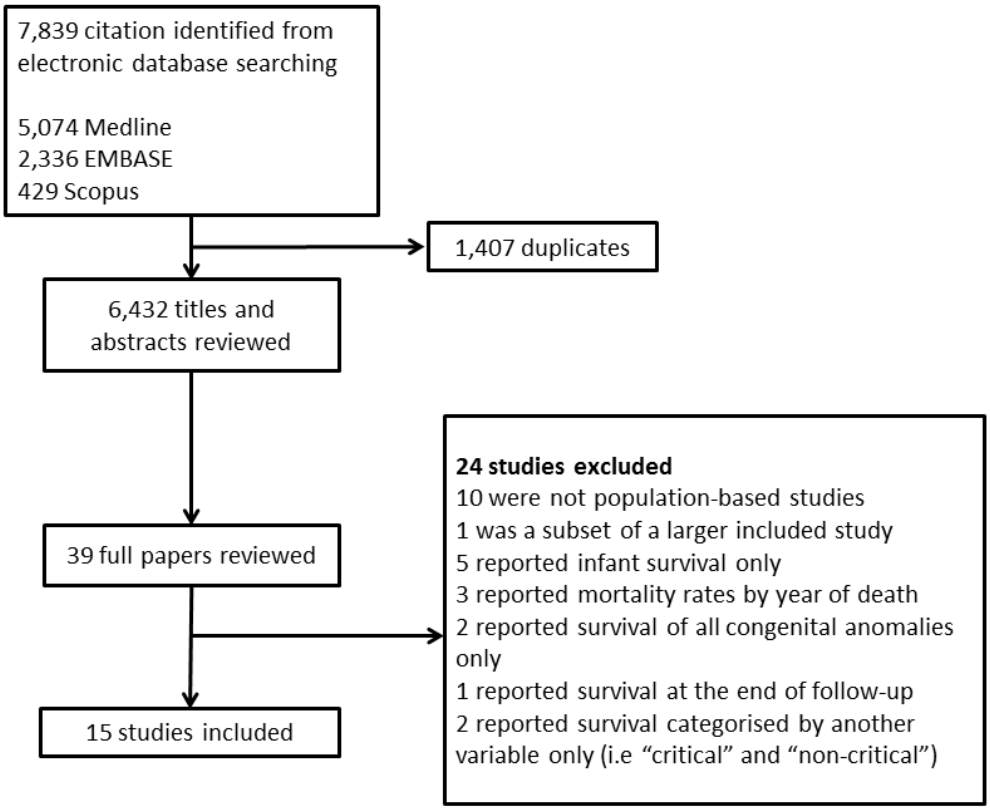
Study	Included birth years	Study location	Included CHD Subtypes (ICD codes)	Inclusion of extra-cardiac anomalies (ECAs)	Age limit for diagnosis	Source of cases	Source of death information	% of traced cases	Prevalence per 1000 live births
			747.9) and ICD-10: Q20 - Q26 (except Q26.5-Q26.6).						
Samanek et al [86]	1980-90	Bohemia	All CHD subtypes (no ICD codes specified)	Not stated.	None stated	Hospital records	Autopsy reports	Not stated	6.2
Tennant et al [116]	1985-2003	North East of England	All CHD subtypes (ICD 10: Q20-26)	Cases with ECAs were excluded unless all anomalies were related to a single subtype	16 years of age (1985–2001) or, from 2001, to 12 years of age.	Northern Congenital Abnormality Survey	Office for National Statistics death registrations	99% (of all congenital anomalies)	6.8
Wang et al (2011) [191]	1983-2006	New York State, USA	TGV (ICD 9 745.10–745.12, 745.19), ToF (745.2), HLH (746.7), AVA/S (746.3), CAT (745.0), AVSD (745.6), CoA (747.10)	Cases with ECAs were included, percentage not stated.	None stated	The Congenital Malformations Registry	Death certificates files maintained by the New York State Department of Health	97% (of all congenital anomalies)	9.5
Wang et al (2013) [192]	1983-2006	New York State, USA	TGV (ICD 9: 745.10–745.12,	Cases with ECAs were included, percentage not stated.	2 years	The Congenital Malformations Registry	Death certificates files maintained by the New York	Not stated	Not stated

Study	Included birth years	Study location	Included CHD Subtypes (ICD codes)	Inclusion of extra-cardiac anomalies (ECAs)	Age limit for diagnosis	Source of cases	Source of death information	% of traced cases	Prevalence per 1000 live births
			745.19), ToF (745.2), HLH (746.7), CoA (747.10)				State Department of Health		

7.3 Results

Figure 7.1 shows a PRISMA diagram for the flow of articles through the review. Of 7,839 identified articles, 15 met the inclusion criteria [67, 86, 116, 181-192].

Figure 7.1 PRISMA flowchart



7.3.1 Study characteristics

Study characteristics are shown in Table 7.2. All the included studies were conducted in high income, western populations, with 10 set in Europe (three in the UK [116, 181, 186], one in Sweden [183], one in Norway [187], one in Belgium [189], one in Bohemia [86], three in Denmark [67, 184, 185]) and five in the USA (two in Texas [182, 190], one in Metropolitan Atlanta [188], two in New York State [191, 192]). Although several of the articles reported survival on subsets of the same population, all were included as survival was reported for different CHD subtypes. The oldest article included cases born between 1973-1997 [183] and the most recent articles between 1983-2006 [185, 191]. Of the 15 included articles, eight included cases with ECAs, with approximately 20% of cases occurring with other congenital anomalies in each article [67, 184-187, 189, 191, 192]. Four articles excluded cases with trisomy 13 and 18 but included cases with all other ECAs [182, 183, 188, 190]. Two articles

reported survival for isolated cases of CHD (i.e. CHD with no ECAs) [116, 181] and one study did not state whether or not cases with ECAs were included [86]. Prevalence estimates were reported by most studies and ranged from 3.7 to 10.2 per 1000 live births, when considering all CHD as a composite group [67, 103].

7.3.2 Survival estimates

Five articles reported survival to age five [181, 182, 184, 189, 190], three to age 10 [186-188], two to age 15 [86, 183], one to age 20 [116], three to age 25 [67, 191, 192] and one to age 30 [185].

For all CHD (as a composite group), pooled one year survival from six articles was 87.0% (95% CI: 82.1-91.2), pooled five year survival from eight articles was 85.4% (95% CI: 79.4-90.5) and pooled 10 year survival from four articles was 81.4% (95% CI: 73.8-87.9) (Figure 7.2). It was not possible to pool estimates beyond 10 years as there were too few articles. However, Figure 7.3 shows the survival estimates plotted over increasing age, up to age 25. Here the fitted meta-regression shows that survival decreases very gradually with increasing age over 25 years. There was no evidence of publication bias according to Egger's tests (p=0.748 for one year, p=0.237 for five years and p=0.601 for 10 years). There was significant heterogeneity between articles for one year survival (I^2=99.0%, p<0.001), five year survival (I^2=99.6%, p<0.001) and 10 year survival (I^2=99.5%, p<0.001). Meta-regression showed that more recent study period was significantly associated with increased one, five and 10 year survival (p=0.047, p=0.013 and p=0.046) (Figure 7.4). According to the adjusted R^2 values, study period accounted for 50.9%, 62.8% and 87.0% of the between article variance for one, five and 10 year survival. However, after adjustment for study period, there remained substantial residual heterogeneity attributable to between-study heterogeneity (I^2=98.2% for survival at age one, I^2= 98.4% at age five and I^2=93.7% at age 10).

Table 7.3 shows the survival estimates and pooled survival estimates for individuals with CHD, by subtype. Pooled one year survival was lowest for individuals with HLH (18.5%, 95% CI: 2.8-43.5) and greatest for individuals with VSD (95.5%, 95% CI: 89.0-99.2). There was significant heterogeneity in survival estimates between articles for all CHD subtypes, with the exception of ToF (I^2=37.9%, p=0.169). Heterogeneity between estimates for SV was of borderline statistical significance (I^2=65.0%, p=0.057). Pooled five year survival varied by subtype, with survival for HLH being 14.4% (95% CI: 2.8-32.8) and survival for VSD being 96.3% (95% CI: 93.7-98.2). With the exception of ToF (I^2=0.0%, p=0.612) and SV (I^2=26.9%, p=0.250), there was significant heterogeneity in survival estimates between

articles (Table 7.3). It was possible to calculate pooled 15 year survival estimates for AVA/S, AVSD, CAT and CoA, but not for any other CHD subtypes. There were too few studies to calculate pooled survival beyond age 15, although in the few studies that had reported survival into adulthood, survival was still very gradually declining.

Figure 7.2 Forest plot for all CHD at ages one, five and 10

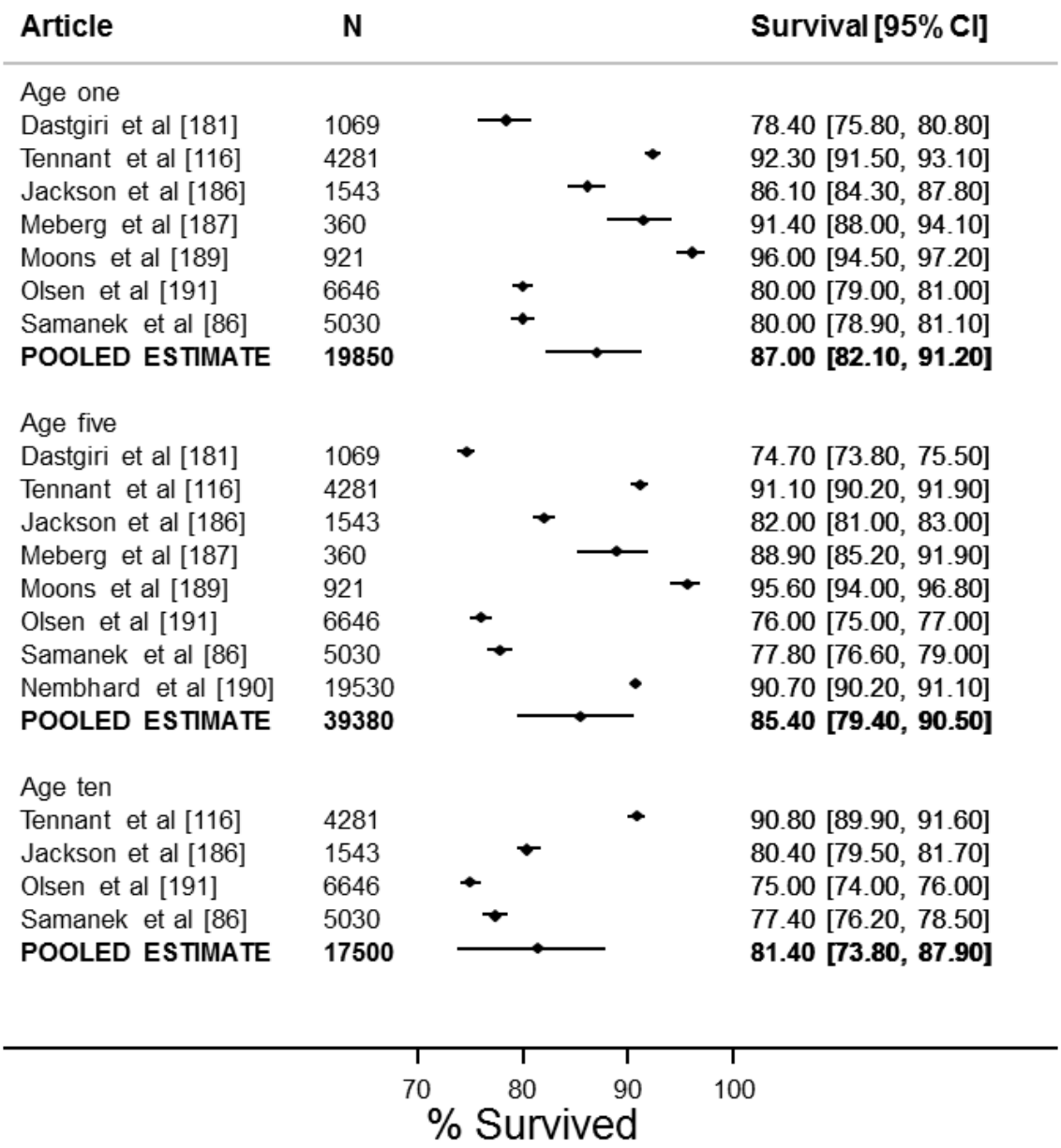


Figure 7.3 Bubble plot of survival estimates for all CHD at ages one to 25

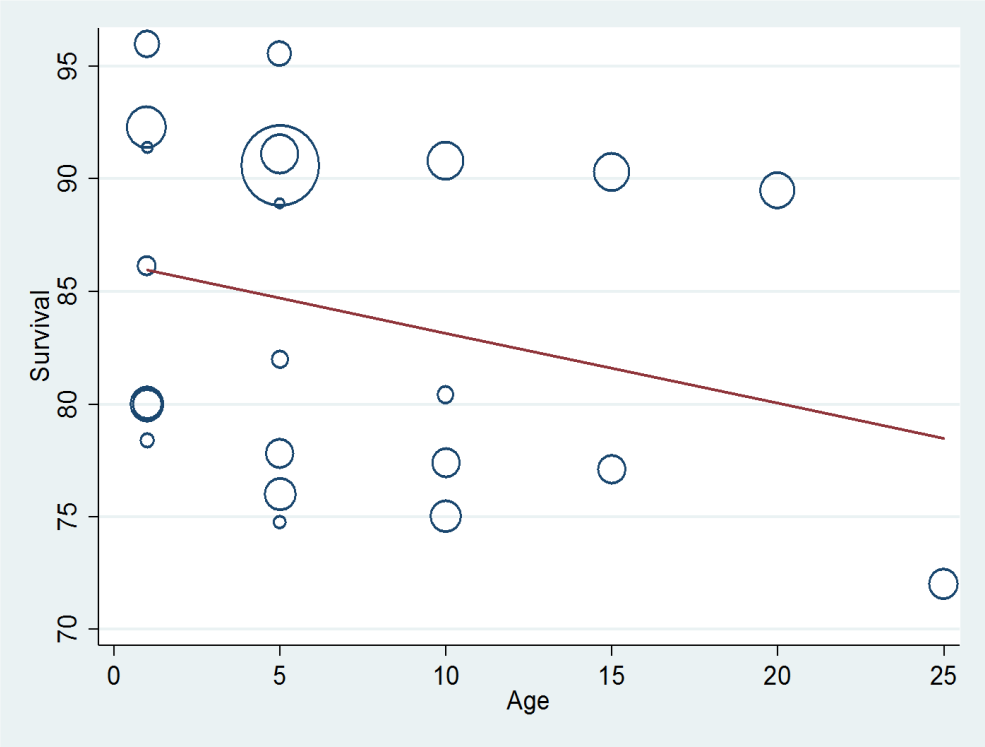


Figure 7.4 Bubble plots showing the association between study period and survival for all CHD

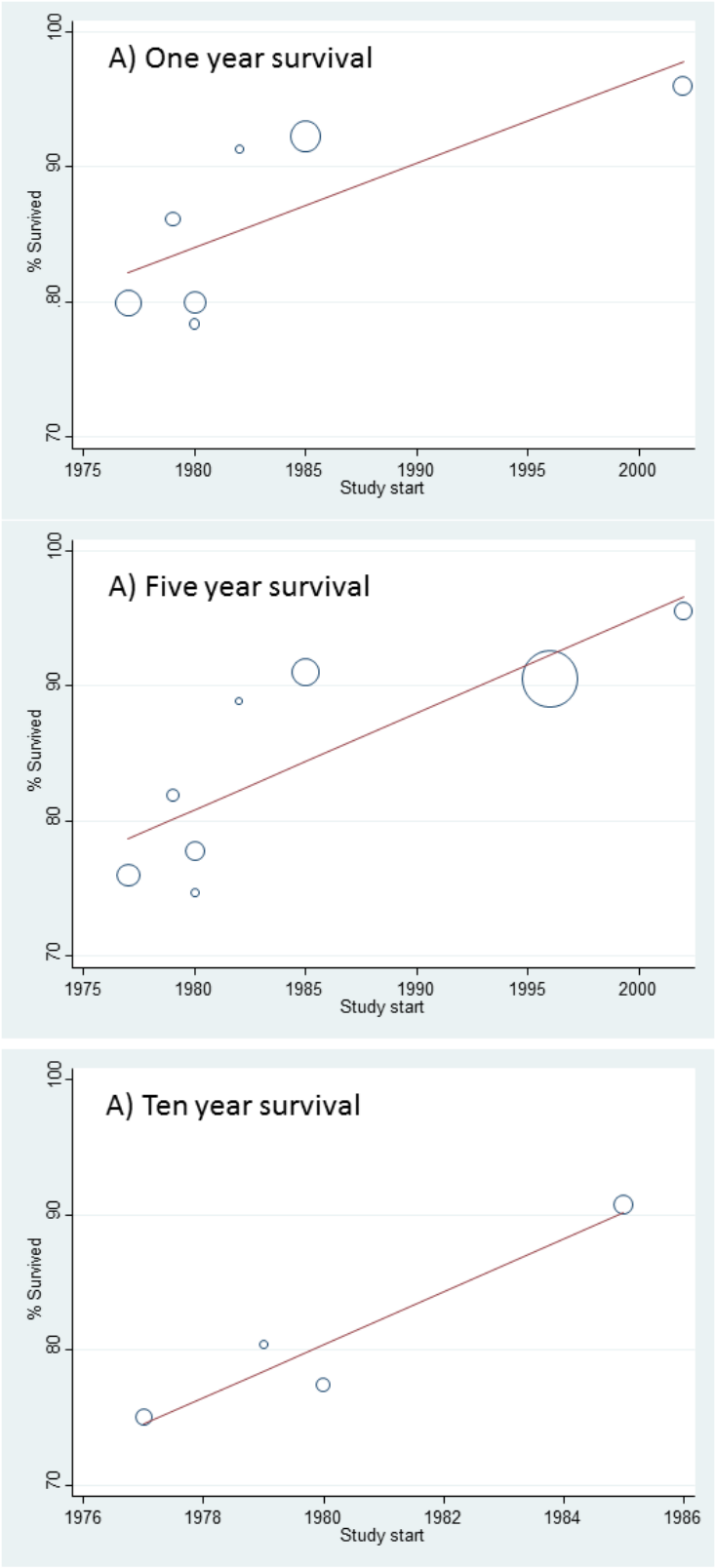


Table 7.3 Survival estimates at age one to 25

Subtype	Article	N	Survival Estimates (95% CI)					
			1 year	5 years	10 years	15 year s	20 years	25 years
All congenital heart disease	Dastgiri et al[181]	1,069	78.4 (75.8-80.8)*	74.7 (73.8-75.5)†				
	Tennant et al [116]	4,281	92.3 (91.5-93.1)	91.1 (90.2–91.9)	90.8 (89.9–91.6)	90.3 (89.3–91.2)	89.5 (88.4–90.6)	
	Jackson et al [186]	1,543	86.1 (84.3-87.8)*	82.0 (81.0-83.0)	80.4 (79.5-81.7)†			
	Meberg et al [187]	360	91.4 (88.0-94.1)*	88.9 (85.2-91.9)*				
	Moons et al [189]	921	96.0 (94.5-97.2)*	95.6 (94.0-96.8)*				
	Olsen et al [67]	6,646	80 (79-81)	76 (75-77)*	75 (74-76)			72 (70-73)
	Samanek et al [86]	5,030	80.0 (78.9-81.1)	77.8 (76.6-79.0)	77.4 (76.2-78.5)	77.1 (75.9-78.3)		
	Nembhard et al [190]	19,530		90.7 (90.2-91.1)*				
	Pooled estimate (95% CI), Heterogeneity I^2 & p-value		87.0 (82.1-91.2) 99.0%, p<0.001	85.4 (79.4-90.5) 99.6%, p<0.001	81.4 (73.8-87.9) 99.5%, p<0.001			
Ventricular septal defect	Tennant et al[116]	1,805	99.2 (98.7-99.5)	99.1 (98.6–99.5)	99·1 (98·5–99·4)	99·1 (98·5–99·4)	98.3 (96.6–99.1)	
	Moons et al[189]	303		99.3 (97.6-99.9)*				
	Nembhard et al [190]	10,382		93.9 (93.5-94.4)*				
	Olsen et al [67]	1,559	94 (93-95)		90 (89-91.7)			
	Samanek et al [86]	2,092	91.1 (89.8-92.3)*			89.4 (88.0-90.7)		
	Garne [184]	195		96.9 (93.4, 98.9)*				
	Pooled estimate (95% CI), Heterogeneity I^2 & p-value		95.5 (89.0-99.2) 99.0%, p<0.001	96.3 (93.7-98.2) 97.1%, p<0.001				

Subtype	Article	N	Survival Estimates (95% CI)					
			1 year	5 years	10 years	15 year s	20 years	25 years
Pulmonary valve stenosis	Tennant et al [116]	382	98.7 (96.8-99.5)	98.1 (96.1-99.1)	98.1 (96.1-99.1)	98.1 (96.1-99.1)	98.1 (96.1-99.1)	
	Garne [184]	33		97.0 (84.2-99.9)*				
	Nembhard et al [190]	1170		91.6 (89.9-93.1)*				
	Samanek et al [86]	292	96.2 (94.0-98.5)	95.6 (93.1-98.0)	95.6 (93.1-98.0)	95.6 (93.1-98.0)		
	Pooled estimate (95% CI), Heterogeneity I^2 & p-value			95.6 (91.1-98.6) 89.6%, p<0.001				
Atrial septal defect	Tennant et al [116]	365	97.3 (95.0-98.5)	97·0 (94·6–98·3)	97·0 (94·6–98·3)	96·3 (93·3–98·0)	96.3 (93.3–98.0)	
	Moons et al [189]	162		99.4 (96.6-100.0)*				
	Nembhard et al [190]	9164		89.9 (89.3-90.5)*				
	Olsen et al [67]	361	93 (90-95.3)		91 (88-95.6)			84 (72-91)
	Samanek et al [86]	436	94.0 (92.4-96.3)		92.9 (90.1-	92.9 (90.1- 95.1)*		
	Garne [184]	78		98.7 (93.1, 100.0)*				
	Pooled estimate (95% CI), Heterogeneity I^2 & p-value		94.9 (92-97.2) 77.4%, p<0.001	96.8 (90.8-99.7) 95.4%, p<0.001	94.0 (89.9-97.1) 81.6%, p=0.004			
Aortic valve atresia/stenosis	Tennant et al [116]	171	92.4 (87.3-95.5)	91.2 (85.9-94.6)	91.2 (85.9-94.6)	89.3 (83.2-3.3)	89.3 (83.2-3.3)	
	Garne [184]	24		87.5 (67.6, 97.3)*				
	Moons et al [189]	36		100.0 (90.3-100.0)*				
	Nembhard et al [190]	560		79.1 (75.5-82.4)*				
	Samanek [86]	391	90.3 (87.3-93.3)			88.4 (85.1-91.7)		
	Wang et al [191]	877	78.8 (75.9-81.4)	76.6 (73.6–79.3)		74.1 (71.0–77.0)		73.4 (70.1–
	Pooled estimate (95% CI), Heterogeneity I^2 & p-value		87.5 (77.6-94.9) 95.0%, p<0.001	88.3 (80-94.6) 93.1%, p<0.001		84.4 (73.1-93.1) 96.8%, p<0.001		

Subtype	Article	N	Survival Estimates (95% CI)					
			1 year	5 years	10 years	15 year s	20 years	25 years
Atrioventricular septal defect	Tennant et al [116]	94	84.0 (74.9-90.1)	80·9 (71·3–87·5)	79.7 (70.1–86.6)	79.7 (70.1–86.6)	79.7 (70.1–86.6)	
	Frid et al [183]	502	77.1 (73.2-80.7)*	66.5 (62.2-70.7)*	64.3 (59.9-68.5)*	63.1 (58.8-67.4)*		
	Miller et al [188]	338	69.9 (61.8-76.0)	60.4 (52.3-67.5)	57.9 (49.7-65.3)			
	Moons et al [189]	37		91.9 (78.1-98.3)*				
	Nembhard et al [190]	853		72.1 (69.0-75.1)*				
	Olsen et al [67]	354	75 (70-79)		65 (59-70)			59 (51-65)
	Samanek et al [86]	201	62.2 (55.4-69.0)	54.7 (47.7-61.8)	54.2 (47.1-61.2)	54.2 (47.1-61.2)		
	Wang et al [191]	1,004	68.4 (65.5-71.2)	62.8 (59.7–65.7)		59.5 (56.3–62.6)	58.1 (56.5-61.4)	56.6 (52.8–60.2)
	Garne [184]	20		50 (27.2-72.8)*				
	Pooled estimate (95% CI), Heterogeneity I^2 & p-value		72.7 (67.5-77.5) 83.9%, p<0.001	67.3 (61.4-73.0) 87.0%, <0.001	64.0 (57.2-70.5) 81.4%, p<0.001	63.4 (56.3-70.3) 85.9%, p<0.001		
Coarctation of aorta	Tennant et al [116]	189	91.5 (86.6–94.7)	91.5 (86.6–94.7)	90.9 (85.8–94.3)	90·9 (85·8–94·3)	89.6 (83.7–93.5)	
	Moons et al [189]	46		91.3 (79.2-97.6)*				
	Nembhard et al [190]	1145		78.6 (76.1-80.9)				
	Olsen et al [67]	334	84 (79-87)		82 (77-85)			78 (61-82)
	Samanek et al [86]	266	68.0 (62.3-73.8)	65.4 (59.6-71.3)	65.0 (59.2-70.9)	65.0 (59.2-70.8)		
	Garne [184]	12		58.3 (27.7-84.8)*				
	Wang et al [191]	2,529	79.4 (77.8-81.0)	77.0 (75.4–78.6)		76.0 (74.3–77.7)		75.2 (73.3-77.0)
	Pooled estimate (95% CI), Heterogeneity I^2 & p-value		81.3 (73.7-87.9) 93.3%, p<0.001	79.5 (73.5-8.05) 91.2%, p<0.001	56.2 (36.3-75.1) 87.3%, p<0.001	78.2 (65.9-88.4) 95.6%, p<0.001		

Subtype	Article	N	Survival Estimates (95% CI)					
			1 year	5 years	10 years	15 year s	20 years	25 years
Common arterial trunk	Tennant et al [116]	36	36.1 (21.0–51.4)	36.1 (21.0–51.4)	36.1 (21.0–51.4)			
	Moons et al [189]	7		85.7 (42.1-99.6)*				
	Nembhard et al [190]	160		56.9 (48.8-64.7)*				
	Olsen et al [67]	78	45 (34-55)	45 (34-55)	45 (34-55)	45 (34-55)	45 (34-55)	45(34-55)
	Samanek et al [86]	55	12.7 (3.7-21.7)	10.5 (4.1-22.2)*	7.3 (0-15.4)	7.3 (0-15.4)		
	Garne [184]	7		14.3 (0.4, 57.9)*				
	Wang et al [191]	460	64.8 (60.2-69.0)	60.8 (56.1–65.1)		59.2 (54.4–63.6)		55.2 (49.5–60.5)
	Pooled estimate (95% CI), Heterogeneity I^2 & p-value		39.2 (17.5-63.4) 93.3%, p<0.001	42.4 (25.0-61.0) 92.6%, p<0.001	28.5 (9.6-52.6) 87.3%, p<0.001	36.5 (14.6-62) 94.5%, p<0.001		
Pulmonary atresia (with IVS)	Idorn et al [185]	75	41.7 (30.1-53.3)*	37.5 (26.4-49.2)*	35.3 (24.0-46.5)*	37.5 (26.4-49.2)*	35.3 (24.0-46.5)*	37.5 (26.4-
	Fixler et al [182]	118	59.3 (49.9-67.6)	55.7 (45.8–64.4)				
	Moons et al [189]	6		83.3 (36.5-99.1)*				
	Samanek et al [86]	53	18.9 (8.1-29.6)	7.6 (0.3-14.8)	7.6 (0.3-14.8)	7.6 (0.3-14.8)		
	Pooled estimate (95% CI), Heterogeneity I^2 & p-value		39.7 (18.5-63.3), 92.1%, p<0.001	41.1 (17.2-67.6) 92.0%, p<0.001				
Pulmonary atresia	Garne et al [184]	5		60.0 (14.7-94.7)*				
Pulmonary valve atresia (with VSD)	Moons et al [189]	6	67 (19-96)*	50 (11.8-88.2)*				
	Samanek et al [86]	55	61.8 (48.7-74.9)	54.5 (41.1-68.0)	45.2 (30.8-59.6)	45.2 (30.8-59.6)		

Subtype	Article	N	Survival Estimates (95% CI)					
			1 year	5 years	10 years	15 year s	20 years	25 years
Tetralogy of Fallot	Tennant et al [116]	190	90.5 (85.4-93.9)	83·7 (77·6–88·2)	83·1 (76·9–87·7)	83.1 (76.9–87.7)	80.8 (72.8–86.6)	
	Wang et al [192]	1,739						86.9 (85.3-
	Moons et al [189]	52	83 (70-92)*	82.7 (69.7-91.8)*				
	Nembhard et al [190]	766		79.1 (76.1-81.9)*				
	Olsen et al [67]	381	83 (79-87)		70 (65-74)			67 (58-74)
	Garne [184]	7		82.6 (61.2-95.0)*				
	Wang et al [191]	2,843	85.7 (84.3-86.9)	80.5 (79.0–81.9)				
	Samanek et al [86]	169	84.6 (79.0-90.2)		76.6 (70.1-83.2)	76.6 (70.1-83.2)		
	Pooled estimate (95% CI), Heterogeneity I^2 & p-value		85.7 (83.3-87.8) 37.9%, p=0.169	81.0 (79.7-82.3) 0%, p=0.612	81.4 (77.5-85) 93.6%, p<0.001			
Total anomalous pulmonary venous return	Tennant et al [116]	54	72.2 (58.2-82.2)	72.2 (58.2-82.2)	72.2 (58.2-82.2)	72.2 (58.2-82.2)	72.2 (58.2-82.2)	
	Garne [184]	5		20 (0.5-71.6)*				
	Samanek et al [86]	40	52.5 (36.7-8.23)	50.0 (34.2-65.8)	50.0 (34.2-65.8)	50.0 (34.2-65.8)		
	Pooled estimate (95% CI), Heterogeneity I^2 & p-value			53.7 (30-76.6) 76.6%, p=0.014				
Transposition of the great vessels	Tennant et al [116]	189	82.5 (76.3-87.3)	81·0 (74.6–85.9)	80.3 (73.8–85.3)	78·4 (71.6–83.9)	74.1 (64.4–81.5)	
	Wang et al [192]	1,840						74.5 (72.4-
	Wang et al [191]	2,622	75.7 (74.1-77.3)	70.8 (69.0–72.5)				
	Moons et al [189]	29		100.0 (88.1-100.0)*				
	Olsen et al [67]	461	74 (70-78)		62 (38-67)			50 (41–59)
	Samanek et al [86]	271	61.6 (56.7-67.5)	56.5 (50.3-62.4)*	53.9 (46.8-60.9)	53.9 (46.8-60.9)		
	Garne [184]	21		76.2 (52.8, 91.8)*				
	Fixler et al [182]	225	90.7 (86.0-93.8)	89.7 (85.0-93.1)				

Subtype	Article	N	Survival Estimates (95% CI)					
			1 year	5 years	10 years	15 year s	20 years	25 years
	Pooled estimate (95% CI), Heterogeneity I^2 & p-value		77.5 (69.9-84.3) 94.5%, p<0.001	75.5 (67.9-82.4) p<0.001	66.1 (46-83.5) p<0.001			
Tricuspid atresia	Tennant et al [116]	24	83.3 (61.5-93.4)	66.7 (44.3–81.7)	62.5 (40.3–78.4)	62.5 (40.3–78.4)		
	Idorn et al [185]	106	68.0 (58.2-76.7)*	61.7 (51.4-70.6)*	60.5 (50.4-69.7)*	57.4 (47.6-67.1)*	57.4 (47.6-67.1)*	57.4 (47.6-67.1)*
	Fixler et al [182]	67	76.1 (64.0-84.6)	74.6 (62.4–83.4)				
	Moons et al [189]	4	100 (39.8-100.0)*	100 (39.8-100.0)*				
	Samanek et al [86]	39	46.2 (30.2-62.1)		35.9 (20.5-51.3)	35.9 (20.5-51.3)		
	Pooled estimate (95% CI), Heterogeneity I^2 & p-value		71.4 (57.2-83.7) 74.4%, p=0.004	53.7 (30.0-76.6) 93.9%, p<0.001	53.1 (36.5-69.2), 72.4%, p=0.027	53.3 (37.2-69.1), 72.9%, p=0.025		
Hypoplastic left heart	Tennant et al [116]	73	4.1 (1.1-10.5)	2.9 (0.5-8.9)				
	Wang et al [192]							35.6 (32.6-39.7)
	Wang et al [191]	1315	40.1 (37.47-42.7)	34.1 (31.5-36.6)				
	Idorn et al [185]	252	12.5 (8.9-17.5)*	10.4 (6.9-14.8)*	10.4 (6.9-14.8)*	8.8 (5.6-12.9)*		
	Fixler et al [182]	311	41.8 (36.3-69.9)	38.0 (32.6-43.5)				
	Moons et al [189]	10	50 (18.7-81.3)*	40.0 (12.2-73.8)*				
	Samanek et al [86]	172	0 (0.0-2.1)*	0 (0.0-2.1)*	0 (0.0-2.1)*	0 (0.0-2.1)*		
	Pooled estimate (95% CI), Heterogeneity I^2 & p-value		18.5 (2.8-43.5) 98.7%, p<0.001	14.4 (2.8-32.8) 97.8%, p<0.001				

Subtype	Article	N	Survival Estimates (95% CI)					
			1 year	5 years	10 years	15 year s	20 years	25 years
Single ventricle	Tennant et al [116]	31	83.9 (65.5-93.0)	74.2 (55.0–86.2)	74.2 (55.0–86.2)	64.5 (43.1-80.0)		
	Fixler et al [182]	286	64.7 (58.8-69.9)	56.1 (49.9-61.7)				
	Garne [184]	16		56.3 (29.9- 80.2)*				
	Moons et al [189]	9	56 (21-86)*	55.6 (21.2-86.3)*				
	Pooled estimate (95% CI), Heterogeneity I^2 & p-value		70.4 (54.1-84.4) 65.0%, p=0.057	59.8 (50.4-68.8) 26.9%, p=0.250				
Ebstein`s anomaly	Tennant et al [116]	55	67.3 (53.2-78.0)	58.0 (43.8-69.7)	58.0 (43.8-69.7)	54.6 (39.7-67.2)	54.6 (39.7-67.2)	
	Garne [184]	5		60.0 (14.7-94.7)*				
	Moons et al [189]	3		100 (29.2-100.0)*				
	Nembhard et al [190]	160		68.8 (61.0-75.8)*				
	Samanek et al [86]	22	67.9 (50.2-86.5)	64.3 (46.2-82.4)	64.3(46.2-82.4)	64.3(46.2-82.4)		
	Pooled estimate (95% CI), Heterogeneity I^2 & p-value			64.8 (55.5-73.6) 25.5%, p=0.255				

* Indicates that 95% CIs were not reported in the study, but 95% binomial exact 95% CIs were calculated by the authors.
† 95% CIs obtained from author
TGV in Fixler et al's study relates to dextro-TGV only
VSD=ventricular septal defect
IVS= intact ventricular septum

7.3.3 Quality assessment

Quality assessment is shown in Table 7.4. All articles satisfied the study ascertainment domain because by definition, population-based studies are representative of the population. The attrition domain was satisfied by a third of articles, due to studies failing to report the proportion of untraced cases. However, many of the articles classed unmatched cases as alive and so it is possible that all cases were traced. The outcome ascertainment domain was satisfied by 93.3% of studies and the analysis domain by 80%. Studies that did not satisfy the analysis domain were those that did not perform survival analysis and instead reported the proportion alive, which does not account for case censorship. This may have slightly inflated the survival in these studies.

Table 7.4 Quality assessment

Domain	Quality items, potential bias	Yes	Not stated	Number of studies, %
Study ascertainment	The study population is adequately described for key characteristics (i.e CHD subtype frequency, sex distribution, ethnicity).	[67, 182-184, 186, 188, 190-192]		9 (60%)
	Ascertainment is adequately described, including: method of ascertainment, included birth years, study location	[67, 86, 116, 181-192]		15 (100%)
	Inclusion and exclusion criteria are adequately described (i.e ICD codes stated and inclusion of extra-cardiac anomalies.	[67, 116, 182-188, 190-192]		12 (80%)
	There is adequate ascertainment.	[67, 86, 116, 181-192]		15 (100%)
	POTENTIAL BIAS: The study sample represents the population of interest on key characteristics sufficient to limit potential bias to the results.	**[67, 86, 116, 181-192]**		**15 (100%)**
Study attrition	The proportion of traced cases is stated and adequate	[116, 181, 183, 184, 190]	[67, 86, 182, 185-189, 191, 192]	5 (33.3%)
	Reasons for untraced cases are provided	[116, 181, 184, 190]	[67, 86, 182, 185-189, 191, 192]	4 (60%)
	Untraced cases are adequately described for key characteristics (i.e CHD subtype)	[116, 181, 183, 184, 190]	[67, 86, 182, 185-189, 191, 192]	5 (33.3%)
	There are no important differences between key characteristics and		[67, 86, 116, 181-192]	0 (0%)

Domain	Quality items, potential bias	Yes	Not stated	Number of studies, %
	outcomes in participants who were traced and untraced.			
	POTENTIAL BIAS: Untraced cases are not associated with key characteristics (i.e., the study data adequately represent the sample), sufficient to limit potential bias.	**[116, 181, 183, 184, 190]**	**[67, 86, 182, 185-189, 191, 192]**	**5 (33.3%)**
Outcome ascertainment	Frequency of outcome is recorded	[116, 181-192]		13 (86.7%)
	The method of ascertainment of deaths is valid and reliable to limit misclassification bias	[67, 86, 116, 181-192]	[186]	14 (93.3%)
	POTENTIAL BIAS: The outcome of interest is adequately measured in study participants to sufficiently limit potential bias.	**[67, 86, 116, 181-192]**	**[186]**	**14 (93.3%)**
Analysis	There is sufficient presentation of results (i.e number of cases and 95% CIs).	[67, 86, 116, 182, 185, 186, 188, 190-192]		10 (66.7%)
	The analysis is adequate for the design of the study.	[67, 86, 116, 181, 182, 185, 186, 188-192]		12 (80%)
	Results are not selectively reported	[67, 86, 116, 181-192]		15 (100%)
	POTENTIAL BIAS: The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results.	**[67, 86, 116, 181, 182, 185, 186, 188-192]**		**12 (80%)**

7.3.4 Risk factors for mortality

Crude and adjusted hazard ratios are shown in Table 7.5.

Considering all CHD subtypes as a composite group, three studies showed that the risk of mortality significantly decreased with more recent year of delivery [67, 184, 191]. The risk of mortality also decreased with increasing year of delivery among cases of SV physiology [182, 185], AVSD [183, 188], TGA [192], CoA [192], HLH [192] and ToF [192].

Considering all CHD subtypes combined, two studies reported twice the proportion of deaths amongst children born preterm compared to term [184, 190]. Two articles also reported increased risks of mortality among children with UV physiology who were born preterm, with a greater effect amongst those born severely preterm [182, 185]. There was no significant association between survival and preterm delivery in children with AVSD [188].

Considering children with all CHD subtypes combined, two studies reported that low birthweight was associated with increased mortality, with the risk being greater amongst preterm cases [190, 191]. Two studies reported a significant increased risk of mortality amongst low birth weight babies with UV physiology [182, 185]. In both articles, the effect was greater in extremely low birth weight babies, although this only reached significance in one study [182]. There was no evidence of an association between mortality and birthweight in cases of AVSD [188]. Among cases of TGV, ToF, HLH and CoA, low birth weight was associated with increased risk of mortality, with greater effect sizes among preterm cases [192].

Considering all CHD subtypes, five studies reported an increased risk of mortality amongst cases with ECAs compared to isolated cases of CHD [67, 184, 190, 191]. Two further studies reported similar increased risks of mortality in cases with UV physiology with ECAs compared to isolated cases [182, 185]. Wang et al reported increased risks of mortality in children with CoA, TGV and ToF and ECAs, but not amongst cases with HLH. Frid et al reported no significant difference in mortality rates between cases of AVSD with ECAs compared to those with isolated AVSD [183]. Miller et al reported a significant increased risk of mortality amongst cases of AVSD with two non-chromosomal ECAs (compared to isolated AVSD), but not amongst cases with just one non-chromosomal ECA [188].

Frid et al reported that children with isolated AVSD who underwent surgical intervention, were at increased odds of mortality at age five. The effect size increased with more recent year of delivery (OR=0.97 in 1973-77 and OR=0.02 in 1993-97) [183], however, confidence

intervals were not reported, so it was not possible to assess whether the association reached statistical significance. Garne et al did not formally assess the risk of mortality associated with surgical intervention (in all cases of CHD combined), but commented that surgery was not performed in the majority of deaths [184].

One article examined the association between mortality and socioeconomic status, among children with AVSD, finding no significant association (p=0.506) [188]. However, survival decreased linearly over the four categories of socioeconomic status (0-4.9% in poverty=62.3% survival, 5.0%-9.9% in poverty=60.4% survival, 10-19.9% in poverty= 57.9% survival and ≥20% in poverty= 56.9%). There were also no significant associations between mortality and maternal education in any of the studies of all CHD, UV physiology, TGV, ToF, HLH and CoA [182, 190, 192]. However, there was a linear decrease in mortality with increasing maternal education in each study.

Considering all CHD subtypes, Nembhard et al reported that the risk of mortality was significantly increased in males [190]. Females with UV physiology were at 27% significant increased risk of mortality, the association was no longer significant after adjustment for confounders [182]. Idorn et al also reported no significant association between infant sex and mortality among individuals with UV physiology [185]. Females with TGV were at 16% significant increased risk of mortality after adjustment for potential confounders [192]. There were no significant associations reported between infant sex and mortality amongst cases of AVSD [188], ToF [192], HLH [192] and CoA [192].

Considering all CHD subtypes, Nembhard reported improved survival amongst children born in urban compared to rural areas [190]. For children with TGV, HLH and CoA, Wang et al did not find a significant association although the risk of mortality was lower amongst those born in the city [192]. Idorn et al reported no association between mortality and being born in tertiary centres (compared to “Other” place of birth) in children with UV physiology [185].

Wang et al was the only study to report on plurality as a risk factor for mortality, finding no significant association after adjustment for potential confounders [191].

