



**The Prevalence and Survival of Children with Congenital Septal
Defects in the UK Using CPRD**

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Abstract

Background

Congenital heart disease (CHD) is a major contributor to infant mortality worldwide, accounting for a third of total congenital defects and a fifth of total global early neonatal mortality. Congenital septal defects (SD) are the most common CHD. This study assesses the prevalence and survival of children diagnosed with congenital septal defects in the UK.

Methods

All children who survived to at least the first 30 days after birth and registered with a GP within their first year of birth diagnosed with any CHD at any time in England between January 1998 and June 2017 were extracted from Clinical Practice Research Datalink (CPRD). Similar records for children diagnosed with other congenital anomalies were also obtained as well as children without any congenital anomaly constituting as the control group. These records were matched with the Office for National Statistics (ONS) death registration data, and the Index of Multiple Deprivation (IMD) data to allow assessment of death records and deprivation records, respectively. Prevalence risk ratios were calculated according to specific sociodemographic factors such as gender, year of birth, ethnicity, socioeconomic status, and geographical location for SD and its variants. Mortality risk ratios were calculated by gender, ethnicity, and socioeconomic status for SD and its variants. Also, in the absence of Hospital Episode Statistics (HES) data, I assessed the recording of CHD-related procedures/interventions in children's GP records as a measure of disease severity within the CPRD-based birth cohort used in this thesis.

Results

The prevalence of any CHD was 86.1 per 10,000 live GP-registered births (95% CI, 83.7 – 88.4). SD accounted for 53.4% of the total CHD within this population and the overall prevalence of SD was 48.64 per 10,000 live GP-registered births (95% CI 46.90-50.44). Of all SD diagnosis identified, 59.1% had a VSD diagnosis (35.50 per 10,000 live GP-registered births, 95% CI 34.02-37.04), 28.8% ASD (17.31 per 10,000 live GP-registered births, 95% CI 16.29-18.40), 6.5% for ToF (3.91 per 10,000 live GP-registered births, 95% CI 3.44-4.45), 0.3% for AoSD (0.17 per 10,000 live GP-registered births, 95% CI 0.09-0.31), 3.2% for AVSD (1.93 per 10,000 live GP-registered births, 95% CI 1.61-2.32), and 2.1% for unspecified SD (1.28 per 10,000 live GP-registered births, 95% CI 1.02-1.60). For any SD, gender was significantly associated with occurrence, with the prevalence in females being 15% more than males (PR (Male-Female) 1.15, 95% CI 1.07-1.24), however, there was considerable variation across specific SD variants. Whilst there was no evidence of an association with the year of birth, ethnicity, or socioeconomic status on the prevalence of overall SD, specific sub-analysis of the SD variants showed some associations. The prevalence of SD and its variants varied by geographical regions in England with the highest prevalence of any SD observed in the East Midlands.

The total number of deaths due to CHD from 30 days after birth to 19 years between January 1998 and June 2017 was 166 and the mortality rate was 5.6 (95% CI, 4.8-6.5) per 1,000 person-years. By SD variants, children with Aortopulmonary septal defect (54.9; 95% CI 13.7-219.6), Atrioventricular septal defect (7.2; 95% CI, 3.0-17.3), and Tetralogy of Fallot (8.1; 95% 4.6-14.3) had the highest mortality rates compared to other defects, although small numbers of children resulted in large confidence limits for some of these estimations.

The hazard of death for children with any septal defect was over 16-fold higher than for children without a CA (HR 16.2; 95% CI, 12.8-20.6); aHR 16.4, 95% CI, 13.0-20.9, $p<0.001$). Of this, children with Aortopulmonary septal defect had the highest hazard of death with a 160-fold increase compared to children without a CA (HR, 164.6, 95% CI, (41.1-659.5); aHR 159.3, 95% CI, 39.7-641.4, $p<0.001$) and was lowest for children with VSD (HR, 15.5, 95% CI, (11.7-20.5); aHR 14.9, 95% CI, 12.0-21.0, $p<0.001$). For overall septal defects, whilst there was no difference in the hazard of death or mortality rate by ethnicity, there was a significant association with socioeconomic status largely driven by ASD. Mortality rates by age groups between 0 and 9 years were also considered; whilst there was substantial variation within the various defects and age groups, there was a 12-fold increased risk of post neonatal death for all SD compared to children with no CA across age groups.

Of the total SD cases in this dataset, 5% were recorded to have had an intervention within the first year of life. Of the SD sub variants, 4% of each of the total VSD and ASD had an intervention recorded in population. The proportion of interventions was higher for the other SD sub variants with ToF, AVSD and AoSD at 29%, 36% and 40% respectively. Of the 381 CHD patients who had a recording of at least one CHD-related intervention, only eight (8) patients died. The subsequent analysis of the severity of SD variants in relation to mortality was therefore precluded as for all variants the number of deaths recorded was less than 5.

Conclusion

Using a study population derived through data linkage between CPRD, ONS, and IMD in England, this study reinforces broadly that AoSD, ToF, AVSD whilst being the least prevalent SD, constitute the highest mortality variants of SD whilst VSD and ASD (the more

prevalent forms) are not as lethal. Regardless, all SD variants considered had higher mortality than children without SD. Considerable effort is required to further improve the survival rates of children with these defects and ultimately improve the prognosis for children diagnosed with these defects. This study further raises the need for the consideration and development of region-specific and ethnicity-specific strategies to improving diagnosis and disease outcomes for children with a septal defect in England. As the dataset was not linked to HES, the ability to adequately assess the severity of septal defects in the study population was impaired. Using the limited codes for recording of CHD-related procedures within the GP-based dataset as a measure of severity unmasked the likely under-reporting of hospital events or procedures as children who should have received interventions based on their diagnosis did not always have this recorded in their GP record. Further studies incorporating the available information from HES are required to effectively determine the severity of septal defects and its variants especially with regards to how it affects mortality and mortality rates.

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Dedication

I dedicate this study to the memory of my brother, Raphael Olusola Lewis (PAPA), who died of an officially undiagnosed Atrial Septal Defect. And to all Nigerian children living with a congenital heart defect without adequate plan or provision for their survival.

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Abbreviations

AoSD	Aortopulmonary septal defect
ASD	Atrial septal defect
AVSD	Atrioventricular septal defect
AVV	Atrioventricular Valve
CA	Congenital anomalies
CHD	Congenital heart defects
CHF	Congestive heart failure
CoA	Coarctation of Aorta
CT	Computerized tomography
DORV	Double outlet right ventricle
GUCH	Grown-up Congenital Heart
HCM	Hypertrophic cardiomyopathy
HES	Hospital Episode Statistics
HLHS	Hypoplastic Left Heart Syndrome
HRHS	Hypoplastic Right Heart Syndrome
IAA	Interrupted aortic arch
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICV	Inferior vena cava
L-TGA	Congenitally corrected transposition of the great arteries
LA	Left atrium
LV	Left ventricle
MS	Mitral stenosis
MVP	Mitral valve prolapse
miRNA	MicroRNA
NorCAS	Northern Congenital Abnormality Survey
OCA	Other congenital anomalies
PAPVR	Partial anomalous pulmonary venous return
PDA	Patent ductus arteriosus
PFO	Patent Foramen Ovale
PPS	Peripheral pulmonary stenosis
PS	Pulmonary Stenosis

PVS	Pulmonary valve stenosis.
QoL	Quality of Life
RA	Right atrium
RV	Right ventricle
SD	Septal defect
SVAS	Supravalvular aortic stenosis
SVC	Superior vena cava
TA	Truncus arteriosus
TAPVR	total anomalous pulmonary venous return
TEE	transoesophageal echocardiography
TGA	Transposition of Great Arteries
ToF	Tetralogy of Fallot
TOPFA	Termination of Pregnancy for Foetal Anomaly
VSD	Ventricular Septal Defect

Chapter 1: Introduction to Congenital heart defects

1.1 Congenital heart defects

Congenital heart defects (CHD) also called congenital heart anomalies or congenital anomalies of the circulatory system refers to abnormalities in the heart structure and function which are usually present at birth although detection may not occur till post neonatal stages (1). The definition of Mitchell *et al.* has been generally adopted for CHD and it is, “a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance” (2). CHD are considered to be one of the key medical challenges present in this century (3).

1.1.1 Burden of CHD

CHD are a major contributor to infant mortality worldwide, accounting for a third of total congenital defects and a fifth of total global early neonatal mortality (4). CHD is known to significantly impair the quality of life (QoL), social, and educational participation of affected patients (5). The available data on the prevalence and long-term survival of CHD is quite contentious as there is huge variability in the reported prevalence across different settings ranging from 4-50 per 1000 live births (4). Therefore, this remains an area of active research.

Marked advances in paediatric cardiac care have led to an increase in survival and the transitioning of children with CHD into adulthood constituting a sub-specialty of cardiology referred to as Grown-up Congenital Heart (GUCH) disease (4,13,14) where there are now more adults living with CHD than children. These advances in technology include early detection, which includes prenatal diagnosis, prenatal preparation for optimal post-natal intervention, optimal perioperative care, and surgical and catheter interventions (4,13–15).

Currently, the adult CHD prevalence is thought to hover around 3000 in every 1 million people with an ever-growing trend in this group (6).

In a recent assessment of the global burden of CHD using the Global burden of disease database, comprising 195 countries in total, the worldwide CHD incidence was 17.9 per 1,000 births, with the incidence marginally higher in males than females (19.1 per 1000 births in males compared to 16.6 per 1,000 births in females) (7). Of the sub-variants of CHD, the variant with the highest incidence was ventricular septal defect (VSD) and atrial septal defects (ASD) accounted for a third of all cases (7). In Wu et al, other variants of CHD were broadly categorised into severe or critical malformations, but specific defects like aortopulmonary septal defects, tetralogy of Fallot, and atrioventricular septal defects were not considered. Whilst the overall CHD incidence was relatively steady between 1990 and 2017, the incidence varied by national socioeconomic growth status where there was an overall decline across all socio-economic statuses except in the highest socio-economic regions driven largely by an increase in VSD and ASD (average annual percentage change, AAPC=0.14, 95%CI: 0.10, 0.18) (7). Wu et al, showed that the global mortality rate from CHD dropped by almost 40% between 1990 and 2017, with the age-standardized mortality rate (ASMR) lower in females than males (7). The highest CHD-related deaths occurred in children under 5 years, with a 2% decrease in mortality rate from 1990 to 2017 (7). The highest death rates were recorded in countries with the lowest socioeconomic index (7). Although this study highlights the global trends in CHD, more evidence is needed for specific congenital anomalies in specific populations. For example, in Wu et al, the highest mortality rates from CHD were observed in low and middle-income countries in Africa and parts of Asia compared to more developed countries in Europe and North America (7). Although the

global decrease in CHD-linked mortality is often quoted, this masks a disproportionate increase occurring in the poorest parts of the world.

Within the same time frame, another study assessing the global burden of CHD reports a 34.5% reduction in global mortality from 1990 to 2017 (8). This decline was steeper with increasing socioeconomic index (8). Furthermore, about 70% of all recorded deaths in 2017 occurred in 1-year-old infants (8). Other studies also suggest the increased likelihood of mortality before the age of one in children with complex forms of CHD such as transposition of the great arteries (9). This suggests that the continuous understanding of the prevalence and survival of children diagnosed with CHD remains an important question. This need is further emphasised by the observation that there was about a 20% increase in the number of people living with some form of CHD globally in the 27 years between 1990 and 2017 (8). This correlates with advancement in medical management resulting in an overall increase in a global aging population.

There remain conflicting results for the prevalence of CHD globally between the last 30 years. Whilst Zimmerman et al. reported a 4.2% increase in birth prevalence of all CHD when specific variants are considered, they observed a decrease in the prevalence of VSD and ASD within the study population between 1990 and 2017 (8). Furthermore, a meta-analysis by Liu et al. of 260 studies comprising of over 130 million births found the average prevalence of CHD was 8 /1000 births with an increase from 4.547/1000 (95 CI, 3.664 - 5.526) in 1970–74 to 9.410/1000 (95 CI, 8.602-10.253) in 2010–17 ($P < 0.001$) (10). In contrast to Zimmerman et al.'s findings, Liu et al. reported an increase in the prevalence of all CHD including ASD and VSD. This suggests a need for continuous research into the prevalence trends in CHD, especially in specific populations.

The survival rate for children with CHD beyond the first year of life is now reported to be above 80% (11). With the increasing number of children and adolescents living with CHD, it is important to continuously study factors affecting their long-term prognoses such as ethnicity and socioeconomic status.

The epidemiology of SD relating to prevalence and mortality is explored further in chapters 4 and 5, respectively. But first, the aetiology of specific septal defects is explored in more detail in this chapter.

1.1.2 The physiology of the heart

In an embryo, the heart is believed to be the first organ to develop due to its necessity in nutrient circulation and waste removal. Anatomically, CHD affects various parts of the heart (12,13). To evaluate this, it is important to consider the anatomy and optimum functioning of the heart. The human heart beats approximately 100,000 times a day to allow the circulatory system to circulate oxygen and nutrients around the body as well as removing carbon dioxide and unwanted materials for clearance (14). The heart is divided into 4 chambers consisting of 2 upper atrial chambers (right atrium and left atrium) and 2 lower ventricular chambers (right ventricle and left ventricle) (Figure 1.1). The right atrium and ventricle act to collect and pump deoxygenated blood to the lungs via the pulmonary artery where gaseous exchange occurs whilst the left atrium and left ventricles act to collect oxygenated blood and pump it throughout the body via the aorta. Coronary arteries supply the heart itself with oxygenated blood. The septum is the wall that separates the right side from the left side of the heart. Veins are important for circulating blood from the rest of the body to the heart. The inferior vena cava (IVC) is a large vein that carries deoxygenated blood from the lower body into the

heart, while the superior vena cava (SVC) carries deoxygenated blood from the upper part of the body (above the diaphragm) to the heart. Both empty into the right atrium. The pulmonary veins carry oxygenated blood from the lungs to the heart via the left atrium (14).

Blood flow in the heart is tightly regulated by heart valves which open and close in a one-way direction. There are multiple heart valves such as the tricuspid valve, the mitral valve, the pulmonary valve, and the aortic valve. The tricuspid valve is the valve between the right atrium [RA] and the right ventricle [RV]. The mitral valve is the valve between the left atrium [LA] and the left ventricle [LV]. The pulmonary valve is the valve that controls outflow from the RV into the pulmonary artery, while the aortic valve is the valve controlling the outflow from the LV into the aortic artery (14). CHD can occur in either the heart's walls, valves, arteries, veins, and blood circulation, causing an obstruction in the physiological circulation of blood in the heart or an alteration in the direction of blood flow (12,13). The classification of CHD is usually done based on the structural aetiology or pathophysiology of the disease.

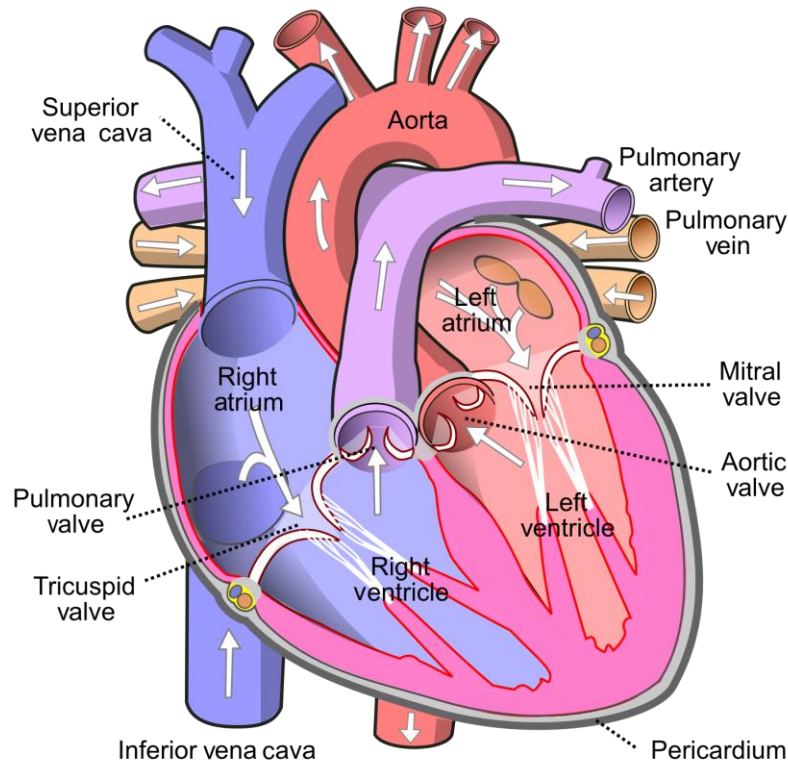


Figure 1.1 The physiology of the human heart. "Diagram of the human heart (cropped).svg" by Wapcaplet is licensed under CC BY-SA 3.0.

1.1.3 Classification of congenital heart disease

Many different classifications of CHD have been suggested, based on size, complexity, structure, aetiology, or clinical presentation of the disease without a consensus method. One classification system of congenital anomalies (CA) is found in chapter XVII (Congenital malformations, deformations, and chromosomal abnormalities [Q00-Q99]) of the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). The Q20-Q28 sub-chapter details nine types of CHD classified based on the heart's anatomy affected and comprising 73 subtypes of CHD (15). CHD is also classified as either cyanotic or acyanotic (12), isolated or complex, and simple or major/severe/ critical (16,17).

CHD is cyanotic when a child turns blue due to lack of oxygen either because the defect prevents proper oxygenation of blood or inhibits the circulation of oxygenated blood (12) whilst, CHD is acyanotic when the defect does not affect the distribution of oxygen in the blood (Figure 1.2). Isolated CHD refers to a single type of CHD while complex CHD can be either more than one CHD subtype or a CHD subtype in conjunction with other congenital anomalies (OCA) (16,17). A simple (minor, non-critical) CHD is an asymptomatic one that may not require any form of intervention while major/severe/critical is symptomatic and requires interventions early in life to forestall fatality. Size also defines the simplicity or complexity of defects with small defects needing no interventions classified as minor or simple and large defects needing intervention referred to as major or severe. CHD is often associated with a distinguishable pattern of anomalies that are causally related called syndromes (18). Some CHDs are defined as rare; these are defects with <5 per 10,000 in prevalence (18,19).

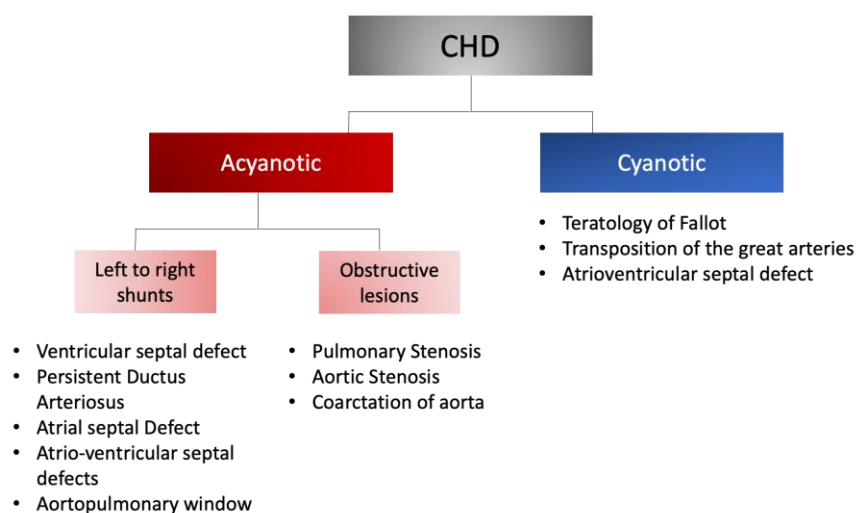


Figure 1.2 Classification of congenital heart defects. Image drawn by author according to information from (20).

There is also an anatomical classification that is dependent on the affected component of the heart. Examples of anatomical classifications are atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA) (21). A simple/mild CHD consists of small holes in the walls of the heart or the slight narrowing down of valves, arteries, or veins. Symptoms are often absent in most isolated simple CHD and when incidentally diagnosed, treatments may not be required (1,10). CHD becomes moderate when there is more than one simple CHD, holes in heart walls are larger, and/or valves are stenotic (fuse or thicken), or insufficient (regurgitates) enough to affect blood circulation. Thus, ASD, VSD, PDA, and Pulmonary Stenosis (PS) can all constitute moderate CHD if the holes are large enough or valves restrict blood movement enough (21). Symptoms of moderate CHD can be seen pre or perinatally and treatment is commenced shortly after birth (21). CHD is said to be severe when valves are absent (atresia), chambers are not well developed (hypoplastic), arteries are switched, or there are multiple defects associated in an individual (21). Symptoms are often diagnosed prenatally, e.g., Hypoplastic Left Heart Syndrome (HLHS), Hypoplastic Right Heart Syndrome (HRHS), Tetralogy of Fallot (ToF), and Transposition of Great Arteries (TGA). In these defects, systemic blood circulation is greatly impaired that the neonate turns blue (cyanotic). Cyanotic CHD patients require immediate surgery for survival (12,21).

Congenital heart defects have different degrees of severity, with varying degrees of associated mortality and morbidity. About 70 years ago, only 1 in 5 infants born with a moderate/complex/severe form of CHD would survive their first year; in recent years this has increased to over 9 out of 10 with advances in diagnosis and interventions (22). CHD diagnosis, treatment, outcomes, and survival are dependent on the severity of the subtype (23). Defects could be simple, complex, or critical (24). In relation to SD, though VSD and ASD are considered simple defects, duplicity and/or large size of these simple defects or the

presence of another subtype of CHD can easily make these defects complex. Within the SD variants of CHD, ToF is a complex CHD, and depending on the size and duplicity of defects encountered, AVSD could constitute a complex CHD, AoSD is rare but in most cases is both complex and critical (25). ToF babies are most often cyanotic at birth, while depending on the size and/or duplicity of defects, AVSD and AoSD could be as well (26). For these three defects, the only treatment is often interventional as soon as possible after diagnosis which in most cases is when the child is either a neonate or an infant (25).

SD are the most encountered subgroup of CHD for a quantifiable study. The natural history of CHD has been studied more in variants of SD (27–34) simply because these variants present different severity/complexity of the total defects and the available numbers allow for quantifiable and significant analysis. It has been possible to compare a mild untreated case of VSD to a complex case of VSD with intervention (27), VSD in infancy (35), and treated and untreated ASD over a long period of time (27,32). In comparison, severe defects like the Hypoplastic Left Heart Syndrome (HLHS) and/or Hypoplastic Right Heart Syndrome (HRHS) have such high neonatal mortality that studies on them often end at most in infancy. Historically, the study of the variants of SD has added novel knowledge to the total knowledge of CHD and has made long term studies possible.

1.1.4 Aetiology and management of CHD

Causes of CHD include genetic or chromosomal abnormalities as seen in syndromes, maternal factors which can be excessive alcohol intake during pregnancy, medication intake, or maternal existing diabetes or infection during the first trimester of pregnancy, for example, Rubella virus or measles (36,37). CHD can be diagnosed prenatally by foetal echocardiogram

or postnatally using echocardiogram, electrocardiogram, chest X-ray, pulse oximetry (in cases of low blood oxygen), and cardiac catheterization (12,36,37). Some are diagnosed in childhood, adolescence, and adulthood; sometimes, diagnosis is only made as part of an autopsy (12). Symptoms include a blue tinge to the skin, rapid breathing, rapid heartbeat, oedema in the ankles/legs, tummy or around the eyes, shortness of breath, extreme tiredness, and fatigue after birth (12,36). Other symptoms include retardation in growth, infections in the throat, respiratory tract, lungs, and sinuses, heart infection, endocarditis, pulmonary hypertension, high blood pressure, and deficient heart function which may lead to heart failure later in life (37). Major or severe CHD require intervention which can either be surgical or catheter; in most cases, patients are monitored for life either for the primary defect or for associated long-term outcomes (12).

Each subtype of CHD has a management protocol including the optimal time of diagnosis and sequence of treatment (12). There is no cure for CHD; care is palliative with life-long expert management required to optimize outcomes in critical/major and/or moderate defects (38). However, studies have shown that the timing of diagnosis and timely intervention is related to both short and long-term outcomes and survival (24,39–41). Despite being a congenital anomaly, many more studies have been done on the adult population than on the child population with most of the studies done on health outcomes and survival being on the adult population (24,42). The few studies on health outcomes and survival in the child population have been limited to very severe CHD (43–45) and to immediately after perinatal surgery (44,46,47). Some studies have assessed survival in both the adult and child populations within the same study (48,49) while others have looked at congenital anomalies in general, thereby only focussing on few CHD subtypes (28). Other studies have been done

using non-UK population (50,51), have a short follow-up time (44), or based on the quality of life of children and their cognitive and developmental growth after the intervention (49).

Whilst there is an increasing number of studies evaluating the prevalence of congenital defects generally and developing strategies to improve health outcomes in this population, a similar analysis of individual septal defects remains sparse. Since heart defects are so varied in anatomy and aetiology, it is helpful to consider specific anatomical subgroups (52). Thus, the focus of the study from this point on is congenital cardiac septal defects, and references to other subtypes of CHD will be for comparison purposes only.

1.2 The biology of congenital cardiac septal defects

CHD is caused when there is a disruption in the normal development of the foetal heart (36). In congenital cardiac septal defects (SD), there is a disruption in the development of the wall (septum) that separates the right part from the left part of the heart creating an opening (53). The variants of SD diagnoses described in Q21 of chapter XVII of ICD-10 (Table 1.1) are unique in the location of the opening created by this disruption (15). Thus, for example, an opening between the lower chambers of the heart (ventricles) results in a VSD.

Table 1.1: Types of congenital malformations of the cardiac septa according to ICD-10-CM (15)

Congenital malformations of the cardiac septa	ICD-10-CM
Ventricular septal defect (VSD)	Q21.0
Atrial septal defect (ASD)	Q21.1
Atrioventricular septal defect (AVSD)	Q21.2
Tetralogy of Fallot (ToF)	Q21.3
Aortopulmonary septal defect (AoSD)	Q21.4
Other congenital malformations of cardiac septa (other SD)	Q21.8
Unspecified congenital malformation of the cardiac septum (Unspecified SD)	Q21.9

SD are the commonest CHD (54). They fit into the defining terms used for all CHD subtypes. Thus, SD can be either simple (minor, non-critical) or severe (major, critical), isolated or complex, cyanotic or non-cyanotic, and common or rare. The size of the SD can be the difference between a simple or severe SD. The size of the defect determines the haemodynamic consequence and symptoms exhibited, which will, in turn, determine the timing of diagnosis and management protocol employed for treatment. Thus, small-sized defects without haemodynamic consequences constitute simple defects and large-sized defects with haemodynamic consequences constitute severe defects. When defects exist solely, they are termed isolated. When defects exist, on one hand, in association with other cardiac defects, they constitute a complex defect or on the other hand, isolated septal defects may exist in association with other non-cardiac genetic/chromosomal anomaly to constitute either a complex defect or be a part of a syndrome. For example, a multiple of the same isolated defect in one individual can constitute a complex defect as seen in the “Swiss-

cheese” type VSDs where there are several holes along the ventricular septum (54). Various isolated defects may constitute a major defect as seen in the case of ToF which comprises a VSD and pulmonary stenosis (PS) in combination with an overriding aorta and right ventricular hypertrophy (12).

1.2.1 Ventricular Septal Defect (VSD)

1.2.1.1 Presentation

VSD is an opening in the ventricular septum which is the wall dividing the two lower chambers (ventricles) of the heart and it is the most common CHD (12,21,55). This opening or hole in the wall between the ventricles causes oxygen-rich blood from the left ventricle to mix with oxygen-poor blood in the right ventricle. The earliest classification of isolated forms of VSD by Bloomfield was based on the size, amount, and direction of blood movement and resistance to blood flow in the pulmonary circulation (56). Based on this classification, VSD would be classified as complicated if there is an elevated pulmonary vascular resistance and as uncomplicated in the absence of pulmonary vascular resistance. Soto et al. classified VSDs based on the ventricular septum having muscular and membranous portions (57). Thus, defects seen around the muscular septum are referred to as muscular VSDs (inlet, trabecular, or outlet (infundibular)). Those found around the membranous portions but having rims of muscular attachment are referred to as peri membranous defects while those found in the septum adjacent to the arterial valves are referred to as sub arterial infundibular defects.

Penny and Vick posited that there is no universally agreed consensus on the classification for VSDs and based theirs on the location of the defect as either within the muscular septum or at its margins (58). Like the classification of Soto et al., they divided VSDs into muscular

defects, those of the margins of the muscular septum related to the atrioventricular valves (peri membranous) or those of the arterial valves (juxta-arterial or sub arterial) or both.

Generally, VSDs are classified based on their location on the ventricular septum (55,57–60) while the severity and thus, the prognosis, is based on the size, haemodynamic shunt, and complications resulting from these and other associated defects (55,56,58,61–63). The size of the opening determines the volume of blood that passes from the left ventricle (LV) into the right ventricle (RV) and the lungs; the larger the volume of blood that passes through, the bigger the pressure built in the RV and the lungs. VSD is an intrinsic feature in Tetralogy of Fallot (ToF) or univentricular atrioventricular connection and is seen in association with Transposition of the Great Arteries (TGA), congenitally corrected transposition, Coarctation of Aorta (CoA), or interruption (12,58). In their study in the Netherlands, Menting et al. found 27 of their 91 VSD patients to have one or more associated cardiac lesions. This included 11 with patent foramen ovale (PFO: included as a defect only if the intervention had been carried out to close it), 10 pulmonary stenoses (PS), six patent arterial duct, five CoA, four atrial septal defects (ASD), two mitral stenoses (MS), and one aortic stenosis (AS) (63).

The overall CHD prevalence is dependent on VSD prevalence especially in the age of echocardiographic diagnosis that makes the identification of very small muscular VSDs possible. There is some form of controversy on which VSD sub-type is seen more frequently. Congenital Heart Defects UK posits that peri membranous VSD is seen in 75% of all VSD cases while muscular VSD is seen in 20% of all VSD cases (12) although the age of the population was not mentioned. In a study of 3,240 infants to determine CHD prevalence, Reller et al. found muscular VSD to be prevalent with 27.5/10,000 births as against 10.6/10,000 births for perimembranous VSD (67). The size of the opening will determine the

symptoms seen, the severity of the condition, and the age symptoms will be presented (1). Though symptoms often occur in infancy, each child may present differently with VSD symptoms. Symptoms include fatigue, sweating, rapid breathing, heavy breathing, congested breathing, lack of interest in feeding or tiring out while feeding, and poor weight gain (1, 33, 34).

1.2.1.2 Diagnosis

The size of the hole in a VSD will determine the symptoms, if any, that are exhibited (33). A physician may hear a murmur in the heart, the loudness, and location of which may require confirmatory tests (1, 34). A chest x-ray will show the image of the heart which may show the RV to be enlarged or might have changed due to the pressure it is handling; an electrocardiogram (ECG or EKG) records the electric activities of the heart and may show arrhythmias or spot heart muscle stress (1, 33, 34). An echocardiogram (echo) uses sound waves to evaluate the structure and function of the heart and its valves; it can show the size of the opening and the pattern and volume of blood flow through the opening (1, 33, 34). Cardiac catheterization is an invasive procedure that gives thorough information on the inside of the heart (1, 33, 34).

1.2.1.3 Treatment

The course of treatment will depend on the child's age, overall health, medical history, and extent of disease, tolerance for medications, procedures or therapies, the prognosis of the defect, and consent from parents (1). A fairly-sized VSD that is symptomatic and likely to cause right ventricular and lung damage will require surgery to close the opening (1, 33). Interventional cardiac catheterization may also be used instead of surgery (1, 33). A catheter is passed into the heart through the groin. Once in place, a septal occluder is passed through

to close the VSD. Treatment may simultaneously require medications that strengthen the heart muscles to work better (digoxin) or one that helps the kidney retain more fluids in the body (diuretics); antibiotics are needed for infection control during procedures or for such activities as dental work to prevent endocarditis. Painkillers are given to manage pain (1, 32-34).

1.2.1.4 Outcomes

Outcomes are dependent on the type of VSD and the timing of diagnosis (1). With early diagnosis and repair, the outcome is tremendous and requires minimal follow-up. When diagnosed later in life, if left untreated or if there is a complication after the procedure, outcomes are poor including pulmonary hypertension; Eisenmenger's syndrome (an irreversible and progressive pulmonary and vascular obstructive disease)(1, 32, 34); aortic insufficiency or regurgitation (the leaking of the aortic valve) (34), infective endocarditis and heart failure (also referred to as congestive heart failure [CHF]) which is the inability of the heart to pump blood sufficiently to maintain blood circulation in the body) (34).

1.2.2 Atrial Septal Defect (ASD)

1.2.2.1 Presentation

ASD refers to birth defects featuring holes in the wall that separates the two upper chambers (atria; singular: atrium) of the heart (12,68,69). Depending on the size of the hole, considerable amounts of oxygen-rich blood from the left part of the heart mixes with oxygen-poor blood in the right side of the heart (12,70). This movement of blood from the left to the right is called a shunt (12,71). An opening between the atria referred to as the foramen ovale is normal in foetal circulation, however, this is expected to close around birth (12,70,71). An

asymptomatic unclosed opening between the atria can be leftover in healthy adults and this is called a Patent Foramen Ovale (PFO) (70,71). Symptoms are often absent in children, and thus, ASD is often diagnosed in adolescence or adulthood and the majority (over 70%) is diagnosed in the fifth decade of life; there is a 2:1 female: male approximate ratio of ASD (35).

There are four types of ASD: ostium secundum ASD, ostium primum ASD, sinus venosus ASD, and coronary sinus ASD (72). The four main ASD types (ostium secundum [75% of all ASD cases, 7% of all CHD, and 30-40% of CHD in patients >40years]; ostium primum [15-20% of all ASD cases]; sinus venosus [5-10% of ASD cases]) account for 10% of all CHD and 20-24% of CHD in adults (72).

Earlier studies put ASD as the second most common CHD (73) whereas a more recent study puts it as the third most common type of CHD (74). Depending on the size of the defect and its location, spontaneous closure may or may not happen; the size and location also determine if the defect will be symptomatic (12,75). Treatment choice is also based on the size and location of the defect (74). Hoffman and Kaplan categorized ASD as moderate in severity if the defect is large and as mild if small or spontaneously closes (4). ASD can occur on its own or in conjunction with other CHD or other non-cardiac congenital defects (69). ASD is seen more in females than in males (12,69) and it can be diagnosed anytime from birth until adulthood. This is due to the silent murmurs (the movement of blood in the heart) produced in these defects that could be mistaken for normal blood movement in the heart. Historically in some cases, ASD was diagnosed a bit later in life because children with these defects appeared symptom-free. ASD is often asymptomatic and murmurs from this defect are often very soft thus, diagnosis is often delayed till later in life (4,12,76,77). A study done in Japan

from 1989 to 1998 on first-year elementary children (n=86,142) or junior high school children (n=80,632) detected 33 newly diagnosed asymptomatic ASD subjects (76) with 31 of them requiring surgical closure. The authors concluded that though national screening and medical care were widely available in Japan, it is common for patients of ASD to both be missed until school age and to remain asymptomatic even though intervention is required. Although the authors stated that the incidence of ASD in school children will decrease due to the advent of echocardiography as a diagnostic tool earlier in life, Hoffman and Kaplan posited that this late diagnosis would affect ASD incidence and prevalence estimates in childhood (4).

There are several types of ASDs depending on the location of the defect on the heart septum and the development of the defect (69,77); however, in all types, there is communication between the right side of the heart (pulmonary circulation) and the left side of the heart (systemic circulation) (74).

Coronary sinus ASD: is one of the rarest forms of ASD. It occurs when there is a hole in the wall between the coronary sinus in the right atrium and the left atrium (22,24,26). Sinus venosus ASD: occurs in the upper part of the atrial septum near where the superior vena cava enters the heart (69,75,78). Secundum ASD (ostium secundum ASD): this defect occurs right in the middle of the atrial septum and is the most common ASD (21,23,25,56). Patent Foramen Ovale (PFO): In normal foetal circulation there is a hole between the two upper atria that allows blood communication to bypass the lungs (12,69,78). This hole should close by the time a baby is born; if this does not happen, a patent foramen ovale is formed (PFO) (4). Not all current literature classifies PFO as an ASD (69). However, PFO is listed in the same sub-category as ostium secundum ASD in the ICD-10 (15)

These first three types of ASDs are listed as ASD (Q21.1) within the ICD-10 2016 version (15). Primum ASD (ostium primum ASD): this defect occurs in the lower part of the atrial septum in association with abnormal development of the endocardial cushions (78) and near the mitral and tricuspid valves (69). It is often associated with mitral and tricuspid valve malformation and abnormalities of the upper part of the interventricular wall (78). The ICD-10 2016 version classifies the primum ASD separately as an atrioventricular septal defect (Q21.2: Common atrioventricular canal, Endocardial cushion defect, or Ostium primum atrial septal defect (type I)) (15). When ASD size is large, symptoms can be seen in infants and children and these include: poor appetite, poor growth, fatigue, exertional dyspnoea (shortness of breath) and repeated respiratory infections (1, 35)

1.2.2.2 Diagnosis

Due to subtle findings, diagnosis is not done till either the 2nd, 3rd, 4th, or 5th decade of life, is dependent on the amount of left-right shunt, even though earlier detection and intervention is most desirable and recommended (35). Chest radiography (x-ray) shows cardiomegaly (enlarged heart) and surrounding organs; transthoracic echocardiography (echo) (transoesophageal echocardiography [TEE] is needed for a sinus venous ASD); Doppler echocardiography is useful in validating flow across the atria; a Continuous-wave Doppler and Contrast echocardiography can offer additional confirmation; a heart Magnetic Resonance Imaging (MRI) identifies the size and position of the ASD although this is limited to small defects; and an EKG gives an electrical activity and can indicate volume overload of the right side of the heart (1, 35).

1.2.2.3 Treatment

There is no definitive medical therapy for ASD; however, surgical and transcatheter closures are available for ASD for both children and adults (1, 35). Treatment is dependent on the age, size, and location (type) of the ASD, the volume and hemodynamic impact of the shunt, and the extent of the pulmonary arterial hypertension (35). Presentation with substantial volume overload and atrial arrhythmias require medications and preventive antibiotics are given to prevent infections in dental procedures (1, 35). Spontaneous closure in childhood is seen in secundum ASD but not in adulthood. Treatment is contraindicated when ASD size and shunt is small, in pulmonary arterial hypertension, prenatal diagnosis, and in severe left or right ventricular dysfunction (35).

When surgical or transcatheter treatment is given in childhood, it prevents later adulthood challenges (1) and though surgical closure can still be achieved in the elderly with a subsequent good prognosis, long-term prevention of death and morbidity is best achieved before 25 years of age (35).

1.2.2.4 Outcomes

ASD patients will generally survive into adulthood without treatment though natural survival beyond 40-50 years is less than 50% and the attrition rate after age 40 years is about 6%/year (35). Chronic left-to-right shunts result in an increased pulmonary overload of the RV, pulmonary arterial hypertension, a reversal of the shunt, arrhythmias, and Eisenmenger syndrome (35). Paradoxical embolism can arise from catheter treatment and the risk of infective endocarditis exists during the first 6 months of surgery (35). Post-operative incidental arrhythmias are seen in 1-4% of patients, especially in those who had arrhythmias pre-operation (35, 37). Although often asymptomatic, when left untreated or uncorrected,

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ASD may lead to premature death in the 4th decade from congestive heart failure (CHF), or non-reversible pulmonary hypertension (37). Later complications include stroke and atrial fibrillation (irregular atrial beat) (35). Age at the closure of ASD in adulthood is the most important predictor of the development of atrial arrhythmias (both atrial flutter [regular but faster atrial beats] and atrial fibrillation) (35, 37). ASD repair is optimally completed at 2-4 years of age if found early; if not, surgery before 25 years of age results in 30-year survival and if done between 25-40 years, survival is reduced (35).

Another factor that affects the prevalence of ASD is the ability of some types of ASDs to close spontaneously. Spontaneous closure is not often seen in the sinus or coronary as often as it is seen in secundum ASD (77) and mostly, whenever the specific subtype is mentioned in studies, reported spontaneous closures have been in secundum ASD (75,77,79,80).

1.2.3 Tetralogy of Fallot (ToF)

1.2.3.1 Presentation

Tetralogy of Fallot named after Étienne-Louis Arthur Fallot is the most common cyanotic heart disease. It is estimated to occur in 3 per 10,000 live births and accounts for one-tenth of the total CHD burden (81). In 1888, the French physician linked the deoxygenation blue patient phenotype to the characteristic anatomic features of the disease (82). It is a complex condition that consists of four pathological components, namely, ventricular septal defect, pulmonary valve stenosis, overriding aorta, and right ventricular hypertrophy. The severity of the different components occurs to varying degrees consequently impacting the clinical manifestation in patients.

Clinically, children with ToF present with cyanosis, which means a bluish tint in their skin and extremities. Arising due to the four components of ToF working in synergy to obstruct in the rightwards region of the heart and reducing the efficiency of communication between the heart and the pulmonary system. This obstruction arises due to a combination of factors such as the misalignment of the anterior or top outlets of the ventricular septum or a malformation in the muscularization of the outflow cushions (83). Thus, allowing the mixing of oxygenated and deoxygenated blood from both the left and right ventricles.

In the case of the overriding of the aorta, since the outlet septum into the right ventricles is usually misaligned, the resulting obstruction of blood flow through the pulmonary system leads to a forced ejection of deoxygenated blood through the systemic circulation (83). The pulmonary valve stenosis component of ToF refers to the sub-pulmonary obstruction caused by the Antero-cephalad malalignment of the muscular outlet septum which causes the narrowing in the tract that takes blood towards the lungs (83). This narrowing is dynamic and can be exacerbated by the release of some hormones from the adrenal glands leading to acute episodes of hyper cyanotic spells such as during crying or any unusual strenuous activity. The last component of ToF, right ventricular hypertrophy, is the thickening of the right ventricular walls due to it experiencing excessive blood through the defective septum.

There are several variants of ToF such as ToF where the pulmonary valve is absent occurring in 5% of all cases (84). Here, there is usually the presence of tangled valvar leaflets at the interface between the ventricles and the pulmonary system culminating in the regurgitation of blood back from the pulmonary system (83). Furthermore, some ToF patients have right ventricles with a double outlet usually occurring due to severe cases of an aortic override. More so, some 1-6% of ToF patients also have an atrioventricular septal defect (84). These

diversities impact the symptoms and clinical management of these defects. Because the ToF occurs from multiple factors as described above, the symptoms of the disease are known to vary widely between patients depending on the severity of each contributing component. Cyanosis at rest or upon exertion in babies is the most common symptom. Other symptoms include dyspnoea, heart murmurs, excessive load of red blood cells, stunted growth, and bouts of temporary paralysis (85).

1.2.3.2 Diagnosis

Clinical examination involving specialist tests is required for its diagnosis. Common diagnostic tests include chest radiograph, electrocardiogram, and echocardiogram (83). the electrocardiogram usually shows right ventricular aberrations that do not normalise with time. Chest radiographs also usually show a classic boot-shaped heart structure in these patients due to the typical right ventricular hypertrophy that occurs (83). The echocardiography is usually able to delineate the extent of the sub-pulmonary obstruction and any problems with blood flow to the lungs, therefore, proving a definitive diagnosis for ToF. About 50% of ToF patients are diagnosed antenatally during prenatal scans (86) although patients who are diagnosed or show suspicions of ToF antenatally usually show severe forms of the defect upon birth (86).

1.2.3.3 Treatment

The clinical management of ToF is dependent on the extent of sub pulmonary obstruction. Treatment is usually aimed at promoting the pulmonary circulation of blood. One of the definitive treatments of ToF is corrective surgery with the best outcomes obtained if surgery is performed in infancy (87). The first corrective surgery was documented in 1954 and since then treatment continues to improve (88). To promote blood flow to the lungs, a modified

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Blalock-Taussig (mBT) shunt which is a systemic to pulmonary shunt is used (89). Another way of performing a systemic to pulmonary shunt is via stenting of the ductus arteriosus. Whilst the success of this procedure is around 83%, the ambiguity in the anatomy of the ductus arteriosus in ToF patients means this procedure is not always the appropriate approach (89). Furthermore, a stent is sometimes used in the right ventricular outflow tract (RVOT) to promote sub pulmonary blood flow. When medium health outcomes were accessed, there was no significant difference between the use of a stent in RVOT in comparison to the systemic to pulmonary shunt but there were favourable measures to perioperative outcomes (90).

1.2.3.4 Outcomes

With the early treatment and advances in diagnosis and treatment, immediate and long-term outcomes for ToF are quite excellent. The treatment approaches used to treat ToF currently give about 85% survival rate in patients born 30 years ago (87), but this comes with lifelong monitoring and management in some patients due to lingering problems that often exist needing further interventions (87). These residual problems include reoccurring pulmonary stenosis, long-lasting pulmonary regurgitation, and irregular ventricular heartbeats (83). Whilst the current strategies promote survival in this group, more studies are required to optimise personalised approaches to minimise the need for further interventions.

1.2.4 Atrioventricular Septal Defect (AVSD)

1.2.4.1 Presentation

Atrioventricular septal defect (AVSD) consists of various congenital abnormalities characterised by defective atrioventricular valves and septation. AVSD is also known as

atrioventricular canal defects, endocardial cushion defects, or atrioventricular commuins (91).

AVSD affects the atria, ventricles, atrioventricular septum, and valves to varying degrees.

The incidence of AVSD is estimated to be between 2.4 to per 10,000 live births to 3.1 per 10,000 live births (92). AVSD is strongly correlated with Down's syndrome, where co-occurrence of Down's syndrome and AVSD occurs in up to 42% of all AVSD cases (92).

AVSD has been classified into incomplete, transitional, complete, and AVSDs with ventricular imbalance (93,94). Partial AVSDs or ostium primum atrial septal defects constitute incomplete AVSDs. Complete AVSD is further sub-categorised using the Rastelli classification based on the localisation of the superior bridging leaflet. In Type A AVSD, the superior bridging leaflet is attached to the LV and tightly connected to the ventricular septum by multiple muscular loops, in Type B, the superior bridging leaflet is situated over the ventricular septum by an anomalous papillary muscle of the RV and in Type C, the superior bridging leaflet is unattached and free-floating (95).

AVSD accounts for up to 5% of all CHDs, with an estimated prevalence of 4% per 10,000 live births (67,96). AVSD is known to progress to heart failure and death in many patients. In this regard, the prevalence prenatally is thought to be a lot higher at 18% of all CHD occurrences and falls sharply in childhood due to a high death rate within this population (97). Down's syndrome and Heterotaxia are two co-morbidities prevalent within this group (98). In a cohort study, about three-quarters of all AVSDs were complete and 50% were incomplete AVSD (99).

AVSD is characterised by a left-to-right shunting process between the atria and ventricles and particularly atrioventricular valve (AVV) regurgitation (91). As with other septal defects, the clinical presentation of AVSD in infants is dependent on the severity of the abnormality to

the morphology of the heart and any other co-morbidity present. In complete AVSD, ostium primum ASD coexists with a form of VSD with a shared AV valve, allowing shunting to occur in both the atria and ventricle (94). Complete AVSD account for up to 75% of all AVSDs. Partial AVSD is where the shunting is restricted to only the atria and is then known as ostium primum ASD or is restricted to the ventricles. Intermediate AVSD refers to defects that fall in between partial and impartial forms of the condition (94). In the case of AVSD with ventricular imbalance, the shared valve between the ventricles exhibits a bias to one side of the ventricles leading to a decrease in the size of one of the ventricles. Symptoms of AVSD include dyspnoea, lethargy, failure to thrive and congestive heart failure (94).

1.2.4.2 Diagnosis

The four-chamber view of the heart during antenatal scans can detect AVSD lesions and show the presence of a non-demarcated left and right atria and ventricles, however, the detection rates remain quite low. A UK cohort study showed that less than a third of AVSD cases were detected antenatally with ultrasounds (100). Although this is constantly evolving with a suggestion that including a measurement of atria to ventricular length increases the detection rate to more than 80% (92).