Six articles examined maternal age at delivery as a risk factor for mortality [182, 185, 188, 190-192]. In two studies, there was no evidence of an association in individuals with UV physiology, but both studies reported elevated risk amongst mothers aged under 20 [182, 185]. In children with AVSD, there was no significant association between mortality and maternal age, but mortality rates were greater with maternal age<29 [188]. Considering all CHD subtypes combined, Wang et al and Nembhard et al reported a linear decrease in the risk

of mortality with increasing maternal age, although Wang et al reported that the effect was only significant amongst mothers aged ≥35 (aHR= 0.88) [191]. There were no significant associations with maternal age among children with CoA, HLH and ToF, although maternal age ≥35 appeared protective among children with TGV [192].

Two studies examined paternal age as a risk factor for mortality and found no significant association, one in children with UV physiology and the other with children with AVSD [185, 188].

Considering all CHD subtypes combined, one study investigated the association between parity and mortality, finding that multiparous individuals were at significant increased risk of mortality compared to nulliparous individuals, after adjusting for potential confounders (aHR= 1.19, 95% CI: 1.10-1.28).

Five studies investigated the influence of maternal ethnicity as a risk factor for mortality, all using non-Hispanic white ethnicity as the reference category [182, 188, 190-192]. Hispanic maternal ethnicity was not associated with mortality in all CHD subtypes combined [190, 191], CAT [190], TGV [190, 192], ToF [190, 192], TA [190], PVS [190], PVA-IVS [190], EA [190], HLH [190, 192], AVA/S[190], CoA [192], VSD [190] or ASD [190]. However, cases of UV physiology born to Hispanic mothers were at borderline significant increased risk of mortality [182]. Non-Hispanic Black ethnicity was not associated with mortality in cases of CAT [190], TA [190], PVS [190], EA [190], HLH [190], AVA/S [190], AVSD [188, 190] or HLH [190] and CoA [190]. but was associated with an increased risk of mortality in cases of UV physiology [182], TGV [190, 192], ToF [190, 192], PVA-IVS[190], VSD [190] and ASD [190]. There was conflicting evidence on the association between non-Hispanic Black ethnicity and mortality for CoA and all CHD subtypes combined [190, 192].

Table 7.5 Risk factors for mortality

Study	CHD subtypes	Risk factor	Reference category	Comparison category	HR (95% CI), or % died & log-rank test	aHR (95% CI)
Fixler et al [182]	UV physiology	Year of delivery	1996-2000	2001-2003	0.60 (0.49-0.73)	0.53 (0.43-0.66)
Frid et al [183]	AVSD		N/A	1973-77/ 1993-97	63% vs 8%, p=0.003	
Garne[184]	All CHD		1986-93	1994-98	21% vs 13%, p<0.05	
Idorn et al [185]	UVP		1990-99	1977-89 2000-09	2.04 (1.63-2.55) 0.85 (0.64-1.12)	2.65 (2.06-3.42) 0.77 (0.57-1.05)
Miller et al [188]	AVSD		1979-1991	1992-2003		0.59 (0.3-0.98)
Olsen et al[67]	All CHD		1977-86	1997-05	0.42 (0.37-0.49)	
Wang et al (2011) [191]	All CHD		2001-06	1983-88 1989-94 1995-2000		2.06 (1.83-2.33) 1.81 (1.61-2.04) 1.43 (1.27-1.62)
Wang et al (2013) [192]	TGA		2001-06	1983-88 1989-94 1995-2000		2.87 (2.29-3.59) 2.22 (1.77-2.77) 1.59 (1.25-2.01)
[192]	CoA		2001-06	1983-88 1989-94 1995-2000		2.65 (2.05-3.43) 2.09 (1.63-2.70) 1.67 (1.29-2.17)
[192]	HLH		2001-06	1983-88 1989-94 1995-2000		3.41 (2.76-4.20) 2.74 (2.22-3.39) 1.77 (1.41-2.21)
[192]	ToF		2001-06	1983-88 1989-94		2.58 (1.97-3.37) 2.23 (1.72-2.91)

Study	CHD subtypes	Risk factor	Reference category	Comparison category	HR (95% CI), or % died & log-rank test	aHR (95% CI)
				1995-2000		1.49 (1.11-2.00)
Fixler et al [182]	UV physiology	Gestational age	37-44 weeks	20-31 weeks 32-36 weeks	2.80 (1.80-4.34) 1.69 (1.32-2.18)	
Garne [184]	All CHD		≥37 weeks	<37 weeks	32% vs 15%, p<0.05	
Idorn et al [185] [188]	UV physiology AVSD		> 37 weeks > 37 weeks ≥37 weeks	<32 weeks 32-37 weeks <37 weeks	2.34 (1.16-4.73) 1.51 (1.10-2.08)	0.53 (0.09-2.99) 1.68 (1.13-2.51) 1.65 (0.96-2.8)
Nembhard et al [190]	All CHD		≥37 weeks	<37 weeks	7.6% vs 14.0%	
Miller et al [188]	AVSD	Birth weight	<2500g	2500g	47.4% vs 38.8%, p=0.197	
Fixler et al [182]	UV physiology		≥2500g	<1500 1500-2499	6.22 (4.00-9.65) 2.85 (2.22-3.65)	6.27 (3.95-9.96) 2.08 (1.61-2.70)
Idorn et al [185]	UV physiology		≥2500g	<1500g 1500-2499g	4.15 (1.95-8.84) 1.13 (0.82-1.54)	6.21 (1.24-31.15) 0.84 (0.56-1.25)
Wang et al (2011) [191]	All CHD		≥37 weeks, 2500-3999g	<37 weeks, <1500g <37 weeks, 1500-2499g <37 weeks, 2500-3999g <37 weeks, ≥4000g ≥37 weeks, <1500g ≥37 weeks, 1500-2499g ≥37 weeks, ≥4000g		2.89 (2.47-3.39 1.76 (1.56-1.99) 1.22 (1.06-1.41) 0.56 (0.25-1.25) 2.23 (1.36-3.66) 1.74 (1.55-1.94) 0.80 (0.67-0.95)
[192]	CoA		≥37 weeks, 2500-3999g	<37 weeks, <1500g <37 weeks, 1500-2499g <37 weeks, 2500-3999g <37 weeks, ≥4000g ≥37 weeks, <1500g		2.71 (1.91-3.83) 2.26 (1.73-2.96) 1.39 (0.95-2.04) 1.22 (0.30-4.94) 0.79 (0.20-3.20)

Study	CHD subtypes	Risk factor	Reference category	Comparison category	HR (95% CI), or % died & log-rank test	aHR (95% CI)
				≥37 weeks, 1500-2499g		2.21 (1.70-2.87)
				≥37 weeks, ≥4000g		0.65 (0.43-0.97)
[192]	HLH		≥37 weeks, 2500-3999g	<37 weeks, <1500g		3.55 (2.31-5.46)
				<37 weeks, 1500-2499g		1.87 (1.46-2.39)
				<37 weeks, 2500-3999g		1.07 (0.76-1.49)
				<37 weeks, ≥4000g		0.34 (0.05-2.54)
				≥37 weeks, <1500g		2.23 (0.91-5.47)
				≥37 weeks, 1500-2499g		1.31 (1.01-1.69)
				≥37 weeks, ≥4000g		0.94 (0.70-1.25)
[192]	TGV		≥37 weeks, 2500-3999g	<37 weeks, <1500g		4.97 (3.61-6.84)
				<37 weeks, 1500-2499g		2.36 (1.84-3.03)
				<37 weeks, 2500-3999g		1.49 (1.12-1.99)
				<37 weeks, ≥4000g		0.65 (0.09-4.63)
				≥37 weeks, <1500g		2.43 (1.20-4.92)
				≥37 weeks, 1500-2499g		1.95 (1.55-2.45)
				≥37 weeks, ≥4000g		0.77 (0.55-1.07)
[192]	ToF		≥37 weeks, 2500-3999g	<37 weeks, <1500g		2.77 (2.02-3.80)
				<37 weeks, 1500-2499g		1.51 (1.16-1.97)
				<37 weeks, 2500-3999g		1.11 (0.75-1.64)
				<37 weeks, ≥4000g		-
				≥37 weeks, <1500g		1.44 (0.46-4.52)
				≥37 weeks, 1500-2499g		1.85 (1.46-2.35)
				≥37 weeks, ≥4000g		0.41 (0.21-0.79)
Fixler et al [182]	UV physiology	ECAs	Isolated CHD	ECAs	2.32 (1.84-2.9)	1.84 (1.46-2.34)
Frid et al [183]	AVSD		Isolated CHD	Down syndrome	37.7% vs 40.4%, p=0.7	

Study	CHD subtypes	Risk factor	Reference category	Comparison category	HR (95% CI), or % died & log-rank test	aHR (95% CI)
Garne [184]	All CHD		Isolated CHD	ECAs	13% vs 35%, p<0.05	
Idorn et al [185]	UVP		Isolated CHD	ECAs	1.80 (0.35-2.41)	1.95 (1.40-2.71)
Miller et al [188]	AVSD		Isolated CHD	1 ECA 2 ECAs		1.28 (0.6-2.5) 3.32 (1.7-6.3)
Olsen et al [67]	All CHD		Isolated CHD	ECAs	27% vs 36%, p<0.05	
Wang et al (2011) [192]	All CHD CoA		Isolated CHD	ECAs Down syndrome ECAs (not Down syndrome)		1.37 (1.25-1.51) 2.31 (1.52-3.51) 2.07 (1.74-2.46)
Wang et al (2013) [192]	HLH		Isolated CHD	Down syndrome ECAs (not Down syndrome)		1.00 (0.46-2.15) 1.10 (0.95-1.28)
Wang et al (2013) [192]	TGV		Isolated CHD	Down syndrome ECAs (not Down syndrome)		1.86 (1.10-3.12) 1.80 (1.56-2.08)
[192]	ToF		Isolated CHD	Down syndrome ECAs (not Down syndrome)		2.33 (1.76-3.09) 2.81 (2.34-3.36)
Fixler et al [182]	UV physiology	Infant sex	Male	Female	1.27 (1.04-1.55)	
Idorn et al [185]	UV physiology		Male	Female	1.14 (0.94-1.38)	
[188]	AVSD		Male	Female	39.2% vs 41.7%, p=0.491	
Wang et al (2011) [191]	All CHD		Male	Female	1.07 (1.00-1.15)	

Study	CHD subtypes	Risk factor	Reference category	Comparison category	HR (95% CI), or % died & log-rank test	aHR (95% CI)
Wang et al (2013) [192]	TGV		Female	Male		0.84 (0.73-0.97)
[192]	ToF		Female	Male		0.90 (0.76-1.06)
[192]	HLH		Female	Male		0.97 (0.84-1.12)
[192]	CoA		Female	Male		1.00 (0.85-1.18)
Fixler et al [182]	UV physiology	Maternal age	20-29	<20 ≥40 30-39	1.15 (0.87-1.53) 0.64 (0.32-1.31) 0.93 (0.74-1.17)	
Idorn et al [185]	UV physiology		20-29	>40 <20 30-39	1.12 (0.42-3.01) 1.05 (0.65-1.69) 0.89 (0.73-1.10)	
Miller et al [188]	AVSD		<29	≥29	45.3 vs 34.9%, p=0.3802	
Wang et al (2011) [191]	All CHD		25-29	<20 20-24 30-34 ≥35		1.15 (0.99-1.34) 1.02 (0.91-1.14) 1.03 (0.93-1.14) 0.88 (0.79-0.98)
Wang et al (2013) [192]	CoA		25-34	<25 years ≥35 years		0.98 (0.80-1.19) 0.84 (0.68-1.03)
[192]	HLH		25-34	<25 years ≥35 years		1.06 (0.90-1.24) 0.99 (0.84-1.17)
[192]	TGV		25-34	<25 years ≥35 years		1.04 (0.88-1.22) 0.84 (0.71-1.00)
[192]	ToF		25-34	<25 years ≥35 years		0.96 (0.79-1.17) 0.96 (0.78-1.19)
	UVP	Maternal ethnicity		Hispanic	1.19 (0.97-1.47)	1.26 (1.00-1.58)

Study	CHD subtypes	Risk factor	Reference category	Comparison category	HR (95% CI), or % died & log-rank test	aHR (95% CI)
Fixler et al [182]			Non-hispanic White	NON-HISPANIC black	1.59 (1.15-2.20)	1.41 (1.01-1.97)
Miller et al [188]	AVSD		Non-hispanic White	Black/African American Other		0.87 (0.50-1.5) 2.35 (0.95-5.8)
Wang et al (2011) [191]	All CHD		Non-hispanic White	Asian, Pacific Islander Hispanic Non-Hispanic Black		1.01 (0.83-1.22) 1.00 (0.89-1.12) 1.07 (0.97-1.18)
Wang et al (2013) [192]	TGV		Non-hispanic White	Hispanic Non-Hispanic Black		1.20 (0.96-1.49) 1.31 (1.07-1.60)
[192]	CoA		Non-hispanic White	Hispanic Non-Hispanic Black		1.12 (0.86-1.47) 1.40 (1.10-1.79)
[192]	ToF		Non-hispanic White	Hispanic Non-Hispanic Black		1.24 (0.96-1.61) 1.34 (1.06-1.69)
Nembhard et al [190]	HLH		Non-hispanic White	Hispanic Non-Hispanic Black		0.85 (0.68-1.06) 0.92 (0.76-1.11)
[190]	CAT		Non-hispanic White	Hispanic Non-Hispanic Black		1.76 (0.88-3.49) 1.88 (0.62-5.66)
[190]	TGV		Non-Hispanic White	Hispanic Non-Hispanic Black		1.16 (0.87-1.55) 2.04 (1.40-2.97)
[190]	ToF		Non-Hispanic White	Hispanic Non-Hispanic Black		1.39 (0.92-2.10) 1.85 (1.09-3.12)
[190]	TA		Non-Hispanic White	Hispanic Non-Hispanic Black		0.97 (0.66-1.43) 1.41 (0.90-2.21)
[190]	PVS		Non-Hispanic White	Hispanic Non-Hispanic Black		1.15 (0.68-1.96) 1.13 (0.57-2.22)
[190]	PVA-IVS		Non-Hispanic White	Hispanic Non-Hispanic Black		1.76 (1.06-2.91) 2.60 (1.32-5.12)

Study	CHD subtypes	Risk factor	Reference category	Comparison category	HR (95% CI), or % died & log-rank test	aHR (95% CI)
[190]	EA		Non-Hispanic White	Hispanic Non-Hispanic Black		1.88 (0.74-4.79) 1.42 (0.43-4.70)
[190]	HLH		Non-Hispanic White	Hispanic Non-Hispanic Black		1.51 (1.13-2.02) 1.06 (0.67-1.66)
[190]	AVA/S		Non-Hispanic White	Hispanic Non-Hispanic Black		0.92 (0.56-1.51) 1.02 (0.49-2.13)
[190]	CoA		Non-Hispanic White	Hispanic Non-Hispanic Black		0.73 (0.53-1.02) 1.12 (0.71-1.76)
[190]	VSD		Non-Hispanic White	Hispanic Non-Hispanic Black		0.96 (0.79-1.18) 1.56 (1.19-2.03)
[190]	ASD		Non-Hispanic White	Hispanic Non-Hispanic Black		0.94 (0.80-1.11) 1.34 (1.08-1.66)
[190]	AVSD		Non-Hispanic White	Hispanic Non-Hispanic Black		0.98 (0.71-1.37) 1.02 (0.68-1.54)
[190]	All CHD		Non-Hispanic White	Hispanic Non-Hispanic Black		0.96 (0.85-1.08) 1.32 (1.14-1.54)

7.4 Discussion

In this systematic review and meta-analyses, I found that 87.0% of children born with CHD survived to age one, 85.4% to age five and 81.4% to age 10. Few articles reported survival beyond age 10, but survival appeared to continue gradually decreasing into adulthood. There was substantial variation in survival estimates between articles, some of which was accounted for by study period, which positively impacted on survival. Articles consistently showed that less recent year of delivery, preterm delivery, presence of ECAs and low birth weight negatively impacted on survival. There was some evidence that maternal ethnicity and being born in more rural environments negatively influenced survival. There was inconsistent or little evidence surrounding socioeconomic status and maternal age as risk factors for mortality.

The main strength of this systematic review is its restriction to population-based studies. Although including hospital-based studies would have increased the amount of data available, these studies under-ascertain milder CHD subtypes that do not require major medical intervention. Additionally, children with severe CHD may travel to centres with specialist expertise. Therefore, the survival estimates reported by hospital-based studies can be unrepresentative of the general population of individuals with CHD. The robustness of the individual rates to bias was examined using a quality assessment with previously published domains and items [180]. While each study failed to satisfy at least one quality item, due to the population-based study designs, the potential for bias in each domain remained low. Moreover, for all CHD, I did not identify any significant publication bias according to Egger's test.

A further strength is the comprehensive nature of my search strategy. Three databases were searched for relevant citations along with key journals and reference lists, thus the likelihood of missing key studies was limited. Full articles were reviewed by two researchers to ensure they fully met the inclusion criteria and that data was extracted correctly.

There were also several limitations. The maximum follow-up was just 30 years, with five of the included studies reporting survival to just five years. The greatest risk of death appeared to occur within the first year, but survival continued to decrease over the follow-up, although at a lesser rate. A study of CHD related mortality rates between 1999-2006 in the USA showed a high mortality rate of 41.5 per 100,000 in infancy, which decreased to 1.38 between ages 1-4 and

stabilised at approximately 0.55 between the ages of 5-65. After age 65 however, the mortality rate doubled to 1.10 per 100,000 [193].

A further limitation is that longer-term survival estimates may not be representative of children born with CHD today. Even in the most recent studies, 25-year survival rates related to individuals born in the 1990s; in my meta-regression of one, five and 10 year survival, I showed that survival estimates improved over time.

Given that the primary aim of this systematic review was to identify survival estimates, the search strategy may not have included all articles that reported risk factors for long-term CHD mortality. However, it is unlikely that studies of risk factors were missed, as all of them should also report long-term survival in line with my inclusion criteria.

All the included articles were performed in high income western populations. Evidence suggests that infant mortality rates associated with congenital anomalies are greater in low income countries [8]. Therefore, the survival estimates in this review are not likely to be globally representative. While I only included articles written in the English language, I did not identify any relevant articles written in other languages.

Most of the included articles included cases with ECAs [67, 86, 181-192]. It is therefore difficult to assess how much of the mortality is accounted for by CHD as opposed to the co-occurring congenital anomalies. However, cases with ECAs accounted for only 20% of all cases, some of which are not likely to be life threatening. Additionally, all articles used all-cause mortality, meaning the deaths may not have been directly related to the CHD diagnosis.

While this review provides an insight into long-term mortality associated with CHD, I have not accounted for morbidity. Research suggests that quality of life is lower in those with CHD and survivors are subject to morbidities such as endocarditis, cerebrovascular accidents, myocardial infarctions and arrhythmias [194-196]. The American Heart Association has also reported that children with CHD are at increased risk of developmental disorders [27].

Using meta-regression, I found more recent study period positively impacted on survival. However, despite the adjustment for study period, there was still a high degree of heterogeneity. While I adjusted for study period using the year of study commencement, the lengths of the study periods varied by article. Therefore, my adjustment for the year of study commencement is not

likely to have fully accounted for the changes in survival over time. Study period is likely to have had a greater impact than that shown in the meta-regression models. Further heterogeneity is likely attributable to a variety of sources. Firstly, case ascertainment is likely a major cause of heterogeneity. Olsen et al report lower survival estimates even after accounting for study period, but their prevalence of CHD is almost half that of other studies. Given that they included only cases diagnosed before age one, it is likely they under-ascertained cases with milder CHD subtypes, such as VSD [67]. The data sources used may also have contributed to variation in ascertainment, with articles using hospital records as opposed to CARs (which use multiple sources for ascertainment), contributing to lower survival estimates, likely due to the milder cases being under-ascertained [86]. Additionally, articles that used CARs may have had better ascertainment of individuals with ECAs. This is likely to worsen prognosis among these studies when compared to say Moons et al, who ascertained cases from a paediatric cardiology register [189]. The classification of ECAs is also a source of heterogeneity. Two articles excluded all cases with ECAs [116, 181]. Unfortunately too few articles excluded cases with ECAs and so a meta-regression could not be performed.

Variation in study periods is arguably the greatest source of heterogeneity in survival estimates. Survival has improved over time due to advances in surgical correction. For example, the Fontan operation for repair of SV, HLH and TA and the conduit repair for cases of CAT were introduced in the late 1970s and developed across the 1980s-90s [197, 198]. The arterial switch operation for treatment of TGV was introduced in 1975 [199], and fully replaced the atrial switch operations in the early 1990s resulting in improved long-term survival [200]. Although at first the arterial switch operation resulted in greater mortality [201], eventually this led to improved survival among cases of TGV [200]. Survival is also likely to have improved over time due to advances in prenatal diagnosis. Greater prenatal diagnosis rates may have led to an increase in termination (for fetal anomaly) rates. If cases with the more severe subtypes are terminated, this will have resulted in better survival. Prenatal diagnosis also allows quicker intervention at birth or even in utero, which may also improve survival [202]. Survival is also likely to have improved due to the introduction of prostaglandin, which was trialled in neonates with cyanotic CHD in the 1970s [203, 204], although was not frequently administered until the 1980s.

Further research is required to examine survival in non-western countries. Although I aimed to examine long-term survival, the longest follow-up was 30 years. Mortality rates suggest that the

mortality rates remain stable between age five and 65 [193]. However, after age 65 there is evidence that mortality rates increase; therefore studies with follow-up longer than thirty years are required.

Chapter 8. Survival and risk factors for mortality among individuals with congenital heart disease: a data-linkage study

8.1 Introduction

In Chapter 7, a systematic review showed that a limited number of population-based studies have reported survival of children born with CHD. In particular, there was a paucity of information on the survival of children with isolated CHD and beyond the age of five years.

Research regarding risk factors for mortality is limited. Studies consistently demonstrated that less recent year of delivery, preterm delivery, presence of ECAs and low birth weight negatively impacted on survival. There was some evidence that maternal ethnicity and being born in more rural environments negatively influenced survival. However, there was inconsistent or little evidence surrounding socioeconomic status and maternal age as risk factors for mortality. Most of the studies examined all CHD subtypes combined. Given that the subtypes are diverse in terms of aetiology and severity, this is not particularly informative and can be misleading.

8.1.1 Aim

The aim of this chapter is to report the long-term survival and risk factors for mortality among individuals born with CHD, using high quality population-based register data.

The original aim was to conduct a national study of long-term survival for individuals born with CHD between 1985-2010; involving the linkage of data from six BINOCARs to death registrations. The linkage was to be performed by the Health and Social Care Information Centre (HSC IC, previously known as the NHS Information Centre) using several patient identifiable variables. In 2013, I submitted full ethics applications to the Confidentiality Advisory Group (CAG) and the Research Ethics Committee (REC) [205, 206]. Although I gained ethical approval from both CAG and REC in November 2013 (CAG 5-08(b) 2013 and 13/NE/0188, Appendix B), the application could not be progressed by the HSC IC between 2013-2014 due to their moratorium while they reviewed their policies on patient identifiable data. After the moratorium ended, HSC IC would not progress the application because Newcastle University did not have an Information Governance (IG) toolkit. I spent several months writing a System Level Security Policy, with a member of Newcastle University IT. Once this had been approved, the BINCOAR's CAG approval, (which allows the BINOCARs

to collect data without consent) expired and therefore my application with HSC IC was further halted until this was fully renewed in April 2015. The HSC IC then reviewed my application and requested some further changes. These changes required an update to my original CAG approval, which was accepted in September 2015. I am currently waiting for final approval from the HSC IC, before the data-linkage can commence. Due to time constraints, I had to find an alternative data set to investigate long-term survival of CHD. I therefore analysed an existing data set consisting of individuals born between 1985-2003 and notified to one BINOCAR (the NorCAS) and linked to death registrations in 2008. Some of this data has already been published, although survival was not reported for every CHD subtype, cases with multiple CHD subtypes or ECAs were excluded, and there was no analysis of risk factors for mortality [116].

8.1.1.1 Objectives

- To produce Kaplan-Meier survival estimates for each CHD subtype at one week, one month, one year, five years, 10 years, 15 years and 20 years of age.
- To examine at what age cases were at greatest risk of mortality, according to CHD subtype.
- Using Cox regression, to describe risk factors for mortality including: the presence of ECAs, year of delivery, gestational age at delivery, standardised birth weight, maternal age, infant sex, deprivation, prenatal diagnosis, plurality and annual TOPFA rates, according to CHD subtype.
- To predict 30 year survival associated with each CHD subtype.
- To predict 20 year survival for individuals with CHD born in 2003, 2010 and 2015.

8.2 Methods

8.2.1 Case inclusion

All live born cases (any plurality) with a final diagnosis of CHD (ICD 9: 745, 746, 7470-7474) born between 1st January 1985-31st December 2003 and notified to the NorCAS before January 2008 were included in this study.

8.2.2 Data

The NorCAS (one of the BINOCARs) was linked to the PMS to obtain data on infant deaths. Any cases that were not recorded on the PMS were then linked with ONS death registrations. Cases were linked to death registrations on 28th January 2008 using "fuzzy" matching of the following variables: infant forename and surname, infant sex, last known address and infant's date of birth. Traced cases that were matched to a death registration were classed as dead and traced cases that were unmatched to death registrations were classed as alive. Cases were classed as traced if they were found on the civil registration system, for example in the form of a birth certificate. Untraced cases were further examined on NorCAS records, hospital records and through the National Tracing System. Cases that were untraced by PMS, ONS, hospital records and the National Tracing System were excluded from the analysis (n=22).

The variables included in the analysis are shown in Table 8.1. Using a fetal growth formula to predict birth weight at 40 weeks gestation (according to regional birth weight references) [125], birth weight was standardised for gestational age at delivery, sex and plurality. From mothers' postcode at delivery, the IMD 2004 was calculated (see Chapter 4, section 4.1.1). The IMD for the whole of England is ranked from 0 to 32,482. Cases were therefore assigned to national tertiles of most, moderately and least deprived.

There were too few cases of triplets and higher order pregnancies to examine these separately from twins. Therefore, plurality was classed as singleton or multiple.

Information on the exact timing of prenatal diagnosis was not available, so prenatal diagnosis was simply categorised as "prenatally diagnosed" or "not prenatally diagnosed". In this chapter, prenatal diagnosis refers to the diagnosis of the *specific* type of CHD. For example, cases of TGV would only be classed as prenatally diagnosed if TGV specifically was suspected.

Table 8.1 Description of variables used in analysis

Variable	Classification
Year of delivery (years)	Continuous variable
Gestational age at delivery (weeks)	Continuous variable
Annual TOPFA (varies by CHD subtype)	Continuous variable
Sex	Male (reference category) Female
Maternal age at delivery (years)	Continuous variable
Extra-cardiac anomalies (ECAs)	Isolated CHD CHD with structural ECAs CHD with chromosomal/ genetic ECAs
Prenatal diagnosis	Prenatally diagnosed (subtype specific), Not prenatally diagnosed (subtype specific)
Standardised birth weight (SD from the mean)	SD<-1 -1 ≤ SD ≥1 SD>1
Plurality	Singleton Multiple
IMD rank	Tertile 1 (most deprived, reference category) Tertile 2 (moderately deprived) Tertile 3 (least deprived)

Statistical analysis

8.2.2.1 Kaplan-Meier survival estimates

Kaplan-Meier survival estimates and corresponding 95% CIs were estimated at age one week, one month, one year, five years, 10 years, 15 years and 20 years. In order to produce precise survival estimates in the tail of the Kaplan-Meier curves, estimates were reported where there were at least 10 cases at risk at the beginning of the interval, at least five cases at risk at the end of the interval and at least five deaths during the interval [207].

8.2.2.2 Cox regression models

For each CHD subtype, unadjusted HRs representing the risk of mortality associated with year of delivery, gestational age at delivery, standardised birth weight, maternal age at delivery, sex, deprivation, prenatal diagnosis, plurality and annual TOPFA rate were estimated using univariable Cox regression models [208]. The unadjusted models were fitted with three strata for: 1) isolated CHD; 2) CHD with structural ECAs; 3) CHD with chromosomal/ genetic ECAs. This was because these groups of CHD are diverse in terms of aetiologically, prognosis, and intervention. The strata allows the hazard function to vary between strata, but the HR for each risk factor is assumed to be the same in each strata [209]. Interactions between the ECAs variable and the other risk factors were examined to ensure this was appropriate. In terms of interpretation, the HRs produced in the Cox regression models with strata are essentially pooled estimates across the three ECA categories. Where there were < 10 cases at risk within a strata, this strata was excluded.

Adjusted HRs (aHRs) were estimated using multivariable Cox regression models. While a formal sample size calculation was not performed (due to this being a secondary analysis on a population-based data set), Peduzzi et al's guideline on the minimum number of events per variable entered into the Cox regression was utilised [210]. Here, multivariable analysis was performed if, for the CHD subtype in question, the number of cases was 10 times the number of variables divided by the probability of a death. As case numbers were limited, only variables that were significantly associated with mortality for all CHD subtypes combined were included in the multivariable analyses. Hence, multivariable analyses was carried out for cases of AVA/S, AVSD, ToF, TGV, VSD and all CHD subtypes combined only.

Interactions between the risk factors were also tested. However, this was only possible for the models for all CHD subtypes combined, due to there being too few cases and therefore not enough power to test interactions for the individual CHD subtypes.

The proportional hazards assumption was checked by examination of the Schoenfield residuals and the application of the Grambsch-Therneau test for the linearity of the log(HR) [211].

Cox-Snell residuals were also examined to investigate model fit. If the model is of a good fit to the data, then the cumulative hazard function should have an exponential distribution with a HR equal to one [212]. This can be checked by using the Cox-Snell residuals as the analysis time and plotting the cumulative hazard function. If this cumulative hazard function follows a

45 degree line then the function approximately follows the exponential distribution and the model is a good fit to the data [212].

Martingale residuals were examined for each continuous explanatory variable in order to ensure the linearity of the association [213]. Here a flat Lowess curve of the Martingale residuals over the explanatory variable of interest is indicative of a linear association between the variable and mortality [214].

8.2.2.3 Graphing the hazard function

The hazard functions were examined in order to assess when the greatest risk of mortality occurred. Cox regression produces very unstable estimates of the hazard function. Therefore, the hazard functions were produced from Royston-Parmar models, which uniquely model the baseline hazard function using cubic splines (i.e. piecewise polynomials joined at pre-specified time-points called knots) [215]. In this analyses, one knot placed at the 50^{th} percentile was sufficient for modelling the baseline hazard.

All statistical analysis was performed in Stata 13. As all analyses were conducted for each of the 20 subtypes, a Bonferroni adjustment was used. Therefore, $p<0.003$ was considered statistically significant. As this is arguably over-conservative, associations significant at the $p<0.05$ level are also discussed and described as having "some evidence of an association".

8.2.2.4 Prediction and extrapolation

From the Cox regression model adjusted for year of delivery only, survival estimates were predicted for cases born in the last year of the study period (2003), the last year of the study period for the data in Chapters five and six (2010) and the current year (2015).

Using multivariable Royston-Parmar models (adjusted for the same variables as in the multivariable Cox models), baseline survival (i.e. the average risk of death) was extrapolated to age 30. The predicted survival curve was compared to the Kaplan-Meier survival curves to ensure the models were of good fit up to age 20 and therefore if the estimated 30 year survival was feasible.

8.3 Results

There were 5,092 live born cases of CHD notified to the NorCAS between 1985-2003, of which 5,070 (99.5%) were traced. Of these, 4,181 (82.5%) were isolated CHD, 287 (5.7%) occurred with structural ECAs and 602 (11.9%) occurred with chromosomal/ genetic ECAs. The frequency of each CHD subtype is shown in Table 8.2.

Table 8.2 CHD subtypes in live births according to presence of ECAs, 1985-2003

CHD subtype	Isolated CHD n (% of 4,181)	CHD with structural ECAs n (% of 287)	CHD with chromosomal/ genetic ECAs n (% of 602)	Total n (% of 5,070)
SV	34 (0.8)	1 (0.3)	1 (0.2)	36 (0.7)
HLH	73 (1.7)	2 (0.7)	4 (0.7)	79 (1.6)
HRH	11 (0.3)	0 (0)	1 (0.2)	12 (0.2)
EA	24 (0.6)	1 (0.3)	2 (0.3)	27 (0.5)
TA	27 (0.6)	5 (1.7)	2 (0.3)	34 (0.7)
PVA	30 (0.7)	4 (1.4)	7 (1.2)	41 (0.8)
CAT	36 (0.9)	6 (2.1)	10 (1.7)	52 (1.0)
AVSD	107 (2.6)	20 (7)	137 (22.8)	264 (5.2)
AVA/S	226 (5.4)	6 (2.1)	15 (2.5)	247 (4.9)
TGV	202 (4.8)	14 (4.9)	6 (1)	222 (4.4)
ToF	191 (4.6)	36 (12.6)	44 (7.3)	271 (5.3)
TAPVR	55 (1.3)	5 (1.7)	4 (0.7)	64 (1.3)
CoA	216 (5.2)	18 (6.3)	24 (4)	258 (5.1)
IAA	19 (0.5)	1 (0.3)	13 (2.2)	33 (0.6)
DORV	14 (0.3)	3 (1)	5 (0.8)	22 (0.4)
MVA	75 (1.8)	1 (0.3)	4 (0.7)	80 (1.6)
VSD	1922 (46)	96 (33.6)	164 (27.2)	2,182 (43.0)
ASD	337 (8.1)	19 (6.6)	66 (11)	422 (8.3)
PVS	382 (9.1)	16 (5.6)	30 (5)	428 (8.4)
PDA	11 (0.3)	8 (2.8)	20 (3.3)	39 (0.8)
Other	189 (4.5)	25 (8.7)	30 (5)	244 (4.8)
All CHD	**4,181 (100)**	**287 (100.3)**	**602 (100)**	**5,070 (100)**

8.3.1 Survival estimates and mortality rates

Table 8.3 shows the Kaplan-Meier survival estimates, by CHD subtype. Survival estimates are also displayed graphically in Figure 8.16 (red curves). Overall, 85.2% lived to age 20, which was significantly lower than survival in the general population (98.9%, 95% CI: 98.9-99.0; $p<0.001$) [216]. The rate of mortality was highest during the first week of life, decreased steeply until approximately age 6 months and gradually declined thereafter, attenuating towards zero (Figure 8.1).

Survival estimates varied by CHD subtype (Table 8.3): for children with isolated HLH, survival was 22.8% at age one month (with no cases surviving beyond age 11), whereas for children with isolated ASD, 20 year survival was 94.0%. Twenty year survival for all CHD subtypes was significantly lower than that of the general population. For all CHD subtypes, the predicted mortality rate was greatest during the first week of life (Figure 8.1). The predicted mortality decreased monotonically with increasing age and attenuated towards zero. The rate of the decrease in mortality and the age at which the rate started to approach zero varied by CHD subtype (Figure 8.1).

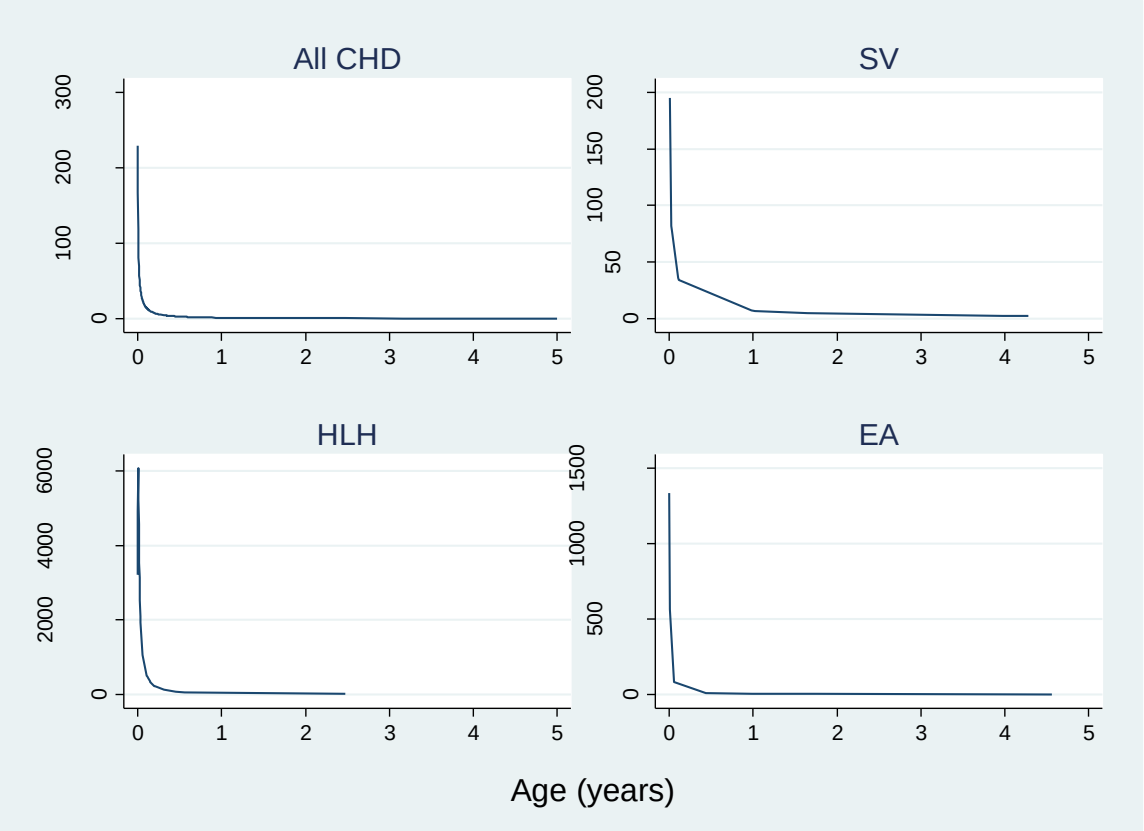
Table 8.3 Survival estimates up to age 20, by CHD subtype

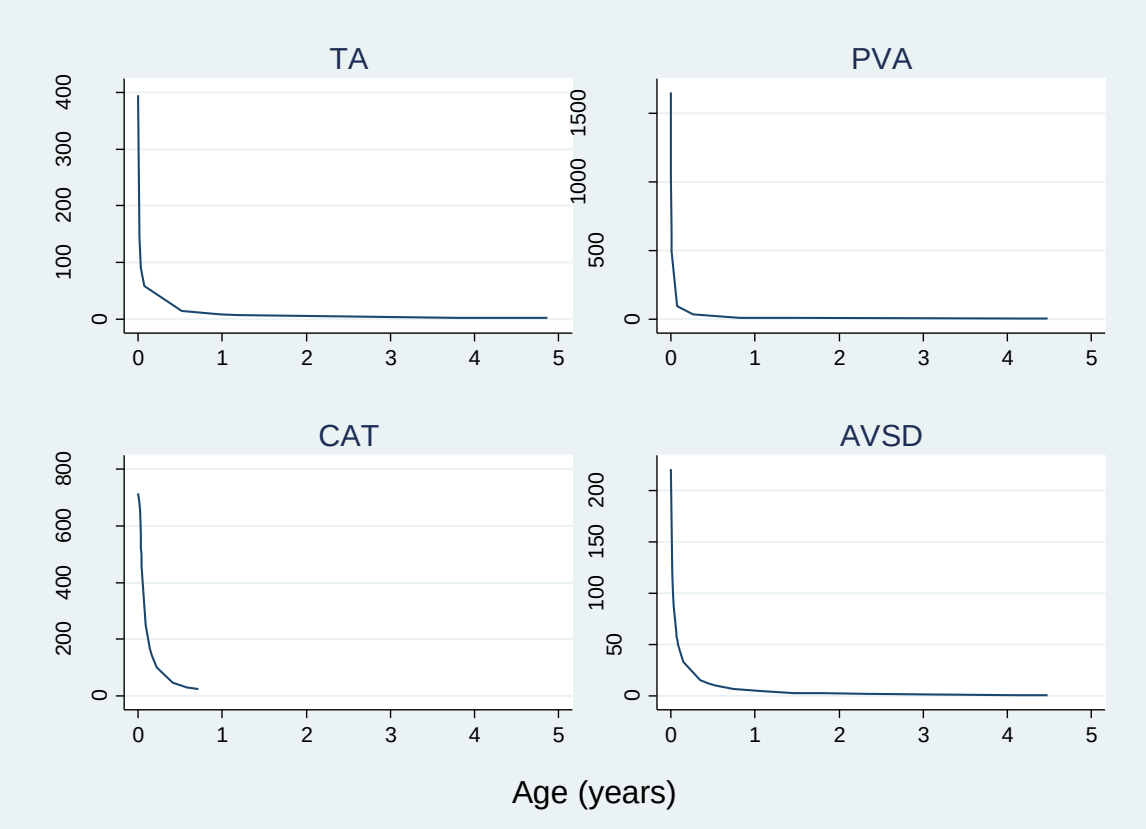
Age	Subtype	No at risk†	% Survival (95% CI)	Subtype	No at risk†	% Survival (95% CI)
1 week	CHD	4867	96.0 (95.4-96.5)	TOF	256	94.5 (91.0-96.6)
1 month		4756	93.8 (93.1-94.4)		251	92.6 (88.8-95.2)
1 year		4516	89.1 (88.2-89.9)		231	85.2 (80.4-89.0)
5 years		4131	87.1 (86.2-88.0)		200	77.1 (71.6-81.7)
10 years		2910	86.7 (85.7-87.6)		145	76.7 (71.2-81.3)
15 years		1591	86.0 (85.0-87.0)		84	76.0 (70.3-80.7)
20 years		515	85.2 (84.1-86.3)		27	74.4 (67.8-79.8)
1 week	SV	34	94.4 (79.6-98.6)	TAPVR	60	93.8 (84.2-97.6)
1 month		32	88.9 (73.1-95.7)		55	85.9 (74.7-92.4)
1 year		28	77.8 (60.4-88.2)		45	70.3 (57.5-79.9)
5 years		24	69.4 (51.7-81.8)		42	70.3 (57.5-79.9)
10 years		18	66.4 (48.5-79.4)		37	70.3 (57.5-79.9)
15 years		10	57.7 (38.4-73.0)		24	70.3 (57.5-79.9)
20 years						70.3 (57.5-79.9)
1 week	HLH	28	35.4 (25.1-45.9)	CoA	246	95.4 (92-97.3)
1 month		18	22.8 (14.3-32.5)		231	89.5 (85.1-92.7)
1 year					218	84.5 (79.5-88.4)
5 years					202	82.2 (76.9-86.3)
10 years					161	81.7 (76.4-85.9)
15 years					91	81 (75.6-85.4)
20 years					30	80.1 (74.3-84.7)
1 week	HRH	12	83.3 (48.2-95.6)	IAA	30	90.9 (74.4-97.0)
1 month		12	83.3 (48.2-95.6)		30	72.7 (54.1-84.8)
1 year		10	66.7 (33.7-86)		24	60.6 (42.0-74.9)
5 years					20	60.6 (42.0-74.9)
10 years					17	60.6 (42.0-74.9)
15 years					13	60.6 (42.0-74.9)
20 years						
1 week	EA	24	88.9 (69.4-96.3)	DORV	19	86.4 (63.4-95.4)
1 month		23	85.2 (65.2-94.2)		18	81.8 (58.5-92.8)
1 year		21	77.8 (57.1-89.3)		15	68.2 (44.6-83.4)
5 years		17	70.4 (49.4-83.9)		12	59.1 (36.1-76.2)
10 years		13	70.4 (49.4-83.9)		10	59.1 (36.1-76.2)
15 years						
20 years						
1 week	TA	30	88.2 (71.6-95.4)	MVA	80	100 (-)
1 month		27	79.4 (61.6-89.6)		79	98.8 (91.5-99.8)
1 year		23	67.7 (49.2-80.6)		77	96.3 (88.8-98.8)
5 years		18	52.9 (35.1-68.0)		73	96.3 (88.8-98.8)
10 years		12	46.4 (29.0-62.1)		57	96.3 (88.8-98.8)
15 years					35	96.3 (88.8-98.8)
20 years						
1 week	PVA	32	78.1 (62.1-87.9)	VSD	2152	98.6 (98-99)