In the case of complete AVSD, echocardiography is usually vital for diagnosis, as it can delineate the ostium primum atrial septal defect, any existing defunct atrioventricular valve, and defective ventricular inflow due to damaged or non-existing septation (93). Furthermore, echocardiography can identify abnormalities in the obstruction of inflow and outflow in the affected heart chambers (93). Echocardiography is also used to assess suitability for surgery and estimate long-term outcomes. Chest radiographs and electrocardiograms are often used to identify other features of AVSD. Where a significant left to right shunt occurs, a clinical

examination is sometimes able to uncover an inconsistent diastolic systolic murmur and pan systolic murmur due to AVV regurgitation (101). Nonetheless, other tests like electrocardiograms, echocardiography, and chest radiographs are often required for a more definitive diagnosis.

1.2.4.3 Treatment

The first complete correction of AVSD was documented in 1955, and since then the combination of the improvement in the understanding of the aetiology of the disease, physiology of the heart, and diagnostic tools continues to improve the success of medical interventions for children with AVSD (88). The critical point of surgery for children with AVSD is to correct the abnormal anatomy and promote septation of the heart, ensuring minimal residual left to right shunt, and restoring the function of the atrioventricular valves.

In some cases, congestive heart failure is managed pharmacologically with a combination of vasodilators and diuretics (92). In the case where there is a failure to thrive in neonates, feeding tubes are sometimes required (92). Nonetheless, medical interventions of this nature are usually for short-term care whilst correctional surgery is often preferred for long-term care. Where possible, surgery is conducted within the first six months of the infant's life to prevent long-term pulmonary hypotension (92). The mortality from the operation procedures is reported to be less than 10% (102). Therefore, this remains relatively preferable to lack of treatment.

To repair the lack of septation, one- or two-pericardial patch techniques are often used. One-patch surgery involves the closure of the atrial and ventricular components by dividing the shared valve leaflets and connecting them to a single patch whilst, in the two-patch surgery the ventricular compartments are closed independently using one patch, and the atria septal

defect is closed with another patch (103). Both one and two patch techniques have been shown to provide similar results (104,105). Separate surgeries are sometimes required when AVSD occurs with other cardiac malformations such as AVSD with unbalanced ventricles, ostium primum ASD, and Down's syndrome.

1.2.4.4 Outcomes

If surgical repair is not carried out, the risk of significant morbidity and mortality increases significantly with only a quarter of this population surviving beyond 40 years old (92). Where surgery is delayed significantly, within two years some children develop irreversible pulmonary hypotension due to the prolonged left to right shunt and instead of a tightly regulated systemic circulation to the lung (92). Conversely, a significant improvement in the 20-year survival in children with complete AVSD has been reported following timely corrective surgery (106,107). It is important to note that even with the improved survival following surgery, there remains reports of reoperation due to remaining AVV regurgitation and persistent obstruction to the outflow of blood from the left ventricles (91). Therefore, continued medical monitoring is sometimes required even when survival is improved.

1.2.5 Aortopulmonary Septal Defect (AoSD)

1.2.5.1 Presentation

Aortopulmonary Septal Defect (AoSD) is a rare form of CHD resulting in 0.1% to 0.2% of total CHD (108). AoSD which often develops at the embryonic stage is characterised by partial septation of the aorta, which carries oxygenated blood from the left ventricles to the rest of the body, and pulmonary arteries which carry deoxygenated blood to the lungs (108). AoSD arises when the connection between the aorta and the pulmonary artery doesn't

develop properly even though the semilunar valves occur normally (109). AoSD is usually classified according to the location of the defective window between the aorta and pulmonary artery.

Symptoms in children with AoSD are usually evident neonatally and include increased sweating, abnormally rapid breathing, fast heart rate, slow weight gain, and increased susceptibility to viral infections (109). These symptoms reflect the over-exertion of the pulmonary circulation that occurs due to a fall in pulmonary vascular resistance. Children with AoSD have also been reported to show an abnormally increased circulatory volume around the precordium with a detectable diastolic murmur arising from the mitral valve in some cases (109). AoSD can present with ToF where murmur arising from pulmonary regurgitation can be identified (110). AoSD can occur as isolated defects or concurrently with other cardiac lesions such as coarctation of the aorta, other arch anomalies, and sometimes VSD and ToF (108).

1.2.5.2 Diagnosis

As with other septal defects, a combination of chest radiography, electrocardiography, CT scan, and echocardiography is used in the diagnosis of AoSD. Chest radiography can reveal abnormal enlargement of the heart. Electrocardiography can identify increase heart rate and abnormal voltages in the heart chambers. Echocardiography is usually used to obtain a more definitive diagnosis, as it can measure the efficiency of the communication between the aorta and the pulmonary arteries (108). If AoSD is left undetected, Eisenmenger syndrome may develop, requiring catheterization to assess the pulmonary vascular resistance (109). Often a combination of these different techniques is required to fully evaluate the presence and severity of the defect.

1.2.5.3 Treatment

Clinically, diuretics, ACE inhibitors, and digoxin are used either as palliative care or to temporarily alleviate symptoms, but these are not curative (109). In cases where AoSD results in shock, some preoperative management such as resuscitation procedures is required (108). Due to the risk of developing pulmonary hypertension over time, surgery is often quickly considered if appropriate for the child as the overall outcome is otherwise dire for affected children. The goal of the surgery in children with AoSD is to allow the separation of the aorta and the pulmonary artery either using direct suturing or using a pericardial patch (111). Surgical repair procedures have been shown to have low mortality especially when there are no other comorbidities. When other CHD are present, corrective surgery of the different components is considered to avoid a reintervention where possible.

1.2.5.4 Outcomes

With existing technologies used in the management of AoSD, outcomes are very good for children with isolated AoSD but more cautious where other comorbidities exist. Here, the prognosis is then based on the nature of other existing anomalies. However, early intervention is paramount as the prognosis if left untreated is otherwise dire, with a fatality rate of 40% before the age of one (111).

1.3 General risk factors for congenital heart defects

To fully understand the factors affecting the prevalence, survival, and long-term health outcome in children affected by CHD, it is important to understand the risk factors that affect its predispositions. Genetic, environmental and lifestyle factors have been linked to disease incidence.

1.3.1 Genetic risk factors

The understanding of the genetic risk factors has grown rapidly due to advancements in scientific technologies such as next-generation sequencing. The genetic risk factors implicated in CHD can be monogenic, i.e., arising from a single gene, or polygenic i.e., arising from multiple genes (101). However, models are reporting that the genetic predispositions need to interact with environmental factors or teratogens for defects to occur (28,39). An underlying genetic cause has been found for a fifth of all CHD cases and a significant proportion of these are syndromic CHD (112,113).

Syndromic CHD refers to defects that occur concurrently with large chromosomal aberrations such as occurs in Down syndrome (114). The chromosomal abnormalities that occur have been shown to involve in part clusters of genes that are involved in the normal fetal heart development as well as other biological systems (Table 1.2). For non-syndromic multiple genes coding for transcription factors, receptors, muscle contraction proteins, or yet unidentified functions have been implicated in the aetiology of non-syndromic CHD (Table 1.2). In familial CHD, autosomal dominant/recessive or X chromosome-linked mutations are expressed with high penetrance in the offspring (112). Due to the effects of natural selection, autosomal dominant or X-linked mutations are predicted to be quickly eliminated from the population whilst newly occurring mutations continue to contribute significantly to sporadic familial forms of CHD (112). There are various reports of the prevalence of the 'de novo' mutations. Rare de novo mutations were observed in 5% of CHD in a study conducted following genome-wide studies (115). Following the exome sequencing in a cohort of probands identified 8% of cases (116). Examples of high penetrance genetic and chromosomal aberrations and the manifesting SD are listed in Table 1.2

Apart from chromosomal and direct genetic mutations, small non-coding microRNA (miRNA) which regulate the expression level of mRNAs are important for heart development in the fetus are also implicated in the aetiology of CHD. For example, miRNA-84 is downregulated in cyanotic CHD patients in a mechanism that involves a decrease in the proliferation and enhanced hypoxic sensitivity of cardiomyocytes (117). Other miRNAs implicated in the pathophysiology of CHD include miRNA-499 (118), miRNA-1(119), and maternal upregulation of miRNA- 19b, miRNA-22, miRNA-29c, and miRNA-375 (120).

The genetics of CHD is quite heterogenous as a single genetic aberration can result in various defects hence the occurrence of various forms of CHD in the same child and conversely, specific mutations in various genes can amount to the same disease phenotypes.

Table 1.2: List of mutated genes or aberrations associated with syndromic and non-syndromic septal defects adapted from (101,121,122)

<i>Syndromic or non-syndromic</i>	<i>Syndrome/genes mutated</i>	<i>Septal defect</i>
<i>Syndromes from chromosomal aberrations</i>	Edwards	VSD, ASD, TOF,
	Velocardiofacial	ToF
	Patau	ASD, VSD, AVSD
	Down's	AVSD, ASD, VSD, ToF
	Klinefelter	ASD
	Pallister-Killian	VSD, ASD
	Heterotaxy	AVSD
	Alagille	TOF, ASD
	Noonan	ASD
	Holt-Oram	ASD, VSD, AVSD, ToF
<i>Syndromes from single-gene mutations or small-scale chromosomal deletions</i>	CHARGE	ASD, VSD
	Ellis-van Creveld	Primum ASD, common atrium, AVSD
	Smith-Lemli-Opitz	AVSD, primum ASD, VSD
	Kabuki	ASD, VSD
<i>Non-syndromic</i>		
	NKX2.5	ASD
	MEF2C	VSD
	GATA4	VSD, ASD
	CFC1	ToF, AVSD

ANKRD1	Septal Defects
HAND2	ToF, VSD
CASZ1	VSD
MYH6	ASD
MYH7	ASD

1.3.2 Non-genetic risk factors

There are other modifiable factors associated with CHD such as maternal exposure to teratogens in early pregnancy. The transmission of rubella from mother to child either in pregnancy or during breastfeeding has been linked to multiple congenital defects such as patent ductus arteriosus, ToF, and VSD (123). Maternal viral infections such as influenza have also been linked to the development of coarctation of the aorta in infants (124). A five-fold increase in the risk of AoSD has been noted in infants born to mothers with pregestational diabetes (125). Furthermore, other maternal illness, such as phenylketonuria is also linked to an increased incidence of CHD (126,127). In a cohort study of over 3,000 infants, maternal smoking within one month before conception was associated with an increased risk of having infants with ASD, and a stronger association was observed when heavier smoking was reported (128).

Furthermore, exposure to certain pharmacological drugs has been shown to increase the relative risk of CHD in various studies. Whilst maternal folic acid supplementation was linked with an increased risk of septal defects (129), these findings have been contested in other findings that reported a decrease in the prevalence of severe CHD following

population-wide exposure to folic acid (130,131). The risk of VSD was reported to increase following drug exposure, chemical hair treatments, and exposure to paint fumes (132). Whilst ibuprofen was associated with Transposition of Great Arteries (133), there has been a report of the use of ibuprofen in treating patent ductus arteriosus in infants (134). Therefore, more studies are needed on the link of ibuprofen in causing or managing CHD. The modifiable risk factors have not only been restricted to maternal exposure alone, as paternal use of marijuana and paternal anaesthesia has been linked to the Transposition of Great Arteries with intact ventricular septum and ToF respectively (133). In the next chapter, the global and national burden of CHD, SD and its variants will be considered.

Chapter 2: Thesis rationale

Congenital septal defects (SD) are the most common congenital heart defects (CHD). An increase in the diagnosis of very small ventricular septal defects (VSD) has been held culprit for the high prevalence seen in CHD recently as advancements in paediatric cardiology have made such identifications possible.

There have been more studies done on short and long-term outcomes of CHD in the adult population than has been done in the child population. Studies on the assessment of long-term prognosis done in the child population have mostly been restricted to more severe cases of CHD, or children undergoing treatments with survival and outcomes assessed almost immediately after treatment. Death and its cause at a population level in these patients beyond the very sick and post-intervention have not been thoroughly investigated. Assessing the long-term survival of children with septal defects is required in shaping management strategies for this class of diseases.

There is no UK population study looking at the prevalence and survival of all SD variants concomitantly in this population and comparing them within the same setting to children with other congenital anomalies, and children without any congenital anomalies. Thus, this study sets out to assess the prevalence and survival of children with congenital septal defects in the UK using the GP data (CPRD).

2.1 Aims and objectives

1. Assess the prevalence of CHD, SD, and SD variants within the current primary care data CPRD and compare to EUROCAT and other already published data.

Objectives on the first aim:

- What is the prevalence of CHD and SD within the current data? Assess the number, percentage, and prevalence of CHD that is contributed by SD and compare this to literature and EUROCAT. Report CHD prevalence per 10,000LB.
 - Separate SD into its variants and report prevalence per 10,000LB.
 - Assess the effect of gender, year of birth, ethnicity, geographical location, and socioeconomic status on the prevalence of SD and its variants.
2. Assess survival in SD; subsequently, assess survival trends in SD variants and compare with survival in children with other major CA and children without any CA; assess the cause of death in the SD cohort.

Objectives on the second aim:

- Assess mortality rates in CHD, overall SD, and SD variants.
- Assess the effect of gender, ethnicity, and socioeconomic status on mortality rates.
- Assess survival and cause of death in infants (30 days- 1 year), children (1 year-16 year), and those 16 years and above within the current data and compare the rates with the general population and other major CA?
- Explore the feasibility of assessing the severity of CHD cases by evaluating the recording of CHD-related procedures/interventions within the CPRD based dataset.
- Assess the frequent cause(s) of death in SD?

2.2 Outline of the thesis

The subsequent chapters in this thesis are as follows:

Chapter 3 describes the three different databases used to build the study population in this thesis namely, the Clinical Practice Research Datalink (CPRD), the Office for National Statistics (ONS) death registration data, and the Index of Multiple Deprivation (IMD) data. Furthermore, this chapter also includes a brief discussion on study ethics, data management for dataset build-up, and statistical software.

Chapter 4 describes the prevalence of septal defects and the various variants namely, VSD, ASD, ToF, AVSD, AoSD, and unspecified SD. Furthermore, the effect of gender, year of birth, ethnicity, and socioeconomic status on the prevalence of these defects is enunciated. Furthermore, the prevalence of SD in well-defined geographical areas in England is also described here.

Chapter 5 describes the evaluation of the mortality from any septal defect and septal defect variants and the effect of gender, ethnicity, and socioeconomic status on the mortality rates. Furthermore, the survival of children with these defects is compared with survival in children with other major CA and no CA. The cause of death for children with septal defect variants is evaluated.

Chapter 6 summarises the key findings from this thesis and elucidates avenues for future research.

Chapter 3: Data source and management

This chapter describes the three different databases used for analyses in this thesis which are, the Clinical Practice Research Datalink (CPRD), the Office for National Statistics (ONS) death registration data, and the Index of Multiple Deprivation (IMD) data. A brief discussion on study ethics, data management for dataset build-up, and statistical software used is also included.

3.1.1 Clinical Practice Research Datalink (CPRD)

3.1.1.1 History

CPRD is an electronic collection of anonymised patients' observational health records from primary care general practices (GP) in the UK captured using the Vision® software system (135). The CPRD has been used in over 2,600 peer-reviewed published articles spanning a wide range of health-related topics, such as clinical epidemiology, disease patterns, disease management, outcomes' research, and drug usage (136,137). The CPRD is an ongoing collection of GP data (136); invariably, patient and practice numbers are expected to change with and over time. Thus in 2013, Herrett et al. documented that the CPRD covered 11.3 million patients from 674 practices with 4.4 million active patients representing approximately 6.9% of the UK population in age, sex, and ethnicity (136). In this current study, the CPRD July 2017-build data contain 17,148,866 patients' records across 718 practices.

The CPRD was launched in 2011 and fully established on the 1st of April 2012 (138,139); before then, the CPRD, formerly named GPRD, has been collecting primary care data since 1987 (136). An Essex general practitioner developed a system to assist in the daily

management of patients' data in his practice; this became so successful that Value Added Medical Products Ltd. (VAMP) was set up in 1987 to recruit other practices to form an information base (140). In 1993, Reuters Health Information acquired VAMP and donated it to the Department of Health in 1994 and it became GPRD (140–142). As a part of the Office for National Statistics (ONS), the Office of Population Censuses and Statistics (OPCS) took over the maintenance of GPRD on behalf of the Department of Health. In 1999, the Medicines Control Agency (MCA) took over the management and relocated operations of GPRD from ONS and a major redevelopment of the programme to enhance the wider utility of the data within and outside of the UK was commenced (142).

3.1.1.2 Quality of data

CPRD carries out an internal data quality check both at the patient and practice levels (136,143). Patients are deemed “acceptable” to be included in research by a process that detects and omits patients with non-continuous follow-up or poor recording of data while practices are deemed “up-to-standard” on a date that practice has had a continuous high standard of data fit for research purposes as stipulated in the recording guidelines provided by the Vision system (136,143). The quality of data collected by the CPRD has been studied for validity, representativeness of population, accuracy, and completeness of diagnostic coding and applicability of CPRD in comparison to primary care, hospital records, and other databases for various health questions such as eating disorders, septal defects, ulcers and diabetes (144–148). CPRD has been validated for use in the assessment of VSD, ToF, and Coarctation of the Aorta with a positive predictive value of 90-100% for all 3 defects (149). Khan et al. did a systematic review of the literature on the validity of the then GPRD for diagnostic coding in 49 studies (148). Here, when compared with a gold standard, diagnoses

of various disorders including some congenital heart defects (VSD, ToF, CoA) were correctly documented within the GPRD (so named at the time the study was published); however, acute cardiac conditions such as angina, heart attack, or ventricular arrhythmias that had PPV lower than 50% were not so accurately recorded (148). Nonetheless, 12 papers within this review that compared the prevalence rates of common conditions such as chickenpox, hay fever, asthma, and diabetes in the then GPRD and available national morbidity statistics or other databases found relatively comparable rates for all diseases considered except diabetes and musculoskeletal conditions, which were underestimated in GPRD (148), and in agreement with the study by Lawson et al. (140). As a means of drug safety and pharmacovigilance, the then GPRD was found to be practically complete for records on drug prescription with over 90% of drugs newly prescribed and 95% of changes in prescription recorded within the database (145).

3.1.1.3 Structure of CPRD, data collected, and how they are recorded.

Data within CPRD are structurally separated into patient, clinical, referral, immunisation, tests, and therapy files (136). Data are captured against the practice and patient identifiers to protect anonymity (136,143). The CPRD harnesses the fact that over 98% of the UK population is registered with a GP under the National Health Service (NHS) (136,141,142). GPs are the first port of call for all health-related issues in the UK; they are responsible for referrals to emergency or secondary care, which also feed GPs back on patients' information including diagnoses (136).

Patient-level data collected by GPs include demographics (including sex and age), medical symptoms (signs, diagnoses, and comments), therapy (medicines, vaccines, devices), treatment outcomes, withdrawal from drug or treatment, referrals to hospitals and specialists,

laboratory tests and pathology results, and lifestyle factors (height, weight, BMI, smoking and alcohol consumption) (136,140,142). The demographics are contained within the patient file and medical symptoms and dates of diagnosis and/or referrals are contained within the clinical and referral files respectively; laboratory tests and pathology results are contained within the test files while all treatments, change and/or withdrawal from treatments are contained in the therapy files. Furthermore, practice-level data capture geographical region as one of 10 regions in England with Wales, Scotland, and Northern as stand-alone regions; a practice-level deprivation score is calculated based on the practice's lower super output area (136).

Data are recorded within CPRD using Read codes (136,150). Read codes (named after Dr. James Read who developed the codes) are broad medical codes with over 250,000 codes with 150,000 synonyms (150) and were originally based on the International Classification of Diseases (Ninth Revision, Clinical Modification: ICD-9-CM) (148). The coding system codes diseases, history, symptoms, examination findings and signs, diagnostic procedures, preventive, operative, therapeutic, and administrative procedures; drugs and appliances; and occupation and social information. The Read codes consist of five alphanumerical characters with clinical classification based on six criteria: it is comprehensible; it is hierarchical; employs codes; it is computerized, can be cross-referenced, and it is dynamic (150). This classification aids in clinical care by helping in the collection and recovery of medical information; it makes statistical analyses easier and aids planning and research, and the electronic transmission of health data (150). Read codes were created with enough flexible redundancy to allow for further development of entities and synonyms. The ICD codes are constantly updated with definitions of terms and alphanumerical codes retained or easily mapped between the editions.

The covariates assessed in this study are ethnicity and social-economic status (SES). These variables have been recognized to address inequalities in health service utilization and outcomes (151). SES is calculated as an aggregate of lower super output area and supplied by CPRD as the Index of Multiple Deprivation (IMD) or Townsend Score (152). The IMD is one of the data sources for this study and will be discussed in section 2.1.3. Ethnicity, however, is recorded within the clinical files of CPRD using Read codes. Only 27% of all patients between 1990 and 2012 have their ethnicity recorded, however, since the incentivization of ethnicity recording under the Quality Outcome Framework (QOF), 90% of newly registered patients have their ethnicity recorded, and the proportion of ethnicity recording overall increased by 78.3% since 2010 (151). Since 2006, the proportion of ethnicity recording within CPRD has been comparable to that of the UK population. To pull the various ethnic breakdowns across England, Wales, Scotland, and Northern Ireland together, Mathur et al. collapsed all 16 ethnic categories in CPRD coding into the five higher-level categories of the 2011 census (Table 3.1), and this categorisation is used for this thesis (151).

Table 3.1 Ethnic category collapse adapted from (19)

CPRD 16 groups	2011 census 5 categories
1 British 2 Irish 3 Any other White background	1. White
4 White and Black Caribbean 5 White and Black African 6 White and Asian 7 Any other mixed background	2. Mixed
8 Indian 9 Pakistani 10 Bangladeshi 11 Any other Asian background	3. Asian or Asian British
12 Caribbean 13 African 14 Any other Black background	4. Black or Black British
15 Chinese	5. Chinese
16 Any other ethnic group	6

One thing to consider in the utility of ethnicity in CPRD is the risk of multiple ethnicity recordings within CPRD which could either be due to errors in recording or as a result of a patient stating different ethnicities when asked (151). To assess the regularity of ethnicity coding and to gauge the proportion of multiple-ethnicity recording, Mathur et al. in their study of the completeness and utility of ethnicity data in CPRD and hospital database

compared patients with only one ethnic recording in their medical records to those with multiple recordings. They categorised multiple-ethnic recording into three: truly matched (identical multiple ethnic codes); categorically matched (different multiple ethnic recordings but that still fall into the same five higher-level groups); and truly mismatched (multiple ethnicities across different higher-level groups) (151). The authors found that overall, 23.2% of patients had only one code for ethnicity, and 4% had multiple ethnicities: 3.1% (truly matched), 0.5% (categorically matched), and 0.3% (truly mismatched). When assessed using patients registered from April 2006, 67.3% of patients had only one ethnic code recorded while 11% had multiple ethnic recordings: 8.2% (truly matched), 1.6% (categorically matched), and 1.2% (truly mismatched). They also found 72.9% of patients had no usable ethnicity code recorded overall; this reduced to 22.1% when assessed from patients registered from April 2006. Whilst this dataset has been useful in the study of health outcomes such as incidence of fracture in children according to different ethnic groups (153), the authors reported having a lower proportion of children aged 0-4 years in CPRD when compared to the UK Census 2011, and ethnicity records are only available for about half of the population. Therefore, this points to ascertainment and classification bias where ethnic classification is concerned as limitations of using CPRD. I will return to the considerations of these limitations regarding the results obtained in this current study.

3.1.2 Office for National Statistics (ONS) death registration data

3.1.2.1 History and format

The office for National Statistics (ONS) functions and is responsible to collect, analyse, and disseminate statistics about the UK's economy, society, and population (154). The registration of death data thus falls under the sole responsibility of the ONS. The Birth and

Deaths Registration Act of 1836 made it a legal requirement for all deaths to be certified and registered from the 1st of July 1837 in England and Wales (155); mortality statistics are hence compiled as part of this civic practice and death records are deemed complete due to this exercise (156,157). Mortality data represent the number of deaths that are registered in a particular reference period and are published weekly, monthly, quarterly, and annually to ensure timeliness and accuracy (155).