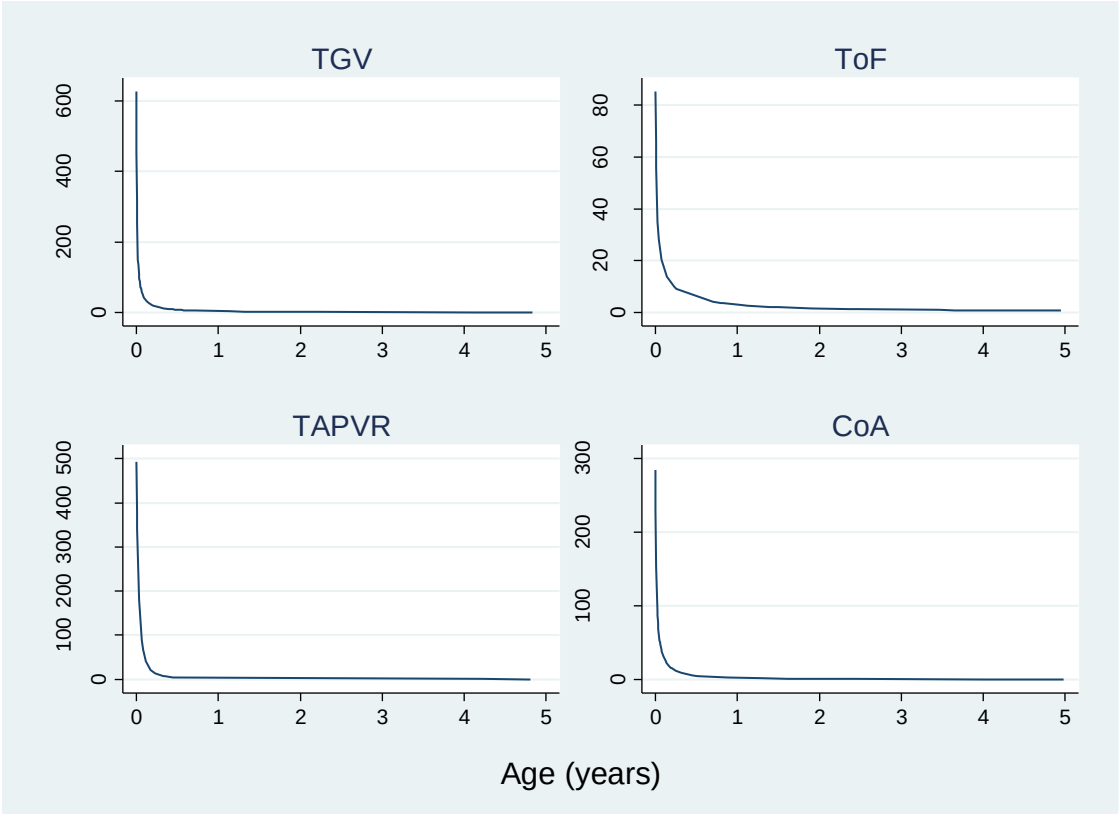
Age	Subtype	No at risk†	% Survival (95% CI)	Subtype	No at risk†	% Survival (95% CI)
1 month		31	75.6 (59.4-86.1)		2142	98.2 (97.5-98.7)
1 year		24	58.5 (42.1-71.8)		2106	96.5 (95.7-97.2)
5 years		18	48.3 (32.3-62.6)		1957	96.0 (95.1-96.7)
10 years		13	48.3 (32.3-62.6)		1308	95.7 (94.7-96.5)
15 years					656	95.6 (94.6-96.4)
20 years					189	94.9 (93.5-96.1)
1 week	CAT	46	88.5 (76.1-94.6)	ASD	417	98.8 (97.2-99.5)
1 month		32	61.5 (47.0-73.2)		416	98.6 (96.9-99.4)
1 year		17	32.7 (20.5-45.4)		407	96.5 (94.2-97.8)
5 years		16	32.7 (20.5-45.4)		365	95.2 (92.7-96.9)
10 years		11	32.7 (20.5-45.4)		225	94.6 (92.0-96.4)
15 years					119	94.0 (90.9-96.1)
20 years					43	94.0 (90.9-96.1)
1 week	AVSD	249	94.3 (90.8-96.5)	PVS	425	99.3 (97.8-99.8)
1 month		238	90.2 (85.9-93.2)		424	99.1 (97.5-99.7)
1 year		193	73.1 (67.3-78.0)		421	98.4 (96.6-99.2)
5 years		165	65.9 (59.8-71.3)		388	97.7 (95.7-98.7)
10 years		124	65.0 (58.9-70.4)		293	97.4 (95.3-98.5)
15 years		63	64.3 (58.1-69.8)		169	97.0 (94.7-98.3)
20 years		22	63.0 (56.4-68.9)		56	97.0 (94.7-98.3)
1 week	AVA/s	240	97.2 (94.2-98.6)	PDA	38	97.4 (83.2-99.6)
1 month		231	93.5 (89.6-96.0)		37	94.9 (81.0-98.7)
1 year		220	89.1 (84.5-92.4)		33	84.6 (68.9-92.8)
5 years		205	87.8 (83.1-91.3)		18	84.6 (68.9-92.8)
10 years		164	87.8 (83.1-91.3)			
15 years		113	85.9 (80.6-89.8)			
20 years		42	85.9 (80.6-89.8)			
1 week	TGV	207	93.2 (89.0-95.9)	Other	233	95.5 (92-97.5)
1 month		195	87.8 (82.8-91.5)		231	94.7 (91.0-96.9)
1 year		176	79.3 (73.3-84.1)		221	90.6 (86.2-93.6)
5 years		158	77.5 (71.4-82.4)		205	88.5 (83.8-91.9)
10 years		111	76.4 (70.2-81.5)		166	88.5 (83.8-91.9)
15 years		66	74.8 (68.3-80.2)		110	87.9 (83.0-91.5)
20 years		29	71.4 (63.1-78.1)		46	87.9 (83.0-91.5)

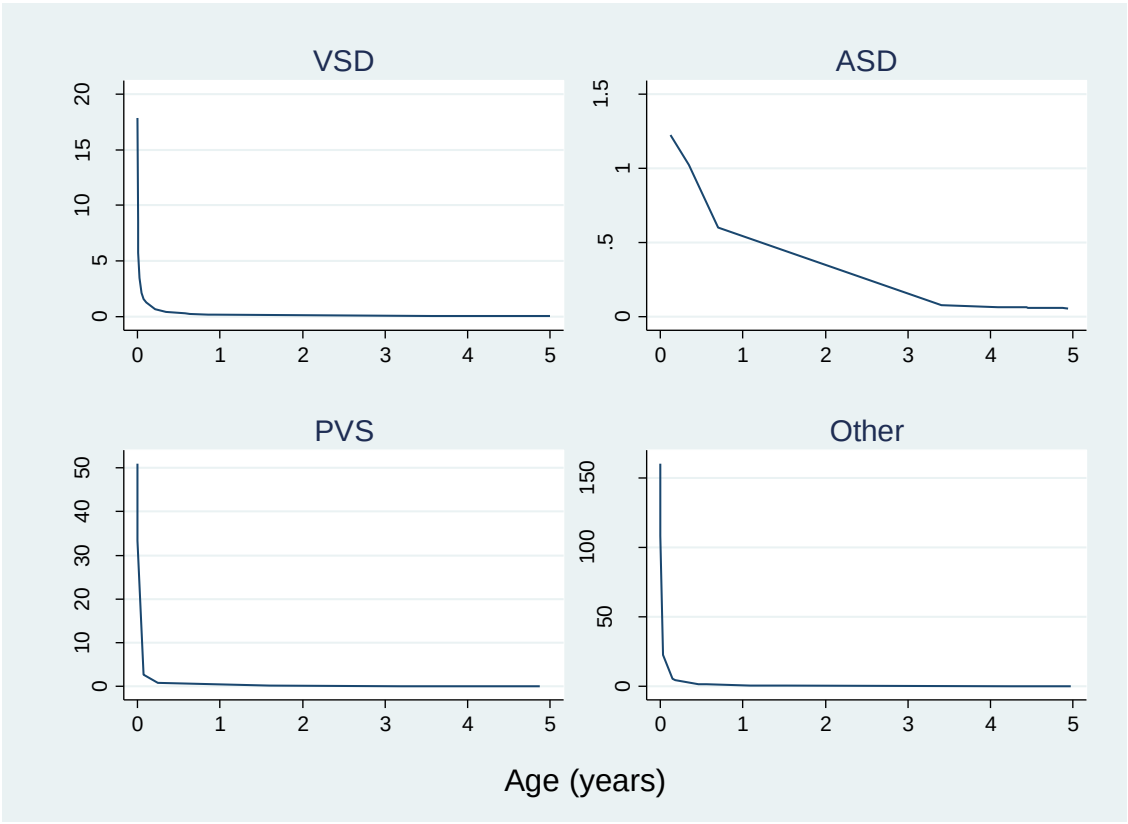
† Where the number at risk was <10 at the start of the interval and/or <5 at the end of the interval, the survival estimates are not presented. Survival estimates are not presented for HRH as there were too few cases at risk even at the first week of survival.

Figure 8.1 Smoothed hazard functions for cases of CHD up to age five, by CHD subtype*









It was not possible to plot the hazard functions for cases of HRH, IAA, MVA, DORV, PDA or "Other" CHD subtypes due to low case numbers. Hazard functions are shown for the first 5 years to better visualise the mortality rates at the time of the greatest risk.

8.3.2 Risk factors for mortality

8.3.2.1 Extra-cardiac anomalies

Survival to age 20 was 89.7% among individuals with isolated CHD, 65.9% among individuals with CHD and structural ECAs, and 63.8% among individuals with CHD and chromosomal/ genetic ECAs (Table 8.4).The risk of mortality varied significantly according to the presence of ECAs ($p<0.001$). Specifically, there was a 4.15 times greater risk of mortality in cases with structural ECAs and a 4.10 greater risk of mortality in cases with chromosomal/ genetic ECAs, compared to isolated cases of CHD (Table 8.5)

There was a significant difference in the unadjusted risk of mortality according to the presence of ECAs in cases of AVA/S ($p=0.002$), ToF ($p<0.001$), VSD ($p<0.001$), ASD ($p<0.001$), PVS ($p<0.001$) and "Other" CHD subtypes ($p<0.001$) (Table 8.5). In the multivariable analysis, the risk of mortality varied according to the presence of ECAs in cases of ToF ($p<0.001$), VSD ($p<0.001$) and all CHD subtypes combined ($p<0.001$) (Table 8.5). The risk of mortality was greater in cases with ECAs than in cases with isolated CHD. Generally, the risk of mortality was greater in cases with structural ECAs compared to cases with chromosomal/ genetic ECAs, although this was not the case for all CHD subtypes.

Table 8.4 Kaplan-Meier survival estimates, by CHD subtype and the presence of ECAs

Subtype	Age	No at risk†	Isolated CHD % Survival (95% CI)	No at risk†	CHD with structural ECAs % Survival (95% CI)	No at risk†	CHD with chromosomal/ genetic ECAs % Survival (95% CI)
CHD	1 week	4,068	97.3 (96.8-97.8)	251	87.8 (83.4-91.1)	548	91.0 (88.5-93.1)
	1 month	3,991	95.5 (94.8-96.1)	238	83.2 (78.4-87.1)	527	87.5 (84.6-89.9)
	1 year	3,865	92.4 (91.6-93.2)	205	71.7 (66.1-76.5)	446	74.1 (70.4-77.4)
	5 years	3,568	91.2 (90.3-92.0)	183	67.5 (61.7-72.6)	380	68.4 (64.5-72.0)
	10 years	2,519	90.9 (90.0-91.8)	131	66.3 (60.8-71.8)	260	66.7 (62.8-70.4)
	15 years	1,383	90.5 (89.5-91.3)	68	65.9 (59.9-71.1)	140	65.1 (60.9-68.9)
	20 years	434	89.7 (88.5-90.7)	32	65.9 (59.9-71.1)	49	63.8 (58.9-67.8)
SV	1 week	33	97.1 (80.9-99.6)				
	1 month	31	91.2 (75.1-97.1)				
	1 year	28	82.4 (64.9-91.7)				
	5 years	24	73.5 (55.3-85.3)				
	10 years	18	70.3 (51.8-82.8)				
	15 years	10	61.1 (40.8-76.3)				
HLH	1 week	26	35.6 (24.7-46.8)				
	1 month	17	23.3 (13.9-33.2)				
EA	1 week	21	87.5 (66.1-95.8)				
	1 month	20	83.3 (61.5-93.4)				
	1 year	18	75.0 (52.6-87.9)				
	5 years	16	70.8 (48.4-84.9)				
	10 years	12	70.8 (48.4-84.9)				
TA	1 week	25	92.6 (73.5-98.1)				
	1 month	23	85.2 (65.2-94.2)				
	1 year	21	77.8 (57.1-89.3)				
	5 years	17	63.0 (42.1-78.1)				
	10 years	12	59.3 (38.6-75.0)				
PVA	1 week	24	80.0 (60.8-90.5)				
	1 month	23	76.7 (60.8-90.5)				
	1 year	19	63.3 (43.7-77.8)				
	5 years	14	52.5 (33.2-68.6)				
	10 years	10	52.5 (33.2-68.6)				
CAT	1 week	36	91.7 (76.4-97.2)			10	90 (47.3-98.5)
	1 month	33	66.7 (48.8-79.5)				
	1 year	24	36.1 (21.0-51.4)				
	5 years	13	36.1 (21.0-51.4)				
	10 years	10	36.1 (21.0-51.4)				
AVSD	1 week	104	97.2 (91.6-99.1)	19	95.0 (69.5-99.3)	126	92.0 (86.0-95.5)
	1 month	97	90.7 (83.3-94.9)	17	85.0 (60.4-94.9)	124	90.5 (84.2-94.4)
	1 year	88	82.2 (73.6-88.3)	12	60.0 (35.7-77.6)	93	67.9 (59.4-75.0)
	5 years	78	76.6 (67.4-83.5)	11	55.0 (31.3-73.5)	76	59.1 (50.4-66.8)
	10 years	58	75.5 (66.2-82.7)	10	55.0 (31.3-73.5)	56	58.2 (49.4-65.9)

Subtype	Age	No at risk†	Isolated CHD % Survival (95% CI)	No at risk†	CHD with structural ECAs % Survival (95% CI)	No at risk†	CHD with chromosomal/ genetic ECAs % Survival (95% CI)
	15 years	33	75.5 (66.2-82.7)			27	56.7 (47.6-64.7)
	20 years					12	56.7 (47.6-64.7)
AVA/S	1 week	220	97.4 (94.2-98.8)			14	93.3 (61.3-99)
	1 month	214	94.7 (90.8-97.0)			11	86.7 (56.4-96.5)
	1 year	205	90.7 (86.1-93.8)				
	5 years	190	89.4 (84.6-92.8)				
	10 years	151	89.4 (84.6-92.8)				
	15 years	103	87.2 (81.7-91.0)				
	20 years	40	87.2 (81.7-91.0)				
TGV	1 week	190	94.1 (89.78-96.6)	12	85.7 (53.9-96.2)		
	1 month	179	88.6 (83.4-92.3)	11	78.6 (47.3-92.5)		
	1 year	163	80.7 (74.5-85.5)				
	5 years	145	78.7 (72.4-83.7)				
	10 years	104	78.1 (71.7-83.2)				
	15 years	62	76.4 (69.7-81.8)				
	20 years	25	72.5 (63.4-79.6)				
ToF	1 week	187	97.9 (94.5-99.2)	31	86.11 (69.8-94.0)	38	86.4 (72.1-93.6)
	1 month	184	96.3 (92.5-98.2)	30	83.3 (66.6-92.1)	37	84.1 (69.5-92.1)
	1 year	176	92.2 (87.3-95.2)	23	63.9 (46.1-77.2)	32	72.7 (57.0-83.5)
	5 years	157	85.3 (79.4-89.6)	17	50.0 (32.9-64.9)	26	63.6 (47.7-75.9)
	10 years	115	84.7 (78.8-89.1)	14	50.0 (32.9-64.9)	16	63.6 (47.7-75.9)
	15 years	67	84.7 (78.8-89.1)				
	20 years	20	82.5 (74.7-88.1)				
TAPVR	1 week	51	92.7 (81.8-97.2)				
	1 month	48	87.3 (75.2-93.7)				
	1 year	40	72.7 (58.9-82.6)				
	5 years	37	72.7 (58.9-82.6)				
	10 years	33	72.7 (58.9-82.6)				
	15 years	21	72.7 (58.9-82.6)				
CoA	1 week	210	97.2 (93.9-98.7)	14	77.8 (51.0-91.0)	22	91.7 (69.5-97.8)
	1 month	200	92.6 (88.2-95.4)	11	61.1 (35.3-79.2)	20	83.3 (61.5-97.9)
	1 year	189	87.5 (82.3-91.3)			18	75.0 (52.6-93.4)
	5 years	174	85.2 (79.7-89.3)			17	70.8 (48.4-87.9)
	10 years	141	84.7 (79.1-88.8)			14	70.8 (48.4-84.9)
	15 years	77	84.7 (79.1-88.8)				
	20 years	25	83.5 (77.4-88.1)				
IAA	1 week	16	84.2 (58.7-94.6)			12	100
	1 month	12	63.2 (37.9-80.4)			10	92.3 (56.6-98.9)
	1 year	10	52.6 (28.7-71.9)				
DORV	1 week	13	92.9 (59.1-99)				
	1 month	12	85.7 (53.9-96.2)				

Subtype	Age	No at risk†	Isolated CHD % Survival (95% CI)	No at risk†	CHD with structural ECAs % Survival (95% CI)	No at risk†	CHD with chromosomal/ genetic ECAs % Survival (95% CI)
	1 year	10	71.4 (40.6-88.2)				
MVA	1 week	74	100				
	1 month	73	98.6 (90.7-99.8)				
	1 year	71	97.3 (89.5-99.3)				
	5 years	54	97.3 (89.5-99.3)				
	10 years	33	97.3 (89.5-99.3)				
VSD	1 week	1,917	99.7 (99.4-99.9)	87	91.6 (83.9-95.7)	148	90.2 (84.6-93.9)
	1 month	1,913	99.5 (99.1-99.8)	85	90.5 (82.6-95.0)	143	87.2 (81.0-91.5)
	1 year	1,903	99.0 (98.5-99.4)	72	86.3 (77.6-91.8)	121	73.8 (66.3-79.8)
	5 years	1,778	98.9 (98.3-99.3)	75	84.2 (75.2-90.2)	104	68.9 (61.2-75.4)
	10 years	1,187	98.8 (98.1-99.2)	52	81.6 (72.1-88.2)	69	68.1 (60.3-74.7)
	15 years	589	98.8 (98.1-99.2)	25	81.6 (72.1-88.2)	42	67.0 (59.0-73.8)
	20 years	166	98.0 (96.4-98.9)	11	81.6 (72.1-88.2)	12	67.0 (59.0-73.8)
ASD	1 week	337	100	18	93.8 (63.2-99.1)	62	93.9 (84.7-97.7)
	1 month	337	100	17	93.8 (63.2-99.1)	60	93.9 (84.7-97.7)
	1 year	333	98.8 (96.7-99.6)	14	81.3 (52.3-93.5)	54	90.9 (80.9-95.8)
	5 years	299	98.2 (96.1-99.2)	12	81.3 (52.3-93.5)	30	86.3 (75.3-92.6)
	10 years	189	98.2 (96.1-99.2)			11	82.5 (70.5-90.0)
	15 years	105	98.2 (96.1-99.2)				
	20 years	38	98.2 (96.1-99.2)				
PVS	1 week	380	99.5 (97.8-99.9)	15	93.8 (63.2-99.1)	30	100
	1 month	379	99.2 (97.5-99.7)	13	93.8 (63.2-99.1)	30	100
	1 year	378	99.0 (97.2-99.6)	11	81.3 (52.5-93.5)	30	100
	5 years	249	98.4 (96.5-99.3)			26	96.7 (78.6-99.5)
	10 years	262	98.4 (96.5-99.3)			20	92.3 (72.1-98.0)
	15 years	149	98.4 (96.5-99.3)			11	86.5 (62.7-95.6)
	20 years	47	98.4 (96.5-99.3)				
PDA	1 week	11	100 (-)			19	95 (69.5-99.3)
	1 month	10	88.9 (43.3-98.4)			19	95 (69.5-99.3)
	1 year	10	88.9 (43.3-98.4)			19	90 (65.6-97.4)
	5 years					18	90 (65.6-97.4)
	10 years					10	85 (60.4-'4.9)
Other	1 week	186	98.4 (95.1-99.5)	20	80.0 (58.4-91.2)	27	90 (72.1-96.7)
	1 month	185	97.9 (94.4-99.2)	19	76.0 (54.2-88.4)	25	90 (72.1-96.7)
	1 year	180	95.7 (91.6-97.8)	16	64.0 (42.2-79.4)	21	83.3 (64.5-92.7)
	5 years	172	94.7 (90.3-97.1)	12	56 (34.8-72.7)	19	80.0 (60.8-90.5)
	10 years	136	94.7 (90.3-97.1)	11	80.0 (58.4-91.2)	12	80.0 (60.8-90.5)
	15 years	95	93.9 (89.1-96.6)				
	20 years	36	93.9 (89.1-96.6)				

† Where the number at risk was <10 at the start of the interval and/or <5 at the end of the interval, the survival estimates are not presented. Survival estimates are not presented for HRH as there were too few cases at risk even at the first week of survival.

Table 8.5 Hazard ratios of the presence of ECAs, according to CHD subtype

Subtype	Type of ECA (compared to isolated CHD)	Univariable models HR (95% CI)	P-value	Multivariable models† HR (95% CI)	P-value
CAT	Structural	-		-	
	Chromosomal	1.29 (0.55-3.00)	0.507	-	
AVSD	Structural	2.11 (0.99-4.49)	0.015	2.05 (0.95-4.44)	0.039
	Chromosomal	1.90 (1.21-3.00)		1.75 (1.1-2.77)	
AVAs	Structural	-		-	
	Chromosomal	3.9 (1.62-9.56)	0.002	3.1 (1.23-7.84)	0.017
TGV	Structural	1.76 (0.70-4.23)	0.209	1.90 (0.70-5.13)	0.271
	Chromosomal	-		-	
ToF	Structural	4.45 (2.50-7.91)	<0.001	3.12 (1.61-6.05)	<0.001
	Chromosomal	2.81 (1.53-5.16)		2.93 (1.55-5.5)	
CoA	Structural	3.22 (1.43-7.27)	0.005	1.67 (0.67-4.14)	0.267
	Chromosomal	2.28 (1.05-4.92)		1.75 (0.8-3.81)	
IAA	Structural	-		-	
	Chromosomal	0.36 (0.10-1.33)	0.126	-	
DORV	Structural	-		-	
	Chromosomal	1.34 (0.26-6.90)	0.730	-	
VSD	Structural	15.1 (8.14-27.91)	<0.001	7.56 (3.99-14.34)	<0.001
	Chromosomal	29.61 (18.39-47.66)		17.68 (10.71-29.18)	
ASD	Structural	18.39 (5.60-60.41)	<0.001	-	
	Chromosomal	11.06 (4.15-29.49)		-	
PVS	Structural	12.76 (3.19-51.09)	0.001	-	
	Chromosomal	6.40 (1.60-25.59)		-	
PDA	Structural	-		-	
	Chromosomal	0.35 (0.08-1.58)		-	
Other	Structural	8.77 (3.86-19.93)	<0.001	-	
	Chromosomal	3.41 (1.28-9.08)		-	
All CHD	**Structural**	**4.15 (3.23-5.19)**	**<0.001**	**2.57 (2.04-3.24)**	**<0.001**
	Chromosomal	**4.10 (3.46-4.85)**		**3.02 (2.54-3.60)**	

*Cases with structural ECAs were excluded for cases of SV, HLH, HRH, EA, TA, PVA, CAT, AVA/S, TAPVR, IAA, DORV, MVA and PDA as there were <10 cases at risk in these strata. Cases with chromosomal/ genetic ECAs were excluded for cases of SV, HLH, HRH, EA, TA, PVA, TGV, TAPVR, DORV and MVA as there were <10 cases at risk in these strata.

†Adjusted for year of delivery, gestational age at delivery, standardised birth weight, prenatal diagnosis and annual TOPFA rate. Multivariable models were only fitted to cases of AVSD, AVA/S, TGV, ToF, CoA, VSD and all CHD subtypes combined, due to low sample sizes.

8.3.2.2 Year of delivery

Overall, the unadjusted risk of mortality decreased by 7% per years increase in year of delivery (HR=0.93, p<0.001) (Table 8.6). The association remained in the multivariable model, but with a slightly stronger effect size (aHR=0.91, p<0.001).

Of the CHD subtypes, there were no significant associations between year of delivery and mortality at the p<0.003 level (Table 8.6). However, there was a suggestion that more recent year of delivery was significantly associated with decreased risk of mortality in cases of CAT (HR=0.92, p=0.020), AVSD (HR=0.94, p=0.004), TGV (HR=0.93, p=0.004) and ASD (HR= 0.91, p=0.017). In the multivariable analysis, the effect sizes generally became greater (Table 8.6).

To summarise, the risk of mortality significantly decreased over time for all CHD subtypes combined. There was some evidence that the risk of mortality decreased over time for cases of TA, CAT, AVSD, TGV, ToF, IAA, MVA, ASD and PVS, although the associations did not reach the nominal significance level.

Table 8.6 Hazard ratios for year of delivery, by CHD subtype*

Subtype	Univariable models HR (95% CI); p-value)	Multivariable models† aHR (95% CI); p-value
SV	0.89 (0.77-1.02); p=0.098	-
HLH	0.95 (0.90-1.01); p=0.090	-
HRH	0.99 (0.82-1.20); p=0.953	-
EA	0.93 (0.80-1.09); p=0.385	-
TA	0.92 (0.81-1.03); p=0.148	-
PVA	1.01 (0.94-1.09); p=0.732	-
CAT	0.92 (0.85-0.98); p=0.015	-
AVSD	0.94 (0.90-0.98); p=0.004	0.91 (0.86-0.97); p=0.006
AVA/S	0.95 (0.88-1.02); p=0.141	0.89 (0.78-1.01); p=0.071
TGV	0.93 (0.88-0.98); p=0.004	0.88 (0.80-0.96); p=0.004
ToF	0.97 (0.93-1.02); p=0.280	0.91 (0.85-0.99); p=0.020
TAPVR	1.03 (0.94-1.13); p=0.486	-
CoA	1.01 (0.95-1.06); p=0.804	1.05 (0.98-1.13); p=0.131
IAA	0.89 (0.78-1.02); p=0.091	-
DORV	0.98 (0.85-1.13); p=0.746	-
MVA	0.88 (0.69-1.12); p=0.306	-
VSD	0.97 (0.93-1.01); p=0.126	0.93 (0.85-1.02); p=0.135
ASD	0.91 (0.85-0.98); p=0.017	-
PVS	0.90 (0.80-1.02); p=0.114	-
PDA	0.96 (0.84-1.10); p=0.535	-
Other	0.95 (0.89-1.03); p=0.202	-
All CHD	**0.93 (0.92-0.95); p<0.001**	**0.91 (0.89-0.93); p<0.001**

*Hazard ratios were estimated using Cox regression with three strata (isolated CHD, CHD with structural ECAs and CHD with chromosomal/ genetic ECAs). Structural ECAs were excluded for cases of SV, HLH, HRH, EA, TA, PVA, CAT, AVA/S, TAPVR, IAA, DORV, MVA and PDA as there were <10 cases at risk in these strata. Chromosomal/ genetic ECAs were excluded for cases of SV, HLH, HRH, EA, TA, PVA, TGV, TAPVR, DORV and MVA as there were <10 cases at risk in these strata.

† Adjusted for gestational age at delivery, standardised birth weight, prenatal diagnosis and annual TOPFA rate. Multivariable models were only fitted to cases of AVSD, AVA/S, TGV, ToF, CoA, VSD and all CHD subtypes combined, due to low sample sizes.

-Case numbers were too low to estimate the hazard ratio

8.3.2.3 Gestational age at delivery

Overall, the unadjusted risk of mortality decreased significantly by 12% per weeks increase in gestational age at delivery (HR=0.88, p<0.001). The association remained in the multivariable model (aHR=0.86, p<0.001) (Table 8.7).

The unadjusted risk of mortality decreased significantly with increasing gestational age at delivery in cases of AVSD (HR=0.85, p<0.001), TGV (HR=0.83, p<0.001), CoA (HR=0.85, p<0.001), VSD (HR=0.81, p<0.001) and "Other" CHD subtypes (HR=0.84, p<0.001). There was a suggestion that gestational age at delivery was associated with decreased risk of mortality amongst cases of HLH (HR=0.90, p=0.006), EA (HR=0.81, p=0.024) and IAA (HR=0.81, p=0.045). In general, the effect sizes decreased slightly in the multivariable models (Table 8.7).

To summarise, there was evidence that increased gestational age at delivery was associated with improved survival overall and in children with AVSD, TGV, CoA, VSD, and "Other" CHD subtypes. There was also some evidence of an association amongst cases of HLH, TA, CAT, IAA and PDA, although these did not reach statistical significance.

Table 8.7 Hazard ratios for gestational age at delivery, by CHD subtype*

Subtype	Univariable models HR (95% CI); p-value)	Multivariable models aHR (95% CI); p-value
SV	1.05 (0.85-1.31); p=0.626	-
HLH	0.90 (0.83-0.97); p=0.006	-
HRH	0.92 (0.74-1.16); p=0.495	-
EA	0.81 (0.68-0.97); p=0.024	-
TA	0.84 (0.68-1.05); p=0.124	-
PVA	0.85 (0.69-1.05); p=0.129	-
CAT	0.90 (0.8-1.01); p=0.066	-
AVSD	0.85 (0.8-0.91); p<0.001	0.84 (0.78-0.9); p<0.001
AVA/S	0.94 (0.8-1.1); p=0.424	0.92 (0.78-1.09); p=0.347
TGV	0.83 (0.76-0.9); p<0.001	0.78 (0.71-0.86); p<0.001
ToF	0.92 (0.83-1.01); p=0.086	0.93 (0.83-1.03); p=0.155
TAPVR	0.94 (0.73-1.21); p=0.641	-
CoA	0.85 (0.78-0.92); p<0.001	0.83 (0.76-0.91); p<0.001
IAA	0.81 (0.66-1); p=0.045	-
DORV	1.16 (0.84-1.61); p=0.37	-
MVA	0.79 (0.56-1.1); p=0.154	-
VSD	0.81 (0.77-0.85); p<0.001	0.79 (0.76-0.83); p<0.001
ASD	0.99 (0.82-1.2); p=0.920	-
PVS	0.94 (0.77-1.16); p=0.581	-
PDA	0.81 (0.61-1.08); p=0.16	-
Other	0.84 (0.76-0.93); p<0.001	-
All CHD	**0.88 (0.86-0.90); p<0.001**	**0.86 (0.84-0.88); p<0.001**

*Hazard ratios were estimated using Cox regression with three strata (isolated CHD, CHD with structural ECAs and CHD with chromosomal/ genetic ECAs). Structural ECAs were excluded for cases of SV, HLH, HRH, EA, TA, PVA, CAT, AVA/S, TAPVR, IAA, DORV, MVA and PDA as there were <10 cases at risk in these strata. Chromosomal/ genetic ECAs were excluded for cases of SV, HLH, HRH, EA, TA, PVA, TGV, TAPVR, DORV and MVA as there were <10 cases at risk in these strata.

† Adjusted for year of delivery, standardised birth weight, prenatal diagnosis and annual TOPFA rate. Multivariable models were only fitted to cases of AVSD, AVA/S, TGV, ToF, CoA, VSD and all CHD subtypes combined, due to low sample sizes.

-Case numbers were too low to estimate hazard ratio

8.3.2.4 Standardised birth weight

Overall, the unadjusted risk of mortality was significantly associated with standardised birth weight ($p<0.001$). The risk of mortality increased by 35% in cases with low standardised birth weight and decreased by 15% in cases with high standardised birth weight (HR=0.85), compared to average standardised birth weight (HR=1.35) (Table 8.8). The association remained significant in the multivariable model ($p<0.001$), although the effect size decreased slightly for cases with low birth weight (aHR=1.28) and increased slightly for cases with high birth weight (aHR=0.71).

There were no significant associations between mortality and standardised birth weight in any of the CHD subtypes. However, in cases of AVSD and VSD, there was a suggestion of an association (at the $p<0.05$ level, $p=0.005$ and $p=0.036$, respectively). Here, low standardised birth weight was associated with an increased risk of mortality in cases of AVSD (HR=1.83) and VSD (HR=1.51) and high standardised birth weight was associated with a decreased risk of mortality in cases of AVSD (HR=0.69) and VSD (HR=0.63). In the multivariable models, the association between standardised birth weight and mortality became significant in cases of AVSD ($p=0.002$). Again, cases with low birth weight were at increased risk of mortality and cases with higher birth weight were at decreased risk.

To summarise, there was evidence of an association between standardised birth weight and mortality in all CHD subtypes combined and in cases of AVSD. There was some evidence of an association amongst cases with CAT and VSD, although these did not reach statistical significance.

Table 8.8 Hazard ratios for standardised birth weight, by CHD subtype

Subtype	Birth weight	Univariable models		Multivariable models	
		HR (95% CI); p-value)	P-value	aHR (95% CI); p-value	P-value
SV	Low	1.70 (0.44-6.61)	0.742	-	
	High	1.22 (0.25-5.93)		-	
HLH	Low	1.20 (0.68-2.09)	0.413	-	
	High	0.72 (0.38-1.38)		-	
EA	Low	3.04 (0.14-66.98)	0.770	-	
	High	0.88 (0.11-7.35)		-	
TA	Low	0.82 (0.26-2.64)	0.946	-	
	High	0.98 (0.12-7.9)		-	
PVA	Low	1.81 (0.69-4.71)	0.396	-	
	High	0.79 (0.17-3.68)		-	
CAT	Low	0.74 (0.36-1.54)	0.510	-	
	High	0.56 (0.18-1.7)		-	
AVSD	Low	1.83 (1.2-2.79)	0.005	1.76 (1.15-2.69)	0.002
	High	0.69 (0.30-1.63)		0.46 (0.19-1.11)	
AVA/S	Low	1.22 (0.59-2.52)	0.493	1.42 (0.66-3.06)	0.379
	High	0.49 (0.11-2.13)		0.52 (0.12-2.33)	
TGV	Low	1.03 (0.52-2.04)	0.801	1.01 (0.5-2.05)	0.796
	High	1.27 (0.62-2.58)		0.78 (0.37-1.65)	
ToF	Low	1.10 (0.64-1.88)	0.929	0.98 (0.56-1.74)	0.892
	High	0.97 (0.4-2.35)		0.81 (0.33-1.99)	
TAPVR	Low	0.39 (0.11-1.4)	0.172	-	
	High	0.26 (0.03-1.96)		-	
CoA	Low	0.68 (0.34-1.37)	0.294	0.72 (0.36-1.44)	0.396
	High	1.35 (0.65-2.8)		1.32 (0.62-2.77)	
IAA	Low	1.74 (0.47-6.48)	0.682	-	
	High	1.72 (0.31-9.49)		-	
VSD	Low	1.51 (0.98-2.33)	0.036	1.28 (0.83-1.97)	0.018
	High	0.63 (0.30-1.34)		0.42 (0.19-0.91)	
ASD	Low	1.74 (0.73-4.14)	0.355	-	
	High	0.79 (0.17-3.62)		-	
PVS	Low	4.09 (1.14-14.62)	0.068	-	
	High	0.98 (0.11-8.76)		-	
PDA	Low	2.91 (0.48-17.8)	0.248	-	
	High	-		-	
Other	Low	2.84 (1.20-6.72)	0.050	-	
	High	2.34 (0.83-6.59)		-	
All CHD	**Low**	**1.35 (1.15-1.59)**	**<0.001**	**1.28 (1.08-1.51)**	**<0.001**
	High	**0.85 (0.67-1.09)**		**0.71 (0.56-0.91)**	

*Hazard ratios were estimated using Cox regression with three strata (isolated CHD, CHD with structural ECAs and CHD with chromosomal/ genetic ECAs). Structural ECAs were excluded for cases of SV, HLH, HRH, EA,

TA, PVA, CAT, AVA/S, TAPVR, IAA, DORV, MVA and PDA as there were <10 cases at risk in these strata. Chromosomal/ genetic ECAs were excluded for cases of SV, HLH, HRH, EA, TA, PVA, TGV, TAPVR, DORV and MVA as there were <10 cases at risk in these strata.

†Adjusted for year of delivery, gestational age at delivery, prenatal diagnosis and annual TOPFA rates. Multivariable models were only fitted to cases of AVSD, AVA/S, TGV, ToF, CoA, VSD and all CHD subtypes combined, due to low sample sizes.

-Case numbers were too low to estimate hazard ratio

8.3.2.5 Maternal age at delivery

Overall, there was a suggestion of an association between mortality and maternal age at delivery, with the risk of mortality decreasing by 2% per years increase in maternal age at delivery (HR=0.98, p=0.016). There was no association with maternal age in the multivariable model (aHR=1.00, p=0.542) (Table 8.9).

In the univariable models, there were no statistically significant associations between mortality and maternal age in any of the CHD subtypes. However, for the majority of the subtypes, the unadjusted risk of mortality appeared to decrease slightly with increasing maternal age at delivery (Table 8.9). In the multivariable models, the effect sizes remained broadly similar and none of the associations reached statistical significance.

To summarise, there was evidence of a decreased risk of mortality with increasing maternal age, although this was likely caused by confounding. There was no evidence of an association when CHD subtypes were considered separately.

Table 8.9 Hazard ratios for maternal age at delivery, by CHD subtype

Subtype	Univariable models HR (95% CI); p-value)	Multivariable models aHR (95% CI); p-value
SV	1.02 (0.91-1.14); p=0.724	-
HLH	1.01 (0.97-1.05); p=0.646	-
HRH	0.93 (0.77-1.13); p=0.474	-
EA	1.01 (0.9-1.13); p=0.904	-
TA	0.93 (0.84-1.02); p=0.120	-
PVA	1 (0.94-1.06); p=0.895	-
CAT	1.01 (0.95-1.06); p=0.853	-
AVSD	1 (0.97-1.03); p=0.934	1.01 (0.98-1.04); p=0.484
AVA/S	0.99 (0.93-1.05); p=0.698	1.00 (0.93-1.07); p=0.891
TGV	0.97 (0.92-1.02); p=0.271	0.97 (0.92-1.03); p=0.348
ToF	1.02 (0.98-1.07); p=0.319	1.03 (0.98-1.07); p=0.284
TAPVR	1.04 (0.96-1.13); p=0.341	-
CoA	1.01 (0.96-1.06); p=0.716	1.00 (0.95-1.05); p=0.936
IAA	1.08 (0.98-1.19); p=0.137	-
DORV	1.00 (0.88-1.13); p=0.946	-
MVA	0.79 (0.56-1.11); p=0.169	-
VSD	0.97 (0.94-1.01); p=0.101	0.99 (0.96-1.02); p=0.602
ASD	0.97 (0.9-1.04); p=0.342	-
PVS	0.95 (0.85-1.06); p=0.343	-
PDA	0.96 (0.84-1.10); p=0.596	-
Other	0.96 (0.89-1.03); p=0.255	-
All CHD	**0.98 (0.97-1); p=0.016**	**1.00 (0.98-1.01); p=0.542**

*Hazard ratios were estimated using Cox regression with three strata (isolated CHD, CHD with structural ECAs and CHD with chromosomal/ genetic ECAs). Structural ECAs were excluded for cases of SV, HLH, HRH, EA, TA, PVA, CAT, AVA/S, TAPVR, IAA, DORV, MVA and PDA as there were <10 cases at risk in these strata. Chromosomal/ genetic ECAs were excluded for cases of SV, HLH, HRH, EA, TA, PVA, TGV, TAPVR, DORV and MVA as there were <10 cases at risk in these strata.

† Adjusted for year of delivery, gestational age at delivery, standardised birth weight, prenatal diagnosis and annual TOPFA rate. Multivariable models were only fitted to cases of AVSD, AVA/S, TGV, ToF, CoA, VSD and all CHD subtypes combined, due to low sample sizes.

-Case numbers were too low to estimate hazard ratio

8.3.2.6 Sex

Overall, there was no evidence that infant sex was associated with mortality (HR=0.98, p=0.840). This remained the case in the multivariable model (aHR=1.01, p=0.870)

In the univariable models, infant sex was not significantly associated with mortality in any of the CHD subtypes. However, there was a suggestion that male cases of CoA and TGV were at increased risk of mortality compared to female cases (HR=2.41, p=0.003 and HR=1.85, p=0.023, respectively) and that male cases of TAPVR were at decreased risk of mortality compared to female cases (HR=0.09, p=0.023). In the multivariable analysis, the effect size for cases of TGV decreased and the association was no longer significant at the $p<0.05$ level (aHR=1.26, p=0.454). However, the association remained similar for cases of CoA (aHR=2.35, p=0.006).

To summarise, there was some evidence that male cases of TGV and CoA were more likely to survive than their female counterparts. There was some evidence that male cases of TAPVR were less likely to survive compared to females.