The ONS and CPRD provide documentation on how death records are obtained, recorded, validated, and disseminated; these documentations explain the processes involved and how corresponding data are made available (156,157). The Local Registration Service in collaboration with the General Register Office (GRO) carries out death registration.

Registrars make records on the Registration Online (RON) based on the information given by informants that are often relatives of the deceased and, cause of death obtained and confirmed by the medical practitioner present at the time of death as written in the Medical Certificate of Cause of Death (MCCD) (156).

Registrars validate the correctness of data entered into the RON by asking the informant to verify the data recorded. The ONS carries out regular checks to diagnose errors and contact affected registrars to resolve issues found weekly. Once data are recorded on the ONS database, inconsistencies are highlighted by a range of automatic validation processes (156). The coding for the most common causes of death codes is done automatically using the Automated Cause coding system, the rest is done manually after the inquest. Accuracy of automated codes and overall completeness checks are done to ascertain all death registrations are done before annual mortality data are finalised.

Since January 2001, the cause of death in England and Wales has been coded using ICD-10 (155); this replaced ICD-9 which had been in use since 1979 (156). The change to ICD-10 has allowed for more codes and the accommodation of many more conditions and detailed common diseases. In January 2011, the ONS updated the software used to code for cause of death from ICD-10 v2001.2 to v2010 (156).

The ONS uses ICD-10 codes to record causes of death. The ONS reports mortality rates in several ways: by age, age-structure (5-year age bands), by sex, by broad and specific underlying causes, by area of usual residence, by IMD, by mother's ethnicity, etc., and assessed in live births, stillbirths, early neonatal, post-neonatal, infant, childhood, and adulthood. Early neonatal, neonatal, post-neonatal, and infant deaths are reported in rates/1,000 live births while childhood and adult deaths are reported in rates/100,000 population of the same age (158).

3.1.2.2 The ONS death registration data set 15

The ONS death registration data set 15 was linked to the CPRD Gold July 2017 build used for this thesis. In the set 15, 913,334 persons (98.35%) have a match-rank five and below and those are the patients linked to CPRD Gold 2017 July build. The match-rank variable corresponds to the step at which a patient is considered linkable to the CPRD (Table 3.2).

The ONS death data are made available for studies for which linkage has been approved by the ISAC. These data are supplied as a tab-delimited text file which can be linked to the matching CPRD Gold patient file using the coded patient identifier. No patient identifiers are included in the data to preserve anonymity.

3.1.3 Index of Multiple Deprivation Data (IMD)

Censuses in the UK are done using output areas (OAs) as the lowest level of geography (159). OAs are built from unit postcodes (about 110-140 households) and lower layer super output areas (LSOAs) are built from 4-6 OAs (minimum of 1,000 residents and 300 households with an average of 1,600 residents) (152). OAs contain approximately the same number of residents within the same locality which makes statistical reporting consistent.

Social and economic indicators characteristic of an LSOA are used to measure material deprivation and they include housing, employment, income, access to services, education and skills, crime, and living environment (152); these are either based on the patient or practice postcode. Socioeconomic indicators of material deprivation are weighted and added to give a combined index of multiple deprivations for each LSOA and these indices are used as a proxy for individual-level measures of socioeconomic status (SES) (152). The socioeconomic index of LSOAs is usually ranked as a range from “least deprived to most deprived” (1-5). In this thesis, patient-level index of multiple deprivation (IMD) was used. Practices that have given their consent for linkage to CPRD are linked using the patient’s postcode of residence which is mapped to the 2015 LSOA via a postcode lookup file. Therefore, this thesis uses the IMD quintiles assigned to the patient’s postcode, which is a group between 1500 people or 650 households (152).

3.1.4 Data linkages

Generally, CPRD data have been linked to secondary Hospital Episode Statistics (HES), ONS death registration, socioeconomic classification data, and disease registries. For linkage to happen, English practices that give their consent for the CPRD linkage scheme provide patient-level information which includes patient NHS identifier, postcode, date of birth, and

gender to a Trusted Third Party (TTP) that effects the linkage (136,143). The TTP creates a linkage eligibility file, which contains patients from all consenting practices across England. This file contains flags for the patients who are eligible for linkage and to how many of the data sources they are linked to, none, some, or all databases (160). A “linkdate” is provided in the file that shows the date each practice makes patient-level data available to the TTP.

Not all patients in CPRD Gold are eligible for linkage to death data and the linkage eligibility file flags the subset of CPRD Gold patients who are linked to the death data. There is an eight-step linkage-determining algorithm based on four identifiers used for the linkage between ONS death data and CPRD Gold. These identifiers are exact NHS number, sex, date of birth, and postcode (156). The eight-step process is done consecutively, and a patient matched at one step becomes unavailable for subsequent matching (Table 3.2). Within CPRD, a match rank variable corresponds to the step at which a match is determined; the lower the match rank variable, the stronger the evidence for a positive match (156) (Table 3.2). Patients with a match rank five or less are included in the linked death registration data; others are retained in a separate file. This current study utilises the linked ONS death registration and IMD data to CPRD.

Table 3.2: ONS linkage to GP records-determining algorithm adapted from (156)

Step	Match
1	Exact NHS number, sex, date of Birth (DOB), postcode
2	Exact NHS number, sex, DOB
3	Exact NHS number, sex, postcode, partial DOB
4	Exact NHS number, sex, partial DOB
5	Exact NHS number, postcode
6	Exact sex, DOB, and postcode (the NHS number must not refute the match, DOB is not 1 st of January and postcode is not on the communal establishment list)
7	Exact sex, DOB, and postcode (the NHS number must not refute the match, DOB is not 1 st of January)
8	Exact NHS number

This current study did not link the CPRD to HES. First, linkage to HES would mean over half of the study population would be lost as research has shown that only about half of the CPRD population is linked to HES (148). As HES Out-Patient data has limited diagnostic information, it is unclear whether this data source could support the current study.

Furthermore, linking CPRD to HES for this study would bring in a level of complexity to the research beyond the scope of an MPhil.

3.2 Building the thesis dataset.

3.2.1 Defining and identifying children with congenital anomaly

As stated in section 3.1.1.3 above, medical diagnoses are recorded in CPRD using Read codes. Read codes, like EUROCAT CHD categories, are based on the International Classification of Diseases (Ninth Revision, Clinical Modification: ICD-9-CM). At the start of this study (2017), CHD categorisations for Read codes and EUROCAT were based on categories as listed in the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). A patient is defined as having a CA if they have a Read code in their medical record for a CA or a cause of death due to CA in their ONS death record. Read codes are used within CPRD to record diagnoses, interventions, and procedures while ICD-codes are used to record causes of death within the ONS death data.

The CPRD Read Hierarchy Chapter Headings and Subheadings is a document that delineates how Read codes are used within CPRD to record diagnoses, interventions, procedures, and administrative incidents. Chapter “P” of the CPRD Read Hierarchy Chapter Headings and Subheadings is designated to “Congenital Anomalies” while chapter 7 is designated to “Operation/Surgical Procedures. Subheadings in both chapters’ “P” and “7” relating to diagnoses and interventions specific to CA are used to identify children with CA. The CPRD medical entity is a data file that contains all current Read codes with their corresponding medical codes “medcodes”, and medical terms while the ONS death data contain codes for cause of death. The medical term refers to the names of the defects as delineated in the ICD-10 and recorded in the CPRD data as clinical descriptors of the corresponding Read codes. Because Read codes are very specific, it is possible to have several Read codes relating to the same ICD-10 term. For example, the Read code “P550.00” has the term Atrial septal defect

NOS while the Read code “P55.00” has the term Ostium secundum atrial septal defect; both codes correspond to ASD (Q21.1) in ICD-10.

Within the 2016 ICD-10, chapter XVII is dedicated to “Congenital malformations, deformations, and chromosomal abnormalities” with 11 blocks from Q00 to Q99 (Table 3.3), viz: (15).

Table 3.3: ICD classification for congenital abnormalities is found within Q00 to Q99.

ICD classification	Health problems
Q00-Q07	Congenital malformations of the nervous system
<u>Q10-Q18</u>	Congenital malformations of eye, ear, face, and neck
Q20-Q28	Congenital malformations of the circulatory system
Q30-Q34	Congenital malformations of the respiratory system
Q35-Q37	Cleft lip and cleft palate
Q38-Q45	Other congenital malformations of the digestive system
Q50-Q56	Congenital malformations of genital organs
Q60-Q64	Congenital malformations of the urinary system
Q65-Q79	Congenital malformations and deformations of the musculoskeletal system
Q80-Q89	Other congenital malformations
Q90-Q99:	Chromosomal abnormalities, not elsewhere classified

CHD are listed in Q20-Q28 with SD listed under Q21 “Congenital malformations of cardiac septa”. The Q21 sub-block has seven variants (Q21.0, Q21.1, Q21.2, Q21.3, Q21.4, Q21.8, Q21.9) with each variant having different types/descriptions; hence, several Read codes correspond to each variant of SD. All other CA in chapter XVII excluding Q20-Q28 are hereafter referred to as other congenital anomalies (OCA).

3.2.2 Building the code lists for CA-patient identification within the birth cohort

3.2.2.1 CHD code list

As at beginning of this study, the CPRD medical entity contained 112,856 distinct Read codes mapped to 112,855 medcodes and their corresponding terms. One code was an administrative code and thus, did not have a corresponding medcode. The CPRD Read Hierarchy Chapter Headings and Subheadings is a document that accompanies CPRD data, and it delineates the Read code hierarchical chapter headings and sub-headings. Diagnostic codes in chapter P (Read term: Congenital Anomalies) of the CPRD Read Hierarchy Chapter Headings and Subheadings with the following subheadings were first extracted from the CPRD medical entity data file:

- “P5” (Read term: Bulbus cordis and cardiac septal closure anomalies; cardiac septa defects; congenital heart disease, septal and bulbar anomalies; and heart septal defects).
- “P6” (Read term: Other congenital heart anomalies).
- “P7” (Read term: Other congenital circulatory system anomalies).
- “PK” (Read term: other and unspecified congenital anomalies).
- “Py” (Read term: Other specified congenital anomalies).

- “Pz” (Read term: Congenital anomaly NOS)

A search was done using all the terms in the ICD-10, chapter XVII Q20-Q28 using the Stata “searchrc, keepcat” command. The code for anomalies of the spleen (PK...00) was dropped; this search yielded a total of 258 codes.

A second search was done using terms synonymous to CHD “searchrc *heart* | *cardia* | *pulmonary* | *aort* | *mitral* | *septal* | *atresia* | *tricuspid* | *endocardial* | *transposition* | *charge* | *acyanotic* | *ostium* | *noonan* | *fallot* | *circula* | *pterygium* | *arteriosus* | *ventric* | *duroziez* | *vascular* | *atri* | *scimitar* | *lutembacher* | *cirroid* | *taussig* | *coffin* | *kommerell* | *uhl* | *cor* | *vena* | *catheter* | *hemicardia* | *vein* | *gerbode* | *arteri* | *defribillator* | *eisenmenger* | *holt-oram* | *patent* | *ebstein* | *aneurysm* | *artery* | *arteriovenous* | *cardium* | *diverticulum* | *phlebectasia* | *vessels* | *roger*, keepcat”.

Irrelevant codes were dropped, and 449 codes were left. The diagnostic code-yields from these first two searches were combined, duplicates were dropped and a total of 461 codes were obtained (Appendix 1).

A list of intervention/procedure codes was also developed to use for assessing potential severity. All codes in Chapter seven (7) of the CPRD Read Hierarchy chapter headings, subheadings “79” (Read term: Heart/Cardiac operations), and “7A” (Read term: Artery and vein/ Blood vessel operations) were also extracted from the CPRD medical entity data file. As these may be used in CHD but are not all specific to CHD, the same search terms as for the diagnostic codes were also used and a code list for procedures/interventions more specifically related to CHD corrective procedures or specifying the name of a CHD (i.e., CHD-specific procedure) was created (Appendix 4).

All Read codes were mapped back to ICD-10 codes. All CHD codes were classified as either SD or other CHD; the SD codes were further delineated into the various SD variants of VSD (Q21.0), ASD (Q21.1), AVSD (Q21.20, ToF (Q21.3), AOSD (Q21.4), other SD (Q21.8) and Unspecified SD (Q21.9) following ICD-10 classification. Three hundred and seventy-eight codes were (378) left and this constituted the CHD code list (Appendix 1). Table 3.4 depicts the first 10 Read codes, their corresponding medcodes, and their medical and/or ICD-10 terms in the accrued CHD code list.

Table 3.4: Mapping of Read codes and medcodes to their corresponding ICD-10 terms.

Read code	Medcode	Medical term/ICD-10 term
14H1.00	18820	H/O: cardiac anomaly
14H1.11	17175	H/O: heart anomaly
66g..00	72576	Congenital heart condition monitoring
7902.00	5477	Correction of tetralogy of Fallot
7902.11	12844	Repair of tetralogy of Fallot
7902000	16538	Correct Fallot tetralogy- valved right ventricular outflow conduit
7902100	73029	Correct Fallot tetralogy- right ventricular outflow conduit NEC
7902200	99198	Correct Fallot tetralogy- right ventricular outflow patch
7902300	70857	Revision of correction of tetralogy of Fallot
7902400	88842	Repair of tetralogy of Fallot using transannular patch

3.2.2.2 Other major congenital anomalies (OCA) code list

Using the CPRD medical entity data file, all diagnostic codes in the congenital anomalies chapter (“P chapter”) subheading of the CPRD Read hierarchy were extracted. All codes relating to CHD (“P5”, “P6”, “P7”, “PK”, “Py”, and “Pz” codes, extracted in 4.2.1.1 above)

were first deleted. Then, using all the terms in the WHO ICD-10 Chapter XVII except those referring to CHD (Q00-Q99 and excluding heart terms in Q20-Q28), a search was done using the “searchrc” command in Stata. A second search was done to collate intervention/operational codes using the chapter 7 intervention codes in CPRD Read Hierarchical chapter headings and subheadings. All codes in subheadings “79” and “7A” (heart-related intervention codes) were deleted. All resulting codes were merged, and duplicates were deleted. Codes are flagged as minor or major based on EUROCAT classification (161). A total of 2,580 codes were retained; 2,121 codes for major OCA while 459 codes were for minor OCA; only major OCA patients were included in both prevalence and survival analyses. The final code list used for OCA patient extraction is included in Appendix 2.

3.2.3 Classifying SD variants for prevalence and survival analysis

CHD patients were first extracted from the total birth cohort and then differentiated into children with SD, children with other CHD, and children with OCA. All other children in the birth cohort population without CHD or OCA were regarded as children without CA (Figure 3.2). Furthermore, EUROCAT reports 19 separate prevalence data for CHD subgroups: one for total CHD, one for all severe CHD (13 in total), and 17 individually specified CHD subgroups (162). Within the class comprising the 13 severe CHD, there are two SD: Q21.2 (AVSD) and Q21.3 (ToF). Ventricular septal defect (Q20.1), ASD (Q21.1), AVSD (Q21.2), and ToF (Q21.3) are listed as part of the 17 individually specified CHD subgroups. Also, the EUROCAT lists patent or persistent foramen ovale (PFO) (Q21.11 [a type of ASD Q21.1]) as part of minor CAs and other conditions to be excluded (161); also, studies have excluded

PFO from analyses (163). For this study, all CHD were regarded as major CA, and none was excluded.

SD variants cases were differentiated into isolated variants of SD, cases with other CHD (extra-cardiac associations), and cases with OCA (Figure 3.1)

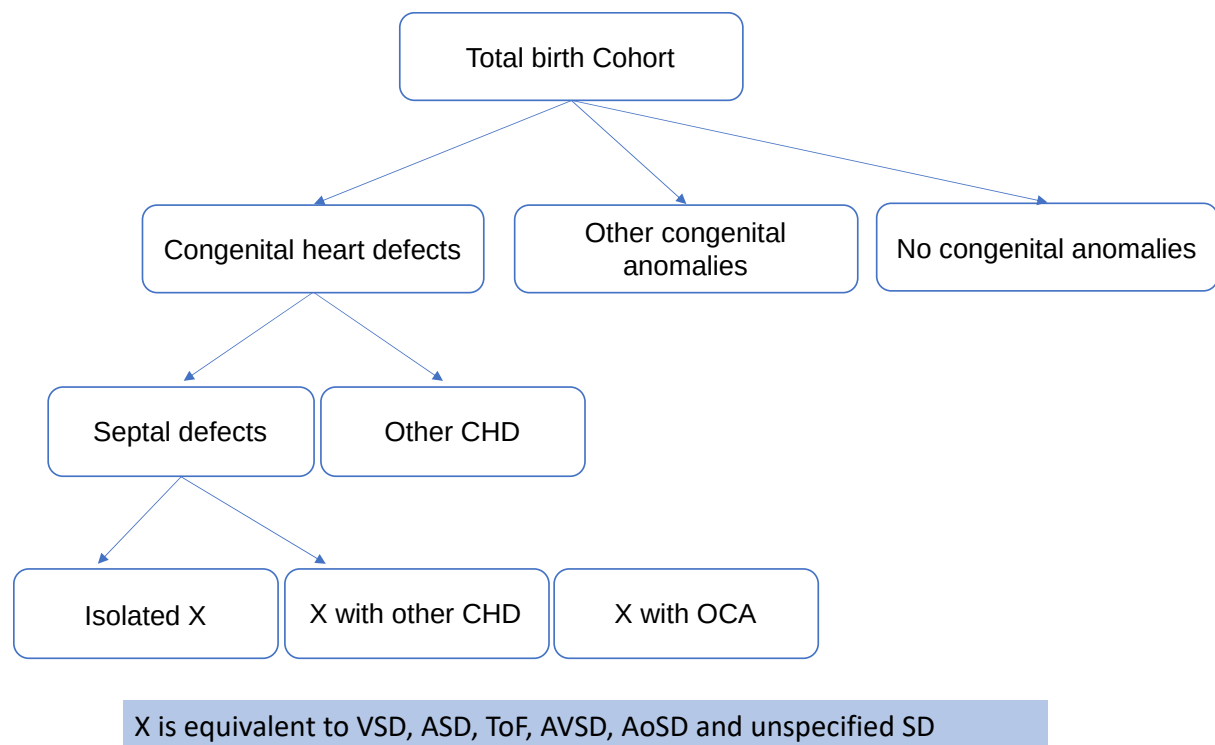


Figure 3.1 Hierarchical classification of congenital heart defects and septal defects for prevalence and survival analysis from the total birth cohort.

3.2.4 Identifying and defining covariates in the data

The covariates considered in this study are socioeconomic deprivation, ethnicity, gender, and region. The region of the GP practices of each record is coded as a variable from 1-10: Northeast, Northwest, Yorkshire and the Humber, East Midlands, West Midlands, East of England, South West, South Central, London, and South East Coast respectively. The IMD data was linked to the birth cohort file. Of the 596,046-birth cohort population, IMD data was available for 595,056 (99.83%) and was missing for 990 (0.17%) patients. As mentioned in section 2.1.3, IMD is supplied as quintiles with one being the least deprived quintile and five being the most deprived quintile.

Codes for ethnicity are recorded in CPRD as part of the patients' clinical records. A code list was generated to extract all codes for ethnic groups. This was compared to an existing code list generated by Lu Ban. All ethnic groups were classified as earlier described (Table 3.1). Of the 596,046-birth cohort population, only 278,482 (46.72) patients have their ethnicities recorded within CPRD and there are 317,564 (53.28%) missing values for ethnicity. The implications of these missing values will be discussed in subsequent chapters.

Data cleaning and management was carried out by the researcher with guidance and assistance from Lu Ban while Jack Gibson gave statistical software guidance. CPRD, ONS, and IMD datasets were supplied in a raw form and zipped when necessary. The researcher imported the raw delimited text files into Stata and extracted the study population. All members of the supervisory team provided guidance on commands and analysis in Stata. The researcher also generated code lists and compared them with codes supplied by Laila Tata. Both were merged and duplicates were deleted. The researcher filled in the ISAC protocol that was submitted by Laila Tata for ethical approval and subsequently requested

corresponding ONS death registration and IMD data from CPRD. Where required, the researcher contacted ISAC directly with enquiries on linked data. Data management procedures and analyses carried out will be outlined under each chapter corresponding to each study. Thus, chapter 4 will focus on the prevalence study and chapter 5 on the survival and cause of death study.

3.2.5 Assessing severity of various septal defects in the dataset

CHD is usually present at birth and can be diagnosed anytime in a lifetime depending on the severity; the very clinically haemodynamic symptomatic CHD (complex, severe, or moderate) will have been diagnosed in-utero, neonatally, or in infancy, and a good proportion of these children would have been registered with a healthcare setting within their first year of birth. A previous study showed that of diagnoses and registration of CHD in early childhood, most happen very early in life (164)

As there was no HES linkage in this current work, the codes in the GP data identifying corrective procedures/interventions for CHD and septal defects were used to investigate if level of severity for these defects could be ascertained, recognising that this information would likely be incomplete. All codes in Chapter seven (7) of the CPRD Read Hierarchy chapter headings, subheadings “79” (Read term: Heart/Cardiac operations), and “7A” (Read term: Artery and vein/ Blood vessel operations) were extracted from the CPRD medical entity data file (as in 3.2.2 above) (appendix 4). All children with these codes in the clinical files were identified as having had a recording of interventions/corrective procedure and were further designated as having interventions between one week of birth, or within day 7 and day 30 of birth, or between 1 month and 12 months of birth.

3.2.6 Extracting the study population from CPRD July 2017 build

There were 17,148,866 patients in the Clinical Practice Research Database (CPRD) July 2017-build of which 14,942,430 patients had an “acceptable” quality of data for research. Patients are said to be “acceptable” when they have “up-to-standard” data records and this population of acceptable patients formed the base for our research population. Up-to-standard (uts) data records refer to the date a GP is regarded as having patient-data quality appropriate for research. The study start date was set at the 1st of February of 1998. This is a month after the Office for National Statistics (ONS) data-linkage start date in the UK; hence, cause of death for all dead subjects can be retrieved. End of study follow-up (eof) was set at 30th June 2017 which is the last collection date for the CPRD July build. Another variable of importance within CPRD is “current registration date” (crd). As the name implies, crd is the patient’s current registration date at the practice.

Each patient’s study start date is taken as their date of birth which must be on or after the study start date of 1st of February 1998. Patients’ study end date is taken as the earliest of their last collection date (lcd), transfer out date (tod), or death date. Last collection date (lcd) refers to the last date data is collected from a GP, transfer-out-date (tod) refers to the date a patient transfers from a GP. To be included in the study, a patient must be registered with a practice on or after the practice’s uts date, must have crd date after their date of birth, must have registered with the practice within their first year of birth, and must have at least one-day follow-up at that practice.

In CPRD, the year of birth (yob) and month of birth (mob) are recorded for children up to the age of 15 years of age. On the date of their 16th birthday, the mob is taken out leaving only the yob for children 16 years and above. Therefore, the date of birth (dob) was set at the 1st

of the given mob and yob for children whose mob and yob are recorded and at the 1st of July for patients whose yob only are recorded. Due to this allocation of dates of birth, it is possible to get current registration dates (crd) before some dates of births. In such situations and after it has been ascertained that such was the case, the crd was taken as the dob for such patients.

Hence, starting with the 14,942,430 accepted patients from up-to-standard practices, all patients linked to ONS death data were retained in the study. Subjects registered within their first year of birth with crd dates after their dob dates, with at least one-day follow-up, and all falling within the start and finish dates of the study, were all retained. Finally, all subjects with indeterminate sex were excluded. This left five hundred and ninety-six thousand and forty-six (596,046) children in the study (Figure 3.2).

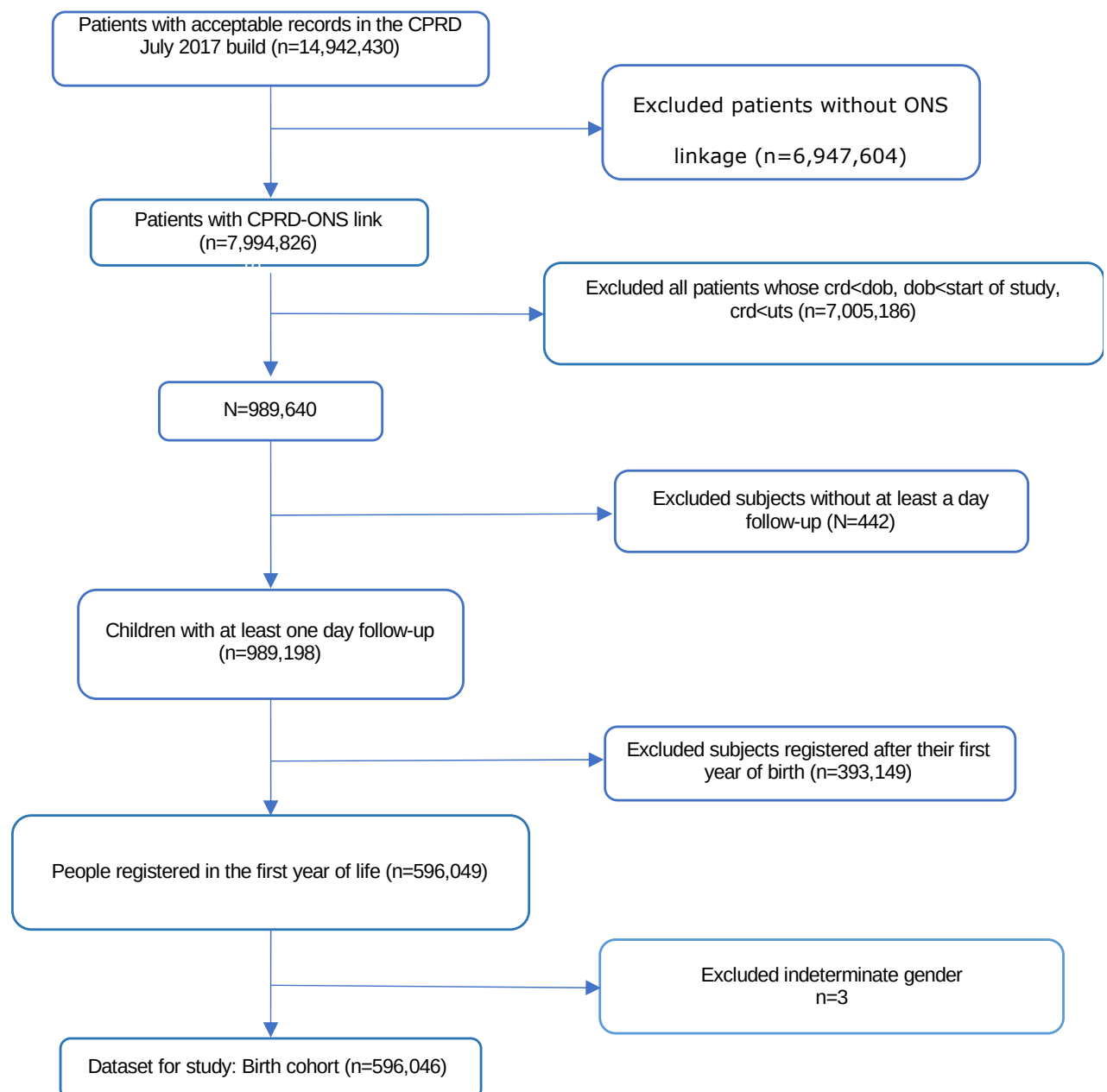


Figure 3.2 Schematics of study population extraction. The study period spans 01/02/1998 to 31/07/2017.

3.2.7 Statistical software

Statistical analyses were carried out using Stata 15 (Stata Corp., TX, USA) for Windows 10 (Microsoft Corporation, Seattle, USA).

3.3 Ethical considerations

The Medicines and Healthcare products Regulatory Agency (MHRA) Independent Scientific Advisory Committee (ISAC) regulates research done using the CPRD (135,136). ISAC approves observational studies that do not require patient involvement. GP practices consent to sharing patient data for public health research with the endorsement of UK medical associations. Furthermore, from the initial stages of data sharing between GPs and CPRD, all patient identifiers are removed including name, address, full date of birth, and any personalised medical notes (135). Also, individual patients can opt-out of being included in data sharing at the point of registering for primary care (135). Ethical approval for this study was obtained from CPRD ISAC under the protocol identification number 17_169RMn.

Chapter 4: The prevalence of septal defect variants

4.1 Epidemiology of septal defects – prevalence

The prevalence of congenital anomalies and congenital heart diseases globally continues to be studied in multiple forms. For example, the reported prevalence of CHD ranges from 2.1 to 10 per 1,000 live births in retrospective studies (8,8,165–170). Septal defects are an important subset of CHDs, accounting for a high proportion of all CHD health burdens (4). Nonetheless, there is less known on the prevalence of the various variants of septal defects in England. Understanding the prevalence of these defects in England is important for appropriate planning and intervention strategies peculiar to this population.

The increase seen in CHD prevalence has been attributed to the technological advancement in paediatric cardiology that has made it possible to diagnose small lesions of VSD (4,171).

Some studies have shown that the prevalence of severe CHD has remained constant and that the increase in CHD prevalence is only due to the diagnosis of small lesions with little or no clinical haemodynamic effect. Roy et al. in their regional population study of the variation in CHD prevalence across 24 years in Canada found that the prevalence of severe lesions (defects) was stable across a decade (1976-1986) (172). Hoffman and Kaplan carried out a meta-analysis of studies reporting that the incidence of moderate to severe CHD forms were about 6/1,000 live births and that this increased to 75/1,000 live birth if very small muscular VSD and other very minor lesions were included. Hence, high SD prevalence drives the increases seen in CHD prevalence.

Cardiac technological advancements however mean that defects can be diagnosed in-utero with the option of termination (Termination of Pregnancy for Foetal Anomaly: TOPFA) (173) or the choice of no-treatment after delivery for pregnancies presenting with defects with very poor prognoses. In essence, the perinatal prevalence of CHD is often different from

prenatal incidence rates. A recent study by Egbe et al. reported an increased CHD prevalence on mild defects from 8.0 to 9.1 per 1,000 live births and a decrease in prevalence for severe CHD lesions from 1.5 to 0.9 (174). This decrease in prevalence in severe CHD was reported to be influenced by TOPFA and/or perinatal mortality (175) and the increase seen is due to diagnosis of small lesions. Dolk et al. carried out a study of CHD in Europe using EUROCAT data during the period 2000-2005. They reported a total prevalence of 8.0/1,000 births (live births, foetal deaths from 20 weeks' gestation, and TOPFA). Total prevalence for non-chromosomal CHD was 7.0/1,000 with 3.6% being perinatal deaths, 20% diagnosed in-utero, and 5.6% TOPFA. Timing of diagnosis also affects prevalence as small muscular VSDs have been reported to close spontaneously (4).

EUROCAT founded in 1979 is a European wide collection of population-based registries for the surveillance of congenital anomalies and currently covers 35 member registries including 9 registries from the United Kingdom spanning 39 years (176). EUROCAT currently holds 750,000 cases of congenital anomalies and is thought to effectively capture 30% of all births in Europe each year, providing annual prevalence figures (177). Information is fed into EUROCAT from individual member registries biannually. EUROCAT captures information on both live births and still births, usually where the latter is reported following a miscarriage that occurs following the detection of an anomaly past 20 weeks' gestation (178). There is no uniformity in how each registry reports data that are fed into EUROCAT; some registries only document cases, where a diagnosis occurs before the age of one whilst others document cases diagnosed at any point in time (179). The classification of anomalies in EUROCAT is done using standardised subgroups based on ICD-10 coding (178). Minor anomalies are excluded from EUROCAT unless they present in association with major anomalies. The defects excluded from EUROCAT include absence or hypoplasia of umbilical artery, single umbilical artery, absence of vena cava superior, functional or unspecified cardiac murmur,

cardiomegaly, cardiomyopathy, deviation of the heart axis, patent ductus arteriosus if GA < 37 weeks, persistent left superior vena cava, persistent right aortic arch, and persistent right umbilical vein (178).

Furthermore, whilst ethnic differences have been reported to impact the birth prevalence of CHDs, where CHD incidence was higher among Black and ethnic minority children compared to white children, no differences were found in the diagnosis or intervention rates between the various ethnic groups in the UK (180). Similar impacts of ethnicity on the prevalence of CHD have also been reported globally (181–184). However, studies on the impact of ethnicity on the prevalence of septal defect variants and especially in the UK, remain sparse. It remains important to assess the prevalence of congenital heart defects, VSD, ASD, ToF, AVSD, and AoSD within the same population and the UK.

This level of interrogation is required to fully understand the comparative prevalence of these various defects and to inform strategies of promoting diagnosis and prompt interventions where required. In this chapter, I consider in the same birth cohort, the prevalence of congenital heart defects, VSD, ASD, ToF, AVSD, and AoSD and, also assess the effect of gender, socioeconomic status, and geographical location on the prevalence of these defects.

4.2 Methods

4.2.1 Study population

The study population was individuals in CPRD born 1998-2017 and registered with their general practice by 12 months of age as described in section 3.2. A 12-month cut-off is based on previous research that showed that amongst a population of children registered later in life, the prevalence for CA was considerably lower and that there is a tendency for their CA information not to be registered (185). Though present at birth and diagnosable anytime in a

lifetime, the very sick CHD child would show symptoms early in life with diagnosis done prenatally for some very complex and/or severe defects. Hence it is expected that the haemodynamically symptomatic defects would have been diagnosed in-utero, neonatally, or in infancy, and that these children, if alive, would have been registered within their first year of birth with a GP. Also, the cut-off at 12 months after birth ascertains those children who were ill perinatally and had to be hospitalized early in life and, who did not get a chance to register with a GP earlier on, would have been registered by age one and thus, be captured in this study population. Children with CA were identified and defined as described in 3.2.1. CHD and SD variants were classified as described in section 3.2.3. All methods for data linkage to ONS and IMD are also described in Chapter 3.

4.2.2 Statistical analysis

4.2.2.1 Prevalence

The birth prevalence was calculated as the number of CHD, SD, or SD variants per 10,000 live GP-registered births. A binominal distribution of the data was assumed in calculating the 95% confidence intervals. For SD and its variants, total cases were further split into isolated cases occurring without other CHD, OCA, and prevalence of all of these was calculated. Following this, the prevalence of SD and its variants was calculated according to gender, year of birth, ethnicity, deprivation, and geographical area. Logistic regression was performed to assess the unadjusted prevalence ratio of the association between gender and total SD, or total VSD, total ASD, or total ToF. Similar analyses were done for year of birth, ethnicity, deprivation, and geographical area. Risk ratios were calculated independently for total SD, or total VSD, total ASD, or total ToF. The sample size for AoSD, AVSD, and unspecified SD was too low to allow for subgroup analysis.

4.2.2.2 Comparison to EUROCAT

For comparison to EUROCAT, the comparison data were downloaded from the EUROCAT website on 30th January 2021 (186). The following parameters were used to allow as close a comparison as possible to the CPRD study population.

- Cases of congenital heart defects, ventricular septal defects, atrial septal defects, Teratology of Fallot, and atrioventricular septal defect
- Live born children from 1998 – 2017
- All registries in England (East Midlands & South Yorkshire, Northern England, South West England, Thames Valley, Wessex, Yorkshire and Humber, Merseyside and Cheshire and NW Thames).

The number of cases, prevalence rates per 10,000 live GP-registered births, and 95% confidence intervals were obtained directly from the EUROCAT database. The 95% confidence intervals on EUROCAT are calculated using the Poisson distribution (176).

To allow comparison of the prevalence rates between CPRD and EUROCAT, prevalence ratios were calculated as the prevalence of SD variant for CPRD divided by the prevalence from EUROCAT. Since the geographical areas in EUROCAT are not exactly parallel to those of CPRD, an exact comparison was not possible.

4.3 Results

4.3.1 Population overview

The total number of children in the study population was 596,046, and of these, 5,129 (0.86%) had a diagnosis of a congenital heart defect between January 1998 to June 2017. Of the total birth population, 46,759 (7.83%) had other congenital anomalies (OCA) whilst 545,454 (91.31%) had no congenital anomaly (CA) and was, therefore, the control group (Figure 4.1). Of the OCA population, 23.14% had major OCA whilst the vast majority (76.86%) had minor OCA and was disregarded concerning analyses for the remaining of this study but were retained in the birth cohort baseline population.

Of the 5,129 with a diagnosis of congenital heart defects, 2,899 (53.4%) had been diagnosed with septal defects whilst 2,533 (46.6%) were diagnosed with other congenital heart defects (Figure 4.1). Of all the children diagnosed with septal defects, VSD had the highest proportion making up 59% of all septal defect cases, followed only by ASD at 29%. Altogether, AVSD, ToF, AoSD, and unspecified SD made up 12% of all septal defect diagnoses (Figure 4.1).

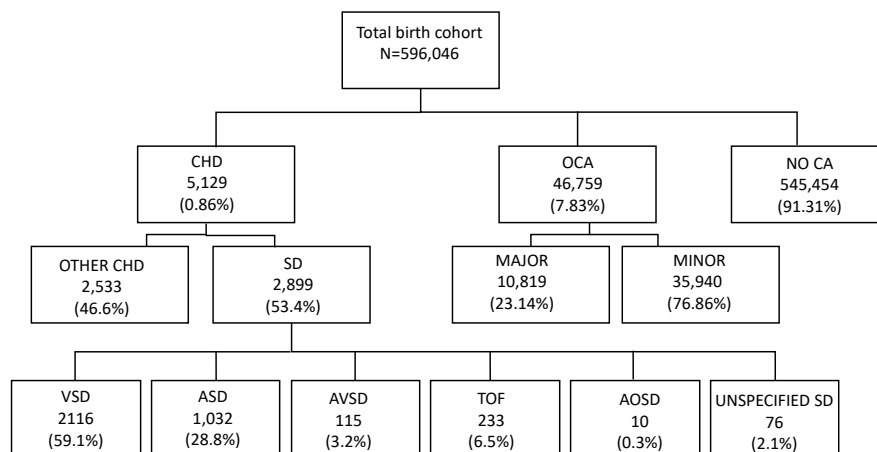


Figure 4.1: Number of cases and prevalence according to congenital anomaly subgroup

In the general study population, the proportion of males (51.24%) was slightly higher than females (48.76%). When investigated further, in children diagnosed with any CHD there was an almost equal split between males and females (50.52% and 49.48% respectively), whereas, for children with major OCA, there were considerably more males (61.35%) than females (38.65%). In children with no CA, there was again about an even split between males and females (50.62% and 49.38%) respectively (Table 4.1).

Table 4.1: Basic demographics of the study population showing numbers and percentages of children with any CHD and major OCA by sex.

		Any CHD		Major OCA		Total
		n	%	n	%	n
Frequency		5,129	0.86	10,819	1.82	596,046
Sex	Male	2,591	(50.52)	6,637	(61.35)	305,412
	Female	2,538	(49.48)	4,182	(38.65)	290,634

4.3.2 Prevalence of Congenital heart defects, other congenital anomalies, and total septal defects

The prevalence of any CHD in the study population was 86.1 per 10,000 live GP-registered births (95% CI 83.7 – 88.4). Furthermore, the prevalence of all septal defects was 48.64 per 10,000 live GP-registered births (95% CI 46.90-50.44), where the total number as earlier reported was 2,899 patients. Of this, the number of isolated SD cases was 1,958 with a prevalence of 32.85 per 10,000 live GP-registered births (95% CI 31.43-34.34). The number of patients with a combined SD and other CHD diagnosis was 182 with a prevalence of 3.10

per 10,000 live GP-registered births (95% CI 2.64-3.53). This number was higher for patients diagnosed with SD and OCA at 638 with a prevalence of 10.70 per 10,000 live GP-registered births (95% CI 9.91-11.57). Children diagnosed with SD, OCA, and other CHD were the lowest component of the total SD at 121 with a prevalence of 2.03 per 10,000 live GP-registered births (95% CI 1.69-2.43) (Table 4.2).

The total number of diagnosed cases of total OCA was 46,759 with a prevalence of 784.49 per 10,000 live GP-registered births (95% CI 777.69-791.34). Of this 10,819 were major OCA with a prevalence of 181.51 per 10,000 live GP-registered births (95% CI 178.16-184.93), whilst there were 35,940 minor OCA cases with a prevalence of 602.97 per 10,000 live GP-registered births (95% CI 596.96-609.05). For this study, only major OCA was considered in further analysis. There were 1,296 combined diagnoses of CHD and OCA and 545,454 records of patients with no CA (Table 4.2).

Table 4.2: Total number, number and percentage by sex, and prevalence of CHD and SD variants per 10,000 live GP-registered births with 95% CI within the birth cohort

	Number of patients (n)	Male (% of n)	Female (% of n)	Prevalence per 10,000 live GP-registered births * (95%CI)
Total CHD	5,129	2,591 (50.52)	2,538 (49.48)	86.1 (83.7 – 88.4)
Total SD	2,899	1,384 (47.74)	1,515 (52.26)	48.64 (46.90-50.44)
Isolated SD	1,958	899 (45.91)	1,059 (54.09)	32.85 (31.43-34.34)
SD with other CHD	182	74 (40.66)	108 (59.34)	3.10 (2.64-3.53)
SD with OCA	638	347(54.39)	291(45.61)	10.70(9.91-11.57)
SD with oca and other CHD	121	64(52.89)	75(47.11)	2.03(1.69-2.43)
Total VSD	2,116	998 (47.16)	1,118 (52.84)	35.50 (34.02-37.04)
Isolated VSD	1,378	626 (45.43)	752 (54.57)	23.12 (21.93-24.37)
VSD with other CHD	233	100(42.92)	133(57.08)	3.91 (3.44-4.45)
VSD with OCA and other CHD	130	63(48.46)	67(51.54)	2.18 (1.84-2.59)
VSD with OCA	375	209 (55.73)	166 (44.27)	6.30 (5.69-6.96)
Total ASD	1,032	478 (46.32)	554 (53.68)	17.31 (16.29-18.40)
Isolated ASD	560	250 (44.64)	310 (55.36)	9.40 (8.65-10.21)
ASD with other CHD	131	54 (41.22)	77 (58.78)	2.20 (1.85-2.61)
ASD with OCA and other CHD	90	45 (50.00)	45 (50.00)	1.51(1.23-1.86)
ASD with OCA	251	129 (51.39)	122 (48.61)	4.21 (3.72-4.77)
Total ToF	233	136 (58.37)	97 (41.63)	3.91 (3.44-4.45)
Isolated ToF	119	67 (56.30)	52 (43.70)	2.0 (1.67-2.39)
ToF with other CHD	42	27(64.29)	15(35.71)	0.71(0.52-0.95)
ToF with OCA and other CHD	17	9(52.94)	8(47.06)	0.29(0.18-0.46)
ToF with OCA	55	33 (60)	22 (40)	0.92 (0.71-1.20)
Total AVSD	115	59 (51.30)	56 (48.70)	1.93 (1.61-2.32)

Isolated AVSD	38	14 (36.84)	24 (63.16)	0.64 (0.47-0.88)
AVSD with other CHD	12	8 (66.67)	<5 (33.33)	0.20 (0.11-0.36)
AVSD with OCA and other CHD	14	9 (64.29)	5 (35.71)	0.24 (0.14-0.40)
AVSD with OCA	51	28 (54.90)	23 (45.10)	0.86 (0.65-1.13)
Total AoSD	10	<5 (40)	6 (60)	0.17 (0.09-0.31)
Isolated AoSD	<5	<5 (33.33)	<5 (66.67)	0.05 (0.02-0.16)
AoSD with other CHD	<5	<5 (66.67)	<5 (33.33)	0.05 (0.02-0.16)
AoSD with OCA and other CHD	<5	0	<5 (100)	0.05 (0.02-0.16)
AoSD with OCA	<5	<5 (100)	0	0.02 (0.002-0.12)
Total Unspecified SD	76	39 (51.32)	37 (48.68)	1.28 (1.02-1.60)
Isolated Unspecified SD	33	12 (36.36)	21 (63.64)	0.55 (0.39-0.78)
Unspecified SD with OCA	17	8 (47.06)	9 (52.94)	0.29 (0.18-0.46)
Unspecified SD with other CHD	12	8 (66.67)	<5 (33.33)	0.20 (0.11-0.36)
Unspecified SD with OCA and other CHD	14	11 (78.57)	<5 (21.43)	0.24 (0.14-0.40)
Total OCA	46,759	27,451 (58.71)	19,308 (41.29)	784.49 (777.69-791.34)
Major OCA	10,819	6,637 (61.35)	4,182 (38.65)	181.51 (178.16-184.93)
Minor OCA	35,940	20,814 (57.91)	15,126 (42.09)	602.97 (596.96-609.05)
CHD + major OCA	1,296	712 (54.94)	584 (45.06)	21.74 (20.59-22.96)
No CA	545,454	276,082 (50.62)	269,372 (49.38)	9151.21 (9144.10-9158.26)

Table 4.3 shows the number and prevalence of any congenital heart defect by gender, year of birth, ethnicity, socio-demographic factors, and geographical region with the unadjusted and adjusted risk ratios for context. Overall, the results show that there is no major difference in CHD occurrence between males and females (RR = 1.03, 95% CI = 0.97-1.09), $p > 0.05$ in unadjusted and adjusted models). The prevalence of any CHD was fairly steady when assessed according to the calendar year of birth from 1998-2002 (82.70 per 10,000 live GP-

90

registered births, 95% CI 77.63-88.15), highest in 2008-2012 at 89.34 per 10,000 live GP-registered births (95% CI 85.29-93.58), and lowest between 2013-2017 with a prevalence of 82.09 per 10,000 live GP-registered births (76.75-87.80) (unadjusted RR = 0.99, 95% CI = 0.91-1.09) (Table 4.3).

The risk of developing any CHD was not so different between the 2nd, 3rd, and 4th deprivation quintiles when compared to the 1st quintile (least deprived); however, there was a difference when compared with the 5th quintile (most deprived) (93.51 per 10,000 live GP-registered births, 95% CI 88.21-99.13), although overall difference was significant in unadjusted analysis (unadjusted RR =1.11, 95% CI 1.03-1.22) $p=0.056$ and insignificant after adjustments for gender, year of birth, ethnicity, and region (adjusted RR = 1.08, 95% CI 0.99-1.17) $p=0.3015$. The prevalence of any CHD varied slightly across geographical areas, with overall CHD occurring mostly in the Northeast than other geographical areas of England (RR = 1.29, 95% CI 1.08-1.55) with a prevalence of 104.87 per 10,000 live GP-registered births. The southeast coast had the lowest prevalence of 72.44 per 10,000 live GP-registered births.

Of all children diagnosed with CHD, 2,627 (51.23%) children had missing data for ethnicity; despite this, there was a significant difference in CHD prevalence across ethnic groups in both unadjusted ($p=0.003$) and adjusted analyses ($p=0.0176$). The prevalence of any CHD was highest in the Mixed population with 95.97 per 10,000 live GP-registered births (95% CI 90.01-102.31) when compared to the White reference group followed by the Asian/Asian British ethnic group with prevalence of 92.54 per 10,000 live GP-registered births (95% CI 79.71-107.41) (Table 4.3).