Table 8.10 Hazard ratios for male versus female, by CHD subtype

Subtype	Univariable models HR (95% CI); p-value)	Multivariable models aHR (95% CI); p-value
SV	0.74 (0.2-2.75); p=0.650	-
HLH	1.09 (0.67-1.78); p=0.718	-
HRH	1.11 (0.16-7.88); p=0.919	-
EA	0.96 (0.22-4.31); p=0.960	-
TA	0.58 (0.2-1.69); p=0.318	-
PVA	1.55 (0.64-3.76); p=0.328	-
CAT	0.87 (0.45-1.69); p=0.682	-
AVSD	0.76 (0.51-1.14); p=0.179	0.91 (0.6-1.4); p=0.681
AVA/S	1.02 (0.48-2.17); p=0.964	0.98 (0.46-2.11); p=0.968
TGV	1.85 (1.09-3.15); p=0.023	1.37 (0.78-2.42); p=0.277
ToF	1.47 (0.9-2.4); p=0.121	1.58 (0.96-2.61); p=0.071
TAPVR	0.09 (0.01-0.71); p=0.022	-
CoA	2.41 (1.35-4.29); p=0.003	2.35 (1.28-4.31); p=0.006
IAA	1.43 (0.45-4.55); p=0.545	-
DORV	2.4 (0.58-9.83); p=0.225	-
VSD	0.93 (0.62-1.39); p=0.712	1.13 (0.75-1.71); p=0.548
ASD	1.26 (0.55-2.91); p=0.581	-
PVS	1.87 (0.58-6.1); p=0.297	-
PDA	3.85 (0.73-20.2); p=0.111	-
Other	1.57 (0.73-3.39); p=0.249	-
All CHD	**0.98 (0.85-1.14); p=0.840**	**1.07 (0.92-1.24); p=0.402**

*Hazard ratios were estimated using Cox regression with three strata (isolated CHD, CHD with structural ECAs and CHD with chromosomal/ genetic ECAs). Structural ECAs were excluded for cases of SV, HLH, HRH, EA, TA, PVA, CAT, AVA/S, TAPVR, IAA, DORV, MVA and PDA as there were <10 cases at risk in these strata. Chromosomal/ genetic ECAs were excluded for cases of SV, HLH, HRH, EA, TA, PVA, TGV, TAPVR, DORV and MVA as there were <10 cases at risk in these strata.

†Adjusted for year of delivery, gestational age at delivery, standardised birth weight, prenatal diagnosis, annual TOPFA rate. Multivariable models were only fitted to cases of AVSD, AVA/S, TGV, ToF, CoA, VSD and all CHD subtypes combined, due to low sample sizes.

-Case numbers were too low to estimate hazard ratio (MVA results not presented as case numbers were too low)

8.3.2.7 Deprivation

Overall, there was no evidence that deprivation was associated with the (unadjusted) risk of mortality (p=0.208). However, the risk of mortality was lower in the least deprived cases (HR=0.82). In the multivariable model, the association remained non-significant (p=0.465) and the effect size corresponding to the least deprived decreased slightly (aHR=0.89).

In both the univariable and multivariable models, there was no evidence of an association between mortality and deprivation in any of the CHD subtypes (Table 8.11).

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Table 8.11 HRs for moderate and least deprived compared to most deprived, by CHD subtype

Subtype	Deprivation	Univariable models		Multivariable models	
		HR (95% CI)	P-value	aHR (95% CI)	P-value
SV	Moderate	0.42 (0.09-2)	0.064	-	
	Least	4.43 (0.9-21.88)		-	
HLH	Moderate	1.25 (0.72-2.17)	0.371	-	
	Least	1.6 (0.8-3.2)		-	
EA	Moderate	1.13 (0.19-6.88)	0.636	-	
	Least	2.13 (0.42-10.8)		-	
TA	Moderate	0.57 (0.12-2.63)	0.350	-	
	Least	1.98 (0.57-6.84)		-	
PVA	Moderate	0.67 (0.25-1.83)	0.581	-	
	Least	0.54 (0.12-2.44)		-	
CAT	Moderate	0.82 (0.33-2.02)	0.159	-	
	Least	0.13 (0.02-1.05)		-	
AVSD	Moderate	0.73 (0.44-1.2)	0.165	0.97 (0.58-1.63)	0.987
	Least	0.59 (0.32-1.09)		1.03 (0.54-1.94)	
AVAs	Moderate	0.73 (0.31-1.7)	0.413	0.95 (0.39-2.31)	0.494
	Least	0.47 (0.14-1.58)		0.47 (0.14-1.64)	
TGV	Moderate	1.29 (0.67-2.47)	0.695	1.54 (0.79-3)	0.449
	Least	1.23 (0.62-2.44)		1.19 (0.59-2.38)	
ToF	Moderate	1.81 (1.06-3.09)	0.035	1.68 (0.93-3.01)	0.060
	Least	0.63 (0.25-1.6)		0.56 (0.21-1.44)	
TAPVR	Moderate	0.6 (0.2-1.86)	0.563	-	
	Least	0.48 (0.06-3.71)		-	
CoA	Moderate	1.12 (0.6-2.09)	0.743	1.21 (0.64-2.26)	0.772
	Least	0.77 (0.32-1.89)		0.89 (0.35-2.24)	
IAA	Moderate	0.61 (0.08-4.93)	0.766	-	
	Least	1.4 (0.36-5.38)		-	
DORV	Moderate	0.65 (0.12-3.62)	0.885	-	
	Least	-		-	
MVA	Least	2.42 (0.15-38.64)	0.533	-	
VSD	Moderate	1.05 (0.66-1.68)	0.738	1.13 (0.7-1.84)	0.598
	Least	0.80 (0.42-1.52)		0.78 (0.4-1.51)	
ASD	Moderate	1.75 (0.74-4.12)	0.164	-	
	Least	0.3 (0.04-2.28)		-	
PVS	Moderate	2.74 (0.77-9.76)	0.236	-	
	Least	0.74 (0.09-6.15)		-	
PDA	Moderate	1.5 (0.12-19.37)	0.313	-	
	Least	5.25 (0.57-48.04)		-	
Other	Moderate	1.19 (0.52-2.74)	0.823	-	
	Least	1.35 (0.48-3.82)		-	
All CHD	**Moderate**	**1.00 (0.84-1.2)**	**0.208**	**1.05 (0.88-1.25)**	**0.465**
	Least	**0.82 (0.65-1.03)**		**0.89 (0.71-1.12)**	

*Hazard ratios were estimated using Cox regression with three strata (isolated CHD, CHD with structural ECAs and CHD with chromosomal/ genetic ECAs). Structural ECAs were excluded for cases of SV, HLH, HRH, EA, TA, PVA, CAT, AVA/S, TAPVR, IAA, DORV, MVA and PDA as there were <10 cases at risk in these strata. Chromosomal/ genetic ECAs were excluded for cases of SV, HLH, HRH, EA, TA, PVA, TGV, TAPVR, DORV and MVA as there were <10 cases at risk in these strata.

HRs were not estimated for HRH due to low case numbers

† Adjusted for year of delivery, gestational age at delivery, standardised birth weight, prenatal diagnosis and annual TOPFA. Multivariable models were only fitted to cases of AVSD, AVA/S, TGV, ToF, CoA, VSD and all CHD subtypes combined, due to low sample sizes.

-Case numbers were too low to estimate hazard ratio

8.3.2.8 Prenatal Diagnosis

Overall, the unadjusted risk of mortality was almost four times greater in cases that were prenatally diagnosed, compared to those that were postnatally diagnosed (HR=3.85, p<0.001). In the multivariable model, the effect size increased and the association remained significant (aHR=4.65, p<0.001).

In the univariable models, the risk of mortality was significantly increased in prenatally compared to postnatally diagnosed cases of AVA/S (HR=7.91, p<0.001), VSD (HR=4.17, p<0.001), PVS (HR=22.51 increased, p<0.001). There was a suggestion that the unadjusted risk of mortality was significantly greater in prenatally compared to postnatally diagnosed cases of EA (HR=7.43, p=0.010), PVA (HR=4.86, p=0.014), AVSD (HR=1.95, p=0.014), ToF (HR=2.25, p=0.020), CoA (HR=2.46, p=0.044) and MVA (HR=51.62, p=0.006). As shown in Table 8.12, the associations remained statistically significant in the multivariable models, although the effect sizes increased.

To summarise, prenatally diagnosed cases of AVA/S, VSD and PVS were less likely to survive than postnatally diagnosed cases. There was some evidence that prenatally diagnosed cases of EA, PVA, AVSD, ToF, CoA and MVA were less likely to survive.

Table 8.12 Hazard ratios for prenatal diagnosis compared to postnatal diagnosis, by CHD subtype

Subtype	Univariable models HR (95% CI); p-value)	Multivariable models aHR (95% CI); p-value
SV	1.58 (0.34-7.22); p=0.557	-
HLH	1.15 (0.67-1.97); p=0.612	-
HRH	9.49 (0.59-151.82); p=0.112	-
EA	7.43 (1.61-34.34); p=0.010	-
TA	1.21 (0.34-4.35); p=0.766	-
PVA	4.86 (1.72-13.75); p=0.003	-
CAT	1.75 (0.48-6.43); p=0.397	-
AVSD	1.95 (1.14-3.32); p=0.014	2.13 (1.13-4.00); p=0.019
AVA/S	7.91 (2.72-23.01); p<0.001	8.65 (2.81-26.67); p<0.001
TGV	0.93 (0.36-2.38); p=0.881	0.67 (0.25-1.80); p=0.426
ToF	2.25 (1.13-4.45); p=0.020	2.83 (1.29-6.2); p=0.010
TAPVR	-	-
CoA	2.46 (1.03-5.89); p=0.044	3.40 (1.34-8.62); p=0.01
IAA	-	-
DORV	0.81 (0.06-11.57); p=0.877	-
MVA	51.62 (3.1-860.41); p=0.006	-
VSD	4.17 (2.42-7.19); p<0.001	3.60 (2.06-6.29); p<0.001
PVS	22.51 (5.62-90.17); p<0.001	-
Other	1.32 (0.31-5.63); p=0.708	-
All CHD	**3.85 (3.13-4.73); p<0.001**	**4.65 (3.75-5.76); p<0.001**

*Hazard ratios were estimated using Cox regression with three strata (isolated CHD, CHD with structural ECAs and CHD with chromosomal/ genetic ECAs). Structural ECAs were excluded for cases of SV, HLH, HRH, EA, TA, PVA, CAT, AVA/S, TAPVR, IAA, DORV, MVA and PDA as there were <10 cases at risk in these strata. Chromosomal/ genetic ECAs were excluded for cases of SV, HLH, HRH, EA, TA, PVA, TGV, TAPVR, DORV and MVA as there were <10 cases at risk in these strata.

† Adjusted for year of delivery, gestational age at delivery, standardised birth weight, and prenatal diagnosis. Multivariable models were only fitted to cases of AVSD, AVA/S, TGV, ToF, CoA, VSD and all CHD subtypes combined, due to low sample sizes.

HRs not estimated for ASD and PDA as these are not possible to diagnose prenatally.

-Case numbers were too low to estimate hazard ratio

8.3.2.9 Plurality

Overall, there was no evidence of an association between plurality and mortality (p=0.667). However, the risk of mortality was increased in cases from multiple compared to singleton pregnancies (HR=1.29). In the multivariable model the association remained non-significant (p=0.267), but the effect changed direction, with cases from multiple pregnancies being at decreased risk of mortality compared to singletons (aHR=0.81).

Of the individual CHD subtypes, there was a significant association between plurality and mortality in cases of VSD only; cases from multiple pregnancies were at almost four-fold increased risk of mortality (aHR=3.54, p=0.001). In the multivariable model, the effect size decreased and the association was no longer statistically significant (aHR=1.43, p=0.368).

Table 8.13 Hazard ratios for cases from multiple compared to singleton pregnancies, by CHD subtype

Subtype	Univariable models HR (95% CI); p-value)	Multivariable models HR (95% CI); p-value
HLH	1.29 (0.40-4.14); p=0.667	-
HRH	1.23 (0.13-11.87); p=0.859	-
CAT	1.51 (0.43-5.31); p=0.523	-
AVSD	0.42 (0.06-3.05); p=0.394	0.18 (0.03-1.37); p=0.098
ToF	0.79 (0.25-2.53); p=0.691	0.60 (0.18-1.99); p=0.406
TAPVR	2.83 (0.57-13.99); p=0.201	-
CoA	1.73 (0.53-5.63); p=0.362	0.53 (0.13-2.21); p=0.381
VSD	3.54 (1.71-7.33); p=0.001	1.43 (0.66-3.11); p=0.368
ASD	0.78 (0.10-5.94); p=0.813	-
PDA	1.37 (0.95-1.97); p=0.096	-
All CHD	**1.29 (0.40-4.14); p=0.667**	**0.81 (0.55-1.18); p=0.267**

† Adjusted for year of delivery, gestational age at delivery, standardised birth weight, prenatal diagnosis and annual TOPFA rate. Multivariable models were only fitted to cases of AVSD, ToF, CoA, VSD and all CHD subtypes combined, due to low sample sizes.

*Hazard ratios were estimated using Cox regression with three strata (isolated CHD, CHD with structural ECAs and CHD with chromosomal/ genetic ECAs). Structural ECAs were excluded for cases of SV, HLH, HRH, CAT, TAPVR, and PDA as there were <10 cases at risk in these strata. Chromosomal/ genetic ECAs were excluded for cases of HLH, HRH and TAPVR as there were <10 cases at risk in these strata.

8.3.2.10 Annual TOPFA rate

Overall, the unadjusted risk of mortality significantly decreased with increasing annual TOPFA rate (p<0.001). Specifically for every percentage increase in TOPFA, the risk of mortality decreased by 15% (HR=0.85). In the multivariable model however, the effect size diminished and the association was not statistically significant (aHR=1.01, p=0.737).

There were no statistically significant associations between mortality and annual TOPFA rate for any of the individual CHD subtypes (Table 8.14). This remained the case in the multivariable models.

To summarise, when considering all CHD subtypes combined, the risk of mortality significantly increased with increasing annual TOPFA rate, but this was likely caused by confounding. There were no significant associations between annual TOPFA rate and mortality in the individual CHD subtypes.

Table 8.14 Hazard ratios for annual TOPFA rate, by CHD subtype

Subtype	Univariable models HR (95% CI); p-value)	Multivariable models HR (95% CI); p-value
SV	0.95 (0.9-1.01); p=0.117	-
HLH	0.99 (0.98-1); p=0.028	-
TA	1.01 (0.99-1.04); p=0.331	-
PVA	1 (0.96-1.04); p=0.935	-
CAT	0.98 (0.94-1.01); p=0.208	-
AVSD	0.99 (0.96-1.02); p=0.523	1.01 (0.83-1.24); p=0.892
AVA/S	1.01 (0.89-1.16); p=0.824	1.28 (0.85-1.92); p=0.234
TGV	0.82 (0.66-1.01); p=0.066	1.19 (0.88-1.6); p=0.258
ToF	1.00 (0.95-1.06); p=0.937	1.18 (0.94-1.47); p=0.155
CoA	0.95 (0.87-1.05); p=0.321	0.6 (0.44-0.83); p=0.002
VSD	1.02 (0.64-1.62); p=0.932	0.99 (0.83-1.18); p=0.919
PVS	1.32 (0.75-2.3); p=0.335	-
All CHD	**0.85 (0.81-0.9); p<0.001**	**1.01 (0.94-1.09); p=0.737**

*Hazard ratios were estimated using Cox regression with three strata (isolated CHD, CHD with structural ECAs and CHD with chromosomal/ genetic ECAs). Structural ECAs were excluded for cases of SV, HLH, TA, PVA, CAT and AVA/S as there were <10 cases at risk in these strata. Chromosomal/ genetic ECAs were excluded for cases of SV, HLH, TA, PVA and TGV as there were <10 cases at risk in these strata.

† Adjusted for year of delivery, gestational age at delivery, standardised birth weight, and prenatal diagnosis. Multivariable models were estimated for cases of AVSD, AVA/S, TGV, ToF, CoA, VSD and all subtypes combined only, due to small sample sizes.

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8.3.3 Sensitivity analysis

8.3.3.1 ECAs as strata

In this chapter, separate strata were fitted to isolated CHD, CHD with structural ECAs and CHD with chromosomal/ genetic ECAs. This approach was used to account for variation in survival between these categories, and variation in the baseline hazards. As shown in Figure 8.2, the proportional hazard assumption would have been violated had the presence of ECAs been simply incorporated into the models as explanatory variables. Specifically, cases with chromosomal ECAs appeared to have a slightly different survival curve over age, compared to isolated cases and cases with chromosomal/ genetic ECAs. Although the baseline hazards can vary between strata, the association with the explanatory variables is assumed to be the same. Therefore, interaction between ECAs and the explanatory variables were investigated.

There were significant interactions between year of delivery and the presence of ECAs ($p=0.001$). The risk of mortality decreased with increasing year of delivery for isolated CHD, CHD with structural ECAs and CHD with chromosomal/ genetic ECAs. However, the effect size was smaller in isolated cases compared to cases with ECAs (Figure 8.3).

Overall, there was a significant interaction between prenatal diagnosis and the presence of ECAs ($p<0.001$). As shown in Figure 8.4, the impact of prenatal diagnosis on mortality was greater in cases of CHD with structural ECAs, compared to cases of CHD with chromosomal/ genetic ECAs.

There were no significant interactions between ECAs and gestational age at delivery, standardised birth weight, maternal age at delivery, deprivation, annual TOPFA rate and infant sex.

Figure 8.2 Log-log plot of survival for all CHD subtypes combined

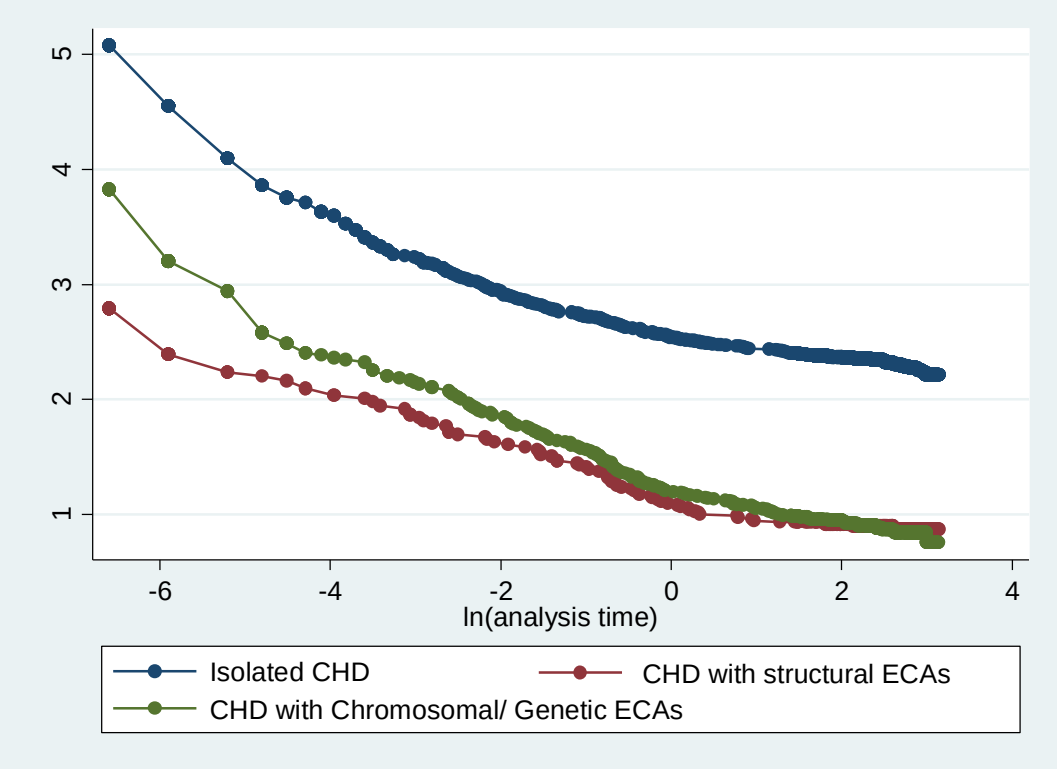


Figure 8.3 Margins for year of delivery according to presence of ECAs

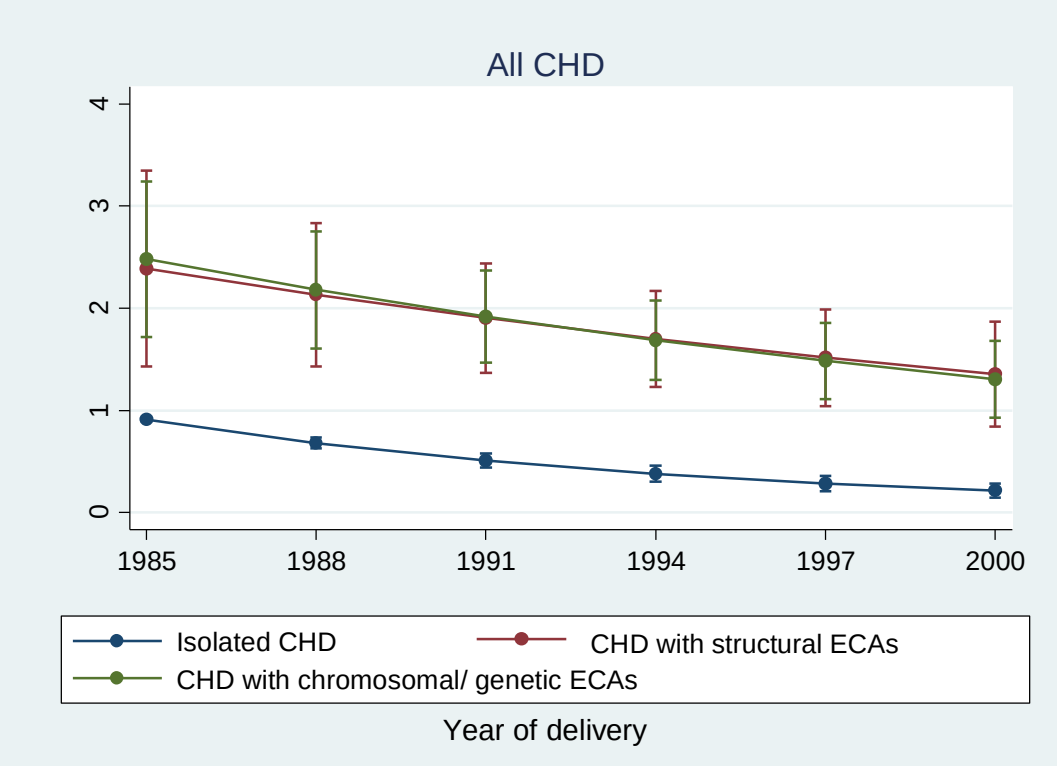
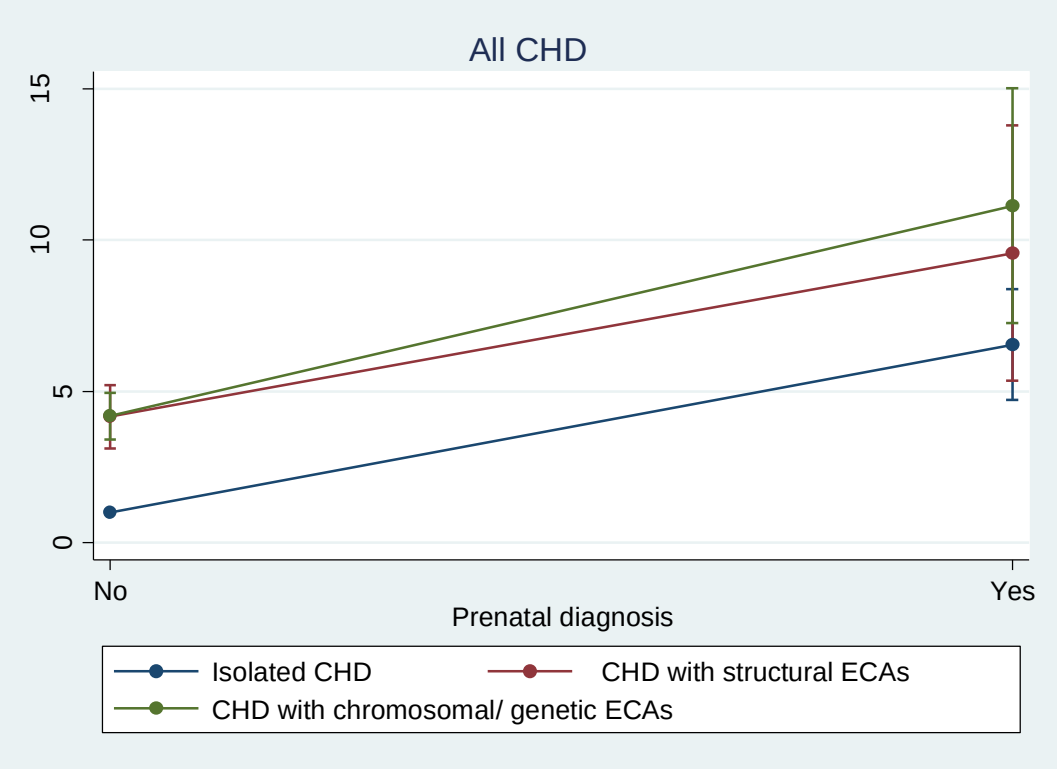


Figure 8.4 Margins for prenatal diagnosis according to the presence of ECAs



8.3.3.2 Interactions between risk factors

Overall, there was a significant interaction between gestational age at delivery and year of delivery ($p<0.001$). As shown in Figure 8.5, the risk of mortality for extremely preterm cases of CHD increased slightly over the study period but, decreased for all other gestational ages. There was also a significant interaction between prenatal diagnosis and year of delivery ($p=0.003$). As shown in Figure 8.6, the decrease in mortality over the study period was very slightly greater amongst postnatally diagnosed cases (aHR=0.91 compared to aHR=0.90).

Figure 8.5 Margins depicting the interaction between year of delivery and gestational age at delivery, for all CHD

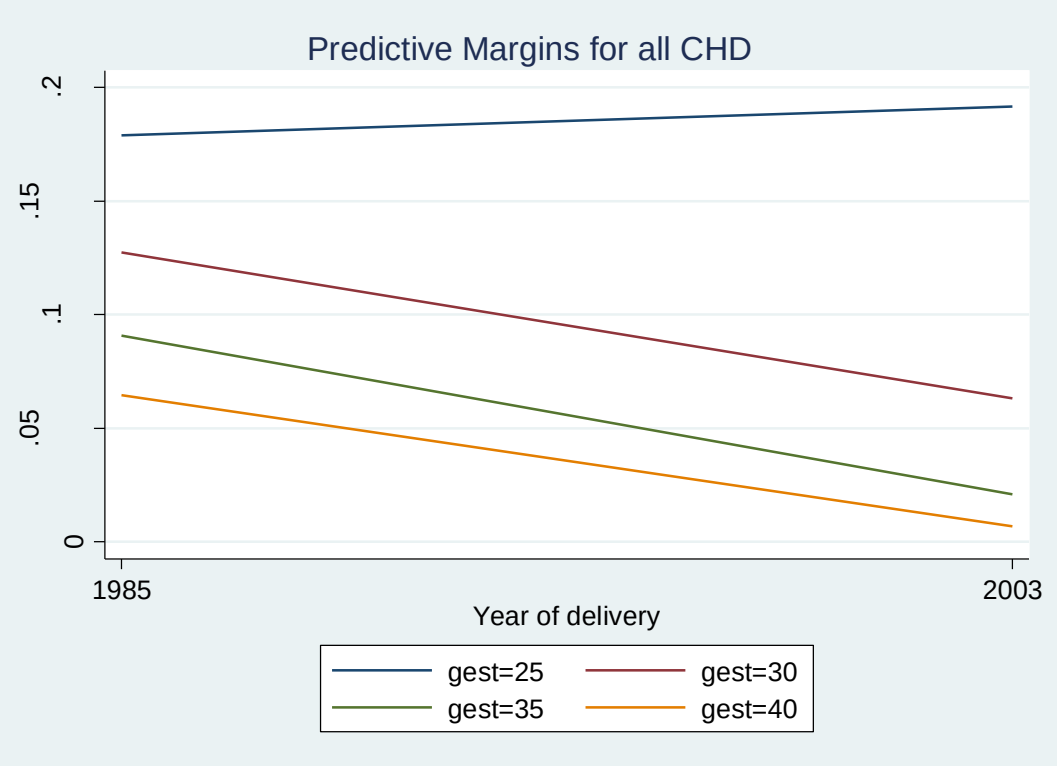
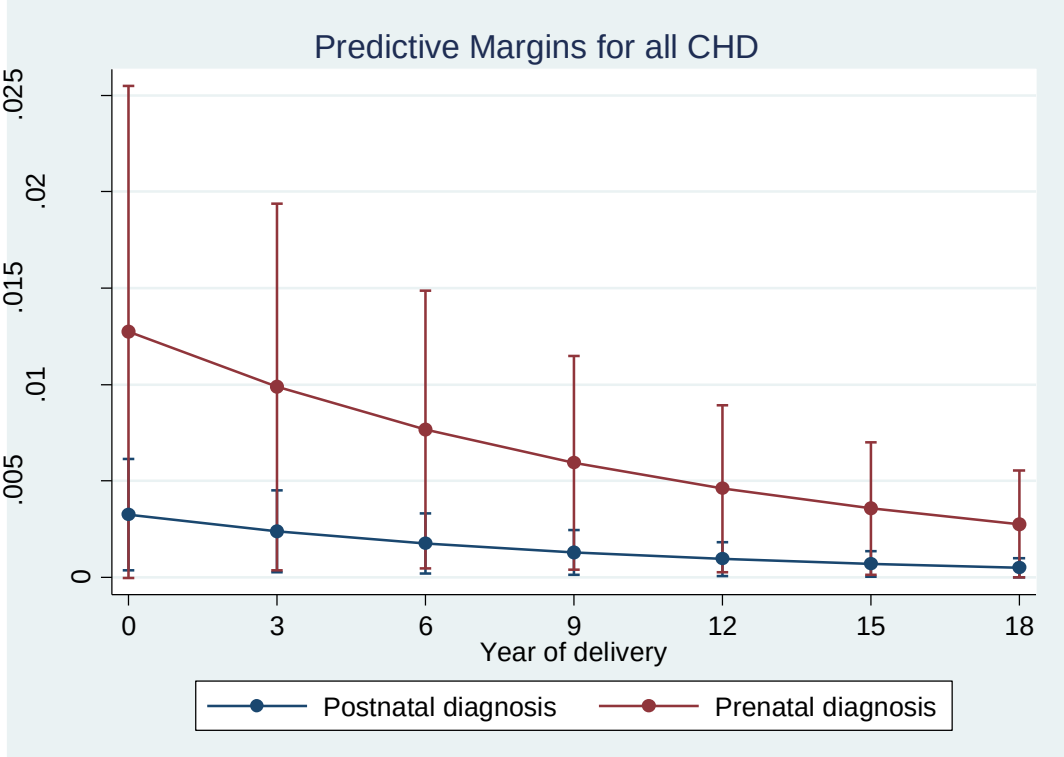


Figure 8.6 Margins depicting the interaction between year of delivery and prenatal diagnosis



8.3.3.3 Proportional hazards assumption

For the univariable models of year of delivery, gestational age at delivery, standardised birth weight, maternal age, sex, prenatal diagnosis and annual TOPFA rate the proportional hazards assumption was satisfied for all CHD subtypes (according to Therneau-Grambsch tests). However, using $p<0.05$ as the nominal significance level, there was evidence that some of the univariable models did not satisfy the proportional hazards assumption for certain subtypes (Table 8.15). The Schoenfield residuals were plotted against age (survival time) for these models (Figure 8.7). Here, standardised birth weight had a slightly greater impact on survival under age five for children born with AVA/S, TAPVR and VSD although the change in effect was relatively small. The effect of maternal age on survival of individuals with AVSD and all CHD combined was relatively stable with increasing age, with perhaps some evidence that maternal age had a slightly greater impact within the first five years of life. The effect of sex on survival of children with TGV and CoA was slightly lower within the first year of life, but remained stable thereafter. In cases of AVA/S, the effect of deprivation became less pronounced with increasing age. However, this effect is likely due to low case numbers of AVA/S at older ages.

With the exception of AVA/S, all of the multivariable models satisfied the proportional hazards assumption, on the basis of the Therneau-Grambsch tests (Table 8.16). But, using $p<0.05$ as the nominal significance level, there was evidence that the multivariable model for CAT did not satisfy the proportional hazards assumption. For both subtypes, the issue with proportionality was caused by standardised birth weight; the proportional hazards assumption was violated by the high birth weight babies (compared to the average birth weight babies) (Figure 8.8). This is likely due to the small proportion of babies with AVA/S and TGV with a high birth weight.

Table 8.15 Univariable models that did not satisfy the proportional hazard assumption at the p<0.05 level

Variable	CHD subtype	Therneau Grambsch test of proportional hazards: p-value
Standardised birth weight	AVA/S	0.034
	TAPVR	0.039
	VSD	0.017
Maternal age	AVSD	0.017
	All CHD	0.022
Sex	TGV	0.032
	CoA	0.016
Deprivation	AVA/S	0.043

Table 8.16 Test of proportional hazards assumption for all multivariable models, by CHD subtype

CHD subtype	Test of proportional hazards assumption; p-value
AVSD	0.887
AVA/S	<0.001
TGV	0.938
ToF	0.887
CoA	0.207
VSD	0.126
All CHD	**0.060**

Figure 8.7 Schoenfield residuals plotted against age for univariable models

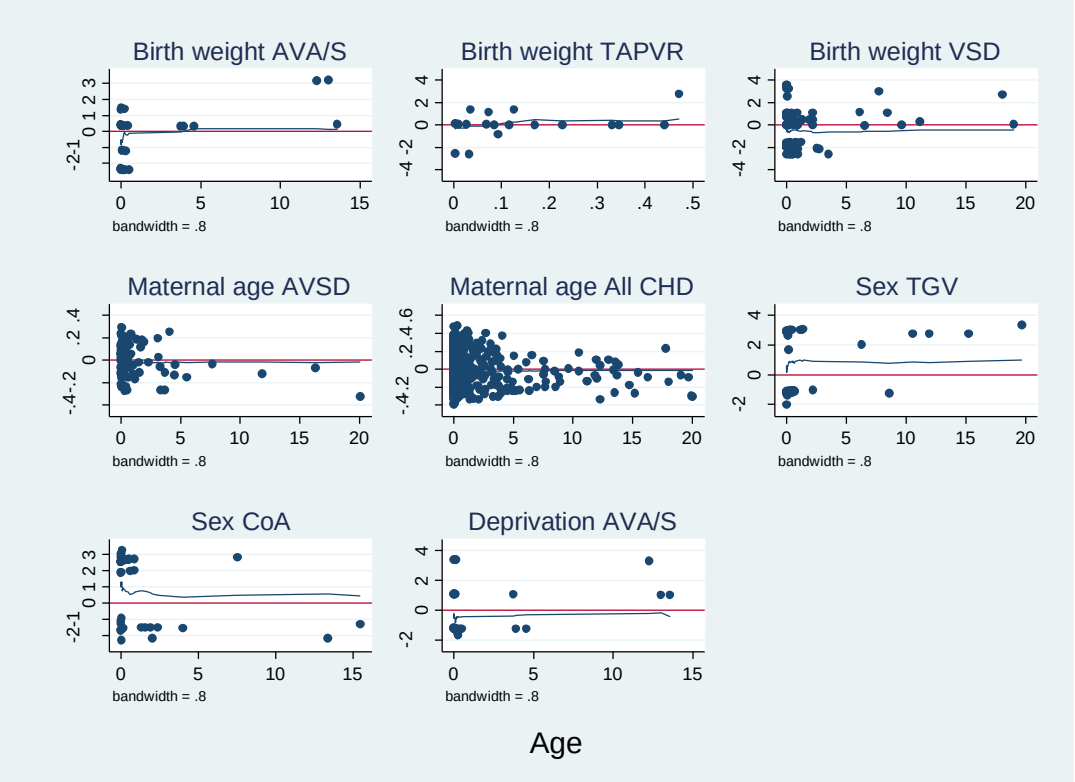
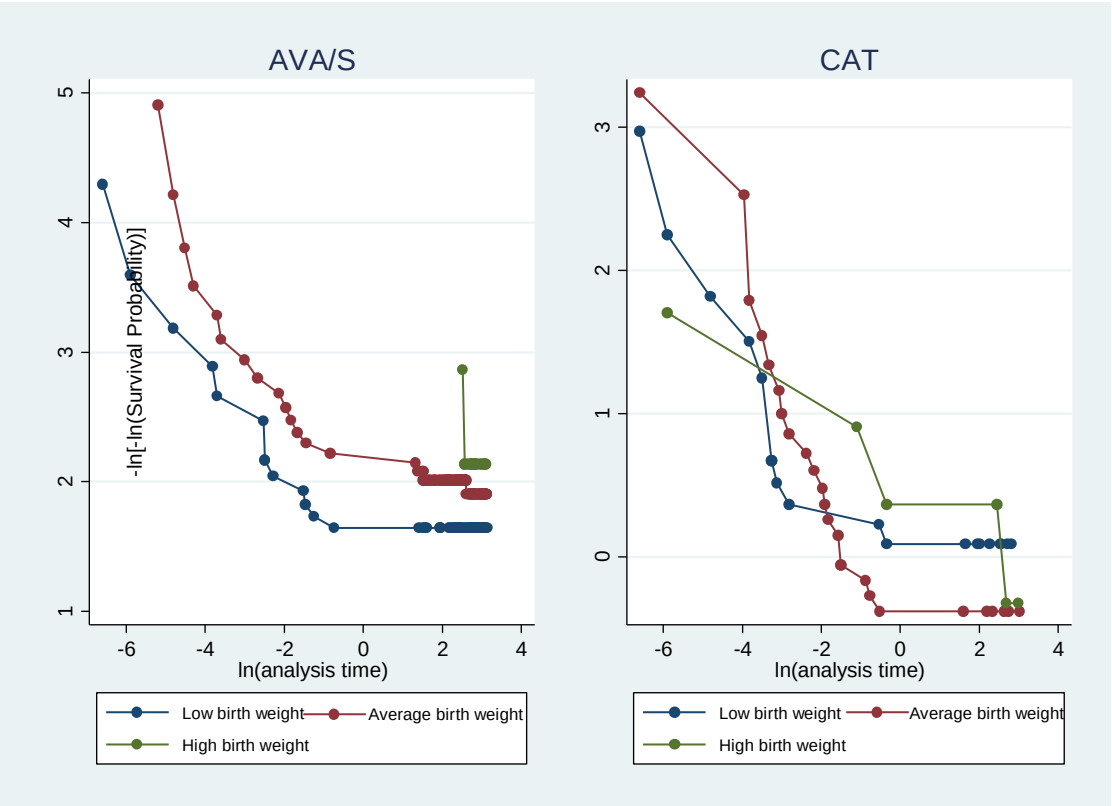


Figure 8.8 Log-log plot of survival according to standardised birth weight

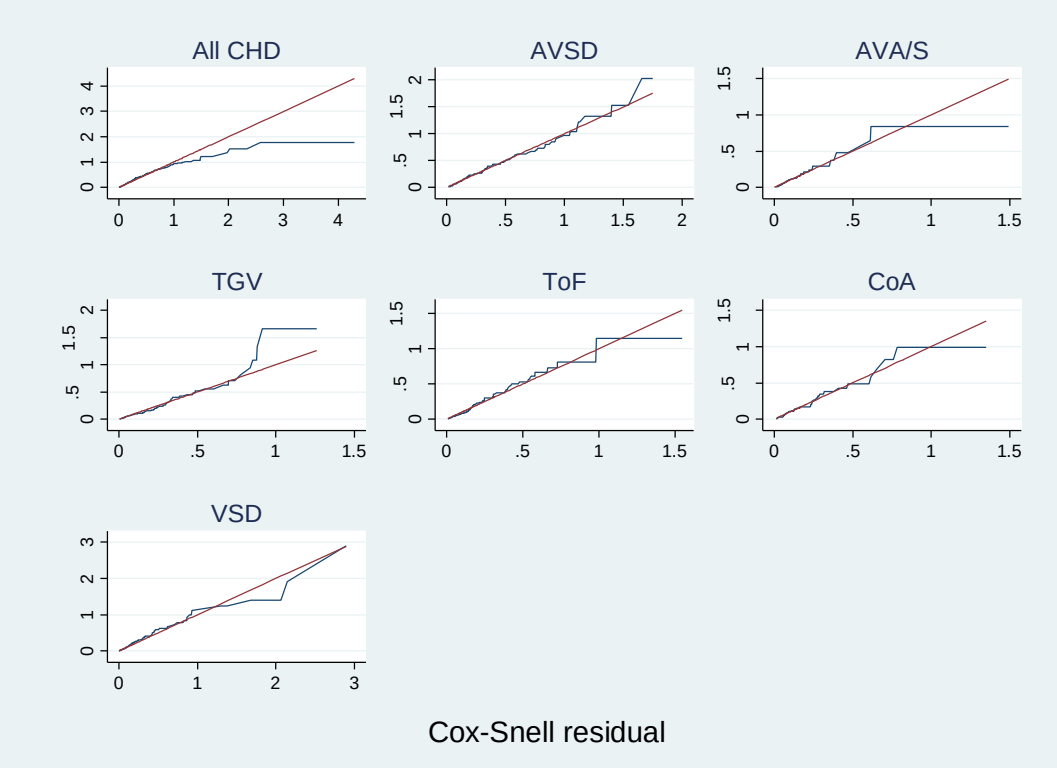


8.3.3.4 Model fit

Considering all CHD subtypes combined, the multivariable model fitted the data well for the smaller values of the Cox-Snell residuals (Figure 8.9). However, for older ages, the cumulative hazard function decreases and becomes lower than one, and the distribution does not follow the exponential function. This is perhaps unsurprising given that the CHD subtypes that comprise this composite group are very diverse.

For the individual subtypes, the multivariable models fit the data reasonably well (Figure 8.9). At older ages, the cumulative hazards functions deviate from the 45 degree line somewhat for AVA/S and TGV. However, this is expected due to high case censoring and low sample sizes in the tail of the data.

Figure 8.9 Cox Snell residuals plotted against the cumulative hazard, by CHD subtype



Cox Snell residuals were predicted from the multivariable models adjusted for year of delivery, gestational age at delivery, standardised birth weight, prenatal diagnosis and annual TOPFA rate. The blue line represents the cumulative hazard function. If the models are a good fit to the data, the hazard functions will have an exponential function with a hazard rate of one, graphically this means the hazard function will follow the forty five degree line (shown in red).