Table 4.3: Number, prevalence/10,000LB, unadjusted and adjusted prevalence ratio, and P values of any of congenital heart defect

	Prevalence			Prevalence ratio			Adjusted Ratio	Prevalence ratio	
	Number	Per 10,000 live GP-registered births	95% CI	Unadjusted Ratio	95% CI	Chi squared P value		95% CI	Adjusted P value
Total	5,129	86.05	(83.74-88.43)						
Sex									
Male	2,591	84.84	(81.65-88.15)	ref			ref		
Female	2,538	87.33	84.01-90.76)	1.03	(0.97-1.09)	0.298	1.03	(0.97-1.09)	0.2981
Year of birth									
1998-2002	954	82.70	(77.63-88.09)	ref			ref		
2003-2007	1,562	86.83	(82.65-91.23)	1.05	(0.97-1.14)		1.04	(0.96-1.13)	
2008-2012	1,771	89.34	(85.29-93.58)	1.08	(1.0-1.17)		1.05	(0.97-1.15)	
2013-2017	842	82.09	(76.75-87.80)	0.99	(0.91-1.09)	0.109	1.02	(0.93-1.12)	0.6738
Ethnicity									
White	1,043	87.93	(82.78-93.41)	ref					
Mixed	928	95.97	(90.01-102.31)	1.09	(1.0-1.19)		1.10	(1.01-1.21)	
Asian/Asian British	171	92.54	(79.71-107-41)	1.05	(0.90-1.24)		1.06	(0.90-1.24)	
Black/Black British	90	89.16	(72.57-109.50)	1.01	(0.82-1.26)		1.04	(0.84-1.30)	
Chinese	10	66.93	(36.05-123.95)	0.76	(0.41-1.42)		0.77	(0.41-1.43)	
Other	260	78.55	(69.59-88.65)	0.89	(0.78-1.02)		0.90	(0.78-1.03)	
Missing	2,627	82.72	(79.63-85.93)	0.94	(0.88-1.01)	0.003	0.97	(0.89-1.04)	0.0176
Deprivation									

1	1,060	83.57	(78.70-88.73)	ref			ref		
2	993	85.47	(80.34-90.93)	1.02	(0.94-1.11)		1.02	(0.94-1.11)	
3	987	84.43	(79.34-89.84)	1.01	(0.93-1.10)		1.00	(0.92-1.09)	
4	965	83.50	(78.41-88.91)	1.0	(0.92-1.09)		0.98	(0.90-1.07)	
5	1,118	93.51	(88.21-99.13)	1.11	(1.03-1.22)		1.08	(0.99-1.17)	
Missing	6	60.61	(27.25-134.23)	0.73	(0.33-1.61)	0.056	0.72	(0.32-1.61)	0.3015
Region									
London	776	81.13	(75.64-87.02)	ref			ref		
Northeast	135	104.87	(88.66-124.01)	1.29	(1.08-1.55)		1.29	(1.07-1.55)	
Northwest	810	93.84	(87.63-100.50)	1.16	(1.05-1.28)		1.14	(1.03-1.26)	
Yorkshire & The Humber	183	85.71	(74.19-99.01)	1.06	(0.90-1.24)		1.06	(0.90-1.25)	
East Midlands	179	102.54	(88.62-118.61)	1.26	(1.08-1.49)		1.29	(1.10-1.52)	
West Midlands	592	86.61	(79.93-93.84)	1.07	(0.96-1.19)		1.06	(0.95-1.18)	
East of England	578	83.39	(76.89-90.44)	1.03	(0.92-1.14)		1.04	(0.93-1.16)	
Southwest	645	92.65	(85.80-100.05)	1.14	(1.03-1.27)		1.15	(1.04-1.28)	
South Central	657	86.58	(80.23-93.43)	1.07	(0.96-1.18)		1.09	(0.98-1.21)	
Southeast Coast	574	72.44	(66.76-78.59)	0.89	(0.80-0.99)	<0.001	0.90	(0.81-1.01)	<0.0001

Adjusted for gender, year of birth, ethnicity, deprivation, and region.

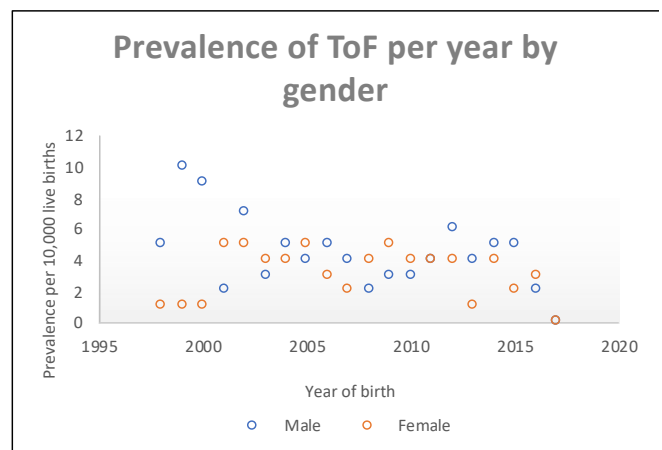
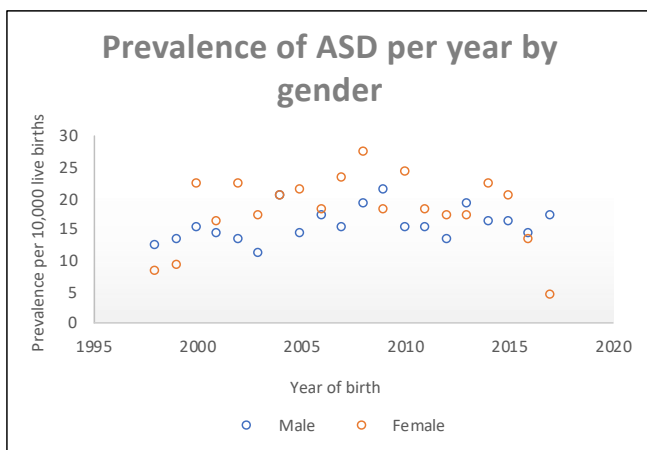
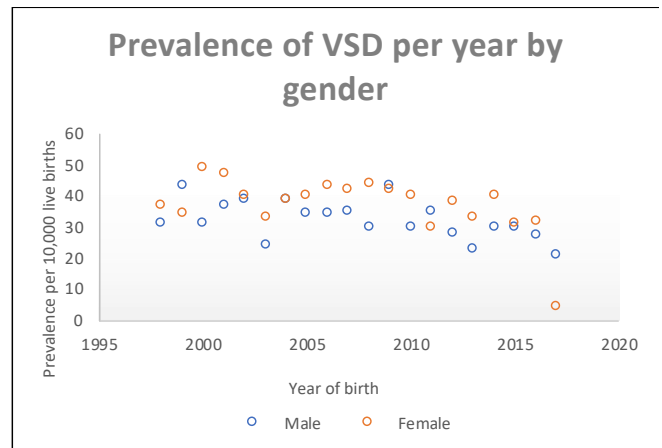
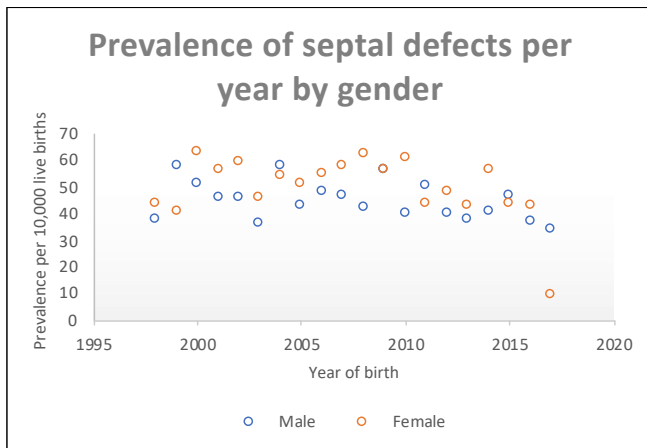


Figure 4.2 Prevalence of Septal defects and its variants per year by sex

Table 4.4 shows the number and prevalence of any septal defects by gender, year of birth, ethnicity, and socio-demographic factors, with the unadjusted and adjusted risk ratios. The results show that total septal defects occurred significantly more frequently in female children compared to male children (RR = 1.15, 95% CI = 1.07-1.24) $p < 0.05$ in unadjusted and adjusted models). The prevalence of any septal defect was fairly steady when assessed according to the calendar year of birth from 1998-2002 (49.41 per 10,000 live GP-registered births, 95% CI 45.52-53.63), highest in 2003-2007 at 50.25 per 10,000 live GP-registered births (95% CI 47.09-53.63), and lowest between 2013-2017 with a prevalence of 43.09 per 10,000 live GP-registered births (39.26-47.29) (RR = 0.87, 95% CI = 0.77-0.99) (Table 4.4).

The risk of developing any septal defect was not different between the deprivation quintiles when compared to 1 (least deprived). There were 3 records with missing deprivation data, but this did not defer from the least deprived as they had overlapping 95% CI. The prevalence of any septal defects varied slightly across geographical areas, with septal defects occurring mostly in the East Midlands than other geographical areas of England (RR = 1.45, 95% CI 1.18-1.77) with a prevalence of 66.45 per 10,000 live GP-registered births. The southeast coast had the lowest prevalence of 41.77 per 10,000 live GP-registered births.

Of all children diagnosed with septal defects, 1,474 (50.84%) children had missing data for ethnicity. The prevalence of any septal defects was not considerably different in other ethnic groups assessed (mixed, Asian/Asian British, Black/Black British, Chinese, other, or missing) when compared to reference White ethnic group (Table 4.4). Prevalence ranged from the lowest, 45.04 per 10,000 live GP-registered births (95% CI 38.35-52.83) in the ethnic group marked as “other” to the highest 54.81 per 10,000 live GP-registered births (95% CI 50.35 – 59.67) in the ethnic group marked “Mixed”. Although there was a statistical significance of any SD occurring based on ethnicity, in the unadjusted models, this significance was lost in the adjusted models, which accounted for gender, year of birth, and region (Table 4.4).

Table 4.4: Number, prevalence/10,000LB, unadjusted and adjusted prevalence ratio, and P values of any of septal defects.

	Prevalence			Prevalence ratio			Adjusted Ratio	Prevalence ratio	
	Number	Per 10,000 live GP-registered births	95% CI	Unadjusted Ratio	95% CI	Chi squared P value		95% CI	Adjusted P value
Total	2,899	48.64	(46.90-50.44)						
Sex									
Male	1,384	45.32	(43.00-47.76)	ref			ref		
Female	1,515	52.13	(49.57-54.81)	1.15	(1.07-1.24)	<0.001	1.15	(1.07-1.24)	0.0002
Year of birth									
1998-2002	570	49.41	(45.52-53.63)	ref			ref		
2003-2007	904	50.25	(47.09-53.63)	1.02	(0.92-1.13)		1.00	(0.90-1.11)	
2008-2012	983	49.59	(46.59-52.78)	1.00	(0.91-1.11)		0.96	(0.86-1.08)	
2013-2017	442	43.09	(39.26-47.29)	0.87	(0.77-0.99)	0.046	0.90	(0.79-1.02)	0.2485
Ethnicity									
White	593	49.99	(46.14-54.17)	ref			ref		
Mixed	530	54.81	(50.35-59.67)	1.10	(0.98-1.23)		1.11	(0.99-1.25)	
Asian/Asian British	98	53.03	(43.53-64.60)	1.06	(0.86-1.31)		1.09	(0.88-1.35)	
Black/Black British	47	46.56	(35.00-61.92)	0.93	(0.69-1.25)		0.98	(0.72-1.32)	
Chinese	8	53.55	(26.80-106.70)	1.07	(0.53-2.15)		1.10	(0.55-2.20)	
Other	149	45.04	(38.35-52.83)	0.90	(0.72-1.08)		0.90	(0.75-1.08)	
Missing	1,474	46.42	(44.11-48.84)	0.93	(0.84-1.02)	0.041	0.94	(0.84-1.04)	0.0587
Deprivation									
1	617	48.64	(44.96-52.62)	ref			-	-	

2	575	49.49	(45.62-53.70)	1.02	(0.91-1.14)		1.01	(.90-1.14)	
3	521	44.57	(40.91-48.55)	0.92	(0.82-1.03)		0.91	(0.81-1.02)	
4	566	48.97	(45.11-53.17)	1.01	(0.90-1.13)		0.99	(0.88-1.11)	
5	617	51.61	(47.70-55.83)	1.06	(0.95-1.19)		1.02	(0.91-1.15)	
Missing	3	30.30	(9.77-93.52)	0.62	(0.20-1.93)	0.215	0.62	(0.20-1.91)	0.3024
Region									
London	440	46.00	(41.91-50.50)	ref				ref	
North East	73	56.71	(45.11-71.27)	1.23	(0.96-1.58)		1.24	(0.96-1.58)	
North West	453	52.48	(47.88-57.53)	1.14	(1.00-1.30)		1.13	(0.99-1.29)	
Yorkshire & The Humber	109	51.05	(42.33-61.56)	1.11	(0.90-1.37)		1.10	(0.89-1.36)	
East Midlands	116	66.45	(55.42-79.65)	1.45	(1.18-1.77)		1.46	(1.18-1.79)	
West Midlands	318	46.53	(41.69-51.92)	1.01	(0.88-1.17)		1.00	(0.87-1.16)	
East of England	324	46.74	(41.93-52.11)	1.02	(0.88-1.17)		1.02	(0.88-1.18)	
South West	362	52	(46.92-57.63)	1.13	(0.98-1.30)		1.14	(0.99-1.31)	
South Central	373	49.16	(44.42-54.39)	1.07	(0.93-1.23)		1.08	(0.94-1.24)	
South East Coast	331	41.77	(37.51-46.51)	0.91	(0.79-1.05)	0.001	0.92	(0.80-1.06)	0.0026

Adjusted for gender, year of birth, ethnicity, deprivation, and region.

4.3.3 Prevalence of Ventricular septal defects

Of the total septal defects, ventricular septal defects had the highest prevalence of 35.50 per 10,000 live GP-registered births (95% CI 34.02-37.04), where the number of patients was 2,116. Within this, the number of isolated VSD diagnoses was 1,378 with a prevalence of 23.12 per 10,000 live GP-registered births (21.93-24.37), accounting for the majority of the VSD cases. Nonetheless, 233 patients were diagnosed with VSD and other CHD with a prevalence of 3.91 per 10,000 live GP-registered births (95% CI 3.44-4.45). More children had a combined diagnosis of VSD and other CA (375 patients) with a prevalence of 6.30 per 10,000 live GP-registered births (95% CI 5.69-6.96). Of all VSD cases, children diagnosed with VSD, other CHD, and other CA were the least at 130 patients, having a prevalence of 2.18 per 10,000 live GP-registered births (95% CI 1.84-2.59) (Table 4.2).

The prevalence of VSD in females was significantly higher than males at 38.47 per 10,000 live GP-registered births (95% CI 36.28-40.79) for females and 32.68 per 10,000 live GP-registered births (95% CI 30.71-34.77) for males; (RR = 1.18, 95% CI 1.08-1.28, $p < 0.001$ for adjusted and unadjusted models) (Table 4.5, Figure 4.2). The prevalence of VSD was highest in the year of birth between 1998-2002 (37.79 per 10,000 live GP-registered births, 95% CI 34.41-41.51) and progressively dropped to 36.63 per 10,000 live GP-registered births (95% CI 33.95-39.53) in 2003-2007; 35.77 per 10,000 live GP-registered births (95% CI 33.23-38.49) and lowest at 30.42 per 10,000 live GP-registered births (95% CI 27.23-33.98) (Table 4.5). Overall, year of birth was significantly associated with VSD occurring ($p < 0.05$ in unadjusted and adjusted models).

The prevalence of VSD was steady across all ethnic groups assessed with the 95% CI of the OR overlapping across all ethnic groups (Table 4.5). Furthermore, the risk of VSD occurring was not different between the deprivation quintiles when compared to 1 (least deprived). The prevalence of VSD varied across geographical areas in England. Where London was the reference, Northeast was higher (RR = 1.37, 95% CI 1.03-1.83); jointly with the South West (RR = 1.37, 95% CI 1.17-1.61); then followed by the East Midlands

(RR = 1.28, 95% CI 0.99-1.66) and South Central (RR = 1.19, 95% CI 1.01-1.40). Of all the geographical regions London was jointly lowest with Southeast Coast.

Table 4.5: Number, prevalence/10,000 live GP-registered births, unadjusted and adjusted prevalence ratio, and P values of VSD.

	Prevalence			Prevalence ratio			Adjusted Ratio	Prevalence ratio	
	Number	Per 10,000 live GP-registered births	95% CI	Unadjusted Ratio	95% CI	Chi squared P value		95% CI	Adjusted P value
Total	2,116	35.50	(34.02-37.04)						
Sex									
Male	998	32.68	(30.71-34.77)	ref			ref		
Female	1,118	38.47	(36.28-40.79)	1.18	(1.08-1.28)	<0.001	1.18	(1.08-1.28)	0.0002
Year of birth									
1998-2002	436	37.79	(34.41-41.51)	ref			ref		
2003-2007	659	36.63	(33.95-39.53)	0.97	(0.86-1.09)		0.97	(0.86-1.10)	
2008-2012	709	35.77	(33.23-38.49)	0.95	(0.84-1.07)		0.95	(0.85-1.08)	
2013-2017	312	30.42	(27.23-33.98)	0.81	(0.70-0.93)	0.019	0.82	(0.71-0.95)	0.0488
Ethnicity									
White	422	35.58	(32.35-39.13)	ref			-	-	
Mixed	382	39.50	(35.74-43.66)	1.11	(0.97-1.28)		1.12	(0.97-1.28)	
Asian/Asian British	72	38.96	(30.94-49.06)	1.10	(0.85-1.41)		1.12	(0.89-1.48)	
Black/Black British	29	28.73	(19.97-41.31)	0.81	(0.56-1.18)		0.88	(0.60-1.29)	
Chinese	6	40.16	(18.05-89.10)	1.13	(0.51-2.52)		1.18	(0.53-2.63)	
Other	117	35.35	(29.50-42.35)	0.99	(0.81-1.22)		0.96	(0.78-1.18)	
Missing	1,088	34.26	(32.29-36.35)	0.96	(0.86-1.08)	0.254	0.96	(0.85-1.08)	0.2437
Deprivation									
1 (least deprived)	479	37.76	(34.53-41.29)	ref			-	-	
2	408	35.12	(31.88-38.69)	0.93	(0.82-1.06)		0.93	(0.81-1.06)	
3	396	33.88	(30.70-37.37)	0.90	(0.79-1.03)		0.89	(0.78-1.02)	

4	403	34.87	(31.63-38.44)	0.92	(0.81-1.05)		0.92	(0.81-1.05)	
5 (most deprived)	427	35.72	(32.49-39.26)	0.95	(0.83-1.08)		0.93	(0.81-1.07)	
Missing	3	30.30	(9.78-93.52)	0.80	(0.26-2.49)	0.704	0.78	(0.25-2.43)	0.5344
Region									
London	303	31.68	(28.31-35.45)	ref			ref		
Northeast	56	43.50	(33.49-56.49)	1.37	(1.03-1.83)		1.35	(1.01-1.79)	
Northwest	310	35.92	(32.14-40.14)	1.13	(0.97-1.33)		1.12	(0.96-1.31)	
Yorkshire & The Humber	81	37.94	(30.53-47.15)	1.20	(0.94-1.53)		1.17	(0.91-1.49)	
East Midlands	71	40.67	(32.24-51.29)	1.28	(0.99-1.66)		1.23	(0.95-1.60)	
West Midlands	225	32.92	(28.89-37.50)	1.04	(0.88-1.23)		1.03	(0.86-1.22)	
East of England	230	33.18	(29.17-37.75)	1.05	(0.88-1.24)		1.03	(0.87-1.22)	
Southwest	302	43.38	(38.76-48.55)	1.37	(1.17-1.61)		1.36	(1.16-1.59)	
South Central	286	37.67	(33.57-42.31)	1.19	(1.01-1.40)		1.18	(1.01-1.39)	
Southeast Coast	252	31.80	(28.11-35.97)	1.00	(0.85-1.19)	0.002	1.00	(0.85-1.19)	0.0022

Adjusted for gender, year of birth, deprivation, and region.

4.3.4 Prevalence of Atrial septal defect

Atrial septal defect was the next most prevalent SD, constituting 28.8% of the total number of patients diagnosed with SD with a prevalence of 17.31 per 10,000 live GP-registered births (95% CI 16.29-18.40). The number of isolated ASD diagnoses was 560 with a prevalence of 9.40 per 10,000 live GP-registered births (95% CI 8.65-10.21). There were 131 children with a combined diagnosis of ASD with other CHD, having a prevalence of 2.20 per 10,000 live GP-registered births (95% CI 1.85-2.61). Furthermore, 251 children had a combined diagnosis of ASD and other CA with a prevalence of 4.21 per 10,000 live GP-registered births (95% CI 3.72-4.77). More so, 90 children were diagnosed with ASD, OCA, and other CHD showing a prevalence of 1.51 per 10,000 live GP-registered births (95% CI 1.23-1.86) (Table 4.2).

The prevalence of ASD in females was significantly higher than males at 19.02 per 10,000 live GP-registered births (95% CI 17.54-20.72) for females and 15.65 per 10,000 live GP-registered births (95% CI 14.31-17.12); (RR = 1.22, 95% CI 1.08-1.38, $p < 0.05$ for adjusted and unadjusted models) (Table 4.6, Figure 4.2). There was no significant difference in the prevalence by year of birth from 1998 to 2017 in relation to the risk of ASD occurring.

Ethnicity was a modestly important factor in the prevalence of ASD in this study population. Within the ethnic group, White is the reference group with a prevalence of 18.38 per 10,000 live birth (95% CI 16.10-20.99), Asian/Asian British had the highest prevalence at 21.65 per 10,000 live GP-registered births (95% CI 15.88-29.50), followed closely by Black/Black British at 20.80 per 10,000 live GP-registered births (95% CI 13.57-31.89) and Mixed ethnicity at 20.37 per 10,000 live GP-registered births (95% CI 17.72-23.42). The Chinese ethnic group had the lowest prevalence at 6.69 per 10,000 live GP-registered births (95% CI

0.94-47.36) (Table 4.6). It is important to note that 49% of the ASD diagnosed cases had missing ethnicity data. Nonetheless, overall, ethnicity was significantly associated with the prevalence of ASD ($p < 0.05$ in unadjusted and adjusted models). Furthermore, the risk of ASD occurring was not different between the deprivation quintiles when compared to the least deprived group (Table 4.6).

The prevalence of ASD varied across geographical areas in England. Where London was the reference, the East Midlands was the highest (RR = 1.85, 95% CI 1.38-2.47) with the Southwest being the lowest with prevalence much lower than London (RR = 0.64, 95% CI 0.49-0.83) (Table 4.6). Overall, geographical region was significantly associated with ASD occurring ($p < 0.05$ in unadjusted and adjusted models).

Table 4.6: Number, prevalence/10,000 live GP-registered births, unadjusted and adjusted prevalence ratio, and P values of ASD

	Prevalence			Prevalence ratio			Adjusted Ratio	Prevalence ratio	
	Number	Per 10,000 live GP-registered births	95% CI	Unadjusted Ratio	95% CI	Chi squared P value		95% CI	Adjusted P value
Total	1,032	17.31	(16.29-18.40)						
Sex									
Male	478	15.65	(14.31-17.12)	ref			ref		
Female	554	19.02	(17.54-20.72)	1.22	(1.08-1.38)	0.002	1.22	(1.08-1.38)	0.0016
Year of birth									
1998-2002	168	14.56	(12.52-16.94)	ref			ref		
2003-2007	318	17.68	(15.84-19.73)	1.21	(1.01-1.46)		1.19	(0.98-1.44)	
2008-2012	370	18.67	(16.86-20.67)	1.28	(1.07-1.54)		1.23	(1.00-1.50)	
2013-2017	176	17.16	(14.80-19.89)	1.18	(0.95-1.46)	0.063	1.24	(1.00-1.54)	0.1583
Ethnicity									
White	218	18.38	(16.10-20.99)	ref			ref	-	-
Mixed	197	20.37	(17.72-23.42)	1.11	(0.91-1.34)		1.14	(0.94-1.39)	
Asian/Asian British	40	21.65	(15.88-29.50)	1.18	(0.84-1.65)		1.13	(0.81-1.59)	
Black/Black British	21	20.80	(13.57-31.89)	1.13	(0.72-1.77)		1.10	(0.70-1.74)	
Chinese	<5	6.69	(0.94-47.36)	0.36	(0.05-2.60)		0.36	(0.05-2.54)	
Other	47	14.20	(10.67-18.89)	0.77	(0.56-1.06)		0.83	(0.60-1.13)	
Missing	508	16.00	(14.67-17.45)	0.87	(0.74-1.02)	0.022	0.88	(0.75-1.03)	0.0419
Deprivation									
1	191	15.06	(13.07-17.35)	ref			ref	-	-
2	204	17.56	(15.31-20.14)	1.17	(0.96-1.42)		1.16	(0.95-1.14)	
3	192	16.42	(14.26-18.92)	1.09	(0.89-1.33)		1.10	(0.90-1.35)	
4	207	17.91	(15.63-20.52)	1.19	(0.98-1.45)		1.14	(0.94-1.40)	

5	237	19.82	(17.46-22.51)	1.32	(1.09-1.59)		1.22	(1.00-1.14)	
Missing	1	10.10	(1.43-71.34)	0.67	(0.09-4.78)	0.101	0.68	(0.95-4.85)	0.3493
Region									
London	178	18.61	(16.07-21.55)	ref			ref		
Northeast	25	19.42	(13.13-28.73)	1.04	(0.69-1.59)		1.07	(0.71-1.63)	
Northwest	180	20.85	(18.02-24.13)	1.12	(0.91-1.38)		1.12	(0.91-1.39)	
Yorkshire & The Humber	30	14.05	(9.82-20.09)	0.76	(0.51-1.11)		0.77	(0.52-1.14)	
East Midlands	60	34.37	(26.70-44.24)	1.85	(1.38-2.47)		1.97	(1.46-2.64)	
West Midlands	131	19.17	(16.15-22.74)	1.03	(0.82-1.29)		1.04	(0.83-1.30)	
East of England	120	17.31	(14.48-20.70)	0.93	(0.74-1.17)		0.96	(0.76-1.21)	
Southwest	83	11.92	(9.62-14.78)	0.64	(0.49-0.83)		0.66	(0.51-0.86)	
South Central	123	16.21	(13.59-19.34)	0.87	(0.69-1.10)		0.90	(0.71-1.13)	
Southeast Coast	102	12.87	(10.60-15.63)	0.69	(0.54-0.88)	<0.001	0.71	(0.56-0.91)	<0.0001

Adjusted for gender, year of birth, ethnicity, deprivation, and region.

4.3.5 Prevalence of Teratology of Fallot

Teratology of Fallot contributed 6.5% (233 patients) of the total number of patients diagnosed with SD with a prevalence of 3.91 per 10,000 live GP-registered births (95% CI 3.44-4.45). The number of isolated ToF diagnoses was 119 with a prevalence of 2.0 per 10,000 live GP-registered births (95% CI 1.67-2.39). There were 42 children with a combined diagnosis of ToF with other CHD, having a prevalence of 0.71 per 10,000 live GP-registered births (95% CI 0.52-0.95). Furthermore, 55 children had a combined diagnosis of ToF and other CA with a prevalence of 0.92 per 10,000 live GP-registered births (95% CI 0.71-1.20). Finally, 17 children were diagnosed with ToF, OCA, and other CHD showing a prevalence of 0.29 per 10,000 live GP-registered births (95% CI 0.18-0.46) (Table 4.2).

Of the total 233 diagnosed cases of ToF, there were 58.3% male and 41.63% female patients. The prevalence of ToF in males was significantly higher than females at 4.45 per 10,000 live GP-registered births (95% CI 3.76-5.27) for males and 3.34 per 10,000 live GP-registered births (95% CI 2.74-4.07) for females; (RR = 0.029, 95% CI 0.58-0.97, $p < 0.05$ for adjusted and unadjusted models) (Table 4.7, Figure 4.2). There was no significant difference in the prevalence by year of birth from 1998 to 2017 in relation to the risk of ToF occurring.

With the ethnic group, White as the reference with a prevalence of 4.89 per 10,000 live birth (95% CI 3.78-6.32), Asian/Asian British had the highest prevalence at 7.04 per 10,000 live GP-registered births (95% CI 4.09-12.11), followed closely by the Chinese at 6.69 per 10,000 live GP-registered births (95% CI 0.94-47.36). The Black/Black British ethnic group had the lowest prevalence at 0.99 per 10,000 live GP-registered births (95% CI 0.14-7.03) (Table 4.7). Nonetheless, overall, ethnicity was significantly associated with the prevalence of ToF ($p < 0.05$ in unadjusted and adjusted models). Furthermore, the risk of ToF occurring was not

different between the deprivation quintiles when compared to the least deprived group (Table 4.7). The prevalence of ToF was similar across geographical areas in England, with wide-ranging and overlapping 95% CI of risk ratio when compared to London as a reference (Table 4.7).

4.3.6 Prevalence of AVSD

Of the total septal defect diagnosis, atrioventricular septal defects constitute only 3.2% (115 patients) showing a prevalence of 1.93 per 10,000 live GP-registered births (95% CI 1.61-2.32). Only 38 isolated cases of AVSD were recorded with a prevalence of 0.64 per 10,000 live GP-registered births (95% CI 0.47-0.88). Furthermore, there were 12 cases of a combined diagnosis of AVSD with other CHD, with a prevalence of 0.20 per 10,000 live GP-registered births (95% CI 0.11-0.36). More so, 51 cases of AVSD with OCA were recorded with a prevalence of 0.86 per 10,000 live GP-registered births (95% CI 0.65-1.13). A further 14 patients were diagnosed with AVSD with OCA and other CHD, showing a prevalence of 0.86 per 10,000 live GP-registered births (95% CI 0.65-1.13) (Table 4.2). Of the total AVSD diagnosis, 51.30% were male and 48.70%. Because of the overall low prevalence of AVSD, further multiple logistic regression was not performed.

4.3.7 Prevalence of AoSD

Aortopulmonary septal defects constituted the least of the total septal defects with only 10 (0.3%) recorded cases in total in the entire study population with a prevalence of 0.17 per 10,000 live GP-registered births (95% CI 0.09-0.31). The number of cases with AoSD was so small all subsequent interrogation of the contributing sub-groups showed that Isolated AoSD and co-diagnosis with either other CHD or other CA were each all less than recorded 5 cases with a prevalence of 0.05 per 10,000 live GP-registered births (95% CI 0.02-0.16) (Table

4.2). Of the total AoSD diagnosis, 40% were male and 60%. Because of the overall low prevalence of AoSD, further multiple logistic regression was not performed.

4.3.8 Prevalence of Unspecified SD

This is a class of septal defects without a specific classification of the type of SD diagnosed; this constituted 2.1% (76) of the total number of SD with a prevalence of 1.28 per 10,000 live GP-registered births (95% CI 1.02-1.60). There were 33 isolated unspecified SD cases reported with a prevalence of 0.55 per 10,000 live GP-registered births (95% CI 0.39-0.78). Furthermore, 17 children were recorded with unspecified SD with other CA with a prevalence of 0.29 per 10,000 live GP-registered births (95% CI 0.18-0.46). Twelve children had unspecified SD with other CHD with a prevalence of 0.20 per 10,000 live GP-registered births (95% CI 0.11-0.36) whilst 14 children had unspecified SD, OCA and other CHD, with a prevalence of 0.24 per 10,000 live GP-registered births (95% CI 0.14-0.40) (Table 4.2). Of the total unspecified SD diagnosis, 51.32% were male and 48.68%. Because of the overall low prevalence of unspecified SD, further multiple logistic regression was not performed.

Table 4.7: Number, prevalence/10,000 live GP-registered births, unadjusted and adjusted prevalence ratio, and P values of ToF

	Prevalence			Prevalence ratio			Adjusted Ratio	Prevalence ratio	
	Number	Per 10,000 live GP-registered births	95% CI	Unadjusted Ratio	95% CI	Chi squared P value		95% CI	Adjusted P value
Total	233	3.91	(3.44-4.45)						
Sex									
Male	136	4.45	(3.76-5.27)	ref			ref		
Female	97	3.34	(2.74-4.07)	0.75	(0.58-0.97)	0.029	0.75	(0.58-0.97)	0.0290
Year of birth									
1998-2002	54	4.68	(3.59-6.11)	ref			ref	-	
2003-2007	70	3.89	(3.08-4.92)	0.83	(0.58-1.19)		0.76	(0.52-1.09)	
2008-2012	75	3.78	(3.02-4.74)	0.81	(0.57-1.15)		0.66	(0.45-0.97)	
2013-2017	34	3.32	(2.37-4.64)	0.71	(0.46-1.09)	0.429	0.73	(0.47-1.13)	0.1970
Ethnicity									
White	58	4.89	(3.78-6.32)	ref			ref		
Mixed	42	4.34	(3.21-5.88)	0.89	(0.60-1.32)		0.93	(0.62-1.38)	
Asian/Asian British	13	7.04	(4.09-12.11)	1.44	(0.79-2.63)		1.50	(0.81-2.75)	
Black/Black British	<5	0.99	(0.14-7.03)	0.20	(0.03-1.46)		0.21	(0.03-1.52)	
Chinese	<5	6.69	(0.94-47.36)	1.37	(0.19-9.88)		1.40	(0.19-10.16)	
Other	10	3.02	(1.63-5.61)	0.62	(0.32-1.21)		0.62	(0.32-1.22)	
Missing	108	3.40	(2.82-4.11)	0.70	(0.51-0.96)	0.039	0.62	(0.44-0.89)	0.0193
Deprivation									
1	53	4.18	(3.19-5.47)	ref			-	-	
2	46	3.96	(2.97-5.29)	0.95	(0.64-1.41)		-0.93	(0.63-1.39)	
3	39	3.34	(2.44-4.57)	0.80	(0.53-1.21)		0.78	(0.51-1.19)	
4	41	3.55	(2.61-4.82)	0.85	(0.57-1.28)		0.82	(0.54-1.23)	

5	53	4.43	(3.39-5.80)	1.06	(0.73-1.55)		1.03	(0.69-1.54)	
Missing	1	10.10	(1.42-71.34)	2.42	(0.34-17.46)	0.635	2.25	(0.31-16.38)	0.6248
Region									
London	39	4.08	(2.98-5.58)	ref			-	-	
Northeast	8	6.22	(3.11-12.42)	1.52	(0.71-3.26)		1.38	(0.64-2.98)	
Northwest	38	4.40	(3.20-6.05)	1.08	(0.69-1.69)		1.01	(0.64-1.60)	
Yorkshire & The Humber	11	5.15	(2.85-9.30)	1.26	(0.65-2.47)		1.20	(0.61-2.35)	
East Midlands	10	5.73	(3.08-10.64)	1.41	(0.70-2.81)		1.42	(0.70-2.89)	
West Midlands	18	2.63	(1.66-4.18)	0.65	(0.37-1.13)		0.61	(0.35-1.07)	
East of England	27	3.90	(2.67-5.68)	0.96	(0.59-1.56)		0.98	(0.59-1.61)	
Southwest	28	4.02	(2.78-5.83)	0.99	(0.61-1.60)		1.02	(0.63-1.68)	
South Central	32	4.22	(2.98-5.96)	1.03	(0.65-1.65)		1.03	(0.64-1.65)	
Southeast Coast	22	2.78	(1.83-4.22)	0.68	(0.40-1.15)	0.324	0.72	(0.42-1.22)	0.4406

Adjusted for gender, year of birth, deprivation, geographical region, and ethnicity.

4.3.9 Comparison of CHD and SD subtypes in CPRD to EUROCAT

In the compared EUROCAT population there were 20,834 CHD cases. The prevalence of any CHD was 50.75 per 10,000 births (95% CI, 50.00-51.50) which was lower than in this study from CPRD data at 86.1 per 10, 000 live GP-registered births (95% CI, 83.7-88.4) (Table 4.). This corresponds to children in CPRD being 70% more likely to have a CHD diagnosis than in EUROCAT (prevalence ratio (PR) 1.70, 95% CI 1.67-1.72).

There were 9,236 VSD diagnoses. The prevalence of VSD was 21.32 per 10,000 births (95% CI, 20.86-21.79) which was lower than CPRD data at 35.8 per 10, 000 live GP-registered births (95% CI, 34.3-37.3) (Table 4.). This corresponds to children in CPRD being 68% more likely to have a VSD diagnosis than in EUROCAT (prevalence ratio (PR) 1.68, 95% CI 1.64-1.71).

Furthermore, the prevalence of ASD was lower in EUROCAT than in CPRD where children in the CPRD birth cohort were 92% more likely to have an ASD diagnosis than in EUROCAT (prevalence ratio (PR) 1.92, 95% CI 1.87-1.97). The opposite was the case for AVSD, where the prevalence of AVSD was higher than in the CPRD dataset corresponding to children in CPRD being 38% less likely to have an AVSD diagnosis than in EUROCAT (prevalence ratio (PR) 0.62, 95% CI 0.55-0.70).

Lastly, for ToF, the prevalence of ToF was only slightly lower than CPRD dataset. Where, children in CPRD were 24% more likely to have a ToF diagnosis than in EUROCAT (prevalence ratio (PR) 1.24, 95% CI 1.16-1.34). The prevalence of AoSD was not indicated in EUROCAT (Table 4.).

Table 4.8: Birth prevalence of congenital heart defects in CPRD and EUROCAT populations. EUROCAT population consists of live GP-registered births from 1998 – 2017.

	EUROCAT			CPRD (N= 596,046)				
	Number	Prevalence Per 10,000 births	95% CI	Number	Prevalence per 10,000 births	95% CI	Prevalence Ratio*	95% CI
Congenital heart defect	20834	50.75	(50.00-51.50)	5,129	86.1	(83.7-88.4)	1.70	(1.67-1.72)
Septal defect				2,899	48.64	(46.90-50.44)		
Ventricular Septal defect	9236	21.32	(20.86-21.79)	2,116	35.8	(34.3-37.3)	1.68	(1.64-1.71)
Atrial Septal defect	3755	9.02	(8.72-9.33)	1,032	17.31	(16.29-18.40)	1.92	(1.87-1.97)
Atrioventricular septal defect	1748	3.12	(2.94-3.30)	115	1.93	(1.61-2.32)	0.62	(0.55-0.70)
Tetralogy of Fallot	1436	3.14	(2.96-3.32)	233	3.91	(3.44-4.45)	1.24	(1.16-1.34)
Aortopulmonary septal defect				10	0.17	(0.09-0.31)		
Unspecified septal defect				76	1.28	(1.02-1.60)		

*Prevalence ratio – CPRD / EUROCAT

Within EUROCAT, English regions are delineated differently from the sub-classification in CPRD. For ventricular septal defect, the lowest prevalence was recorded in Northwest Thames with a prevalence of 7.11 per 10,000 live births (95% CI, 6.23 - 8.08) whilst the highest prevalence with more than 5 times this prevalence was in northern England with a prevalence of 41.31 per 10,000 live births (95% CI, 39.67 - 43.01) (Table 4.8).

For atrial septal defects, the lowest prevalence was also recorded in Northwest Thames with a prevalence of 2.84 per 10,000 live births (95% CI, 2.30 - 3.48) whilst the highest prevalence 9-fold higher was in Merseyside and Cheshire with a prevalence of 18.87 per 10,000 live births (95% CI, 15.39 - 22.90) (Table 4.8).

Similarly, for atrioventricular septal defect, the lowest prevalence was also recorded in Northwest Thames with a prevalence of 1.66 per 10,000 live births (95% CI, 1.25 – 2.17) whilst the highest prevalence was in Northern England with a prevalence of 4.03 per 10,000 live births (95% CI, 3.53 – 4.59) (Table 4.8).

For Teratology of Fallot, the lowest prevalence was also recorded in Northwest Thames with a prevalence of 1.82 per 10,000 live births (95% CI, 1.39 – 2.34) whilst the highest prevalence was in Yorkshire and Humber with a prevalence of 4.69 per 10,000 live births (95% CI, 3.36 – 6.36) (Table 4.8).

Table 4.8: Birth prevalence of congenital heart defects by English regions as delineated within EUROCAT.

Anomaly	Regions	Number	Prevalence per 10,000 births (95% CI)
VSD	N W Thames	235	7.11 (6.23 - 8.08)
	Merseyside & Cheshire	102	18.87 (15.39 - 22.90)
	Thames Valley	826	19.21 (17.92 - 20.57)
	Wessex	732	12.84 (11.93 - 13.80)
	East Midlands & South Yorkshire	1872	16.37 (15.64 - 17.13)
	Northern England	2376	41.31 (39.67 - 43.01)
	Southwest England	1806	28.13 (26.85 - 29.46)
	Yorkshire and Humber	223	25.50 (22.26 - 29.07)
ASD	N W Thames	94	2.84 (2.30 - 3.48)
	Merseyside & Cheshire	102	18.87 (15.39 - 22.90)
	Thames Valley	618	14.37 (13.26 - 15.55)
	Wessex	289	5.07 (4.50 - 5.69)
	East Midlands & South Yorkshire	1025	8.96 (8.42 - 9.53)
	Northern England	846	14.71 (13.73 - 15.73)
	Southwest England	401	6.25 (5.65 - 6.89)
	Yorkshire and Humber	82	9.38 (7.46 - 11.64)
AVSD	N W Thames	55	1.66 (1.25 - 2.17)
	Merseyside & Cheshire	17	3.14 (1.83 - 5.04)
	Thames Valley	91	2.12 (1.70 - 2.60)
	Wessex	178	3.12 (2.68 - 3.62)
	East Midlands & South Yorkshire	375	3.28 (2.96 - 3.63)
	Northern England	232	4.03 (3.53 - 4.59)
	Southwest England	214	3.33 (2.90 - 3.81)
	Yorkshire and Humber	33	3.77 (2.60 - 5.30)
ToF	N W Thames	60	1.82 (1.39 - 2.34)
	Merseyside & Cheshire	14	2.59 (1.41 - 4.35)
	Thames Valley	128	2.98 (2.48 - 3.54)
	Wessex	175	3.07 (2.63 - 3.56)
	East Midlands & South Yorkshire	417	3.65 (3.31 - 4.01)
	Northern England	211	3.67 (3.19 - 4.20)
	Southwest England	157	2.45 (2.08 - 2.86)
	Yorkshire and Humber	41	4.69 (3.36 - 6.36)

4.4 Discussion

This chapter aimed to assess the prevalence of septal defects and the various variants namely, VSD, ASD, ToF, AVSD, AoSD, and unspecified SD. This study used the CPRD dataset linked to ONS and IMD to allow interrogation of mortality and socioeconomic status. The merits and limitations of the CPRD data set have been discussed in Chapter 2. Furthermore, the use of CPRD allows the interrogation of the prevalence of SD in well-defined geographical areas in England.

Therefore, in this study, I assessed the proportion of isolated cases and co-occurring congenital anomalies in each case. Furthermore, I calculated prevalence ratios for each SD variant as well as adjusted and unadjusted risk ratios following multiple logistic regression analyses to evaluate the effect of factors such as gender, ethnicity, year of birth, deprivation, and geographic location in England on the prevalence rates observed.

4.4.1 Summary of Principal findings

In the entire study population, the prevalence of CHD diagnosed under the age of one was 86.1 per 10,000 live GP-registered births. In all CHD diagnoses, the total SD diagnoses accounted for 56.5% of all CHD whilst other CHDs were 43.5%. Of all the CHDs, VSD was the most prevalent, followed by ASD and then ToF. Other variants were much less prevalent with low numbers for total cases and often less than 5 in subgroup analysis.

For any SD, gender was significantly associated with occurrence, with the prevalence higher in males than females (PR (Male-Female) 1.15, 95% CI 1.07-1.24). Adjusting for the year of birth, ethnicity, and geographical location did not change this ratio. There was an initial significant association of year of birth with the risk of any SD occurring, with the prevalence

fairly steady between 1998 to 2012 and falling between 2013 to 2017. However, after adjusting for other factors such as gender, ethnicity, and geographical location, there was no difference in the prevalence of SD by the year of birth. This was also observed with ethnicity, with there no association with the risk of any SD occurring following similar adjustments of confounding variables listed above. No evidence of association with socioeconomic status and any SD occurring in children. There was an association with geographical regions even following adjustments, with the prevalence of any SD occurring highest in the East Midlands of England.

For VSD, which contributed 59.1% of the total SD diagnosis, there was an association with gender where prevalence was 18% higher in females than males. Also, there was an association with the year of birth, where the prevalence progressively and modestly dropped between 1998 and June 2017. There were no significant associations detected with ethnicity or socioeconomic status. There was however an association of VSD in children according to region. Adjusting for other confounding variables shown to be associated with VSD occurring such as gender and year of birth did not affect this association.

ASD contributed 28.8% to the total SD diagnosis and there was an association with gender where prevalence was 22% higher in females than males. There was no association between the year of birth and the prevalence of ASD. There was an association between ethnicity and the prevalence of ASD. However, a significant proportion of the total recorded diagnosis of ASD had missing ethnicity data. There was no significant association with socioeconomic status. There was however an association of ASD in children according to region with the East Midlands having an 85% increase in prevalence compared to London and Southwest having a 36% lower prevalence than London. Adjusting for other confounding variables

shown to be associated with ASD occurring such as gender and ethnicity did not affect this association.

ToF which contributed 6.5% to the total SD recorded cases showed an association with gender, with the prevalence of ToF higher in males than in females. Furthermore, no association with the year of birth or socioeconomic status, or geographical location was identified. There was an association with ethnicity even after adjusting for gender.

The prevalence of CHD, VSD, ASD, and ToF was less in EUROCAT than this current CPRD-based study by 25-90%, however, the prevalence was higher for AVSD in EUROCAT than in this study.

It is noteworthy however that in all these results, many subgroups had confidence intervals that included one or very near 1. This together with the minimal difference observed between the risk ratios, suggest that the differences observed could be explained by low statistical power resulting from the small number of recorded cases of the septal defect variants in this study population. In lieu of this, further subgroup analysis was not carried out in the least occurring SD variants namely AVSD (3.2% of total SD), AoSD (0.3 % of total SD), and unspecified SD (2.1 % of total SD), where the prevalence was 1.93 per 10,000 live GP-registered births (95% CI 1.61-2.32), 0.17 per 10,000 live GP-registered births (95% CI 0.09-0.31) and 1.28 per 10.000 live GP-registered births (95% CI 1.02-1.60) respectively.

4.4.2 Interpretation in context of previous studies

The total prevalence of CHD in this study was 86.1 per 10, 000 live GP-registered births across the whole of England. There is great variability in the reported prevalence of CHD in the literature. The total prevalence of CHD among the 30 EUROCAT registries ranged from 34.43/10,000 births to 140/10,000 with five registries having prevalence above 100/10,000 births and eight registries having below 60/10,000 births. But specifically, the prevalence of registers corresponding to England from EUROCAT reports a prevalence of 75 per 10,000 births (95% CI, 50.00-51.50). Furthermore, the prevalence of subgroups that are very rare, usually unspecified CHD (like Q21.4 [AVSD], Q21.8 [Other SD], Q21.9 [Unspecified SD], etc.) ranged from 0-19.71/10,000 births and are about 0-22% of all total cases (788 cases in total as of the year of this EUROCAT publication [2013]). Of these, there were 49 cases of Q21.4, Q21.8, and Q21.9 (162).

For the overall comparison with this study, the prevalence of VSD, ASD, and ToF was lower, higher for AVSD, and unreported for AoSD and Unspecified SD when compared to EUROCAT. Although CPRD and EUROCAT delineate English geographical regions differently, I compared the geographical trends in the prevalence of SD variants in both datasets. Using the CPRD dataset, the prevalence of VSD was highest in Northeast and Southwestern parts of England and lowest in London and Southeast Coast, whereas in EUROCAT, the prevalence was highest in Northern England and lowest in North West Thames. The highest prevalence of VSD recorded in our CPRD dataset was 43.50 per 10,000 live GP-registered births for Northeast (95% CI, 33.49-56.49) and not far off 41.31 per 10,000 live births (95% CI, 39.67 - 43.01) recorded for Northern England in EUROCAT. For ASD, whilst the highest prevalence within the CPRD dataset was recorded in the East

midlands at 34.37 per 10,000 live GP-registered births (95% CI, 26.70-44.24), in EUROCAT the East midlands was 8.96 per 10,000 live births (95% CI, 8.42 - 9.53), and the highest was in Merseyside and Cheshire with a prevalence of 18.87 per 10,000 live births (95% CI, 15.39 - 22.90). For ToF, whilst in CPRD the highest prevalence was in the Northeast at 6.22 per 10,000 live GP-registered births (95% CI, 3.11-12.42), the highest prevalence in EUROCAT was in Yorkshire and Humber with a prevalence of 4.69 per 10,000 live births (95% CI, 3.36 – 6.36) (Table 4.8). Due to low numbers of cases within the CPRD dataset, sub-analysis by geographical regions was not performed for AVSD and AoSD. AoSD is also not recorded in EUROCAT.