8.3.3.5 Linearity of continuous variables

The Lowess of the Martingale residuals is linear over maternal age at delivery overall and for the individual CHD subtypes (Figure 8.10 and Figure 8.11). The Lowess of the Martingale residuals over year of delivery is also linear overall and for each CHD subtype (Figure 8.13 and Figure 8.12). This suggests that the associations between mortality and maternal age at delivery, and mortality and year of delivery, are linear. Therefore, these variables can be modelled as a continuous explanatory variables.

The Lowess of the Martingale residuals over gestational age at delivery is linear for all CHD subtypes combined (Figure 8.15). For the majority of CHD subtypes, the Lowess is linear, meaning gestational age at delivery can be modelled as a continuous explanatory variable. However for SV, EA and PVA there is some evidence of non-linearity at the higher gestational ages of delivery. This is likely due to the low frequency of these subtypes, combined with the rarity of a gestational age at delivery >40 weeks.

Figure 8.10 Martingale residuals for maternal age at delivery for all CHD

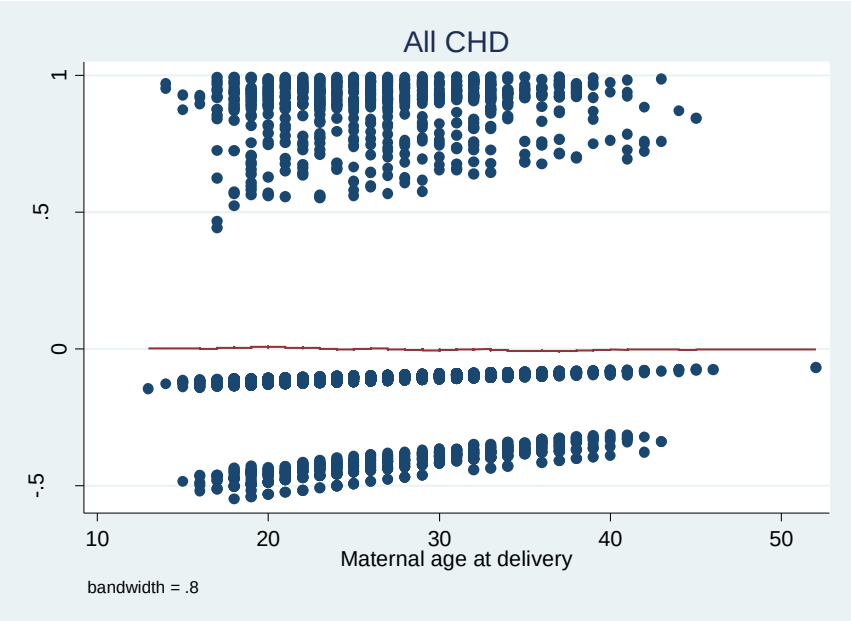


Figure 8.11 Martingale residuals for maternal age at delivery, by CHD subtype

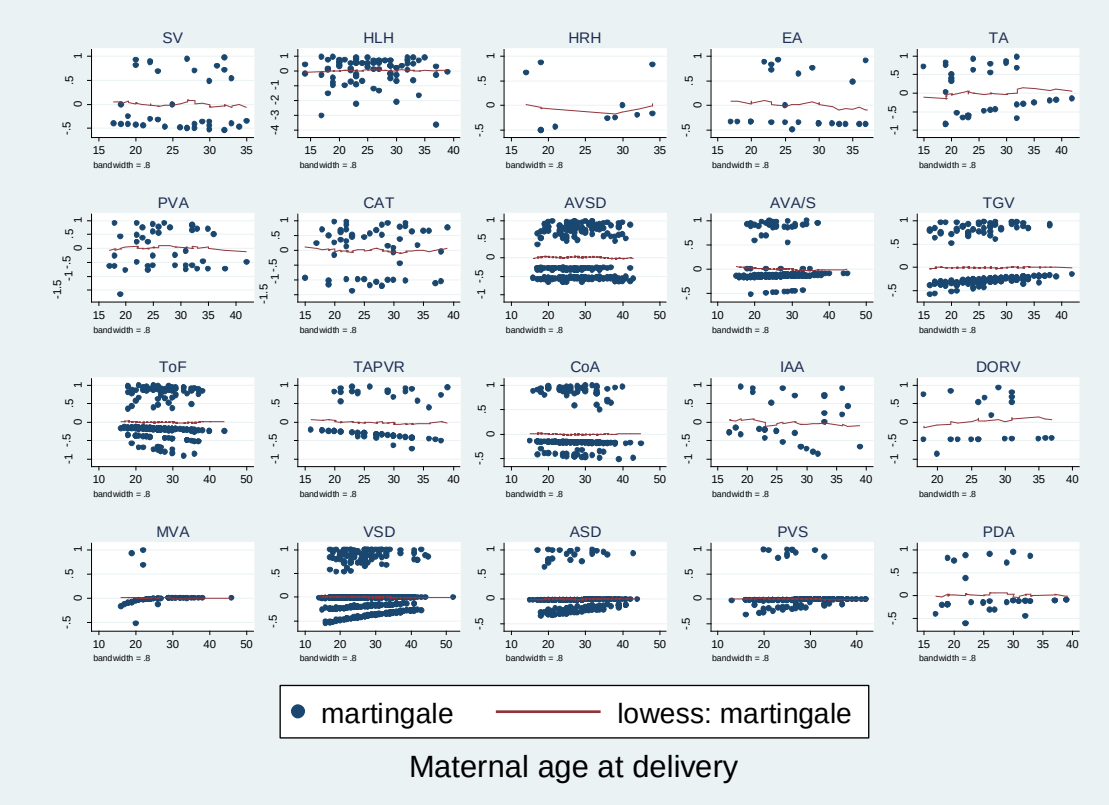


Figure 8.12 Martingale residuals for year of delivery, by CHD subtype

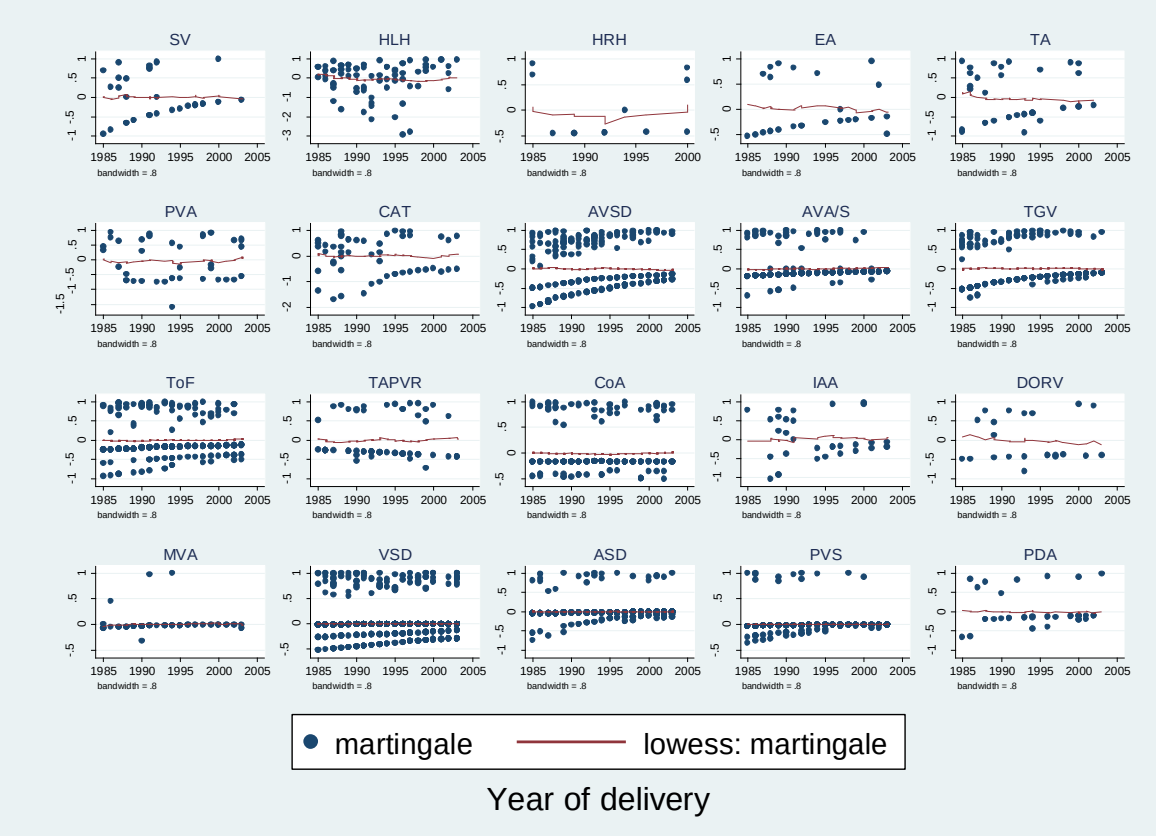


Figure 8.13 Martingale residuals for year of delivery, for all CHD

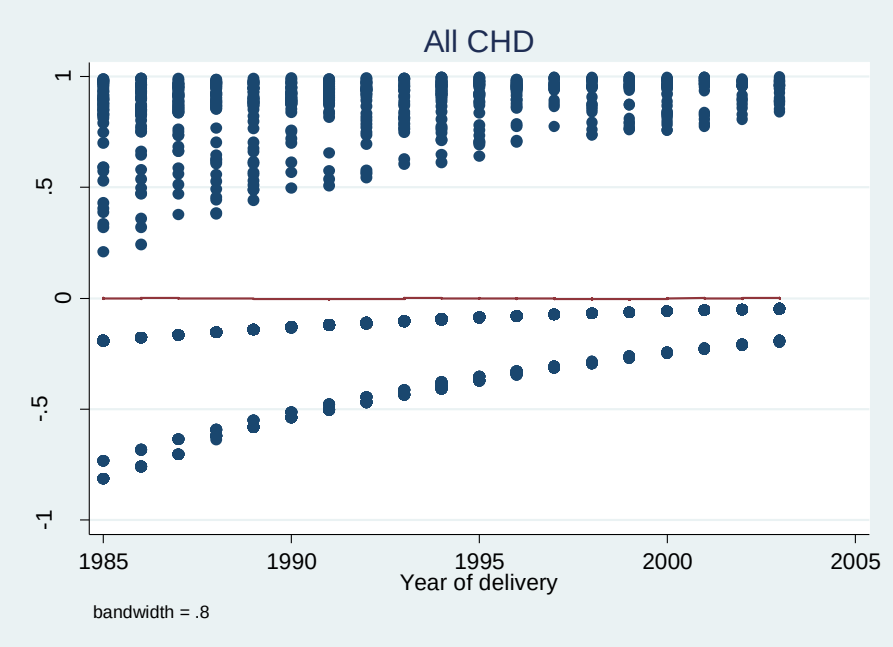


Figure 8.14 Martingale residuals for gestational age at delivery, by CHD subtype

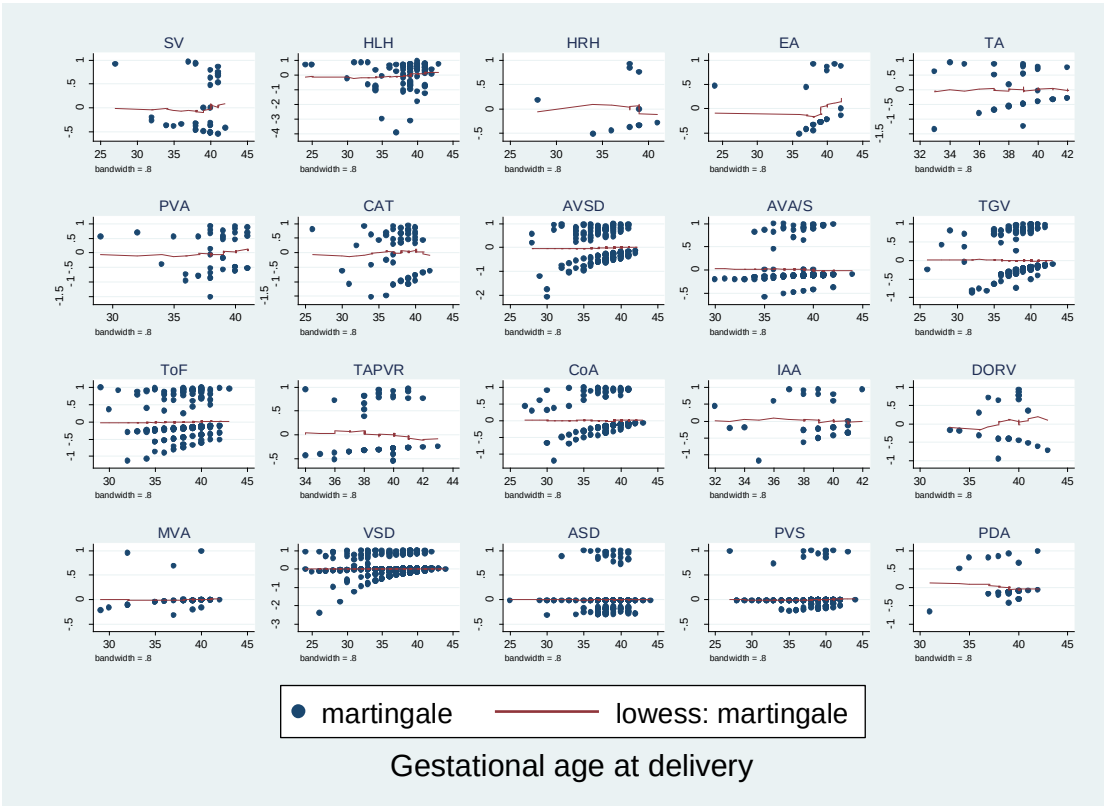
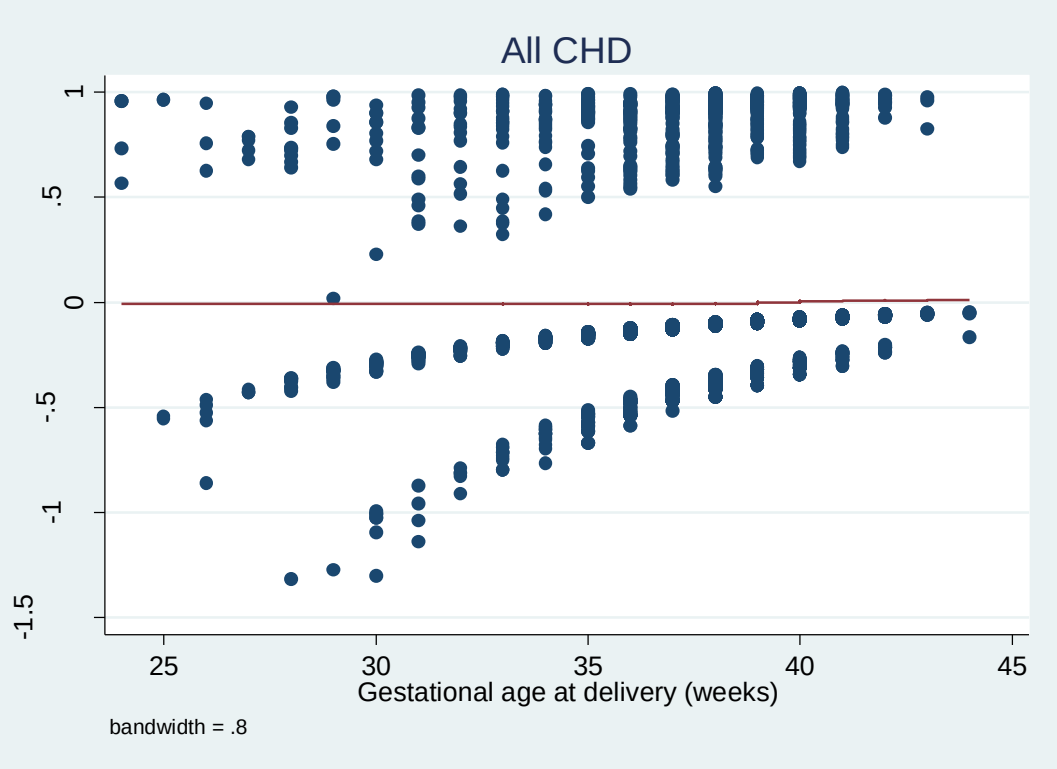


Figure 8.15 Martingale residuals for gestational age at delivery, for all CHD



8.3.4 Predicting survival

8.3.4.1 Predicting survival for cases born in or after 2003

The predicted 20 year survival of children born with isolated CHD (any subtype) in 2003 was 96.0% (Table 8.17). This was substantially higher than the Kaplan-Meier estimate of 89.7%, which was calculated for all cases regardless of year of delivery. With the exception of CoA and DORV, the 20 year survival estimates for children born in 2003 were greater than those produced using Kaplan-Meier estimates (Table 8.17). Indeed, survival of children with ASD (99.3%) and PVS (99.8%) exceeded that of the predicted survival of the general UK population born in 2003 (99.2%) [216].

Assuming the improvements in survival increased at the same rate as in the existing data, the predicted 20 year survival of children born with CHD (any subtype) in 2010 and 2015 was 98.0% and 98.7%, respectively. The predicted survival estimates for cases born in 2010 and 2015, by CHD subtype, are shown in Table 8.17.

Table 8.17 Predicted survival to age 20 for cases born in 2003 and 2010

CHD subtype	Delivered in 2003 Survival (95% CI)	Delivered in 2010 Survival (95% CI)	Delivered in 2015 Survival (95% CI)
SV	88.9 (46.2-98.2)	95.0 (42.8-99.7)	97.2 (40-99.9)
HLH*	8.9 (1.1-27.7)	16.7 (0.9-50.9)	23.7 (0.7-65.7)
HRH	65.3 (3.2-94.8)	66.4 (0-98.4)	67.2 (0-99.4)
EA	84.4 (32.9-97.4)	89.7 (15.4-99.4)	92.5 (6.3-99.8)
TA	95.0 (57.6-99.5)	98.6 (63-100)	99.4 (66.3-100)
PVA*	45.7 (12-74.9)	46.2 (2.8-84.6)	46.5 (0.5-89.6)
CAT	72.6 (31-91.6)	86.5 (36.9-97.9)	92.1 (40.9-99.2)
AVSD	82.2 (61.4-92.4)	86.8 (56.2-96.6)	89.4 (51.8-98.1)
AVA/S	93.1 (82.3-97.4)	95.3 (80.4-99)	96.5 (78.8-99.5)
TGV	85.7 (73-92.7)	90.7 (75.4-96.7)	93.2 (76.8-98.2)
ToF	93.8 (83.9-97.7)	96.9 (86.3-99.3)	98.1 (87.7-99.7)
CoA	62.9 (28.9-84.1)	54 (4.7-88.3)	47 (0.3-90.9)
TAPVR	86.4 (72.9-93.5)	88.1 (65.4-96.3)	89.2 (58.9-97.6)
IAA*	91.2 (37.7-99.1)	97.4 (38.2-99.9)	98.9 (38.1-100)
DORV	23.7 (0-80.1)	3.3 (0-86.7)	0.2 (0-90.5)
MVA	98.2 (60.8-99.9)	98.7 (8.2-100)	98.9 (0-100)
VSD	99.1 (97.5-99.7)	99.5 (97.5-99.9)	99.6 (97.4-99.9)
ASD	99.3 (96.1-99.9)	99.7 (95.2-100)	99.8 (94.4-100)
PVS	99.8 (97.1-100)	99.9 (97.1-100)	100 (97-100)
PDA	78.9 (6.6-98)	86.4 (0.5-99.6)	90.2 (0-99.9)
Other	97.5 (87.5-99.5)	98.6 (84.4-99.9)	99.1 (81.6-100)
All CHD	**96.0 (94.9-96.9)**	**98.0 (97-98.6)**	**98.7 (98-99.2)**

*Eleven year survival was estimated for HLH, survival for children with PVA and IAA was estimated up to age 19 and 6 months.

8.3.4.2 Predicting 30 year survival

Figure 8.16, shows the baseline survival curves at the average prognostic index for all isolated cases, according to CHD subtype. The predicted survival curves fit the raw data, depicted by the Kaplan-Meier curves, reasonably well. For all CHD subtypes combined, predicted survival over-estimated the Kaplan-Meier survival estimates. However, even at 20 years where the difference was greatest, the discrepancy is only 3% (predicted survival estimate: 89.7% (95% CI: 88.5-90.7) and Kaplan-Meier survival estimate: 92.8% (95% CI: 91.8-93.6)). Predicted survival was also over-estimated for cases of TA, TGV, AVSD and VSD, although here the predicted 95% confidence intervals overlapped the Kaplan-Meier 95% confidence intervals.

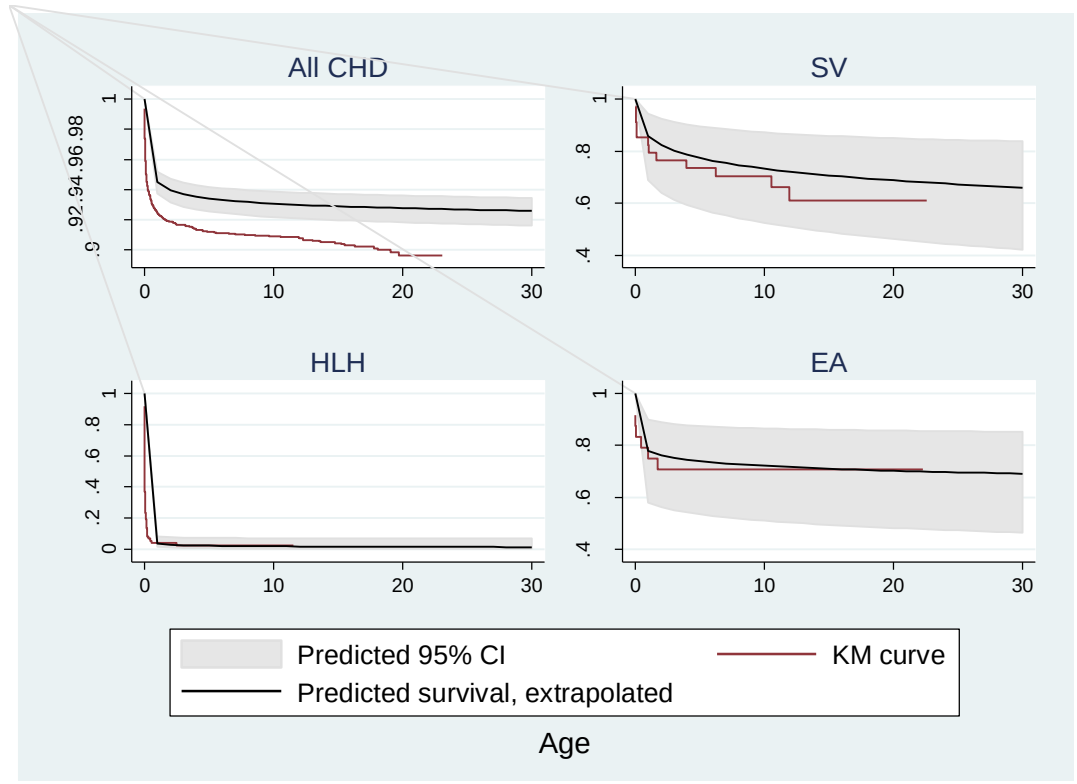
For all CHD subtypes, predicted 30 year survival was lower than predicted 20 year survival (Table 8.18). However, the decrease in predicted survival was relatively minimal.

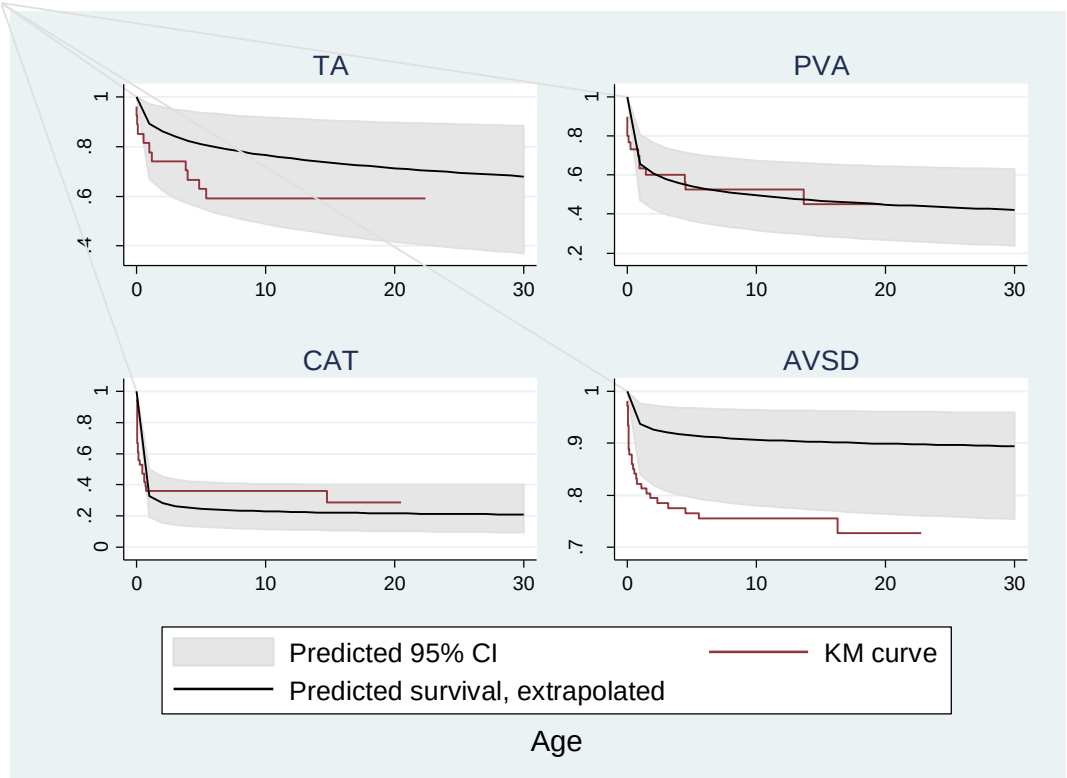
Table 8.18 Predicted 30 year survival of isolated CHD, by CHD subtype

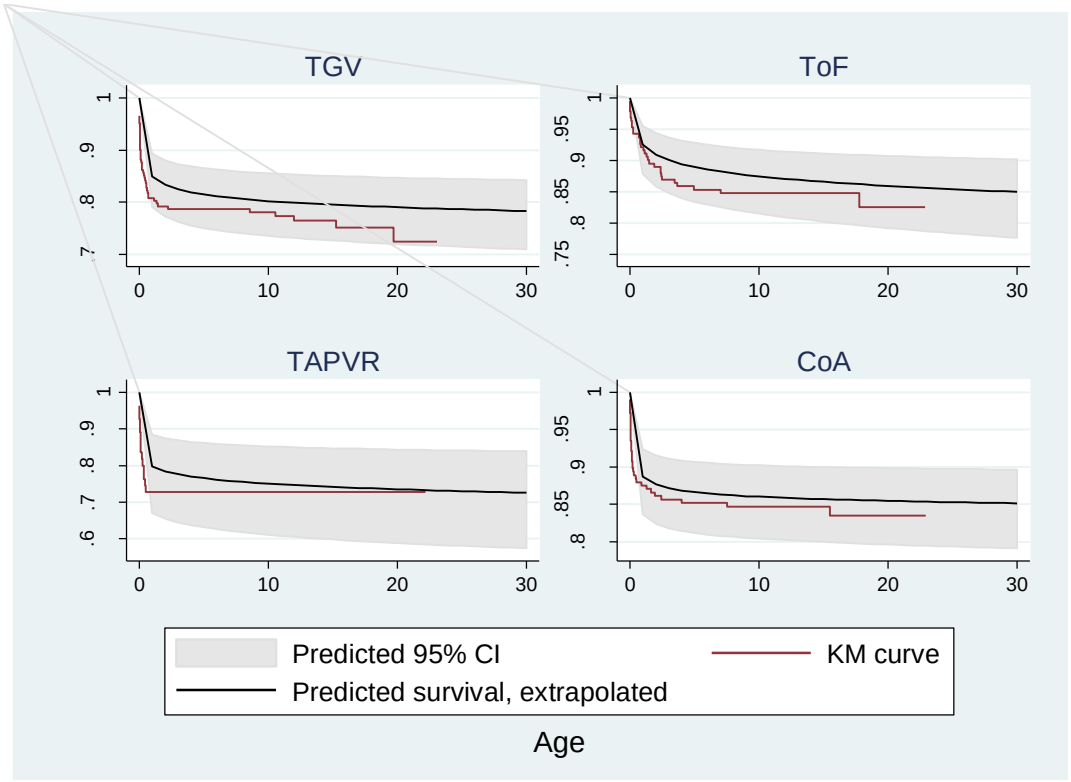
CHD subtype	Predicted 20 year survival (95% CI)	Predicted 30 year survival (95% CI)
SV	68.8 (46.1-85.0)	66.0 (42.1-83.8)
HLH	1.7 (0.4-7.0)	1.5 (0.3-6.9)
EA	70.2 (48.2-85.7)	69.1 (46.5-85.1)
TA	71.3 (41.6-89.7)	68.0 (37.1-88.4)
PVA	44.9 (26.7-64.5)	42.2 (23.8-63.0)
CAT	21.7 (10.3-40.2)	21.0 (9.5-40.1)
AVSD	89.9 (76.4-96.1)	89.4 (75.4-95.9)
TGV	79.0 (71.9-84.7)	78.3 (70.9-84.2)
ToF	85.9 (79.2-90.7)	85.0 (77.6-90.2)
TAPVR	73.5 (58.9-84.4)	72.6 (57.4-83.9)
CoA	85.4 (79.6-89.8)	85.1 (79.1-89.6)
VSD	99.5 (99.0-99.7)	99.5 (98.9-99.7)
ASD	-	-
PVS	98.9 (96.6-99.6)	98.8 (96.4-99.6)
Other	94.1 (88.9-96.8)	93.9 (88.9-96.8)
All CHD	**92.8 (91.8-93.6)**	**92.6 (91.6-93.5)**

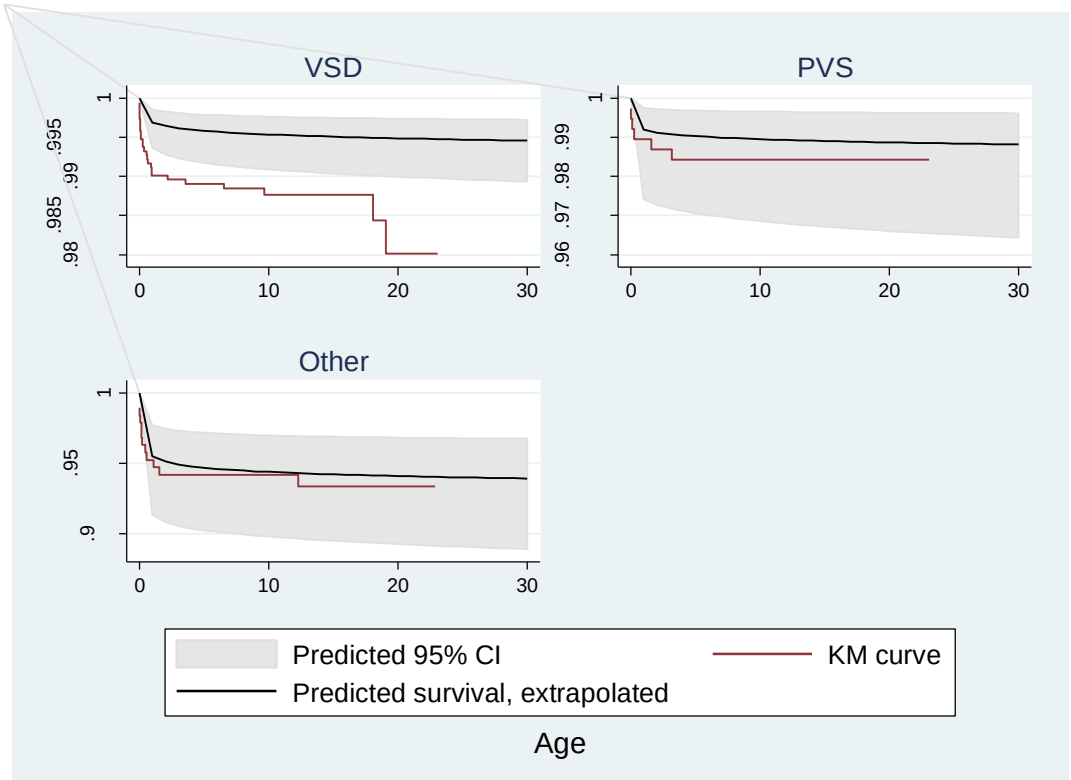
There were not enough cases of HRH, AVA/S, IAA, DORV, MVA and PDA to predict 30 year survival. It was not possible to extrapolate 30 year survival for cases of ASD, due to low frequency of deaths.

Figure 8.16 Extrapolated 30 year survival and Kaplan-Meier curves for isolated CHD









The predicted survival (and 95% CIs): is the baseline survival curve from Royston-Parmar regression (adjusted for year of delivery, gestational age at delivery, standardised birth weight, prenatal diagnosis and annual TOPFA rate), extrapolated to 30 years of age. It was not possible to extrapolate the models for ASD or PDA.

8.4 Discussion

8.4.1 Summary

In this chapter, Kaplan-Meier survival estimates for 20 year survival were calculated for each CHD subtype (where possible). Hazard functions were examined to crudely estimate when children with CHD were at greatest risk of mortality. Several risk factors for mortality were analysed according to CHD subtype. Prediction methods were used to estimate 20 year survival for cases born at the end of the study period and for cases born after the study period. Thirty year survival was also estimated for cases born in the study period.

In total, 89.7% of children born with isolated CHD were alive at age 20. Survival varied substantially according to CHD subtype, with no cases of HLH surviving past the age of 11 but 98.2% of children with isolated ASD surviving to age 20. With the exception of isolated VSD, ASD and PVS, 20 year survival for children with CHD was significantly lower than that of the general population.

Overall, the predicted mortality rate was greatest during the first week of life. The mortality rate decreased steeply within the first year of life and stabilised thereafter. Predicted mortality rates varied considerably by CHD subtype, but were always highest during the first week of life.

Considering all CHD subtypes combined, more recent year of delivery, increased gestational age at delivery, high standardised birth weight and increased annual TOPFA rate all significantly decreased the risk of mortality. The presence of structural or chromosomal ECAs, low standardised birth weight and prenatal diagnosis of CHD increased the risk of mortality. There was some evidence that increased maternal age decreased the risk of mortality, although this did not reach statistical significance at the Bonferroni adjusted level of $\alpha=0.003$ and was likely caused by confounding. The risk factors of mortality varied according to CHD subtype. Increased gestational age at delivery was significantly associated with decreased risk of mortality in cases of AVSD, TGV, CoA, VSD and "Other" CHD subtypes; low standardised birth weight was associated with a significant increased risk of mortality in cases of AVSD; prenatal compared to postnatal diagnosis was significantly associated with increased risk of mortality in cases of AVA/S, VSD and PVS; year of delivery, maternal age at delivery, infant sex, deprivation and annual TOPFA rates were not significantly associated with mortality in any of the CHD subtypes.

The predicted 20 year survival of children with CHD (any subtype) was 96.0% for cases born in 2003, 98.0% for cases born in 2010 and 98.7 for cases born in 2015. The predicted 20 year survival for children born from 2003 onwards with ASD and PVS met that of the general UK population. The predicted 30 year survival of children born with CHD was 92.6% (based on cases being born at the average year of delivery, 1995).

8.4.2 Strengths

This study has a variety of different strengths. Firstly, this is one of few population-based studies to report the long-term survival of children born with CHD. Compared to most studies on long-term survival, this study had a large sample size, therefore, risk factors for mortality could quite uniquely be examined for most of the individual CHD subtypes. Additionally, data was ascertained from a high-quality population-based register which is notified of cases from multiple sources, to ensure high case ascertainment. The NorCAS is cross-validated with the Freeman hospital cardiac database annually. Accurate diagnoses are achieved by the review of complex cases by paediatric pathologists and clinical geneticists and, where relevant, diagnoses are confirmed via post mortem. Cases are included on the NorCAS if they are diagnosed before age 12 (16 before 2001), meaning even mild cases of VSD which are difficult to diagnose are included. Only 17 (0.4%) cases were untraced, reducing the possible incursion of bias. The majority of the untraced cases were VSD (10, 58.8%) or PVS (3, 17.7%). Given that these two subtypes were some of the most common, the proportion untraced was very small and thus not likely to have impacted on the survival estimates.

A further strength is that the assumptions of each Cox regression model were thoroughly checked. All models were robust in that they all satisfied the Cox proportional hazards assumption (using Therneau-Grambsch tests with $p<0.003$ classed as statistically significant). The multivariable models for the individual subtypes were all of good fit to the data, as indicated by the Cox-Snell residuals. However, the multivariable model for all CHD subtypes combined was not a good fit to the data for older ages. However, given that CHD subtypes are very diverse in terms of survival and risk factors of survival, this is not surprising. A further strength is that survival estimates were not reported where there were less than 10 cases at risk at the start of the interval. Therefore only precise, reliable estimates were presented. To decrease the risk of type I errors incurred by multiple testing, a Bonferroni adjustment was used and $p<0.003$ was classed as

statistically significant. But, as discussed in the limitations section, associations significant at the $p<0.05$ level were also highlighted.

8.4.3 Limitations

This study also has a number of limitations. Firstly, survival estimates have previously been reported from this data set for isolated CHD [116]. However, in this study, a more developed coding system was used for cases of CHD. Furthermore, the previous study reported survival estimates relating to isolated cases of CHD only and also did not investigate risk factors of survival of children born with CHD, which are novelly included in this study.

Despite this being one of the largest population-based studies of CHD survival, with 5,092 cases of CHD, only 657 (13.2%) were born 20 years prior to the date of data matching (28th January, 2008). Therefore, 20 year survival estimates could not be reported for all CHD subtypes, due to low sample size. The low proportion of cases at risk between ages five and 20 may also have impacted the validity of the risk factors at the older ages, particularly for the rarer subtypes where the number of deaths were few. Although the proportional hazards assumption was satisfied for all subtypes, suggesting HRs were equal at say, age 20 and at age one, this was analysed by testing the linearity of the Schoenfield residuals over the analysis time. Given that the Schoenfield residuals are only estimated when there is an event, this may not have been a robust test for some CHD subtypes. While I am confident that the risk factors are reliable for survival to age five, where deaths are common, risk factors of survival up to age 20 still require validation in a larger data set.

Additionally, the 20 year Kaplan-Meier estimates relate to survival of cases born between 1985-1988. Due to medical and surgical advances, 20 year survival for cases born today is greater than survival of cases born in the 1980s. This issue was tackled by predicting the survival of cases born in 2010 (after the study period ended) using Cox regression. This approach is somewhat limited in that survival is assumed to have increased at the same rate between 2003-2015 as it did between 1985-2003. Therefore, the Kaplan-Meier estimates should be interpreted as the lower bound of survival and the predicted survival estimates should be interpreted with caution.

A further limitation is that only cases born prior to 2003 were included. Ideally, cases born up to 2010 would have been analysed, to increase the sample size and allow estimation of 30 year

survival. While the original aim for this chapter was to link death registrations to data on cases born between 1985-2010 and notified to six BINOCARs, this was not possible. However, survival was extrapolated in order to provide an estimate of 30 year survival.

While this is one of the larger studies to examine risk factors of CHD survival, there are still issues with small sample size for certain subtypes. Therefore, care should be taken when interpreting non-significant associations as these could have resulted from type I errors. For risk factors such as year of delivery, there were no significant associations in any of the individual CHD subtypes. However, almost all of the HRs showed that the mortality rates decreased over time. Indeed, the associations almost reach statistical significance at the $p<0.003$ level for two of the CHD subtypes (e.g. AVSD and TGV, both $p=0.004$). It was for this reason that both significant associations at the $p<0.003$ (Bonferroni adjusted level of significant) level and at the $p<0.05$ level were discussed. Moreover, due to low sample size, multivariable models were fitted to cases of AVSD, AVA/S, CoA, ToF, TGV, VSD and all CHD subtypes combined only.

In this study, the presence of ECAs, year of delivery, gestational age at delivery, standardised birth weight, maternal age at delivery, infant sex, deprivation, prenatal diagnosis and annual TOPFA rate were examined as possible risk factors for mortality. However, there are many more risk factors that it was not possible to examine. In previous population-based studies, ethnicity, parity and place of delivery were significantly associated with mortality in children with CHD (see Chapter 7). The data notified to NorCAS is that routinely collected in the clinical setting and therefore variables such as ethnicity and parity are poorly recorded and therefore these variables could not be analysed in this chapter. Additionally, surgical and medical interventions are not recorded on the NorCAS. Type of intervention is likely to have influenced survival. In particular, for cases of HLH, survival may be improved with palliative surgery (the three staged Fontan procedure) but many parents still opt for comfort care, resulting in certain death [217]. Moreover, it has been reported that younger age at surgical intervention positively influences survival in children with ASD, AVSD, ToF and HLH [20, 218-221], although a small study found no such association in cases of ToF AVA/S and CoA [222]. Additionally the NorCAS does not hold clinical information on morbidities such as sepsis or hypertension, which increase the risk of mortality in children with CHD [20].

A further limitation is that there was no information available on cause of death. Therefore, it is possible that the mortalities were not related to a cardiac event. However, 20 year survival estimates for children with CHD were compared to 20 year survival estimates for the general population of the UK (98.9%). Given that cause of death was not known, mortality among cases with ECAs may not be a result of a cardiac event. However, this issue was overcome by reporting survival estimates separately for cases with ECAs and isolated cases. But in the more severe CHD subtypes, the effect of other congenital anomalies is likely to be over-powered by the lethality of the CHD.

As discussed in Chapter 1, there are several classification systems used to code CHD into subtypes. The NorCAS uses the ICD classification system, which codes CHD into subtypes based on aetiology. This is clearly useful from an epidemiological perspective. However, the ICD coding system does not provide information on the severity of the CHD, which may vary within subtype. For example, the ICD classification system does not provide detail on the size of a VSD. Such information is important given that larger VSDs have poorer prognoses and are more likely to require surgical intervention [223]. The survival estimates presented for VSDs may therefore be overly optimistic for large VSDs, yet pessimistic for smaller VSDs. However, given the paucity of data on the long-term survival of CHD, particularly isolated CHD, the survival estimates presented in this chapter are still valuable for clinicians counselling parents when their child is diagnosed with a CHD. Had the subtypes been sub-classified there may have been too few cases in each sub-category to analyse meaningfully.

Lastly, I have examined long-term mortality without taking into account morbidity. Several studies have shown that CHD survivors have at increased risk of endocarditis, cerebrovascular events, myocardial infarctions and arrhythmias [194-196]. This information is also important for parents when a diagnosis of CHD is made.

8.4.4 Comparison to previous studies

In this study, 89.7% of children with isolated CHD survived to age 20. As shown in Chapter 7, only one other population-based study reported survival of isolated CHD beyond age 10. This study by Olsen et al reported that just 73% of cases survived until age 25 (73% at age 10) [67]. Olsen et al reported a prevalence of 3.7 per 1000 live births, compared to 7.6 per 1000 in this study. Therefore, it is likely that Olsen et al had a low case ascertainment. If the milder CHD

subtypes were under-ascertained, which is likely given their cases had to be ascertained before age one, this explains why Olsen et al reported a lower survival estimate than in the current study.

In my study, cases with CHD and ECAs were at four-fold increased risk of mortality compared to isolated cases (all CHD subtypes combined). Olsen et al, Wang et al and Knowles et al similarly reported that children with ECAs were at increased risk of mortality, but with much lower effect sizes (HR=1.33, HR=1.37 and HR=1.56) [67, 191]. Given that I identified the greatest effect sizes in cases of VSD, ASD and PVS, Olsen et al are likely to have reported lower effect sizes due to their under-ascertainment of mild CHD subtypes [67]. Similarly, Wang et al did not include cases of VSD, ASD or PVS, and Knowles et al included only those cases that required intervention, so may have under-ascertained these cases with these subtypes [191]. Compared to cases with isolated AVSD, I found a two-fold increased risk among cases with structural ECAs (HR=2.09). Miller et al similarly found that children with AVSD were at 28% increased risk of mortality (HR=1.28) when there was one structural ECA and three-fold increased risk when there was two or more structural ECAs (HR=3.32)[188]. Pooling these results would have produced a comparable HR to that presented in my study. I found that cases of AVSD with chromosomal/ genetic ECAs were at almost two-fold increased risk of mortality (HR=1.91). Similarly, Frid et al reported that cases of AVSD with Down syndrome were at increased risk of mortality (OR=1.26) [183]. While Frid et al reported a lower effect size than in my study, this is likely because they examined Down syndrome only as opposed to all chromosomal/ genetic ECAs. Conversely, Miller et al reported no significant difference in the risk of mortality among cases with Down syndrome compared to those without [188]. This may be because they used "cases without Down syndrome" as their reference category which is likely to have contained cases with structural ECAs. Therefore, the difference between the two categories would have been less pronounced. No other population-based studies have examined the effect of ECAs on the long-term survival of children born with CHD.

In this study, 20 year survival estimates for children with CHD (all subtypes combined) improved significantly over time (HR=0.91), from 85% in 1985-1990 to 95.3% in 1998-2003. This finding reflects that of several population-based studies [67, 117, 171, 191]. Olsen et al reported that one year survival improved from 72% in 1977-1986 to 87% in 1997-2005 (OR=0.42) [67]. Garne et al reported that survival improved from 79% in 1986-1993 to 87% in 1994-1998 [117]. Wang et al also reported improvements in 25 year survival over time, with a two-fold increased risk of

death in cases (with severe/moderate CHD) born in 1983-1988 compared to 2001-2006 (HR=2.06) [191]. Oster et al reported an almost three-fold increased risk of one year mortality in cases (with severe/moderate CHD) born 1979-1993 compared to 1994-2005 (HR=2.65)[171]. Considering the CHD subtypes individually, I found no significant associations with year of delivery (at the $p<0.003$ level). However, the decreasing trends in mortality over time almost reached statistical significance in cases of AVSD, CAT, TGV, VSD, ASD and PVS. Although the trends were not significant, the risk of mortality decreased over time in all CHD subtypes, with the exception of PVA. Among cases of AVSD, Frid et al observed a significant decrease in post-operative mortality over time but no significant change in non-operated cases [183]. Potentially the improved survival in cases of AVSD is related to advances in surgical techniques. Miller et al did not find any significant trend in mortality of children with AVSD, but did report lower survival estimates in 1979-1991 (55.6%) compared to 1992-2003 (72.6%) [188]. Fixler et al reported a 47% significant decrease in the combined mortality of corrected TGV, HLH, SV, PVA (with intact ventricular septum) and TA from 1996-2000 compared to 2001-2003 [182]. Perhaps categorising the years of delivery into just two groups and combining the subtypes provided enough power to detect a significant difference over time.

In this study, greater gestational age at delivery was associated with improved survival for all subtypes combined and for AVSD, TGV, CoA, VSD and "Other" CHD subtypes. Survival was shown to improve with increased gestational age for most CHD subtypes, although this did not reach statistical significance, possibly due to low power. Knowles et al reported an increased risk of mortality in preterm compared to term cases (HR=1.43) [20]. Miller et al reported improved survival in term cases compared to preterm cases of AVSD (63.5% versus 46.1%, respectively) [188]. For cases of corrected TGV, HLH, SV, PVA and TA combined, Fixler et al similarly reported a decreased risk of mortality in term cases compared to very preterm cases (20-31 weeks: HR=2.80) and moderately preterm cases (32-36 weeks: HR=1.69) [182].

In this study, high standardised birth weight was associated with improved survival for all CHD subtypes combined. Wang et al and Oster et al similarly reported that increased birth weight improved survival (in severe/moderate cases combined) [171, 191]. Fixler et al reported that greater birth weight improved survival for combined cases of corrected TGV, HLH, SV, PVA and TA [182]. I found some evidence that standardised birth weight was associated with improved survival in cases of VSD and "Other" CHD subtypes, but no other CHD subtype.

However, despite not reaching statistical significance, high birth weight improved long-term survival for all CHD subtypes, with the exceptions of SV, TGV, CoA, IAA, and "Other" CHD subtypes. Similarly, low birth weight was indicative of poorer survival in all subtypes except TA, CAT, TAPVR, and CoA.

There was some evidence that increased maternal age was associated with improved long-term survival of all CHD subtypes combined. A similar association between maternal age and survival has also been reported by two population-based studies, which examined severe/moderate CHD combined [171, 191]. Wang et al reported a decreased risk of mortality in cases born to mothers aged >35 compared to 30-34 (HR=0.88) [191]. Oster et al reported that maternal age ≥30 was associated with an decreased risk of one-year mortality compared to mothers aged <30 (HR=0.77) [171]. In my study, the effect was not present in the multivariable model, likely due to confounding. If some of the subtypes with a better prognosis were more prevalent amongst older mothers, this may explained why I found an association between maternal age and survival when all CHD subtypes were combined but not for individual CHD subtypes.

In this study, there were no significant associations between infant sex and mortality. Conversely, Wang et al and Fixler et al found borderline significant increases in survival amongst females compared to males (HR=1.07 and HR=1.27) [182, 191]. Additionally, Knowles et al also reported a significant increased risk of mortality among female cases (HR=1.25) [20]. However, all three studies examined composite groups of subtypes and therefore this may be because the more severe subtypes occurred less often in females [20, 182, 191].

I found little evidence of an association between deprivation and survival. However, amongst all CHD subtypes, survival was decreased in the least compared to most deprived tertiles. Amongst cases with AVSD, Miller et al did not find a significant association between socioeconomic status and survival, however, survival decreased linearly with decreasing level of deprivation [188]. The association with deprivation may still exist, perhaps with a small effect size, but requires a larger dataset in order to investigate it with more power.

I established that prenatal diagnosis was associated with an increased risk of mortality in all CHD subtypes combined, and in cases of PVA, AVA/S, VSD and PVS. I also found some evidence of the association in cases of EA, AVSD, ToF, CoA and MVA, although these did not quite reach the significance at the Bonferroni adjusted level. While the direction of this effect may be

surprising, it has been previously reported in the population-based setting. Oster et al reported an increased risk of one-year mortality in cases (severe/moderate CHD subtypes combined) diagnosed before compared to after the first day of life (HR=0.54) [171]. A further study by Oster et al showed that the effect was present among cases of "critical CHD", (a composite group of HLH, TA, CAT, TAPVR, PV, ToF, TGV, IAA, CoA, EA, SV and DORV) but not amongst cases of "non-critical CHD" (VSD, ASD, PVS, AVA/S) [224]. A meta-analysis of eight small hospital-based studies showed an increased risk of preoperative mortality among prenatally diagnosed cases of "critical" CHD. However, prenatally diagnosed cases were more likely to be "high risk" and to opt for comfort care. Excluding these cases, prenatal diagnosis positively impacted survival, but only if the cases were diagnosed in a specialist centre. Additionally, hospital-based studies have previously reported an increased risk of post-operative mortality in prenatally diagnosed cases of PVA and TGV [225, 226]. Four studies have conversely reported no significant association between prenatal diagnosis and post-operative survival in cases of HLH [227-229], TGV[228] and all CHD (combined) [230]. However, three of these small studies were underpowered and actually, survival was lower in prenatally diagnosed cases [228-230]. A further hospital-based study conversely reported greater survival amongst prenatally diagnosed cases of CoA. However, this study excluded cases that were diagnosed after one month of age, citing that these cases were too difficult to diagnose prenatally [231].

8.4.5 Potential mechanisms

Survival of children born with CHD improved over the study period. This improvement is related to a host of factors. Firstly, many surgical interventions were developed over the study period. For example, the Fontan staged operation for repair of SV, HLH and TA and the conduit repair for cases of CAT were introduced in the late 1970s and developed across the 1980s-90s [197, 198]. In the UK however, intervention amongst cases of HLH was introduced in the early 1990s [232]. Similarly, the arterial switch operation was introduced in 1975 [199], and fully replaced the atrial switch operations (i.e. the Mustard or Senning procedures) in the early 1990s [200]. Although at first the arterial switch operation resulted in greater mortality [201], eventually this led to improved survival among cases of TGV [200]. Prior to the development of the Fontan operation, there was no alternative intervention. Therefore, the survival rates for HLH in

particular improved as this anomaly is incompatible with life if left untreated. But even more recently, around 58% of parents elected not to intervene surgically in cases with HLH [233].

Prostaglandin was first trialled in neonates with cyanotic CHD in the 1970s [203, 204], although was not frequently administered until the 1980s. Crucially, prostaglandin prevents the closure of the ductus, which otherwise occurs within the first few days of life, thus allowing oxygenated and deoxygenated blood to mix in circulation [204]. While this is not a permanent solution for cyanotic CHDs, it improves pulmonary circulation and prevents acidosis occurring, enabling children to remain stable prior to surgical intervention and thus more likely to survive [204]. The increased administration of prostaglandin in children with cyanotic CHDs is likely to have improved survival estimates over time.

Increased gestational age at delivery and high standardised birth weight were associated with improved long-term survival for all CHD subtypes combined. Cardiac operative mortality has been shown to increase in infants with low birth weight and low gestational age at delivery [234]. Furthermore, among children with CHD, low gestational age at delivery also poses an increased risk of necrotising entercolitis, which could be another explanation for the increased risk of mortality [235]. Of course, in non-anomalous individuals, the risk of mortality increases as gestational age and birth weight decreases [236, 237]. Potentially, gestational age was a larger contributor to mortality than CHD among the cases delivered extremely preterm, particularly among the milder CHD subtypes. I found that, over the study period, the risk of mortality decreased, except in extremely preterm cases. This could suggest that improvement in survival due to advances in surgical intervention have not impacted upon extremely preterm cases, perhaps because they do not live long enough to undergo intervention.

In this study, prenatally diagnosed cases of CHD were at greater risk of mortality. Even within the same CHD subtype, there is a spectrum of disease severity. Therefore, this paradoxical finding is likely due to the most severe versions of a subtype being prenatally diagnosed [238]. Additionally, compared to postnatally diagnosed cases, prenatally diagnosed cases tend to have a lower birth weight, lower gestational age at delivery, lower APGAR score, ECAs and multiple CHD subtypes [227, 230, 238, 239]. While prenatal diagnosis increased the risk of mortality, studies have shown that prenatally diagnosed cases of HLH are less likely to have early neurologic morbidities and more likely to be stable in the pre-operative period [227-229]. Indeed,

Tworetzky reported that prenatally diagnosed cases of HLH were less likely to experience preoperative acidosis, tricuspid regurgitation and ventricular dysfunction [229]. Bonnet el al also reported that acidosis and multi-organ failure were less common amongst prenatally diagnosed cases of TGV [226]. Escobar-Diaz et al similarly reported a lower rate of acidosis in prenatally diagnosed cases of TGV, although this did not reach statistical significance due to low power [239]. Some of the benefit may be due to the earlier administration of prostaglandins [227].

Chapter 9. Future prevalence of CHD

9.1 Introduction

As shown in Chapter 7 and 8, survival for individuals with CHD has improved over time. This has led to an increase in the population of people living with CHD in the UK [240], and elsewhere [241, 242]. Due to the ongoing medical surveillance, reinvestigation and often reoperation of affected individuals, UK hospital admission rates have therefore risen [26]. Given this increasing need for health services for individuals born with CHD, future prevalence estimates and case numbers could aid health service planning.

Trends in the live birth prevalence of CHD in England and Wales were modelled in Chapter 3, using the yearly prevalence of cases notified to six BINOCARs. However, past trends could be more accurately modelled using the monthly prevalence of CHD, due to the increased number of data points. Furthermore, there is some evidence of seasonality in the prevalence of CHD [243-249], although this has not been shown in all studies [70, 250]. Seasonality, if it exists, should be accounted for in the estimation of future trends.

The aim of this study was to model trends in the live birth prevalence of CHD in the North of England between 1998-2010, and to make estimations of the prevalence of CHD over the next 10 years.

9.2 Methods

9.2.1 Case inclusion and data

Data on the monthly number of live births (any plurality) in the population between 1998-2013 were obtained from PHE. All live born cases (singletons and multiples) with a final diagnosis of CHD notified to the NorCAS between 1st January 1998 and 31st December 2010 were included in this study. In this chapter, month of birth for each case of CHD was available. The other five BINOCAR registers were not able to provide data on month of delivery and so cases notified to NorCAS only are included in this chapter. Case data was available until 2010 only.

9.2.2 Statistical analysis

Analysis was performed for all CHD subtypes combined and for each CHD subtype. Analysis was also performed for all CHD regardless of plurality to maximise case numbers. Analysis corresponds to all cases of CHD (including cases with ECAs) as there were too few monthly case numbers to examine prevalence separately for isolated cases and cases with ECAs. Additionally, for the purpose of estimating future health service requirements for individuals with CHD, modelling the prevalence of all CHD was appropriate.

Wavelet analysis and harmonic regression were performed to analyse trends in the number of live births (in the general population) and in CHD prevalence. These models were then extrapolated to estimate the *future* number of live births and the *future* prevalence of CHD. Both of these figures were then used to estimate the number of live born cases of CHD delivered between 2011 and 2020.

9.2.3 Wavelet analysis

Seasonality in the number of live births and the prevalence of CHD (per 10,000 live births) was analysed using wavelet analysis. Wavelet analysis decomposes the time series of CHD prevalence and estimates how seasonality changes over time. Graphs of the Wavelet power spectrum were produced, where a high wavelet power level occurring at the same period at each age being indicative of seasonality. A random pattern in the wavelet spectrum indicated that there was little evidence of seasonality [251]. More information on the precise formulae used to estimate wavelets can be found in Rosch and Schmidbauer's guide using R [252].

9.2.4 Harmonic regression

The number of live births (in the general population) and the prevalence of CHD (per 10,000 live births) over time were modelled using linear regression. In time series data, there is often autocorrelation between observations (i.e. correlation between data as a function of time, perhaps relating to an unobserved variable), which causes non-constant variance. This non-constant variance violates the assumption of ordinary least squares regression. An alternative is to model the data using generalised least squares (GLS) regression, which accounts for variation in error terms [253]. The number of live births and CHD prevalence (per 10,000 live births) were used as the outcome variables in GLS models. The disadvantage of this method over the Poisson regression used in Chapter 4, is that it is not possible to use an offset term to account for the size of the denominator. However, given that this chapter includes only one BINOCAR, the denominator population is similar for each time point and so this should not cause bias.

The GLS models were fitted with Sine and Cosine terms in order to model seasonality over time. For the model of CHD prevalence, p represents the period (i.e. 12 months):

$$CHD\ prevalence = \beta_1 \cos\left(\frac{2\,\pi\ time}{p}\right) + \beta_2\ sin\left(\frac{2\,\pi\ time}{p}\right) + \beta_3\ time$$

These functions provide linear transformations of time that range between -1 and 1, in relation to the period *p*. The coefficient for time (i.e. β_3), can be interpreted as the trend in CHD prevalence over time, after adjusting for seasonal variation in prevalence. If the addition of linear splines improved the fit of the model (assessed using a LR test), then these were also included. The location of the knots were chosen based on examining time series plots for points of inflection.

These models were used to predict the number of live births or birth prevalence up to 2020. Using the predicted number of live births and the predicted prevalence, case numbers were also estimated up to 2020. Sin and Cos terms were removed from the models where they did not improve fit.

When examining the trends in CHD subtypes, a Bonferroni correction was used in order to reduce the possibility of type II errors relating to multiple testing. Therefore, $p<0.003$ was considered statistically significant.

9.3 Results

9.3.1 Live births

Between 1998-2013, there were 409,875 live births in the North of England. The number of births per month ranged between 2,162 and 2,964. As shown in Figure 9.1 (the blue line representing "actual births"), the number of live births decreased between 1998-2001, increased between 2002-2010 and decreased slightly between 2010-2013. In Figure 9.1, there was also evidence of seasonality in the number of live births, indicated by the repetitive pattern in the monthly live births.

Wavelet analysis showed that the seasonality in live births was constant between 1998-2013, as indicated by high wavelet power (shown in red) occurring at the same time each year (Figure 9.2).

Using harmonic regression, the Sin term significantly improved the fit of the model ($p<0.001$) and the Cos term almost reach statistical significance ($p=0.054$), which implies seasonality in the live births. Linear splines, with knots at December 2001 and December 2009, improved the fit of the model and were therefore included in the harmonic regression model. Accounting for seasonality, the number of live births decreased by an average of six births per month (95% CI: 4-7; $p<0.001$) between 1998-2001, increased by five births per month (95% CI: 4.-5; $p<0.001$) between 2002-2009 and decreased by four births per month (95% CI: 2-5; $p<0.001$) between 2010-2013. Using this model, the number of annual live births were estimated until 2020 (Figure 9.1, red line representing the modelled live births).

Figure 9.1 Number of live births over time, actual and modelled

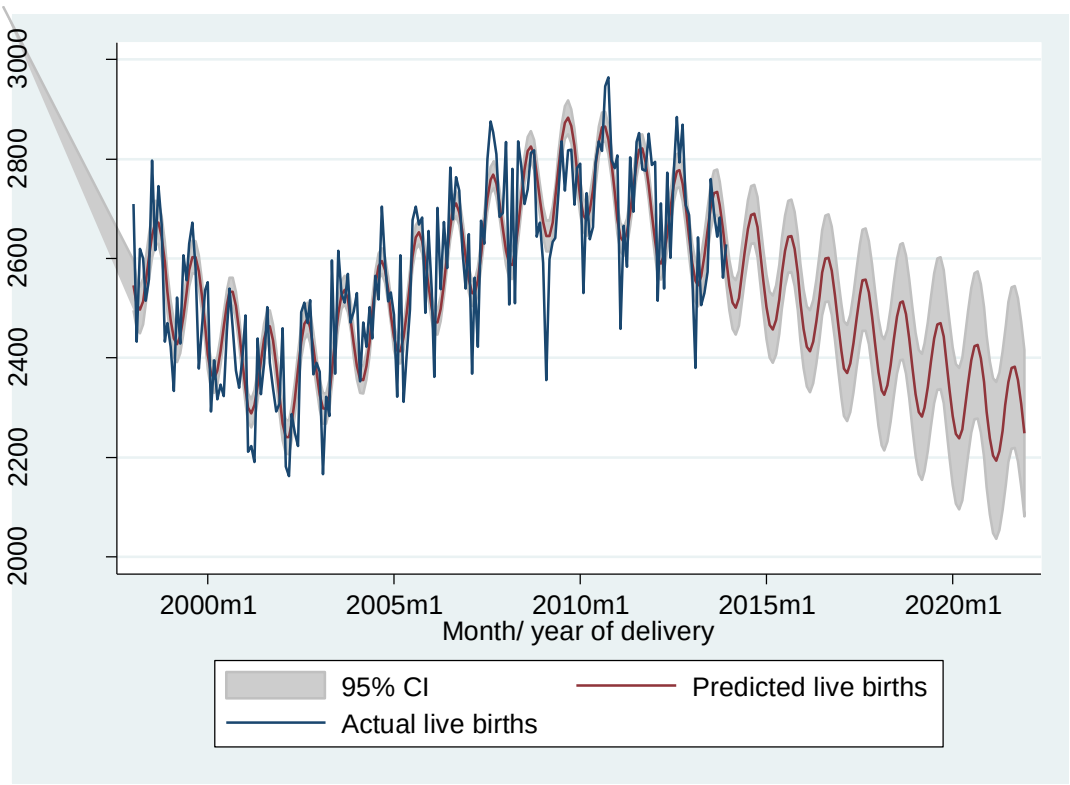
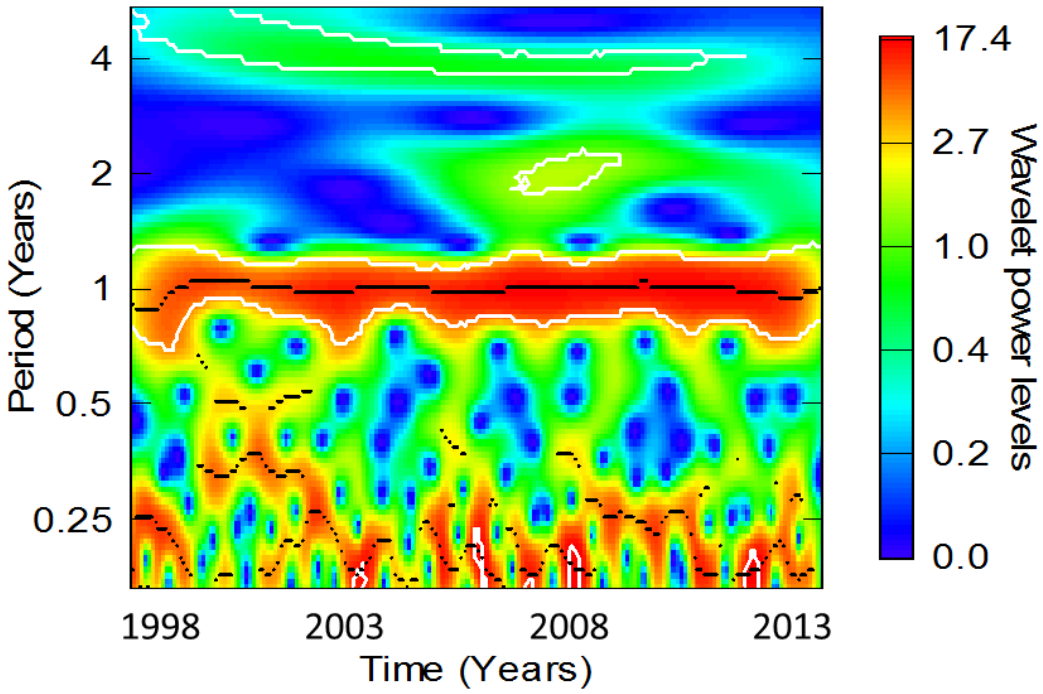


Figure 9.2 Wavelet power spectrum to detect seasonality in live births



9.3.2 Birth prevalence of CHD

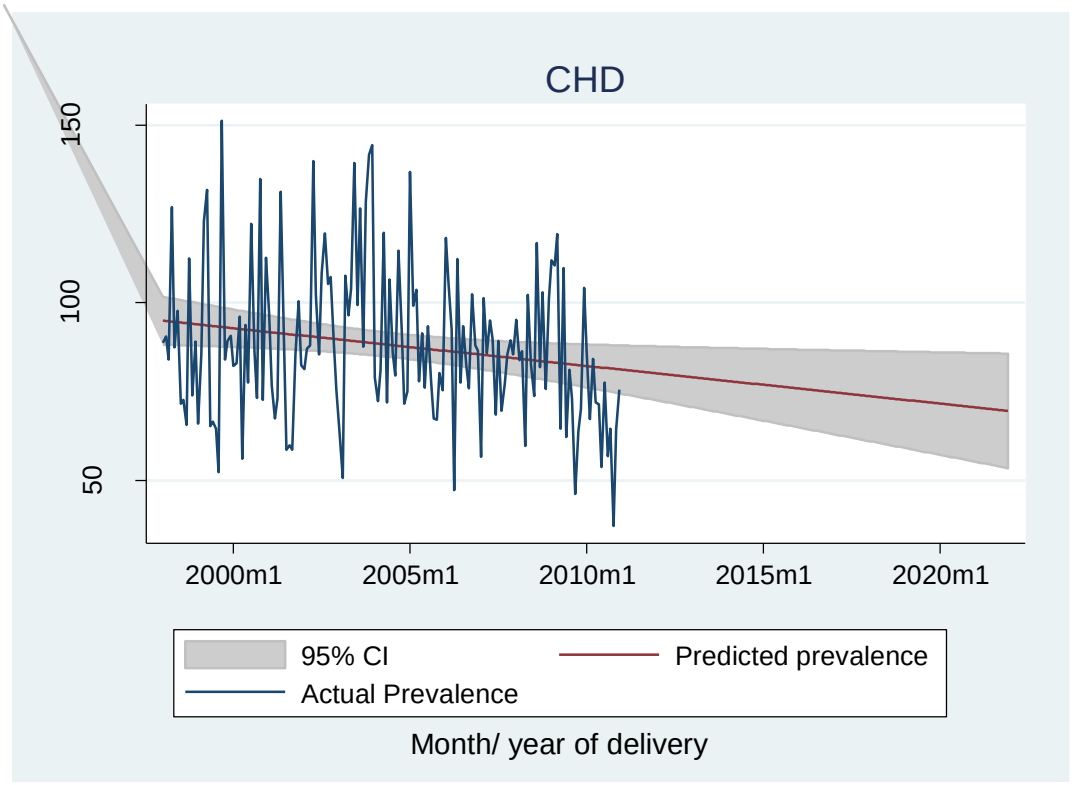
There were 3,682 live born cases of CHD notified to NorCAS between 1998-2010. The live birth prevalence of CHD over time is shown in Figure 9.3 (actual prevalence represented by the blue line), by CHD subtype.

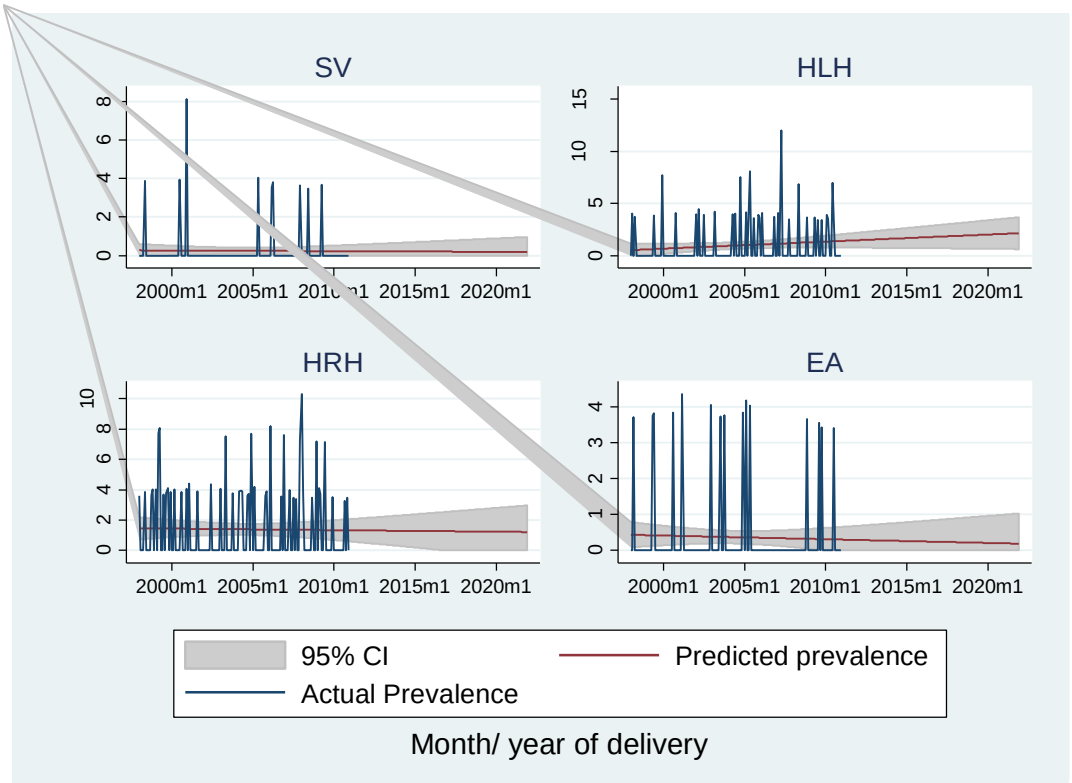
The wavelet power spectrum plots show little evidence of seasonality for all CHD subtypes combined and for each CHD subtype (Figure 9.4). Cos and Sin terms did not significantly improve the fit of the regression models for any of the CHD subtypes (at the $p<0.003$ level), although there was a suggestion of seasonality in the live birth prevalence of HRH (Cos: $p=0.012$), ToF (Sin: $p=0.010$), CoA (Cos: $p=0.042$) and ASD (Cos: $p=0.009$) (Table 9.1).

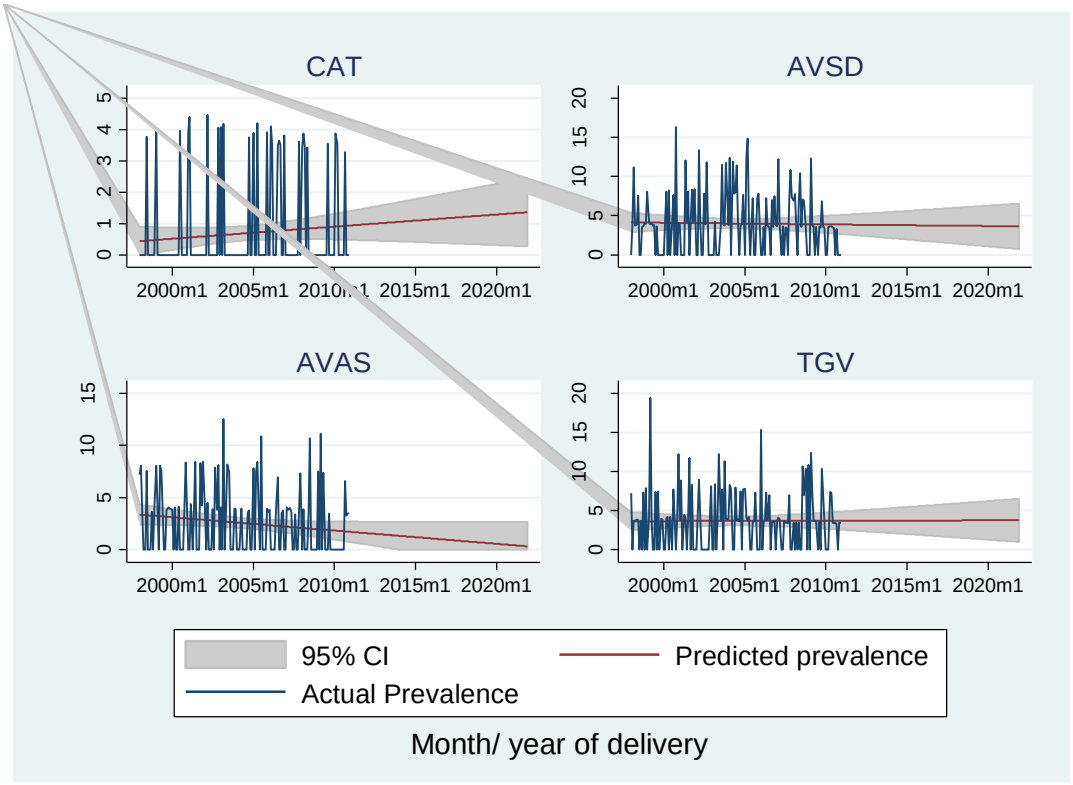
The prevalence of all CHD subtypes (combined) decreased over time, but did not reach statistical significance at the $p<0.003$ level (coef= -0.09, $p=0.022$) (Table 9.1). The prevalence of PDA increased significantly over time (coef= 0.02 (per month), $p<0.001$), the prevalence of VSD and MVA decreased significantly over time (coef= -0.08, $p=0.001$ and coef= -0.08, $p=0.002$, respectively). There was some evidence that the prevalence of ASD decreased over time (-0.02, $p=0.041$). There was no evidence of trends in any of the other CHD subtypes. Splines did not improve the model fit for any of the models and so were not included.

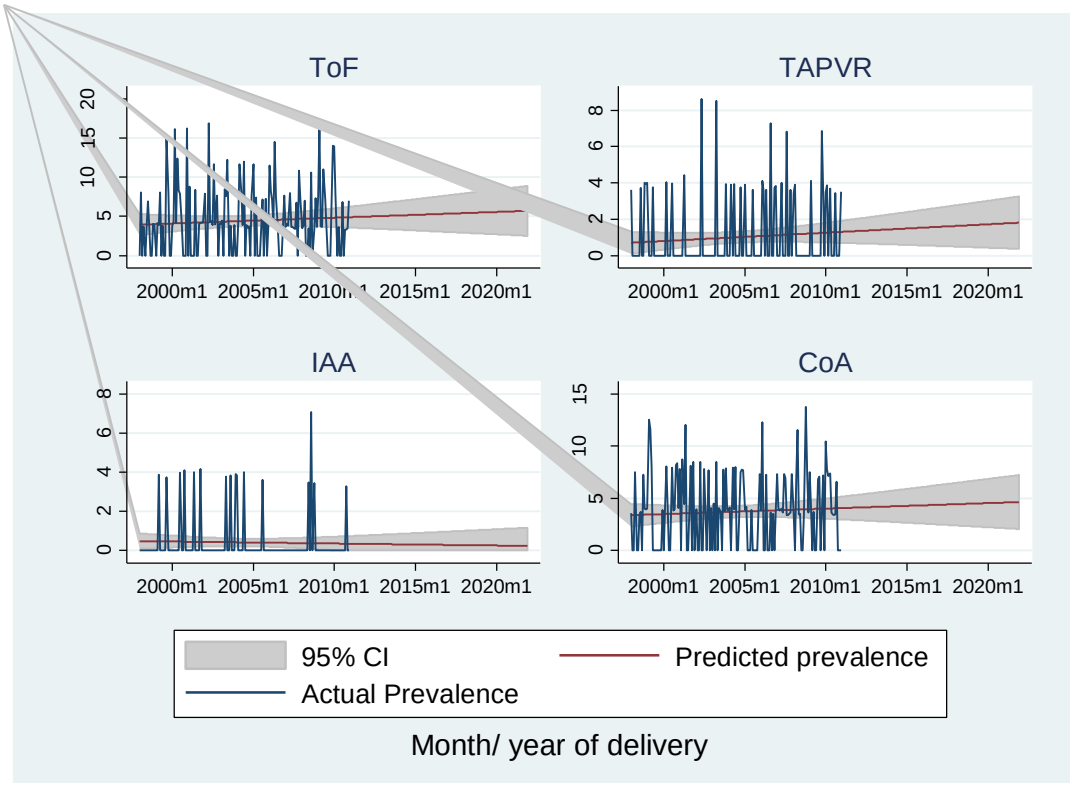
Using the regression models, the prevalence of CHD was estimated for each month until 2020 (Figure 9.3, red line). The predicted monthly case numbers are also shown in Figure 9.5. The predicted number of cases born per year between 2016 to 2020 are shown in Table 9.2, according to CHD subtype.

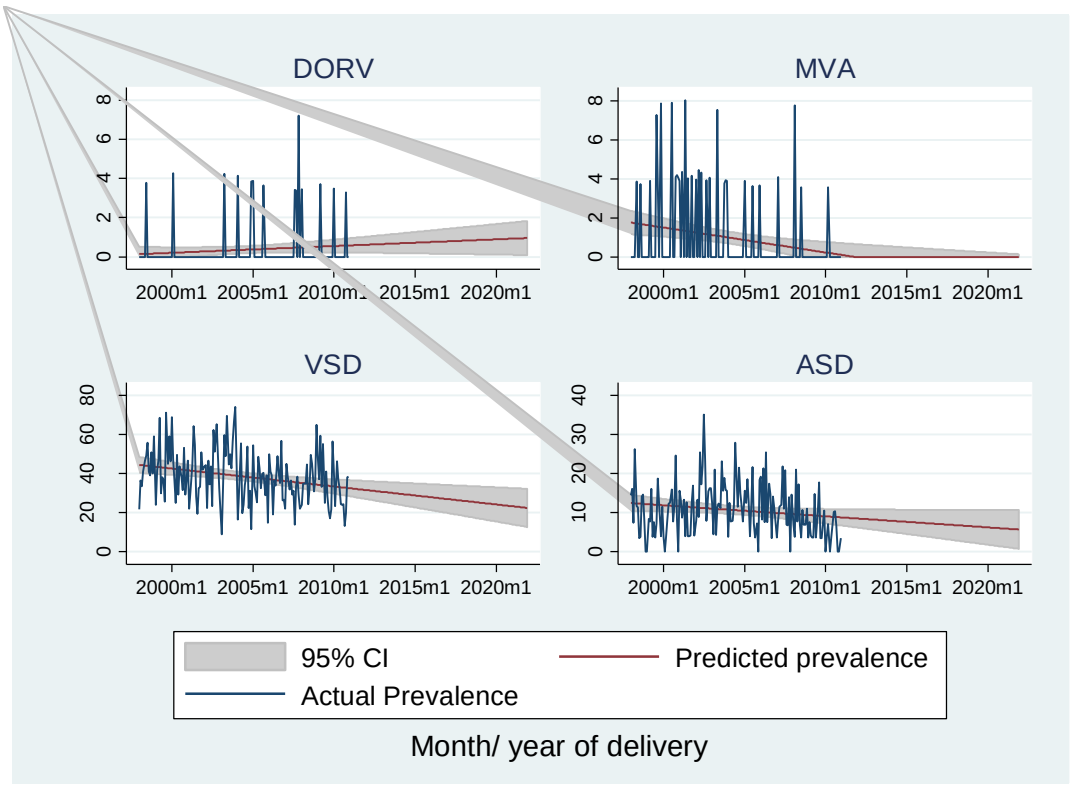
Figure 9.3 Actual and predicted live birth prevalence of CHD over time, by subtype






CAT
AVSD
AVAS
TGV
2000m1
2005m1
2010m1
2015m1
2020m1
95% CI
Predicted prevalence
Actual Prevalence
Month/ year of delivery


ToF
TAPVR
IAA
CoA
2000m1
2005m1
2010m1
2015m1
2020m1
95% CI
Predicted prevalence
Actual Prevalence
Month/ year of delivery


DORV
MVA
VSD
ASD
0
2
4
6
8
0
20
40
60
80
0
10
20
30
40
2000m1
2005m1
2010m1
2015m1
2020m1
95% CI
Predicted prevalence
Actual Prevalence
Month/ year of delivery

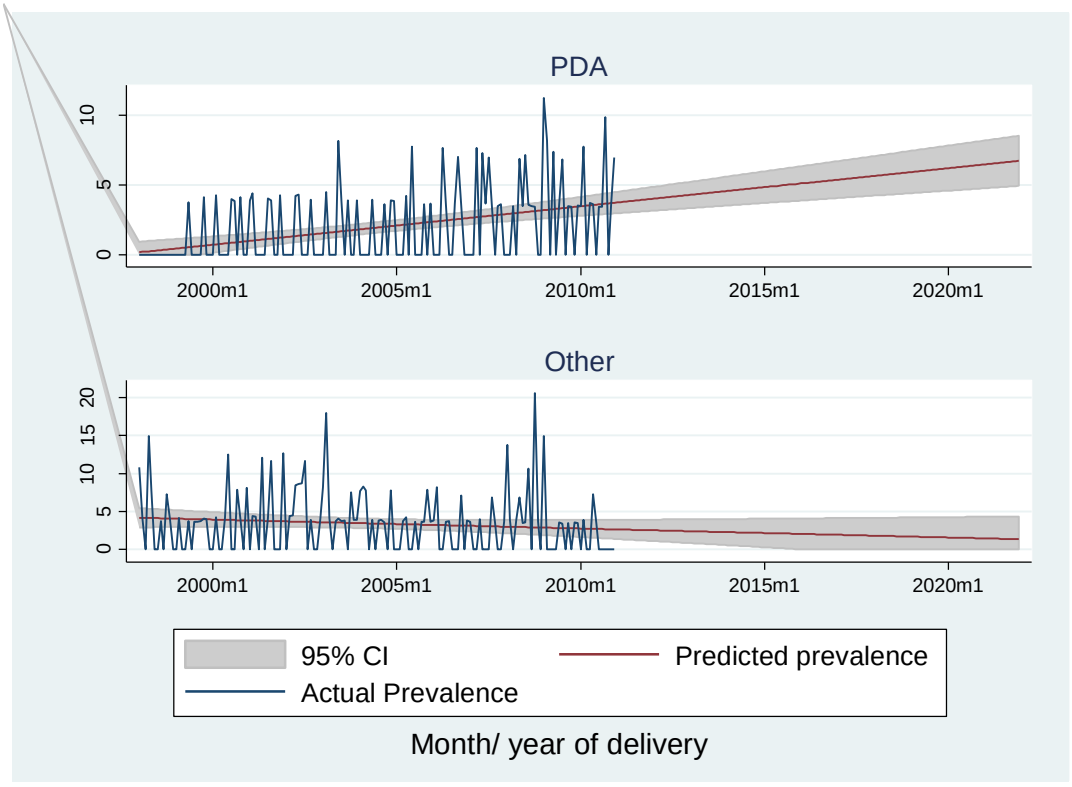
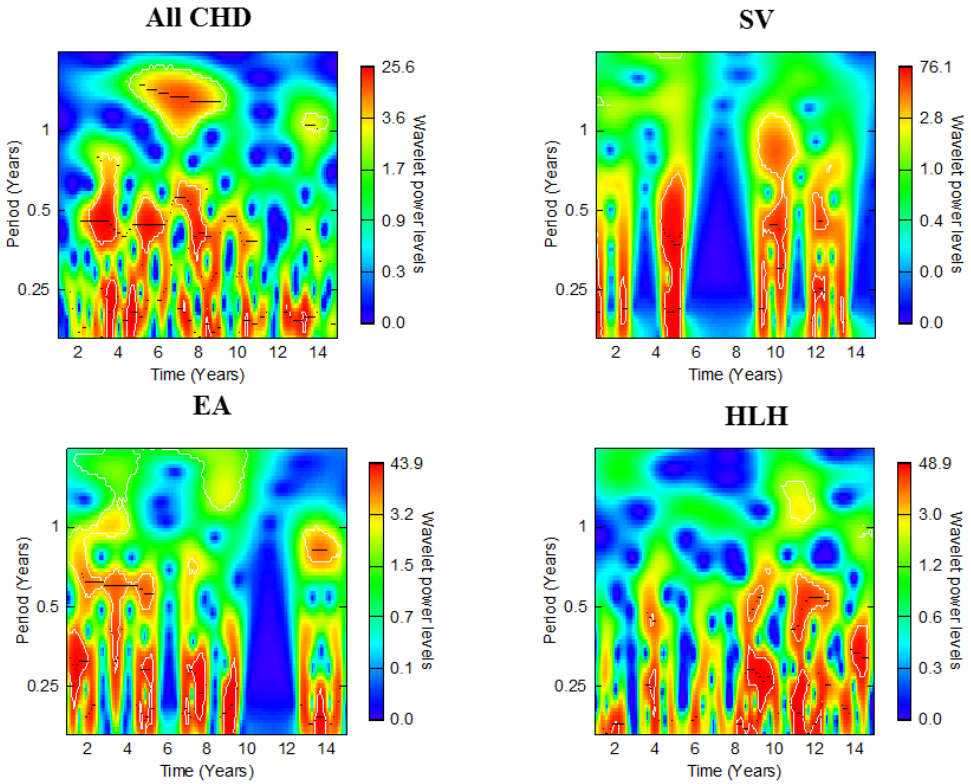
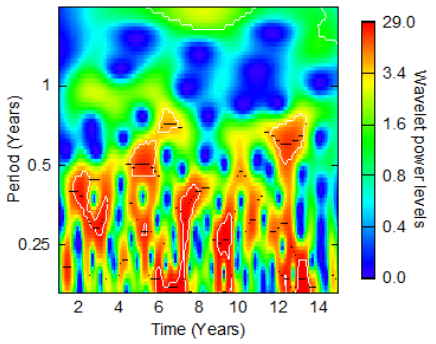

PDA
Other
0
5
10
0
5
10
15
20
2000m1
2005m1
2010m1
2015m1
2020m1
95% CI
Predicted prevalence
Actual Prevalence
Month/ year of delivery

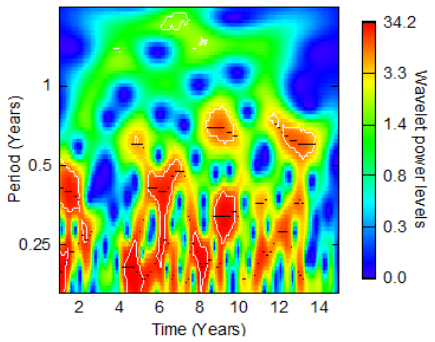
Figure 9.4 Wavelet power spectrum of prevalence per 10,000 live births, by CHD subtype



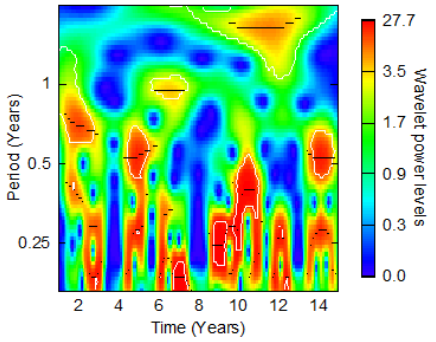
AVA/S



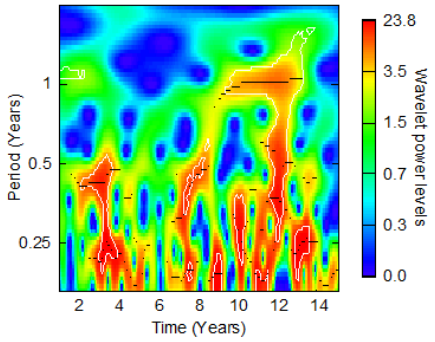
AVSD



CAT



HRH



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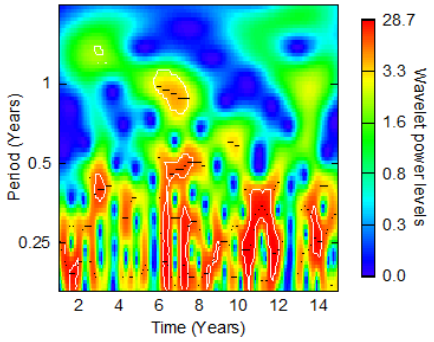
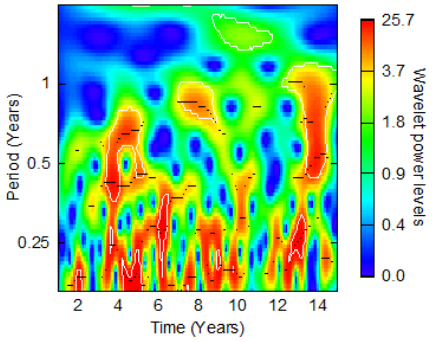
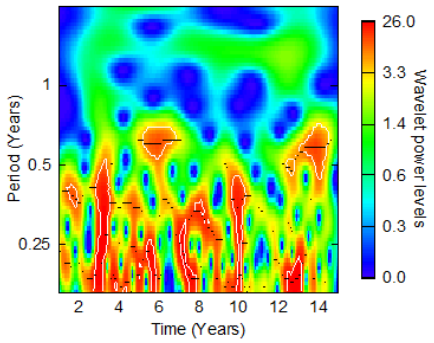
IAA



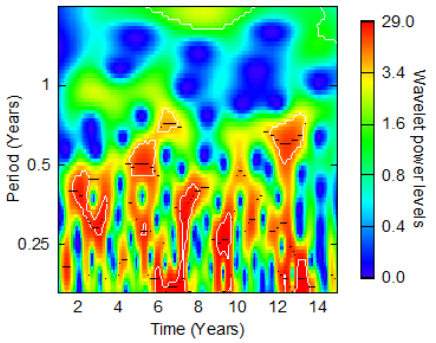
TAPVR



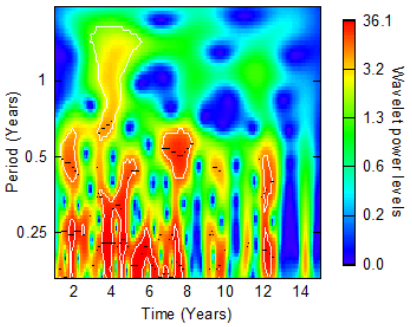
ToF



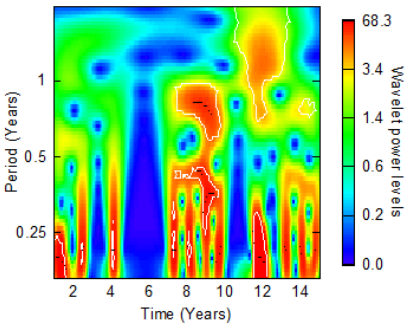
TGV



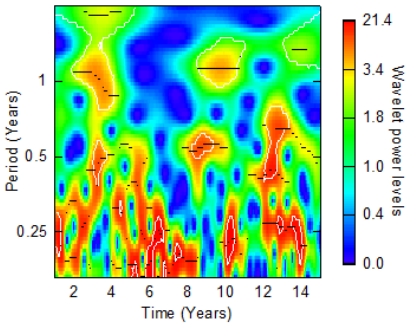
VSD



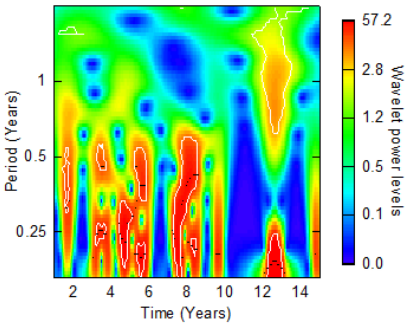
MVA



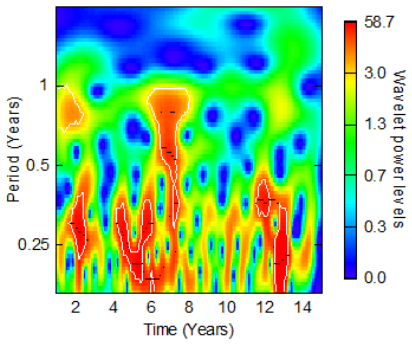
DORV



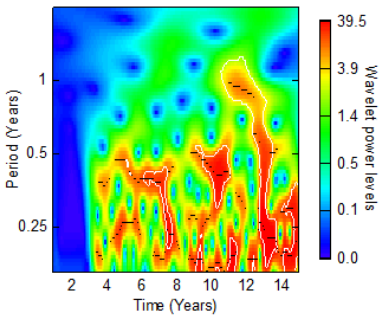
CoA



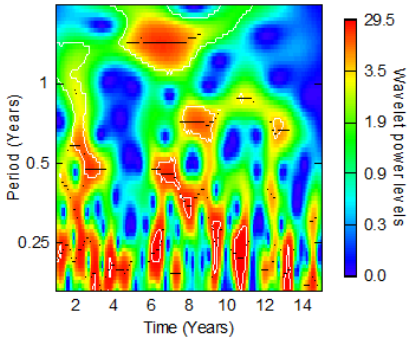
Other



PDA



PVS



ASD

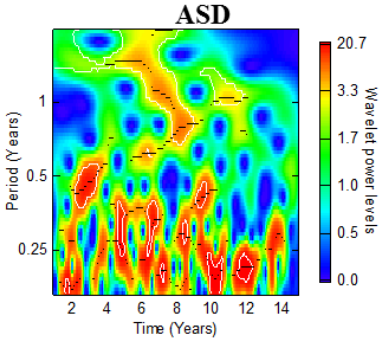
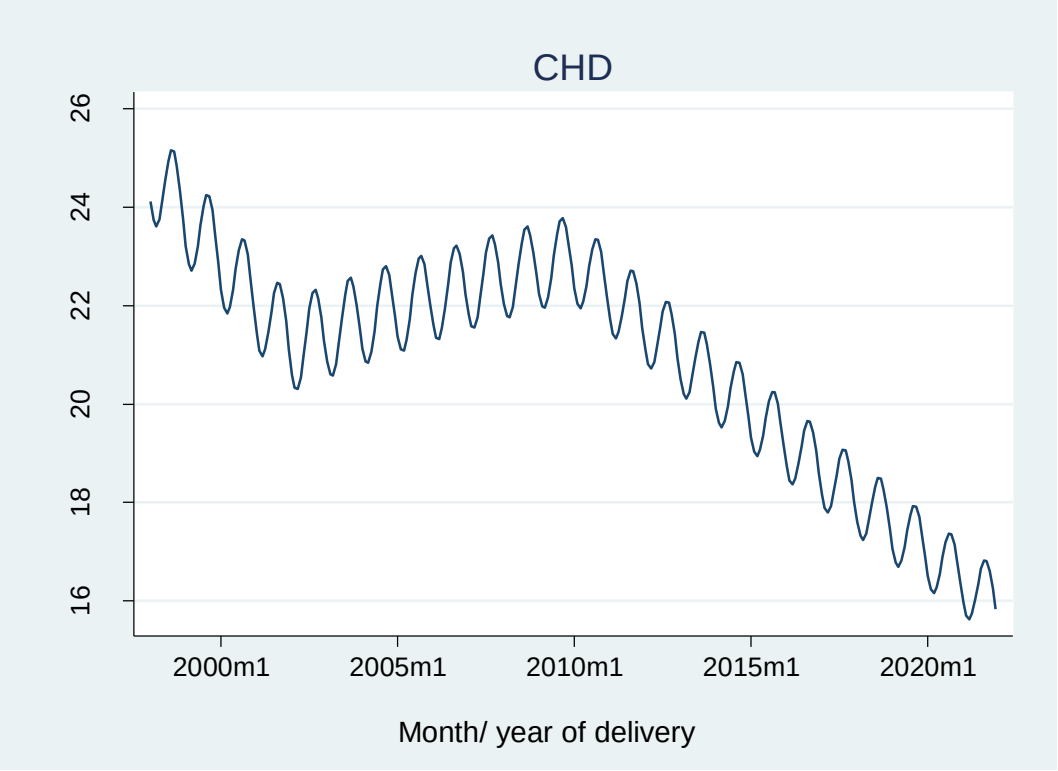
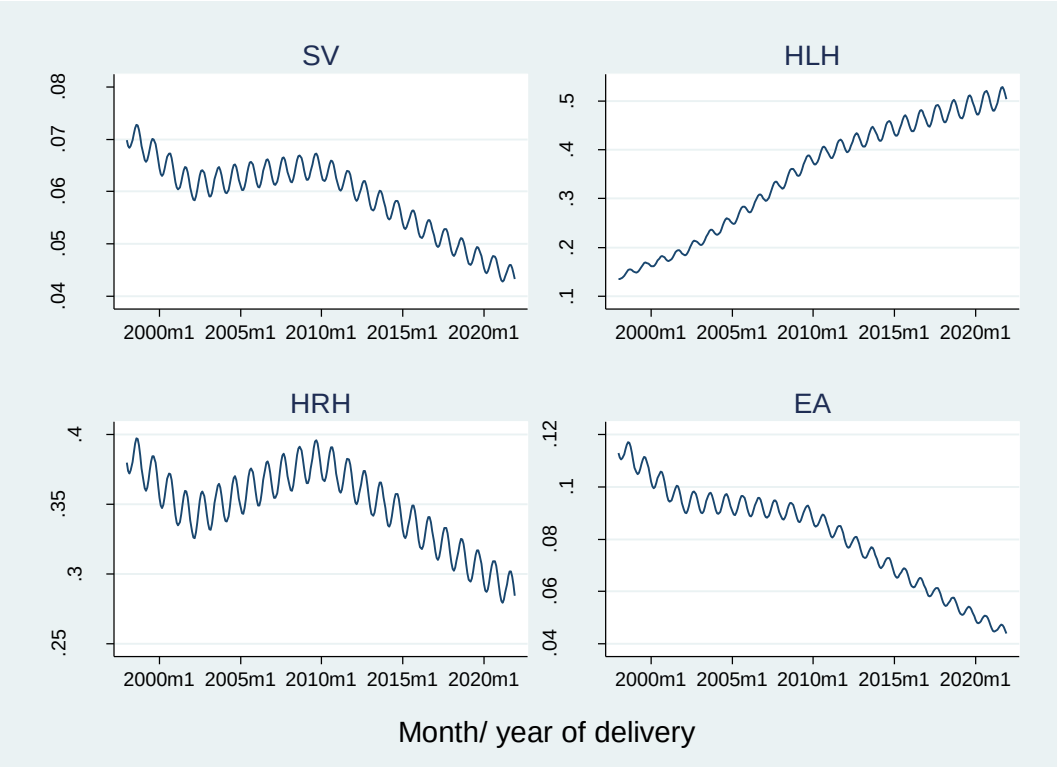


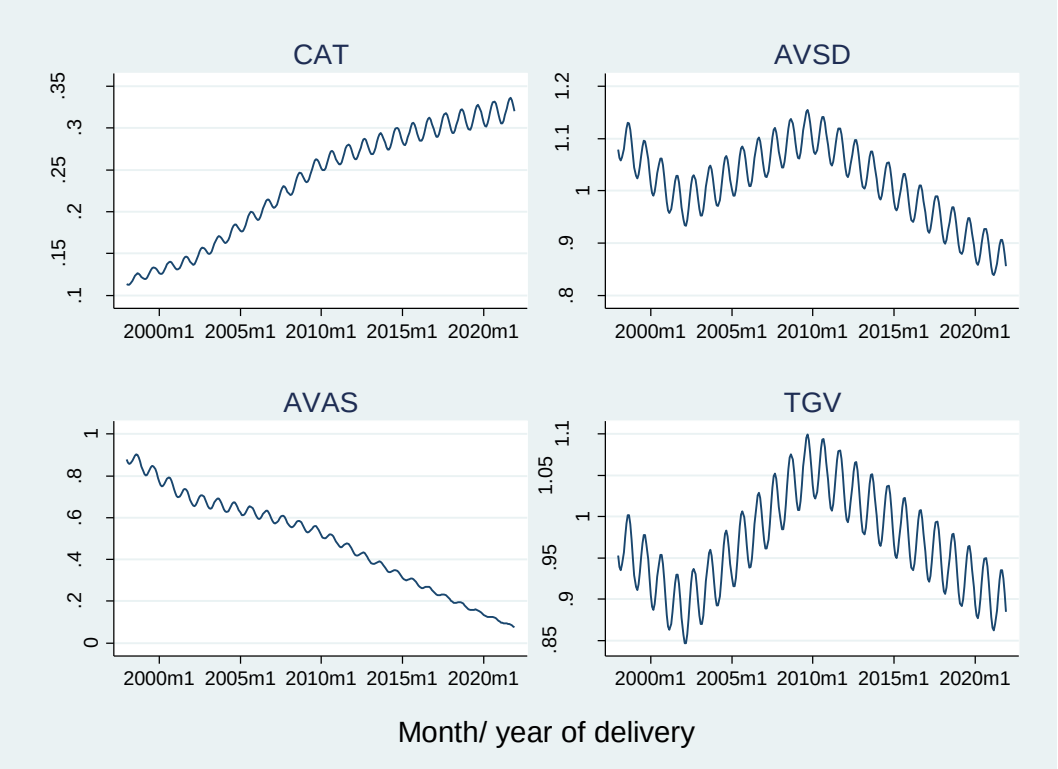
Table 9.1 Harmonic regression models of CHD live birth prevalence, by CHD subtype

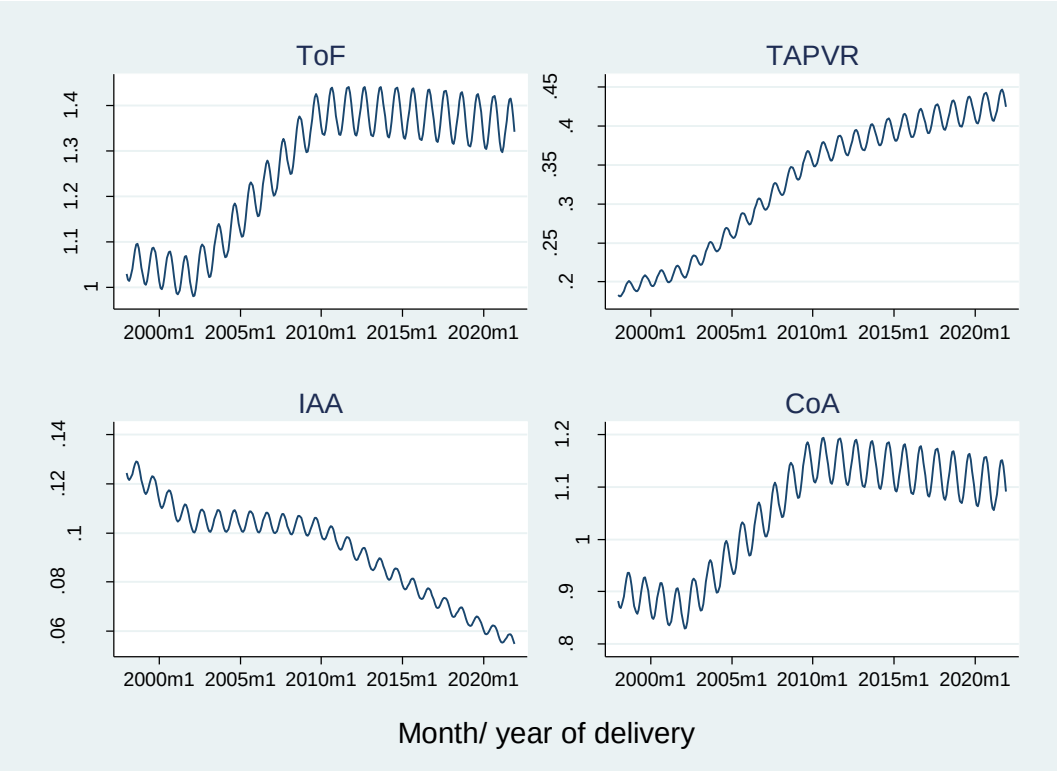
CHD subtype	Cos P-value	Sin P-value	Time of delivery (months) Coef (95% CI); p-value
SV	0.533	0.191	0 (0-0); p=0.943
HLH	0.562	0.062	0.01 (0-0.01); p=0.092
EA	0.716	0.785	0 (0-0); p=0.661
HRH	0.012	0.315	0 (-0.01-0.01); p=0.85
CAT	0.091	0.063	0 (0-0.01); p=0.179
AVSD	0.989	0.700	0 (-0.02-0.01); p=0.822
AVAS	0.266	0.345	-0.01 (-0.02-0); p=0.058
TGV	0.350	0.828	0 (-0.01-0.01); p=0.954
ToF	0.684	0.010	0.01 (-0.01-0.02); p=0.332
TAPVR	0.487	0.182	0 (0-0.01); p=0.233
IAA	0.349	0.043	0 (-0.01-0); p=0.622
CoA	0.042	0.137	0 (-0.01-0.02); p=0.434
DORV	0.087	0.663	0 (0-0.01); p=0.164
MVA	0.585	0.722	-0.01 (-0.02-0); p=0.002
VSD	0.814	0.671	-0.08 (-0.12--0.03); p=0.001
ASD	0.009	0.519	-0.02 (-0.05-0); p=0.041
PVS	0.865	0.947	0 (-0.02-0.02); p=0.929
PDA	0.105	0.656	0.02 (0.01-0.03); p<0.001
Other	0.530	0.599	-0.01 (-0.02-0); p=0.175
All CHD	**0.624**	**0.281**	**-0.09 (-0.16--0.01); p=0.022**

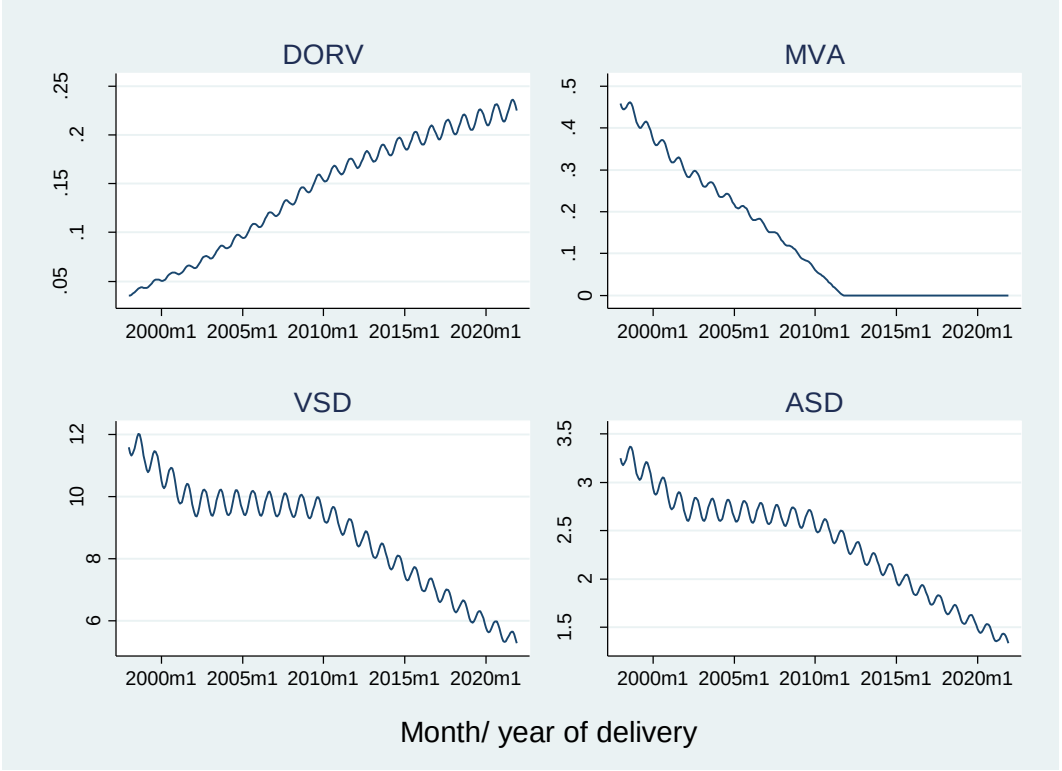
Figure 9.5 Predicted number of live born cases






CAT
AVSD
AVAS
TGV
2000m1 2005m1 2010m1 2015m1 2020m1
Month/ year of delivery


ToF
TAPVR
IAA
CoA
2000m1 2005m1 2010m1 2015m1 2020m1
Month/ year of delivery


DORV
.05
.1
.15
.2
.25
2000m1
2005m1
2010m1
2015m1
2020m1
MVA
0
.1
.2
.3
.4
.5
2000m1
2005m1
2010m1
2015m1
2020m1
VSD
6
8
10
12
2000m1
2005m1
2010m1
2015m1
2020m1
ASD
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2
2.5
3
3.5
2000m1
2005m1
2010m1
2015m1
2020m1
Month/ year of delivery

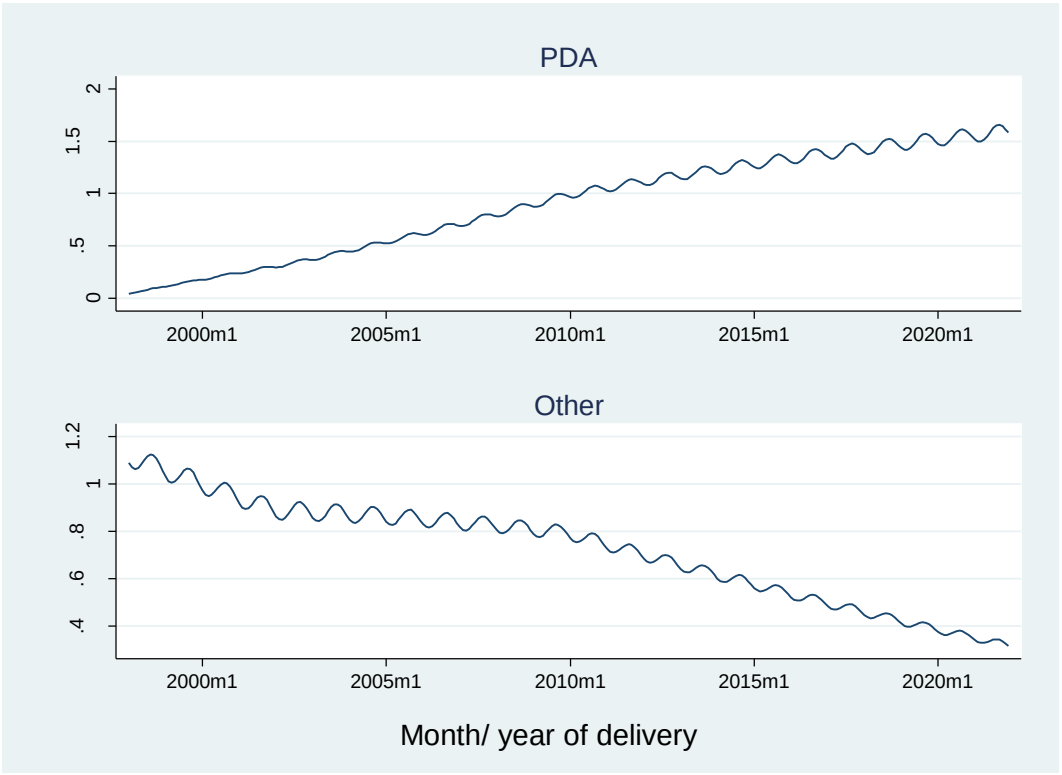
PDA
0
.5
1
1.5
2
2000m1
2005m1
2010m1
2015m1
2020m1
Other
.4
.6
.8
1
1.2
2000m1
2005m1
2010m1
2015m1
2020m1
Month/ year of delivery

Table 9.2 Yearly projected number of cases (95% CI) in the North of England, born 2016-2020

CHD subtype	2016	2017	2018	2019	2020
SV	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-3)
HLH	5 (2-8)	5 (2-9)	6 (2-9)	6 (2-9)	6 (2-10)
EA	1 (0-2)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)
HRH	4 (1-8)	4 (0-8)	4 (0-8)	4 (0-8)	4 (0-8)
CAT	3 (1-6)	4 (1-6)	4 (1-6)	4 (1-6)	4 (1-6)
AVSD	12 (7-18)	12 (6-18)	12 (5-18)	11 (5-18)	11 (4-18)
AVA/s	4 (0-9)	4 (0-8)	3 (0-8)	3 (0-8)	2 (0-8)
TGV	12 (7-17)	12 (6-18)	12 (6-18)	11 (5-18)	11 (5-18)
ToF	17 (10-23)	17 (10-23)	17 (10-24)	17 (9-24)	16 (9-24)
TAPVR	5 (2-7)	5 (2-8)	5 (2-8)	5 (2-8)	5 (1-9)
IAA	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)
CoA	14 (9-19)	14 (8-19)	14 (8-19)	14 (8-20)	13 (7-20)
DORV	2 (1-4)	2 (1-4)	2 (0-4)	2 (0-4)	3 (0-5)
MVA	0 (0-2)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
VSD	94 (75-113)	90 (70-110)	86 (64-107)	81 (59-104)	77 (53-101)
ASD	25 (16-35)	24 (14-34)	23 (12-33)	21 (10-33)	20 (8-32)
PVS	20 (13-28)	20 (12-28)	20 (11-28)	19 (10-28)	19 (10-29)
PDA	15 (12-19)	16 (12-19)	16 (12-20)	17 (13-21)	17 (13-22)
Other	7 (1-13)	7 (0-13)	6 (0-13)	6 (0-13)	5 (0-13)
All CHD	**242 (212-272)**	**235 (203-267)**	**228 (193-262)**	**221 (185-257)**	**214 (176-252)**

9.4 Discussion

9.4.1 Summary

In this chapter, the future prevalence of CHD in the North of England was estimated until 2020. The estimated live birth prevalence of CHD remained relatively stable, with a predicted prevalence of 72.3 per 10,000 live births in 2016, falling to 67.8 per 10,000 live births in 2020. After accounting for seasonality in live births, this equated to 242 cases born to mothers residing in the North of England in 2016, decreasing slightly to 214 cases in 2020.

9.4.2 Strengths

There were several strengths to the analysis performed in this chapter. Firstly, I had access to monthly number of live births. Therefore, it was possible to examine and therefore rule out, seasonality in the live birth prevalence of CHD. This also meant I could model the prevalence of CHD as opposed to the raw counts; this approach may have erroneously shown that there was seasonality in CHD, due to the seasonality in the live births.

Additionally, I modelled the data using GLS regression, which allows for unequal variance. While OLS regression would not have caused biased estimates, it would have given equal weight to all observations, regardless of the error structure [253].

9.4.3 Limitations

There were several limitations to this study. Firstly, it was only possible to estimate future prevalence for a small area of the UK, using one BINOCAR. In Chapter 5, I showed that there was substantial variation in the prevalence of CHD between BINOCARs. However, much of this heterogeneity was likely caused by case ascertainment as opposed to real differences. The NorCAS is the longest established BINOCAR, with the second greatest prevalence (after CARIS). Therefore, the prevalence in this chapter arguably represents a truer estimate when compared to the other BINOCARs. The ONS estimate that there will be 4.0 million births in the UK between 2012-2017 and 4.1 million between 2017-2022 [254]; using my modelled prevalence, this would equate to 30,032 and 27,939 cases of CHD respectively. For more accurate estimates, the model needs to be extended to cover more regions of the UK. The model

needs to be further refined to include information on CHD risk factors, such as maternal age, BMI, diabetes, smoking and ethnicity [4, 80, 96, 97]. I was not able to account for these factors as I did not have the population births categorised according to these variables. These variables may fluctuate over time which could lead to fluctuations in birth prevalence that were not described by my models. Refining the model would lead to more accurate future estimates, which would be important for health care planning. This information could be used to inform health economics research, which would assess the funds required to treat individuals born with CHD.

The model predictions are flawed in that they assume that the future prevalence follow the same trends as the past (or observed) trends in prevalence. Due to low case numbers, it was not feasible to predict the prevalence of singletons and multiples separately. In Chapter 7, I showed that trends in prevalence did not vary in singletons compared to twins overall. However, I showed that the prevalence among MC twins specifically, increased by 8% per year. MC twins account for a small proportion of births (0.6%), meaning the increase of 8% per year accounts for an additional seven cases of CHD per year in England and Wales (approximately).

9.4.4 Comparison to previous studies

In this chapter, I found no evidence of seasonality in the prevalence of CHD. Several studies have previously examined seasonality of CHD, with Luteijin et al's largest and most recent study finding no evidence of seasonality between 2000-2008 in Europe [250]. Smaller studies found a slightly increased prevalence of CHD in the summer months [58, 70, 243, 244, 246-249]. Specifically, seasonality was reported for cases of VSD [58, 243], EA [58], ASD [58, 243], HLH [245], PVS, AVA/S [58] and CoA [58]. But where Luteijin et al used harmonic regression to examine seasonality, many of the other studies more crudely compared the proportion of cases in the summer and winter months [243, 244, 247]. One study that employed several techniques for examining seasonality, reported different findings using each [58]. The aetiology of seasonality in congenital anomalies is still under debate, but is hypothesised to be related to environmental teratogens, such as air pollution, influenza outbreaks, maternal fever, vaccinations and the use of pesticides [250, 255].

Chapter 10. Discussion

The overall aim of this thesis was to examine survival and risk factors for mortality among individuals with CHD. In the discussion below, I will briefly outline the main findings from each of the chapters that make up this thesis. The findings of each chapter have already been compared to previous studies in the respective chapter discussions, so in the summaries of each chapter I will briefly put the results into context of the most relevant literature. I will then outline the implications of these findings for policy and practice in the UK and discuss areas of future research.

10.1 Summary and context of findings

I began this thesis with a review of the international literature on the birth prevalence of CHD. I found that globally, the birth prevalence of CHD ranged between 30-213 per 10,000 total births, varying substantially between studies. In the larger studies, there was evidence that the prevalence of CHD had increased over time [53, 57, 60, 79, 80]. However, increasing trends in these studies were driven by septal defects, which have become easier to diagnose over time due to developments in ultrasound technologies and echocardiography [256]. However, several studies also reported an increase in the prevalence of ToF [53, 60, 79]. A possible cause for this increase is the rise in women undergoing ART [257], as ART has recently been shown to increase the risk of ToF [145, 168]. Trends for other CHD subtypes were more conflicting. There was some evidence that advanced maternal age was associated with an increased risk of non-chromosomal CHD, although this was driven by septal defects and CoA [53, 59, 76, 80]. While there is increasing evidence of a genetic aetiology for some CHD subtypes [45], in many countries, women of advanced maternal age are likely to undergo more prenatal screening during pregnancy [258, 259] and thus case ascertainment is a possible cause. Alternatively, the association may have been confounded by maternal obesity, which is correlated with maternal age and is now a known risk factor for septal defects [4]. Few recent studies reported on CHD birth prevalence and trends in birth prevalence in the UK, which is important given the current reconfiguration of paediatric cardiology services [24].

The analysis of data from six BINOCARs, showed that the singleton birth prevalence of CHD was 65 per 10,000 births between 1991-2010, in England and Wales. I did not find any evidence of trends in CHD (all subtypes combined) or in septal defects, as several studies did in my literature review [53, 57, 60, 79, 80]. However, there was a suggestion of an increasing trend in CHD in five of the BINOCARs; but not in the largest register (CARIS). My more

recent study period may have been a factor for the discrepancy with the previously published literature. Consistent with several studies [53, 60, 79], I identified a small increasing trend in ToF of 3% per year. I also found small decreasing trends in the prevalence of CoA (2% per year) and AVA/S (3% per year). Risk factors have not been described for CoA and AVA/S so it is difficult to assess why these decreases occurred and whether they are real or result from chance findings. Increased maternal age at delivery was associated with an increased risk of CHD, although this was restricted to cases with structural or chromosomal/ genetic ECAs as opposed to isolated cases. Of the individual subtypes, maternal age was associated with ToF, AVSD, VSD and ASD, but again, among cases with chromosomal/ genetic ECAs only. Therefore, the link with maternal age is likely caused by the co-occurring congenital anomaly as opposed to the CHD itself. However, this contradicts several of the studies in my literature review, which found an association with maternal age in isolated cases [53, 59, 76, 80]. Potentially, this difference could relate to the coding systems used and the definitions of ECAs. But notably, a study that did not fit the inclusion criteria for my review also reported that the association with maternal age at delivery was restricted to syndromic cases only [260]. I found that isolated cases of CHD were rarely prenatally diagnosed (30% of cases). However, prenatal diagnosis rates were much higher for the more severe CHD subtypes and increased over the study period. This increase accounted for an increase in TOPFA over the study period.

My analysis of CHD in twins and higher order multiples showed that the prevalence in higher order multiples was 120.7 per 10,000 total births and in twins was 129.7 per 10,000. This equated to a 73% increased risk in twins compared to singletons, which is similar to that described in previous studies [113, 151, 156]. Uniquely, I found that the risk in MC twins exceeded that of DC twins, by around 80%. One hypothesised cause is that placental vascular anastomoses between co-twins' circulations, leads to fluctuations in blood flow during fetal heart development [165, 166]. Potentially, there are confounders such as the use of ART, maternal BMI and folic acid uptake, which may have contributed to the increased risk, but I was unable to investigate these factors. The prevalence of CHD in MC twins increased over time. It is possible that this is a real increasing trend, perhaps caused by increased uptake of ART, which reportedly increases the risk of MZ twinning [261]. Alternatively, this trend may have been caused by changes in the NICE guidelines, to allow increased prenatal screening among MC twins [162].

My systematic review and meta-analysis of the long-term survival of individuals born with CHD, identified 15 studies that had previously examined long-term survival [67, 86, 116,

181-192]. However, the maximum follow-up was 25 years [191, 192] and five of the articles reported five-year survival only [181, 182, 186, 187, 189]. Additionally, all studies were based on population from high income countries. Pooled one year survival was 87.0%, pooled five-year survival was 85.4% and pooled 10-year survival was 81.4%. Survival beyond age 10 was not reported by enough articles to calculate a pooled estimate. Survival varied by CHD subtype, with pooled five year survival being greatest for individuals with VSD (96.3%) and lowest for individuals with HLH (14.4%). Studies consistently showed that less recent year of delivery [67, 184, 191, 192], preterm delivery [182, 184, 185, 190], presence of ECAs and low birth weight [182, 185, 192] negatively impacted on survival. There was some evidence that non-White ethnicity negatively impacted on survival [182, 192]. Associations between mortality and socioeconomic status were non-significant although there did appear to be a linear increase in mortality with increasing deprivation [182, 190, 192]. Therefore, it is likely that the effect size of this association is small and the studies were not large enough to identify a significant difference.

My analysis of data from one BINOCAR linked to death registrations showed that one year survival was 89.1%, five year survival was 87.1%, 10 year survival was 86.7% and twenty year survival was 85.2%. Survival in my study was therefore similar to the pooled survival described in my systematic review. However, some of the data I analysed in my survival chapter also contributed to one of the articles included in my systematic review [116]. Consistent with my systematic review, I found more recent year of delivery, increased gestational age at delivery and high standardised birth weight decreased the risk of mortality. The presence of ECAs increased the risk of mortality. In terms of mechanisms, year of delivery positively impacted survival in the UK due to the improvements in surgical interventions, such as the introduction of the Fontan staged operation, the arterial switch operation and the conduit repair [197, 198] [232] [200]. The administration of new medical interventions, such as prostaglandin, also improved survival [203, 204]. Increased gestational age and birth weight were also protective, due to the decreased chances of co-morbidities such as necrotising entercolitis developing [235]. Cases with ECAs had a worse prognosis, likely due to the co-occurring congenital anomaly as opposed to the CHD. Perhaps the co-occurring anomaly meant that the individual was not stable enough to undergo intervention for CHD. There was some evidence that increased maternal age decreased the risk of mortality, although this did not quite reach statistical significance and was likely caused by confounding, given that there were more mothers of advanced maternal age in the more recent study years. As in my review, I did not find a significant association between deprivation and mortality. But overall, mortality decreased linearly with decreasing deprivation. I also found

that increased annual TOPFA rate decreased the risk of mortality and prenatal diagnosis increased the risk of mortality likely because prenatal diagnosis is a marker for greater CHD severity. There were less statistically significant risk factors for mortality when considering CHD subtypes individually, which in part might be due to low power.

The last phase of my thesis was to predict the future survival and birth prevalence of CHD in the North of England. The predicted 20-year survival of children with CHD was 98.7% for cases born in 2015, although this varied by CHD subtype. The predicted prevalence of CHD was 74.0 per 10,000 live births in 2015 and 68.8 per 10,000 live births in 2020, which equated to 235 and 201 cases, respectively.

10.2 Strengths of the thesis

In this thesis, I used population-based register data to examine the epidemiology of CHD. This approach has several advantages over alternative study-designs, such as hospital-based studies. Firstly, data is collected from multiple sources and therefore ascertainment, even of mild CHD subtypes, is high. All cases are confirmed by echocardiography, catheterisation or post-mortem to ensure that there are no false positives. Cases notified to NorCAS and CARIS are cross-validated with regional cardiac databases within local paediatric cardiology units, to ensure case completeness.

Given that the BINOCARs collect data on a small core set of variables, data is typically very complete for these variables. The BINOCARs receive notifications from prenatal ultrasound, fetal medicine and cytogenetic laboratories and are therefore able to collect data on cases that occur in TOPFAs, late miscarriages and stillbirths. This meant that I could estimate trends in prevalence over time regardless of changes in TOPFA and fetal death rates. Due to the population-based design of the registers, all cases are ascertained regardless of whether they survived until medical intervention or until a certain age. Indeed, NorCAS and CARIS include cases diagnosed up to age 12. This means that cases of CHD are included regardless of where they are on the spectrum of severity. Therefore, the statistics produced in this thesis are representative of all individuals with CHD. Additionally, cases born to mothers who reside in the areas covered by the registers but are born elsewhere are recorded on the CARs, again ensuring complete case ascertainment.

An advantage of using the NorCAS register was that it is linked to the NorSTAMP. This meant that I could examine the risk of CHD in multiple compared to singleton pregnancies, and uniquely, whether the risk was moderated by chorionicity. Using the NorCAS, I was also

able to access the month of birth and the monthly denominator data, which meant I could analyse trends after accounting for seasonality in live births in the general population.

Another strength of my analyses is that I had enough data to examine the prevalence and survival of CHD according to CHD subtype. This is vital given that the subtypes are so diverse in terms of aetiology, prognosis and health service provision. Additionally, analysing risk factors for prevalence and survival on CHD as a composite group can cause bias. For example, investigating the association between CHD survival and say, maternal age, could show that young maternal age is protective if the milder subtypes (with the best prognosis) are those associated with older maternal age.

10.3 Limitations of the thesis

There are several limitations to using population-based register data. For example, the data recorded on the CARs is that routinely recorded in the clinical setting and, therefore, not all variables of interest are available for analysis. For example, given the association between congenital anomalies and maternal BMI [4], it would have been interesting to examine this variable as a risk factor for increased prevalence and for survival. While some of the registers record BMI, it isn't one of the core variables. Additionally, information on ethnicity and smoking status is poorly recorded on the registers as this is not documented well in the clinical setting. Using information from clinical notes, the registers collect information on folic acid uptake. However, this is very incomplete and therefore could not be analysed. According to a recent systematic review, prenatal uptake of folic acid decreases the risk of CHD [262]. However, there are currently no UK studies on this. Furthermore, the BINOCARs do not record data on maternal medications or alcohol uptake which may increase the risk of CHD and potentially influence survival [43].

Another disadvantage is that the registers are not currently allowed to hold data on ART. This would have been interesting to examine as a risk factor for CHD, particularly as a risk factor for ToF, which increased over time in my study and in several others [53, 60, 79]. Moreover, it would have been interesting to see how this contributed to the increased risk of CHD in twins. Although I found the highest risk in MC as opposed to DC twins, there is increasing evidence that MZ twins are more common after ART [261]. MZ twinning may have become more common given the recent changes in the NICE guidelines, stating that one embryo should be implanted in the first round of IVF (in women aged <40) and two if the first round is not successful (or if the woman is aged 40-42) [170]. Previously, up to three embryos could

be implanted, which would have increased the chances of DZ twins or higher order pregnancies.

A further disadvantage of using register data is the detail of the case coding. The BINOCARs code all cases using the ICD coding system, meaning it is not possible to distinguish the severity of individuals with the same subtype. Hospital-based studies are likely to have access to more clinical information which would enable cases to be coded more sensitively, with a coding system such as the ISC which better accounts for severity (see Chapter 1). However, given the small case numbers it is also of benefit to code the subtypes more crudely in order to increase statistical power. A further issue in this thesis was the coding of cases with HRH. Changes between the ICD nine and ICD 10 classification systems meant that a new code was developed for cases of HRH. Because of this, there was an artificial increase in the prevalence of HRH. HRH is technically a secondary anomaly, which results from CHD subtypes such as PVA and TA. The easiest way to deal with this change would have been to code all cases of HRH according to their primary anomaly. Unfortunately, the primary anomaly was not detailed in 60% of HRH cases and therefore HRH had to be treated as a composite group of TA and PVA. While these subtypes are similar in terms of aetiology and treatment, it would have been more useful, in terms of prevalence and birth outcomes, to examine them separately. Fortunately this was not an issue in the survival chapter (Chapter 8) as none of these cases were initially coded under ICD 10 due to the earlier study period.

A major limitation of this work is that I was not able to analyse the impact of medical/ surgical intervention on survival. The type of intervention may impact survival. For example, the Fontan operation for HLH is associated with 47-85% perioperative survival, whereas comfort care results in certain death [217]. Combining all cases of HLH as I have remains informative in terms of health care planning, but may not be useful for parents who want to know post-operative survival of a child with HLH. Additionally, I was not able to examine the impact of morbidities such as sepsis or hypertension, which have been shown to increase the risk of mortality [20].

There is no universally adopted coding system for cases with multiple CHD subtypes. As described in Chapter 1, there are several methods that have previously been used. In this thesis, I used a hierarchy based on that by Khoshnood et al, which favours the CHD subtype of greatest aetiological severity [52]. Different approaches will have produced slightly different results in terms of prevalence and survival. For example, if like Wang et al [191], I had allowed each case to contribute to each of the relevant CHD subtypes, then my prevalence rates would have been greater for the milder CHD subtypes. Additionally, survival

would have been poorer for the milder subtypes if these cases co-occurred with severe subtypes.

A further study limitation is that survival analysis was performed on data from just one BINOCAR (the NorCAS), for cases born between 1985-2003. I had originally intended to link data from the six BINOCARs to death registrations, for cases born between 1985-2010. The data linkage was to be completed by the Health and Social Care Information centre (HSC IC). Unfortunately, at the time of my application, the HSC IC went through a moratorium while they addressed their practises relating to patient identifiable data. As a result, my application is still waiting to be approved by the HSC IC. The NorCAS data I analysed in Chapter 8 was a pre-existing data-set, which is why only cases born prior to 2003 were included. Had I successfully obtained the data from the six BINOCARS, this would have been a much larger data set. Therefore, I could have produced survival estimates to 20 years for the rarer CHD subtypes, such as SV or HLH. Additionally, with this larger dataset I would have had greater power to investigate risk factors for mortality. In the current analysis, multivariable analysis is carried out for only the more common CHD subtypes due to low power. Furthermore, risk factors such as standardised birth weight and annual TOPFA rate, were statistically significant when all CHD was considered as a composite group, but not for individual subtypes. While it is possible that the associations did not exist for the individual subtypes, it is likely that there were some type II errors caused by low power. In particular, it would have been interesting to examine the association between mortality and deprivation, which appears to have a small effect size.

10.4 Implications for practice

The information provided in this thesis has several implications for clinical practice. Firstly, I found that the total and live birth prevalence of CHD and most of its subtypes has remained stable over time amongst singletons. In 2015, the predicted live birth prevalence of CHD is 74.0 per 10,000 (235 cases in the North of England), falling to 68.8 per 10,000 (201 cases in the North of England) in 2020. This information is important for health service planning. However, I also identified an increase in the prevalence of CHD amongst MC twins, of 8% per year. While MC twin births account for just 0.6% of all births, on a population level (England and Wales) this amounts to an excess of approximately seven cases per year. Additionally, while I found a small increasing trend (3% per year) in the live birth of ToF, this equates to an excess of approximately 16 cases per year in England and Wales. While these numbers are relatively low, the diagnosis of CHD in pregnancy has a massive emotional impact on parents, and given the complex surgeries required for individuals with CHD, a

small increase in cases numbers can have large implications in terms of staff, facilities and costs.

Compared to singletons, I found a 49% increased risk of CHD in DC twins and a three-fold increased risk in MC twins. Women with twin pregnancies should be counselled on the risk of having a baby with CHD. This research emphasises the importance of the increased fetal cardiology assessment of women with twin pregnancies. While this was recently introduced in the NICE guidelines for MC twins, there is currently no such guideline for DC twins (see Chapter 1).

In the UK, there is little evidence that women of advanced maternal age are at increased risk of CHD. Therefore, in line with current guidelines (Chapter 1), these women do not need to be referred for fetal echocardiography scans unless other congenital anomalies are suspected.

Among individuals with CHD, the greatest mortality rate was observed within the first few weeks of life. However, after infancy, there remains a gradual decrease in survival which exceeds that of the general population. This information is important for clinicians when counselling parents who have had a prenatal diagnosis, and can aid decision making in terms of whether to continue with the pregnancy. However, the estimated survival for an individual with a prenatally diagnosed CHD was lower than for individuals without a prenatal diagnosis, because the prenatal diagnosis usually occurs for fetuses with the most severe form of a CHD subtype. The information is also important for parents who have child diagnosed prenatally, in order to help manage their expectations.

Long-term survival has been consistently improving for individuals with CHD. This has led to an emerging population of adults living with CHD. Given that these individuals require long-term follow-up and sometimes reoperation, this information is important for health service planning.

10.5 Further research

There are several areas of future research that have been highlighted in this thesis. Firstly, a larger population-based study is required to examine the association between deprivation and long-term survival in individuals with CHD. While my study, along with several others, did not find a significant association with deprivation [182, 188, 190-192], this is possibly due to low power, given that a linear association with a small effect size was observed. A larger study is required before deprivation can be ruled out as a risk factor for long-term survival. Even if the effect size is small, on a population-based level it might be quite important,

particularly if it is a modifiable risk factor. The association with deprivation, if it exists, may be related to uptake of prenatal screening, TOPFA rates, access to health care and time until surgery. A larger study would also be required to properly investigate risk factors for mortality for individual CHD subtypes. In my analysis, many of my univariable models were underpowered for individual subtypes and I did not have the power to perform multivariable regression for all CHD subtypes.

Further research regarding ART as a risk factor for CHD, particularly ToF, is required. Indeed, the increased risk of CHD in twins may be confounded by ART. Currently, it is not possible to link data on ART to CAR data in the UK, but this has been done in other populations [145, 168]. However, even these studies are flawed in that the control group (those without CHD), were those with congenital anomalies that were not hypothesised to be related to ART.

I was not able to examine the impact of ethnicity on survival. Previous studies have shown that non-White ethnicity is associated with improved prognosis [182, 188, 190-192]. However, all of these studies are based on populations in the USA. If this association exists, further research is required to assess whether it is a real difference or a product of confounding. Ethnicity may be acting as a proxy for deprivation, access to healthcare or uptake of screening, for example.

This thesis focuses on mortality among individuals with CHD. However, there remains a paucity of information regarding the quality of life and long-term morbidities among individuals with CHD. This information would be important for parents when a diagnosis of CHD is made prenatally.

Given that few population-based studies have examined surgical interventions or co-morbidities as predictors of CHD, this could be an important area of future research. This would bring together the richness of hospital-based data and the complete case ascertainment of population-based studies. In particular, it would be interesting to investigate how type and timing of surgical intervention impacts long-term survival. This information could also be used to examine the average 'cost' per case of CHD. Additionally, further research is required to examine the association between case volume and survival. A recent systematic review, which was conducted in order to inform the NHS review of CHD services, found some evidence that low case volume was associated with poorer prognosis [263]. However, the results varied between studies and were not hypothesised to be "directly causal" and no UK studies were identified [263].

While I have modelled and extrapolated the birth prevalence of CHD, it would be useful to predict the population prevalence of CHD, i.e. the number of individuals currently living with CHD. Given that these individuals require lifetime follow-up and often reoperation, this would be beneficial in terms of health service planning.

Appendix A) Chapter 6 publication

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Congenital heart disease

OPEN ACCESS

ORIGINAL ARTICLE

Increased risk of congenital heart disease in twins in the North of England between 1998 and 2010

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ABSTRACT

Objective To examine the relative risk (RR) of congenital heart disease (CHD) in twins compared with singletons, according to chorionicity.

Methods Twins and singletons with CHD notified to the Northern Congenital Abnormality Survey between 1998 and 2010 were included in this population-based study. Information on chorionicity was obtained from the Northern Survey of Twins and Multiple Pregnancy. Prevalence was calculated as the number of cases occurring in live births, late miscarriages (20–23 weeks), stillbirths (≥24 weeks) and terminations of pregnancy for fetal anomaly, per 10 000 total births. The risk of CHD in twins compared with singletons was estimated using Poisson regression.

Results There were 399 414 singleton births of which 2984 (0.7%) had CHD. Among 11 871 twin births, 154 (1.3%) had CHD; one twin was affected by CHD in 2.5% of twin pregnancies. Of 8605 dichorionic (DC) births and 2317 monochorionic (MC) births, 96 (1.1%) and 47 (2.0%) were associated with CHD. Compared with singletons, twins were at significantly increased risk of CHD (RR=1.73, 95% CI 1.48 to 2.04; p<0.001). MC twins were at 82% significantly increased risk of CHD compared with DC twins (RR=1.82, 95% CI 1.29 to 2.57; p<0.001). The RR of severe and mild CHD was particularly high in MC twins compared with singletons (292% increased risk, RR=3.92, 95% CI 1.25 to 12.30, p=0.02 and 207% increased risk, RR=3.07, 95% CI 2.20 to 4.28; p<0.001).

Conclusions Compared with singletons, twins were at increased risk of CHD, the risk being substantially higher among MC twins. This information is important for health professionals when counselling women with twin pregnancies.

INTRODUCTION

There is an increased risk of congenital anomalies in multiple compared with singleton pregnancies.[1–4] The risk among twins that share a placenta, monochorionic (MC) twins, exceeds that of twins that do not share a placenta, dichorionic (DC) twins.[1] The risk of congenital heart disease (CHD) among twins is less well researched. While several case series have investigated the prevalence of CHD in twins,[5–8] few studies have compared the rate with singletons.[1 4 9] Of those that have, the risk of CHD was significantly increased by between 47% and 63% in twins.[1 4 9] Even fewer studies have examined the risk of CHD by chorionicity. In Glinianaia *et al*'s[1] study, there was a 30% and 50% increased risk of CHD in MC and DC twins compared with singletons, but this only reached significance in DC twins. Herskind *et al* examined the relative risk (RR) in twins compared with singletons according to zygosity, a proxy for chorionicity given that all dizygotic twins are DC and approximately two-thirds of monozygotic twins are MC. Herskind *et al*[9] reported significantly increased risks of 35% and 30% in monozygotic and dizygotic twins, respectively.

The aim of this study was to examine the RR of CHD in twins compared with singletons, according to chorionicity and CHD severity.

METHODS

Data sources

The Northern Survey of Twin and Multiple Pregnancies (NorSTAMP) collects data on all multiple pregnancies to mothers residing in the North of England (figure 1). The North of England is a geographically defined area with a population of almost three million (with little immigration or emigration) and approximately 32 000 births per year. Multiple pregnancies are ascertained from the prenatal dating scan, the 20-week anomaly scan, and at delivery.[10] In addition to basic maternal and fetal characteristics, chorionicity is recorded by NorSTAMP. Data on chorionicity is collected throughout pregnancy but the final diagnosis of chorionicity for twins of the same sex is based on placental examination and histology.[10] If there is no pathological examination of the placenta, the diagnosis is made based on the prenatal ultrasound determination.

The NorSTAMP records are linked to the Northern Congenital Abnormality Survey (NorCAS). The NorCAS collects data on cases with congenital anomalies delivered to women residing in the North of England. Cases occurring in late miscarriages (20–23 weeks gestation), termination of pregnancy for fetal anomaly (TOPFA; any gestation), stillbirths (≥24 weeks gestation) and live births are notified to NorCAS. Cases are notified from multiple sources including antenatal ultrasound, fetal medicine, cytogenetic laboratories, the regional cardiology centre, pathology and paediatric surgery, ensuring high case ascertainment. Up to eight congenital anomalies per case are recorded.

Cases are coded according to the International Classification of Diseases (ICD) V.10. The European Surveillance of Congenital Anomalies (EUROCAT, a network of 38 registers in 20 European countries) exclusion list for minor anomalies is employed.[11]

Data on the annual number of live and stillbirths to mothers residing in the North of England

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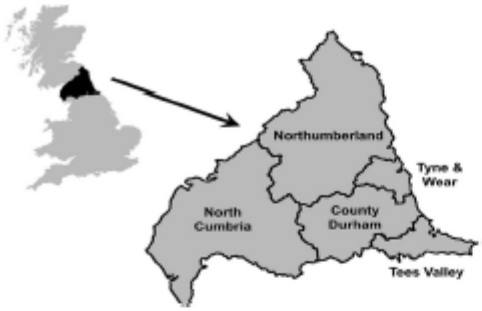

Figure 1 Map showing the region covered by the Northern Congenital Abnormality Survey (NorCAS) and the Northern Survey of Twin and Multiple Pregnancies (NorSTAMP).

(combined and by maternal age) was provided by the Office for National Statistics. Data on the annual number of twin live and stillbirths were provided by the NorSTAMP. The annual numbers of singleton births were calculated by subtracting the annual number of multiple births from the annual number of all births. Maternal age data were missing for 248 (2.1%) twin pregnancies and these were excluded from the denominator for analysis of maternal age.

Ethical approval

Parental consent is required for NorSTAMP. The NorCAS has approval from the Confidentiality Advisory Group of the Health Research Authority (PIAG 2-08(e)/2012), to hold data without consent and ethics committee approval (09/H0405/48) to undertake studies involving the data.

Case definition

All cases with a final diagnosis of CHD (ICD 10: Q20-26) notified between 1 January 1998 and 31 December 2010 were included. Cases with a minor CHD only, such as patent ductus arteriosus (PDA) with a gestational age <37 weeks, were excluded.[11] Cases known to occur with extra-cardiac anomalies (ie, congenital anomalies not of the cardiovascular system) are likely to have different aetiologies than cases with isolated CHD. For example, CHD occurring with chromosomal/genetic anomalies may result directly from chromosomal aneuploidy.[12] These cases are likely to have different risk factors, such as increased maternal age.[13 14] Analysis was performed on cases of isolated CHD only, to investigate the purest possible association between CHD and plurality.

Case coding

Twins were coded as MC or DC. Due to small case numbers, it was not possible to analyse the association between plurality and CHD according to CHD subtype. However, it was possible to analyse groups of CHD subtypes, which were classified according to severity. Based on the classification system outlined by Khoshnood *et al*,[15] cases of CHD were categorised as severe, moderate and mild CHD. However, we also included double outlet RV, interrupted aortic arch and mitral valve anomalies. The groups of CHD subtypes are shown in table 1. Cases with multiple CHD subtypes were categorised according to the CHD in the highest severity group. Cases included in Q20-26 but not described in one of the severity categories (eg, PDA ≥37 weeks gestation) remained unclassified.

Table 1 Frequency of CHD subtypes and severity categories according to plurality and chorionicity

CHD subtype	Twins (any chorionicity) N (% of 154)	Dichorionic twins N (% of 96)	Monochorionic twins N (% of 47)	Singletons N (% of 2984)
Severe CHD	7 (4.6)	4 (4.2)	3 (6.4)	132 (4.4)
Single ventricle	2 (1.3)	1 (1.0)	1 (2.1)	15 (0.5)
Hypoplastic left heart	2 (1.3)	1 (1.0)	1 (2.1)	76 (2.6)
Hypoplastic right heart	3 (2.0)	2 (2.1)	1 (2.1)	41 (1.4)
Moderate CHD	31 (20.1)	25 (26.0)	5 (10.6)	712 (23.9)
Pulmonary valve atresia	5 (3.3)	5 (5.2)	0	32 (1.1)
Common arterial trunk	0	0	0	20 (0.7)
Atrioventricular septal defect	2 (1.3)	1 (1)	1 (2.1)	70 (2.4)
Aortic valve atresia/stenosis	4 (2.6)	3 (3.1)	1 (2.1)	100 (3.4)
Transposition of the great vessels	2 (1.3)	1 (1.0)	1 (2.1)	145 (4.9)
Tetralogy of Fallot	6 (3.9)	5 (5.2)	1 (2.1)	117 (3.9)
Total anomalous pulmonary venous return	2 (1.3)	2 (2.1)	0	34 (1.1)
Coarctation of aorta	10 (6.5)	8 (8.3)	1 (2.1)	132 (4.4)
Double outlet RV	0	0	0	18 (0.6)
Interrupted aortic arch	0	0	0	11 (0.4)
Mitral valve anomalies	0	0	0	33 (1.1)
Mild CHD	106 (68.8)	63 (65.6)	35 (74.4)	1967 (69.9)
Ventricular septal defect	69 (44.8)	39 (40.6)	25 (53.2)	1392 (46.7)
Atrial septal defect	18 (11.7)	12 (12.5)	4 (8.5)	339 (11.4)
Pulmonary valve stenosis	19 (12.3)	12 (12.5)	6 (12.8)	236 (7.9)
Other CHD	10 (6.5)	4 (4.2)	4 (8.5)	173 (5.8)
Patent ductus arteriosus (≥37 weeks)	4 (2.6)	1 (1.0)	2 (4.3)	58 (1.9)
Total	154 (100.0)	96 (100.0)	47 (100.0)	2984 (100.0)

CHD, congenital heart disease.

Statistical analysis

Total birth prevalence was calculated as the number of cases (in live births, late miscarriages, stillbirths or TOPFAs) per 10 000 live and stillbirths (total births).

The unadjusted RR of CHD in twins compared with singletons was estimated using Poisson regression models with the number of cases of CHD as the outcome, log(total births) as the offset and plurality (singleton or twin) as an explanatory variable. Adjusted RRs were estimated by refitting the models to include year of delivery (continuous variable) and maternal age (<20, 20–29, 30–34 and ≥35 years). The interaction between year of delivery and plurality was investigated by refitting the model with a cross-product term. The unadjusted RRs of CHD associated with maternal age and year of delivery were also estimated using Poisson regression.

All statistical analyses were performed in Stata V.13; $p<0.05$ was considered statistically significant.

RESULTS

Between 1998 and 2010, there were 399 414 singleton pregnancies and 6101 twin pregnancies that resulted in (at least one) live or stillbirth in the North of England. This equated to 11 871 total births, given that only one twin was live or stillborn in 331 pregnancies. Of the twins, 4359 pregnancies (8605 births, 72.5%) were DC and 1170 pregnancies (2317 births, 19.5%) were MC, leaving 542 pregnancies (949 births, 8.0%) with unknown chorionicity. The proportion of twin pregnancies increased from 2.6% in 1998 to 2.9% in 2010, although this did not reach statistical significance (test for trend: $p=0.07$).

There were 4160 cases of CHD delivered between 1998 and 2010: 3965 singletons and 187 twins. Of the 187 twins with CHD, 114 (61.0%) were DC, 60 (32.1%) were MC and 13 (7.0%) had unknown chorionicity.

Extra-cardiac anomalies

Of the singletons with CHD, 700 (17.7%) occurred with chromosomal/genetic anomalies and 281 (7.1%) with structural anomalies. Of the twins with CHD, 15 (8.0%) occurred with chromosomal/genetic anomalies and 18 (9.6%) with structural anomalies. Twins with CHD were at significantly decreased risk of chromosomal/genetic anomalies compared with singletons (RR=0.45, 95% CI 0.28 to 0.74; $p<0.001$). The risk of structural anomalies was not significantly different in twins compared with singletons (RR=1.22, 95% CI 0.77 to 1.91; $p=0.40$). Cases with extra-cardiac anomalies were excluded from further analysis, leaving 2984 singletons and 154 twins with isolated CHD.

CHD subtypes, severity and concordance

Of the singletons with isolated CHD, 132 (4.4%) had severe CHD, 721 (23.9%) had moderate CHD, 1967 (65.9%) had mild CHD and 173 (5.8%) were of unclassified severity. Of the twins, 7 (4.5%) had severe CHD, 31 (20.1%) had moderate CHD, 106 (68.8%) had mild CHD and 10 (6.5%) were of unclassified severity. The distribution of CHD subtypes and severity categories according to chorionicity is shown in table 1.

There were eight sets of twins with concordant CHD (four with the same subtype), of which six were DC and two were MC.

Birth prevalence

There were 2984 singletons with isolated CHD, a prevalence of 74.7 per 10 000 total births (table 2); 0.7% of singleton pregnancies were associated with CHD. There were 154 twins with CHD, a prevalence of 129.7 per 10 000 total births; in 2.5% of twin pregnancies, at least one twin was affected by isolated CHD. Of the 154 twins with CHD, 96 occurred in DC and 47 in MC pregnancies, giving prevalence rates of 111.6 and 202.8 per 10 000 total births, respectively. At least one twin was affected by isolated CHD in 2.2% of DC twin pregnancies and 4.0% of MC twin pregnancies. The prevalence of severe, moderate and mild CHD are shown in table 2 by chorionicity. At least one twin was affected by severe, moderate and mild CHD in 0.1%, 0.5% and 1.7% of twin pregnancies, respectively.

Maternal age

Among singletons, there was no evidence that CHD was associated with maternal age ($p=0.53$). Among twins, the association between CHD and maternal age was of borderline significance ($p=0.07$), with mothers aged <20 years having an increased risk of a pregnancy associated with CHD than mothers aged 20–29 years (table 3). Among DC twins, there was no evidence of an association between maternal age and CHD ($p=0.41$) (table 3). Among MC twins, there was evidence of an association between maternal age and CHD ($p=0.01$), with mothers aged <20 years being at increased risk of a pregnancy associated with CHD compared with mothers aged 20–29 years (table 3).

Trends

The risk of CHD among singletons decreased significantly by 2% per year ($p<0.001$) (table 3). There was no evidence of a trend in CHD prevalence over time in twins (any chorionicity) ($p=0.95$) or in DC twins ($p=0.09$). In MC twins, the risk of CHD increased significantly by 8% per year ($p=0.04$) (table 3).

Risk of CHD in twins versus singletons

Twins were at 73% significantly increased risk of CHD compared with singletons ($p<0.001$) (table 4). There was a 78%, 46% and 81% increased risk of severe, moderate and mild CHD in twins (any chorionicity) compared with singletons

Table 2 Prevalence per 10 000 total birth (95% CI) of CHD in twins and singletons, according to CHD severity and chorionicity

	Twins			
CHD severity	Twins (any chorionicity)	Dichorionic twins	Monochorionic twins	Singletons
All CHD	129.7 (110.2 to 151.7)	111.6 (90.5 to 136.1)	202.8 (149.4 to 268.8)	74.7 (72.1 to 77.4)
Severe CHD	5.9 (2.4 to 12.2)	4.6 (1.3 to 11.9)	12.9 (2.7 to 37.8)	3.3 (2.8 to 3.9)
Moderate CHD	26.1 (17.8 to 37.0)	29.1 (18.8 to 42.9)	21.6 (7.0 to 50.3)	17.8 (16.5 to 19.2)
Mild CHD	89.3 (73.2 to 107.9)	73.2 (56.3 to 93.6)	151.1 (105.4 to 209.5)	49.2 (47.1 to 51.5)

CHD, congenital heart disease.

Statistical analysis

Total birth prevalence was calculated as the number of cases (in live births, late miscarriages, stillbirths or TOPFAs) per 10 000 live and stillbirths (total births).

The unadjusted RR of CHD in twins compared with singletons was estimated using Poisson regression models with the number of cases of CHD as the outcome, log(total births) as the offset and plurality (singleton or twin) as an explanatory variable. Adjusted RRs were estimated by refitting the models to include year of delivery (continuous variable) and maternal age (<20, 20–29, 30–34 and ≥35 years). The interaction between year of delivery and plurality was investigated by refitting the model with a cross-product term. The unadjusted RRs of CHD associated with maternal age and year of delivery were also estimated using Poisson regression.

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Severe CHD	5.9 (2.4 to 12.2)	4.6 (1.3 to 11.9)	12.9 (2.7 to 37.8)	3.3 (2.8 to 3.9)
Moderate CHD	26.1 (17.8 to 37.0)	29.1 (18.8 to 42.9)	21.6 (7.0 to 50.3)	17.8 (16.5 to 19.2)
Mild CHD	89.3 (73.2 to 107.9)	73.2 (56.3 to 93.6)	151.1 (105.4 to 209.5)	49.2 (47.1 to 51.5)

CHD, congenital heart disease.

Table 3 RR of CHD according to maternal age and year of delivery

Maternal age at delivery*	N, Unadjusted RR (95% CI)			
	Twins (any chorionicity)	Dichorionic twins	Monochorionic twins	Singletons*
<20	N=14 RR=1.93 (0.96 to 3.88)	N=5 RR=1.06 (0.33 to 3.44)	N=8 RR=3.37 (1.27 to 8.95)	N=290 RR=0.94 (0.83 to 1.07)
20–29	N=66 RR=1 (reference)	N=40 RR=1 (reference)	N=21 RR=1 (reference)	N=1491 RR=1 (reference)
30–34	N=40 RR=0.74 (0.50 to 1.10)	N=25 RR=0.76 (0.46 to 1.26)	N=11 RR=0.64 (0.31 to 1.33)	N=754 RR=1.04 (0.95 to 1.13)
≥35	N=34 RR=0.97 (0.64 to 1.47)	N=26 RR=1.22 (0.75 to 2.01)	N=7 RR=0.63 (0.27 to 1.48)	N=422 RR=1.03 (0.93 to 1.15)
Year of delivery	RR=1.00 (0.96 to 1.04)	RR=0.96 (0.91 to 1.02)	RR=1.08 (1.01 to 1.18)	RR=0.98 (0.97 to 0.99)

*Twenty-nine (0.7%) singletons had missing maternal age data and were excluded. Maternal age data were missing in 2.1% of twins without CHD so these were excluded from the denominator.
CHD, congenital heart disease; RR, relative risk.

(p=0.135, p=0.037 and p<0.001, respectively) (table 4), although this only reached statistical significance for moderate and mild CHD.

MC twins were at 82% significantly increased risk of CHD compared with DC twins (RR=1.82, 95% CI 1.29 to 2.57; p<0.001). Compared with singletons, DC twins were at 49% significantly increased risk of CHD (p<0.001) and MC twins were at 172% significantly increased risk of CHD (p<0.001) (table 4). DC twins were at 41%, 63% and 49% increased risk of severe, moderate and mild CHD, respectively (table 4), although this did not reach statistical significance for severe CHD (p=0.50, p=0.02 and p=0.002, respectively). MC twins were at 292% significantly increased risk of severe CHD (p=0.02) and 207% significantly increased risk of mild CHD (p<0.001). There was no significant effect among moderate CHD (p=0.64) (table 4).

Adjusting for year of delivery and maternal age had little impact on the RR of CHD in twins compared with singletons (table 4).

When considering all twins (any chorionicity) and DC twins, the interaction between year of delivery and plurality was not significant (p=0.45 and p=0.52, respectively). Among MC twins, there was a significant interaction between year of delivery and plurality (p=0.01), with the RR of CHD in MC twins compared with singletons increasing over the study period (interaction term: RR=1.11, 95% CI 1.02 to 1.20).

DISCUSSION

In this population-based study, we found a 73% increased risk of CHD in twins compared with singletons. MC twins were at 172% and DC twins were at 49% increased risk of CHD compared with singletons.

This is one of few studies to examine the RR of CHD in twins compared with singletons. The primary strength of this study is the use of population-based data derived from an established, high-quality, congenital anomaly register. Multiple sources notify the register of cases, ensuring high case ascertainment. Accurate diagnoses are achieved by the review of complex cases by paediatric pathologists and clinical geneticists and, where relevant, diagnoses are confirmed via postmortem. By linking to a population-based register of multiple pregnancies, we were able to estimate the RR of CHD according to chorionicity, which few studies have accomplished.[1 9] Data on chorionicity is unlikely to be misclassified, given that the final diagnosis of like-sex twins is based on placental examination and histology.

A further strength is that CHD occurring in TOPFAs, late miscarriages and stillbirths were included. TOPFAs are less frequent in twin compared with singleton pregnancies, so had they been excluded; our RR of CHD associated with twins may have been overestimated.[16] Stillbirth is more common in twin compared with singleton pregnancies, so excluding stillbirths could have diluted the RR of CHD.[16]

We examined the RR of CHD in twins versus singletons adjusted for confounding factors. Year of delivery is a potential confounder given that the twinning rate increased slightly over the study period. Maternal age may have been a confounder due to the association between increased maternal age and multiple pregnancy[17] and the increased risk of CHD with increased maternal age, which is reported in some, but not all studies.[18–21]

This study has some limitations. First, the sample size was small meaning non-significant results could have resulted from type II errors. Among MC twins, the significant association with maternal age in under 20s should be interpreted cautiously due to low case numbers. Additionally, we were only able to examine severity categories as opposed to subtypes. As NorSTAMP requires parental consent, chorionicity data were not available for all twins. However, chorionicity data were missing for just 7% of cases and 8% of the denominator. Moreover, eight sets of twins with CHD were from the same pregnancy. This violates one of the assumptions of Poisson regression, that all observations should be independent. However, after excluding eight cases (one out of each set), the RR reduced only slightly (unadjusted RR=1.63, 95% CI 1.38 to 1.93; p<0.001, RR=1.40, 95% CI 1.14 to 1.73; p=0.002 and RR=2.60, 95% CI 1.94 to 3.49; p<0.001 for all twins (any chorionicity), DC twins and MC twins, respectively). We did not have data on zygosity as these are not recorded on the NorSTAMP. However, chorionicity can be used as a proxy zygosity given that all MC twins are monozygotic and most (~90%) DC twins are dizygotic.[8] Lastly, we were not able to investigate the risk associated with assisted reproductive technology (ART) as the registers are not able to hold this information.

Our 73% significant increased risk of CHD in twins compared with singletons is slightly greater than previously reported.[1 4 9] Mastroiacovo *et al*[4] reported an increased risk of 51% in Europe and Latin America (1978–1995), Glinianaia

Table 4 RR of CHD in twins versus singletons, according to CHD severity and chorionicity

CHD severity	Twins (any chorionicity) RR (95% CI); p value		Dichorionic twins RR (95% CI); p value		Monochorionic twins RR (95% CI); p value	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
All CHD	1.73 (1.48 to 2.04); p<0.001	1.75 (1.48 to 2.06); p<0.001	1.49 (1.22 to 1.83); p<0.001	1.51 (1.24 to 1.86); p<0.001	2.72 (2.04 to 3.62); p<0.001	2.76 (2.07 to 3.69); p<0.001
Severe CHD	1.78 (0.83 to 3.82); p=0.14	1.82 (0.85 to 3.90); p=0.12	1.41 (0.52 to 3.80); p=0.50	1.39 (0.51 to 3.76); p=0.52	3.92 (1.25 to 12.30); p=0.02	3.90 (1.24 to 12.27); p=0.02
Moderate CHD	1.46 (1.02 to 2.10); p=0.04	1.54 (1.07 to 2.20); p=0.02	1.63 (1.09 to 2.43); p=0.02	1.67 (1.12 to 2.49); p=0.01	1.21 (0.50 to 2.92); p=0.67	1.24 (0.51 to 2.98); p=0.64
Mild CHD	1.81 (1.49 to 2.20); p<0.001	1.80 (1.47 to 2.20); p<0.001	1.49 (1.16 to 1.91); p=0.002	1.50 (1.17 to 1.93); p=0.001	3.07 (2.20 to 4.28); p<0.001	3.12 (2.23 to 4.36); p<0.001

*Adjusted for year of delivery and maternal age. Maternal age was missing in 29 (0.7%) singleton cases and so these cases were excluded. Maternal age data were missing in 2.1% of twins without CHD so these were excluded from the denominator.
CHD, congenital heart disease; RR, relative risk.

et al[1] reported an increased risk of 47% in the North of England (using a subset of the present data, 1998–2002) and Herskind *et al*[9] reported an increased risk of 63% in Denmark (1977–2001). In our study, the RR of CHD in MC twins increased over the study period, so we may have found a greater RR due to our more recent study period. The increase in risk may be a result of increased screening of MC twins, given that the increased risk of congenital anomaly in MC twins has become more widely known over time. In the UK, the National Institute for Health and Care Excellence (NICE)[22] guidelines were updated in 2011 to recommend at least nine antenatal scans for MC twin pregnancy. This may have had particular impact if diagnosis of mild CHD improved, due to technical developments.

We identified a greater risk of CHD in MC compared with DC twins. Conversely, in the study by Glinianaia *et al*,[3] there was no significant difference in the RR by chorionicity, but just nine cases in MC twins were examined. Herskind *et al*[9] estimated the RR of CHD according to zygosity, finding no significant difference in risk. However, bias may have been incurred due to missing zygosity information. Indeed, in their cases with missing zygosity, the RR of CHD was greater than that of all twins (RR=2.41, 95% CI 2.07 to 2.80). Had a higher proportion of monozygotic twins had missing zygosity, this could partly explain why monozygotic twins were not at increased risk. Lastly, Herskind *et al*[9] included only live births, which may have impacted on their results.

We found a significant increased risk of moderate and mild CHD in twins (any chorionicity) compared with singletons. While the risk of severe CHD was increased, it did not reach statistical significance, likely due to low power. The RR was significant among MC twins, due to the larger effect size, although this should be interpreted cautiously due to low sample size. Several studies have examined the RR of CHD in multiples compared with singletons by CHD subtype.[3 4 9] Significant increased risks have been reported for ventricular septal defect (VSD), atrial septal defect, single ventricle, tetralogy of Fallot, atrioventricular septal defect and coarctation of aorta, although the effect sizes vary by study. Herskind *et al* uniquely examined subtypes according to zygosity, but could only examine VSD in monozygotic twins due to low sample size, finding a 73% increased risk compared with singletons.

The aetiology of CHD is becoming more researched and is hypothesised to be of both genetic and haemodynamic origin.[23] The aetiology of the increased risk of CHD in twins is unresolved. Twin to twin transfusion in MC twins was identified as an important risk factor for CHD.[8 24] However, this does not explain why there would be an increased risk in DC twins. Others hypothesise that placental vascular anastomoses between the monozygotic co-twins' circulations may lead to fluctuations in blood flow during fetal heart development, causing CHD.[25 26] If the aetiology of CHD in twins is predominantly haemodynamic as opposed to genetic, this may explain why chromosomal anomalies were less common in twins with CHD compared with singletons. Alternatively, monozygotic twinning itself is hypothesised to be part of a morphogenic anomaly which leads to a congenital anomaly.[27] Given that all MC twins are monozygotic and around 10% of DC twins are monozygotic, this might explain why there was an increased risk in both MC and DC twins and why the effect size was greater in MC twins. However, previous research also found an increased risk among dizygotic twins.[9] Perhaps the increased risk in DC twins could be related to the use of ART, which can result in twin pregnancy and has been linked to an increased CHD prevalence.[28]

Key messages

What is already known on this subject?

- Twins, in particular monochorionic twins, are at increased risk of congenital anomaly compared with singletons.
- Existing research suggests there is an increased risk of congenital heart disease (CHD) in twins compared with singletons.
- The effect of chorionicity and CHD severity on the increased risk in twins is less well researched.

What might this study add?

- Twins are at 73% increased risk of CHD compared with singletons.
- The risk among monochorionic (MC) twins exceeded that of dichorionic twins, with an increased risk of 82%.
- The prevalence of CHD in MC twins has increased over time.

How might this impact on clinical practice?

- Twin pregnancies, in particular MC twin pregnancies, require increased antenatal surveillance for CHD.
- This information is important for health professionals when counselling women with a twin pregnancy.

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Contributors Both authors have read and approved the final version of the manuscript before submission. JR conceived the project and critically reviewed the manuscript. KEB performed the data analysis and drafted the manuscript. Both authors were involved in the interpretation of the data and have given final approval to submit the paper.

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Competing interests None declared.

Ethics approval CAG.

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix B) CAG and REC approval

NHS
Health Research Authority
Confidentiality Advisory Group
On behalf of the Secretary of State for Health

Professor Judith Rankin
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13 November 2013

Dear Professor Rankin

Study title: **Survival of children born with congenital heart disease**
CAG reference: **CAG 5-08(b)/2013**
IRAS Project ID: **134475/481044/4/341**
REC reference: **13/NE/0188**

Thank you for your research application, submitted for approval under the Health Service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent. Approved applications enable the data controller to provide specified information to the applicant for the purposes of the relevant activity, without being in breach of the common law duty of confidentiality, although other relevant legislative provisions will still be applicable.

The role of the Confidentiality Advisory Group (CAG) is to review applications submitted under these Regulations and to provide advice to the approving bodies on whether an application should be approved, and if so, any relevant conditions. Following recent legal advice, please note that research applications covering data generated within England and Wales require an approval decision to be made jointly by the Health Research Authority and the Secretary of State for Health. This application was considered on 8 August 2013.

Secretary of State for Health and Health Research Authority approval decision

The Secretary of State for Health and the Health Research Authority, having considered the advice from the Confidentiality Advisory Group as set out below, have determined the following:

1. The application is approved, subject to compliance with the standard and specific conditions of approval.

This letter should be read in conjunction with the outcome letter dated 22 August 2013.

NHS
Health Research Authority
NRES Committee North East - Newcastle & North Tyneside 2
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2 August 2013

Professor Judith Rankin
Professor of Maternal and Perinatal Epidemiology
Institute of Health & Society
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Dear Professor Rankin

Study title:	**Survival and predictors of survival in children born with congenital heart disease**
REC reference:	**13/NE/0188**
Protocol number:	**N/A**
IRAS project ID:	**117092**

The Research Ethics Committee reviewed the above application at the meeting held on 24 July 2013. Thank you for attending to discuss the application with the student investigator Miss Kate Best.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Gillian Mayer, nrescommittee.northeast-newcastleandnorthtyneside2@nhs.net.

Ethical opinion

The Committee noted that this study involves a worthwhile subject area and members had enjoyed reading the application. The application was very informative and detailed and members were impressed with the information provided.

The Committee noted the independent review queried how robust the study will be in relation to achieving the research objectives.

You informed that the award was granted before the review was shown to you therefore you did not have to answer this question.

The Committee queried why data will only be retained for three months.

You stated that this referred specifically to the identifiable data only. The anonymised data will be retained for a longer period than three months.

The members of the Committee present gave a **Favourable** ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Appendix C) Data extraction form

Study Title:

Included birth years:

Study location:

Included CHD subtypes (ICD codes where possible):

How were cases with multiple CHD subtypes coded?

Were cases with extra-cardiac anomalies included, if so what was the percentage?

What was the maximum age limit at diagnosis?

How many cases of CHD were there?

How were cases ascertained?

What was the source of information on deaths?

Are survival estimates reported?

How are survival estimates reported (e.g. numerically or graphically)?

Survival estimates and 95% CIs

Subtype	1 year survival	5 years survival	10 year survival	15 years survival	20 year survival	25 year survival

Quality Assessment:

Quality items, potential bias	**Yes**	**Not stated**
The study population is adequately described for key characteristics (i.e. CHD subtype frequency, sex distribution, and ethnicity).		
Ascertainment is adequately described, including: method of ascertainment, included birth years, study location		
Inclusion and exclusion criteria are adequately described (i.e. ICD codes stated and inclusion of extra-cardiac anomalies.		
There is adequate ascertainment.		
POTENTIAL BIAS: The study sample represents the population of interest on key characteristics sufficient to limit potential bias to the results.		
The proportion of traced cases is stated and adequate		
Reasons for untraced cases are provided		
Untraced cases are adequately described for key characteristics (i.e. CHD subtype)		
There are no important differences between key characteristics and outcomes in participants who were traced and untraced.		
POTENTIAL BIAS: Untraced cases are not associated with key characteristics (i.e., the study data adequately represent the sample), sufficient to limit potential bias.		
Frequency of outcome is recorded		
The method of ascertainment of deaths is valid and reliable to limit misclassification bias		
POTENTIAL BIAS: The outcome of interest is adequately measured in study participants to sufficiently limit potential bias.		
There is sufficient presentation of results (i.e. number of cases and 95% CIs).		
The analysis is adequate for the design of the study.		
Results are not selectively reported		

Quality items, potential bias	Yes	Not stated
POTENTIAL BIAS: The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results.		

Appendix D) Published abstracts

Best KE, Rankin J. *Are twins at increased risk of congenital heart disease?* BJOG: An International Journal of Obstetrics and Gynecology, 2015. 122: p106.

Best KE, Draper E, Kurinczuk J, Stoianova S, Tucker D, Wellesley D, Rankin J. *Is congenital heart disease on the increase in the UK? A register-based study*. *Archives of Disease in Childhood Fetal and Neonatal Edition, 2014. 99: pA155*

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