Some of these disparities can arise from the way data is recorded in registries and the level of ascertainment of cases. A similar disparity in timeframes covered within this current study between CHD in CPRD (then GPRD) and EUROCAT or National Congenital Anomaly System (NCAS) has been previously reported (149). Furthermore, this disparity may arise as EUROCAT does not include minor CHDs in its registries (178). Furthermore, the total population which is an important factor in the calculation of prevalence differs for EUROCAT and this current study. The study population in this current study comprises children registered with their primary health care provider before the age of one, whereas with EUROCAT, all children within contributing registries account for the total population. CPRD will exclude children who die before they can be registered with a GP; children diagnosed with these congenital anomalies are more likely to have died in this early period of life compared with children who do not have CHD or other congenital anomalies. VSD which is the major contributor of all CHDs in both CPRD and EUROCAT is an important contributor to the reported prevalence rates. Almost half of all VSD anomalies are treated following medical intervention whilst more than 70% of residual shunts in minor defects

disappear on their own (spontaneous closure) (187) while minor heart defects are excluded from the EUROCAT database and only reported when co-existing with other major anomalies (178). Since VSD usually accounts for the least severe forms of SD, there is a risk of under-reporting within the EUROCAT database. Conversely, EUROCAT is likely to capture neonatal cases that are the most severe whilst CPRD misses out the most severe cases who die early before they can be registered with a GP. Nonetheless, one advantage of CPRD is that whilst EUROCAT is reported to capture most anomalies throughout life, most cases are documented around birth or before the age of one and less so if there is a missed diagnosis that occurs later in life, whereas this will most likely be documented within CPRD (179). Understanding the disparities between the various databases is important for effective comparisons.

Moving on, with SD having a high percentage of all CHDs, this study goes into sub interrogation of SD and its subtypes. Liu et al, reports that globally, VSD is the most prevalent CHD, and by extrapolation SD, accounting for 3.071 per 1,000 live births (95% CI, 2.845–3.305) accounting for 35.568 % (95% CI, 33.876-37.278) of all CHDs (10). ASD is the second most prevalent at 1.441 per 1,000 live births (95% CI, 1.215–1.687) and 15.378 % (95% CI, 13.492-17.363) of all CHDs (10). From the Liu et al study, pulling out only the SD subtypes, ToF is the third at 0.356 per 1,000 live births (95% CI, 0.326–0.387) and 4.422 % (95% CI, 4.064–4.794) of all CHDs (10). Following ToF is Atrioventricular septal defect 0.290 per 1,000 live births (95% CI, 0.265–0.316) and 3.595% (95% CI, 3.302–3.900) of all CHDs (10). In agreement to (10), this current study has similar hierarchical positioning for SD using the CPRD database in England; VSD was the first at 59.1% of all SD, followed by ASD at 28.8%, ToF third at 6.5%; AVSD 3.2%, and AoSD the least at 0.3%. The prevalence ratios also described do not differ greatly for VSD, ASD, or ToF. However, for the AoSD,

the prevalence reported in this current study if reported using the same unit of denomination to match Liu et al., is 0.017 per 1,000 live GP-registered births which is a lot less than the 0.295 per 1,000 live births reported in Liu et al (10). Largely, whilst Liu et al. assessed the global prevalence of these defects, the prevalence ratios match the results from this current work and go to validate that CPRD provides a good representation of these congenital anomalies. Furthermore, other differences include the fact that Liu et al. considered a study interval of 1970-2017 whilst this current study considered 1998-2017, a difference of 28 years. Nonetheless, the prevalence ratios are largely similar, suggesting the prevalence in England is similar to the prevalence of these septal defects globally.

Overall, between 1998 and 2017, the prevalence of all SD remained steady, however, there was a progressive decrease in the prevalence of VSD, with a 19% reduction when the period 2013-2017 is compared to 1998-2002. There was no change in prevalence according to the year of birth for ASD or ToF. This is in contrast to a previous meta-analysis study that has shown that overall, CHD, largely driven by milder defects such as VSD and ASD increased between 1970-2017, with the greatest increase seen between 2002 and 2017, whereas the prevalence of more severe forms of CHD decreased within the same study period (10). It is important to note that the prevalence recorded from 1998 and 2017, will be influenced by the rate of diagnosis both pre- and postnatally as well as the rate of termination of pregnancies where antenatal diagnosis occurs. Also, another caveat with this current study is that the data at the extremities of the study period did not cover the entire year (01/02/1998 to 31/07/2017). For example, across the dataset, the prevalence of SD amongst female patients was lowest in 2017 (Figure 4.2). It is important to note that the observed results at the extremities of this timeline could therefore be affected by small numbers at these time points making the corresponding prevalence unstable. Nonetheless, the diagnosis of CHD has been

largely reported to have improved in recent times with the emergence and continuous development of echocardiography, routine real-time ultrasounds, and routine antenatal medical care (188,189). Similarly, termination of pregnancies with antenatal diagnosis of congenital anomalies was reported to increase from 20/100,000 births in 1987-1992 to 78/100,000 births in 2001-2006 (190). Therefore, these factors may affect the prevalence trends observed in the time frame of this current study.

Whilst this study observed an association of any SD prevalence with ethnicity, following adjustments no association was observed ($p = 0.0587$). In the SD subtype analysis of ASD, VSD, and ToF, ethnicity was associated with the prevalence of these defects. This reinforces the importance of subtype analysis which unmasks specific effects in the SD variants that may be masked within the entire population. There are various reports of ethnicity with CHD but minimal studies on SD variants specifically. A previous national study by Knowles et al. had shown that Asian and Black children had a higher incidence of CHD in England and Wales compared to White children (180). Furthermore, a retrospective study has alluded to a higher prevalence of CHD in babies of Pakistani origin compared to non-Asian children in preliminary studies (191). Also, in a retrospective study in the West Midlands, complex CHD was higher in Asian infants compared to non-Asian children, whilst for Coarctation of the Aorta (a non-SD CHD), the prevalence was higher in non-Asians compared to Asians (192). The results on ethnicity in this study need to be taken with caution due to the high proportion of patients with missing ethnicity data in CPRD.

Whilst socioeconomic factors have been reported to influence the incidence of CHD globally (165,193,194), no significant association was detected between socioeconomic studies and the prevalence of SD or any of its variants assessed in this study. A study in Bradford, UK

found no association of occurrence of congenital anomalies with increasing deprivation (195). In contrast to this, in the study by Knowles et al, which showed an increased incidence of CHD in Asian and Black children, the authors reported that a higher proportion of these non-white children had an increased likelihood of living in the most deprived areas in England and Wales (180). More widely, in a population-based study in California, the incidence of CHD was 31% higher in the worst deprived area compared to the least deprived area (odds ratio [OR], 1.31; 95% CI, 1.21–1.41) after adjusting for confounding variables such as ethnicity and age (194). This study also found that maternal comorbidities were an important factor in this association between socioeconomic status and incidence of CHD (194). Further studies are required on these relationships in England. The effects of socioeconomic status on mortality of septal defects and its subtypes will be assessed in chapter 4.

Also, this study explored the regional differences in the prevalence of septal defects and its variants in England. There were differences in the prevalence of all septal defects across the geographical regions in England, where the East Midlands had a 45% higher prevalence than London (RR = 1.45; 95% CI, 1.18-1.77), the Northeast was 23% higher (RR = 1.23; 95% CI, 0.96-1.58). The lowest prevalence was in the Southeast Coast (RR = 0.91; 95% CI, 0.79-1.05). For VSD, the Northeast and Southwest was the joint highest at 37% higher prevalence (RR = 1.37, 95% CI, 1.03-1.83) and (RR = 1.37, 95% CI, 1.17-1.61) respectively. All other regions were higher than London which had the same prevalence as Southeast Coast. For ASD, the East Midlands had the highest prevalence (RR = 1.85, 95% CI, 1.38-2.47). Apart from the Northeast, North West, and West Midlands, all other regions had a prevalence less than London, with the lowest in the South West (RR = 0.64, 95% CI, 0.49-0.83). No association was found for ToF and geographical location. No comparative study was found

for the prevalence of SD and its variants in association with the geographical regions of England in the literature except EUROCAT.

However, a study carried out using register-birth data reported the prevalence of CHD to be 79.7 per 10,000 live births in North of England between 1985-2003 (196). Furthermore, VSD was shown to have a prevalence of 39.3 per 10,000 live births (95% CI, 37.8-40.8), ASD 12.6 per 10,000 live births (95% CI, 11.8-13.5), and ToF 5.5 per 10,000 live births (95% CI, 4.9-6.1) in the North of England (196). One discrepancy is that this current study considers the Northeast separate from the North West whilst Dadvand et al. considered the entire Northern region. Furthermore, the study period differs for both studies by almost a decade. Dadvand et al. used the Northern Congenital Abnormality Survey (NorCAS), a regional population-based register whilst this current study used a CPRD-based dataset, which is a national dataset. Due to the discrepancies, direct comparisons will be flawed. Notwithstanding, the reported prevalence for the Northern regions does not differ enormously between both Dadvand et al. and this current study. Future studies, considering all the regions in England are required to fully understand regional differences arising based on geographical regions. Geographical variations in the prevalence of SD may arise for multiple reasons such as differences in the accuracy and detail of diagnosing these congenital anomalies across the various regions in England. Furthermore, there is sometimes an uneven split of ethnic groups that constitute the population in a geographical area. For example, whilst Redcar & Cleveland and Allerdale in North-Eastern England and Northwest England respectively, are reported to comprise predominantly of white ethnic individuals (up to 97.6%) (197), in certain London boroughs this number of white ethnic individuals are as low as 16.7% (197). These disparities in ethnic proportions across various regions in England can affect the prevalence of SD observed.

Furthermore, health inequalities across English regions are well documented and even though

the English health inequalities strategy was implemented between 1997 and 2010, some inequalities remain across the various regions (198). Understanding these factors allows for the development of region-specific strategies to improving diagnosis and disease outcomes. Further research into other factors that may mediate the associations ascertained in this current study with SD prevalence is needed. It is also important to note that another contributor to the disparity between the different geographical regions observed within the CPRD-based dataset used in this thesis may be due to differences in resources already present, where the prevalence of cases in regions with already existing registries are likely to be higher than in regions without registries dedicated to effectively recording cases of these defects when they do occur. Therefore, even though prevalence may be as high in the other regions, these current results may reflect poor awareness of data capturing where these registries are not set up. Consequently, increased awareness of data capturing across the country may be required to unpick if there is a true difference in prevalence.

4.4.3 Strengths and limitations

This is the first study evaluating the prevalence of an important sub-category of CHD in-depth, assessing the prevalence of SD subtypes and the effect of a range of factors within a single national population over a prolonged time scale (19 years). Linking the data to ONS and IMD allowed the assessment of the relationship between SD, its variants, and factors such as gender, ethnicity, socioeconomic status, and geographical regions, and the potential associations with developing these congenital anomalies. This study also focuses on England which is infrequent in the literature and therefore provides information on an important disease group.

Other studies done in the UK in the literature have been more narrowly focussed, going into more detail on specific regions whereas this current study takes a nationwide approach. For example, Sadiq et al. assessed the effect of ethnic region on the pattern of CHD in the West-Midland region of the UK (192), whilst Sheridan et al. assessed risk factors for the development of CA in Bradford, UK (195). Evaluating the prevalence of SD and its variants across multiple regions in the UK simultaneously provides the avenue of determining nationwide trends that are otherwise difficult to ascertain. Furthermore, conducting this research at a population level rather than using patient registries provides avenues for more suitable controls for relative comparison of risk factors, such as children presenting with other CA and children with no documented CA.

One limitation of this study population was the high proportion of missing data for ethnicity in CPRD which is likely to introduce some bias in the analyses conducted. Another limitation, in general, is that CPRD is reported to have a lower proportion of children aged 0-4 years when compared to the UK Census 2011 (153), although this is likely to have a higher impact on the control group, as children with the defects assessed in this study are more likely to be documented due to the higher chance of needing medical care.

Another limitation is the risk of missing the sickest patients who die before GP registration. Even though CPRD was linked to ONS records, only patients with a GP registration were linked, therefore risking the loss of patients' records that may have died in hospitals quickly after birth. The survival rate in the first month of life has been reported to be 70% less in neonates with CHD, with cardiogenic shock recorded as the predominant cause of death (199). This is particularly so in preterm births and in infants with low birthweights where there is an increased risk of hospital mortality in an Italian cohort study (200).

As this study was not linked to HES, it does not have hospital records for CHD. HES is a database that contains all admissions, Accident, and Emergency (A&E) attendances, and outpatient appointments at NHS hospitals in England (201). The high prevalence, often matching previously reported figures, suggests that the current CPRD-dataset used for this study is unlikely to have missed cases without HES. Nonetheless, linkage to HES could have potentially improved the specificity of the diagnosis, reducing the number of unspecified congenital anomalies in the cohort. Another limitation is that linkage to HES might have improved the ethnicity linkage within this dataset as combining HES and CPRD has been reported to increase the completeness of ethnicity recording to up to 97% from 27.1% in CPRD alone between 1990-2012 (151). A critical reason for not linking HES in this study is that only 50% of patients within our dataset had linked HES data and using the HES-linked data would have excluded half of our study population.

4.4.4 Conclusions and Implications

The prevalence of CHD, SD, and its variants were mostly in accordance with previously reported numbers, although some discrepancies have been described. Furthermore, the distribution of the SD variants contributing to the total CHD burden corresponds to previously published literature. The overall prevalence for CHD was lower in EUROCAT but like CPRD, the proportion of the SD variants contributing to the total CHD burden was of a broadly similar pattern, with some deviations. This study provides England-focused results on a national scale that has previously been sparse.

Data from this study show that the prevalence rates by year of birth between 1998 and 2017 largely remained steady with a drop only in total VSD diagnosis. This suggests that more research is needed to consider the impact of increased diagnosis and probable link to

increased termination of pregnancies in the most severe cases. Additionally, this study provides some insight into the effect of ethnicity on the national scale and demonstrates a limitation in the documentation of ethnicity within the CPRD dataset. More so, the prevalence of SD and its variants differed across the different geographical regions in England. Whilst socioeconomic differences are often cited as an important risk in the development of CHDs, this study found no association with the prevalence of SD or its variants. Instead, this study suggests that more research be done to understand the impact of ethnicity and location across England on the prevalence of SD. Understanding this is important for the development of region-specific and ethnicity-specific strategies to improving diagnosis and disease outcomes.

Chapter 5: Post neonatal mortality in children with a septal defect

In the previous chapter, I evaluated the prevalence of SD and its variants between January 1998 and June 2017. I also assessed the effect of certain demographic factors such as ethnicity, socioeconomic status, geographical location, and gender on the prevalence. In this chapter, I assess the mortality rates of SD and its variants and compare the mortality rates with children with other major CA and children with no CA. I also assess the mortality within specific age groups ranging from birth to 9 years of age for SD and its variants. Finally, I assess the cause of death in children with SD and its variants.

5.1 Epidemiology of septal defects - mortality

There is a global decline in the overall mortality of children under 5, with about a 60% reduction in the mortality rate of children under 5 recorded (202). Furthermore, with improved diagnosis and screening of children antenatally, there has been an improvement in neonatal survival in children with CHD (203). For example, in 2017, the global CHD-related death was reported to be 261,247 deaths (95% CI, 216,567–308,159) down 35% from 1990 (8). CHD accounts for one-tenth of all childhood mortality globally (204), and 30% of all CA-associated deaths within the first year of life (205). The studies assessing the neonatal survival of children with CHD outweigh the studies beyond infancy that look well into adolescence (190,206,207). Particularly, considering that SDs are a significant contributor to the total CHD burden, detailed assessments of mortality rates of specific SD subtypes are sparse especially at a population level.

Studies have evaluated the survival of children with CHDs following various interventions such as following Fontan procedure, intervention for children born with variants of VSD (208,209), arterial switch operation for children with TGA (210), or following any

intervention (211). Whilst this provides information about specific clinical settings, a population-wide comparison of mortality rates of the various septal defect groups particularly in England is needed.

More than 10 years ago, Billett et al., reported an increase in hospital admissions related to CHD in older children with an overall decrease in both hospital fatalities and mortality in the general population in England (212). They reported a decrease in hospital fatalities from 2.1% (95% CI 1.97 to 2.22) in 1997/1998 to 0.83% (95% CI 0.74 to 0.92) in 2003/2004, a drop of more than 50% in the 7-year time period (212). Knowles et al. reported a declining trend in CHD-related mortality across all age groups between 0 and 15 years of age between 1959 and 2009 in England and Wales (213). Similar results have been reported in Canada with an overall decrease in mortality rates and an increase in age when death occurs (214). This decrease in CHD-related mortality is usually attributed to improvement in diagnosis, case ascertainment, intervention procedures, and overall management of CHD. Furthermore, the ethnicity-dependent disparity in mortality and survival in children undergoing CHD surgery has been reported (207). However, these analyses did not include cases that do not require surgeries neither did they delineate the various subgroups of CHD. Also, the survival of children is known to be dependent on the severity of the defect occurring, therefore assessing the relationship between socio-demographic factors with various types of these defects is required. Best et al., in a systematic review of the global evidence on the association of socioeconomic status on CHD-linked mortality, reported that the most deprived children were more likely to die from CHD (215). Children from the most deprived areas were found to have an increased risk of neonatal, post-operative, and long-term mortality (215). Furthermore, in another global study, Zimmerman et al. similarly reported

decreasing mortality rates with increasing socio-demographic index, with the highest death rates occurring in low and middle-income countries (8).

An England-specific estimation of the survival of these defects beyond infancy is important to inform public health planning and designation of long-term resources for CHD patients that may live longer into adulthood with some lingering disabilities, especially where the various defects have varying aetiologies and prognoses.

In this chapter, I address the final thesis objective by estimating the mortality rates of children with SD and its variants and investigating the influence of socio-demographics such as gender, ethnicity, and socioeconomic status on these rates in children aged 0 to 19 years. Furthermore, I compare the risk of mortality between children with these defects and children with no CA or with other major CA. Lastly, I assess the causes of death in children with septal defects.

5.2 Methods

5.2.1 Study population

Only post-neonatal mortality and survival was assessed within this dataset because children who die early in life may not be registered with a GP and a cut-off of 30 days post birth was therefore used from which to assess mortality. Previous research has shown that the death rates from congenital anomalies stabilise after the usually risky neonatal period and the post neonatal data contained within CPRD gives comparable estimates with other studies (185). Therefore, the CPRD cohort used within this thesis is likely to be representative of the general post-neonatal population.

The ONS death dataset was linked to the birth cohort dataset as described previously (section 3.1.4). Within the ONS death database, there were 16 variables for post-neonatal death records (cause, cause1 - cause15) and eight variables for neonatal death records (cause_neon1 – cause_neon8). The post-neonatal cause of death variable “cause” holds the exact cause of death recorded for each patient that died post-neonatally, that is, there could be many causes of death records, however, the primary cause of death is recorded under the variable “cause” with any of the causes of death “cause1 – cause15”, when recorded, being a secondary cause of death. The “cause” variable is empty when the cause of death happens to be a neonatal one, that is when the cause of death is under “cause_neonatal1 – cause_neonatal8”. Also, the “cause” variable is empty when no cause of death is recorded for a patient. On assessment, some causes of death records were recorded using ICD-9 codes and all these were mapped to ICD-10 codes. Cause of death for children with SD was delineated as either CA-related or not CA-related; those that were not CA-related were thereafter delineated using the ICD-10 code and term categorisation.

The start of the mortality analysis was slated for 30 days after each patient’s date of birth, hence, post-neonatal analysis. The end date for survival was either the date of death, the transfer out date (end of follow-up if transferred out from the practice), or, the last collection date (end of follow-up as last collection date). After setting the data for survival, Stata reported that some data ended on or before the survival criteria stated. This is possible because of the date of birth recording in CPRD and how either the day and/or month of birth are allocated for study participants.

5.2.2 Sample size calculation

The required sample size to detect a statistically significant difference in the mortality rates between children with and without CHD was estimated using the Cox proportional hazards power calculation in Stata. A conservative risk estimate of post-neonatal infant mortality in children with CHD compared to those without from the published literature was used (risk ratio 21). Power was set at 80%, significance level at 5% (0.05), and from the birth cohort, a withdrawal probability of 0.55 (proportion of children with less than 5 years follow-up) and a failure probability of 0.0017 (proportion of children in the population who died before 5 years old) was estimated. The required sample size from this calculation was over 1.3m children and 1200 deaths. Given the total birth cohort was only about half of the required sample size, subtypes of SD (AoSD, AVSD, ToF, and unspecified SD) were combined for analysis such as the effect of socio-demographic factors and age-group mortality assessment.

5.2.3 Mortality rate

The mortality in children with CHD, SD and its variants, major OCA, and children without any CA was calculated. Mortality was estimated as the number of deaths per 1,000 person-years. Cox regression model was used to estimate hazard ratios comparing children with all specific variants of septal defects, first, to children with Major CAs, and second, to children with no CA. Regression models were adjusted for sex, deprivation, geographical region, and ethnicity. Also, deprivation was initially fitted into the model as a categorical variable and yielded no significant relationship with outcomes for some SD variants in contrast to literature. Deprivation was then run as a trend and expected significant values were obtained, hence, deprivation was fitted into the final model as a trend. Only the SD variants VSD and ASD were assessed as individual defects. Numbers for ToF, AVSD, AoSD, and Unspecified

SD were too small to allow meaningful individual assessments, hence, all these defects were pooled to assess hazard ratios. To evaluate if the cox proportionality hazards assumption holds for each covariate (sex, ethnicity, and deprivation), log-log plots were examined. No violation of the proportionality assumption was observed (Appendix 3). Furthermore, the birth cohort was divided into age group bands of 30 days – 1 year, 1-4 years, 5-9 years, 10-14 years, and 15-19 years. Mortality rates were calculated for age groups for SD as a whole, for VSD, ASD, a combination of ToF, AVSD, AoSD, and Unspecified SD, and compared with mortality rates in age-group bands of children with major OCA and no CA. Rate ratios with confidence interval and p-values were obtained for SD cases against major OCA and no CA across all assessed age groups. Due to very small numbers giving rise to very wide confidence intervals, age-group assessments were limited to the 0- 9 years of age group.

To explore the feasibility of assessing severity, the number of patients with a recording of at least one intervention within this study population for each septal defect were reported as percentage frequencies. This was obtained by dividing the number of patients with interventions recorded by the total number of cases in the birth cohort for each defect.

5.3 Results

The ONS death data had 1,244 deaths recorded corresponding to patients from our birth cohort. Of this, 693 (55.71%) were males and 551 (44.29%) were females. Thirty-five death records corresponding to 74 patients recorded using ICD-9 codes were mapped to ICD-10 codes and nine (9) patients with no cause of death record were deleted from the dataset; hence, only 1,235 death records were available for survival analysis. Of the total 5,129 CHD patients, 22 were identified using the ONS death data; that is, 22 CHD patients did not have a clinical code for CHD in their clinical files but, they were identified to have CHD using their

primary cause of death in the ONS death data. After setting the data for survival analysis, Stata reported that 754 observations ended on or before the survival parameters set.

The characteristics of the study population and the prevalence of CHD, SD, and its subgroups have been previously described (Chapter 4). In brief, there are 596,046 children in the study population of whom 7.83% had a diagnosis of one or more major CA and 0.86% with a diagnosis of CHD (n = 5,129).

The number of deaths and mortality rates are presented for CHD, SD, and its subtypes (Table 5.1). Mortality risk estimates (adjusted and unadjusted) are presented for all subtypes in comparison to controls (Table 5.2). Furthermore, mortality rates are presented by socio-demographic factors (Table 5.3-5.6).

Of the total 1,235 analysed deaths observed in the birth cohort, 811 of these were children with no congenital anomaly with a mortality rate of 0.27 (95% CI, 0.26 – 0.29) per 1000 person-years and 166 of the total deaths were children with CHD, where the mortality rate was 5.6 (95% CI, 4.8-6.5) per 1000 person-years. Death from any SD accounted for 74 of all deaths. By age group, the number of deaths for any SD was 22 in the post-neonatal group, 10 between 1 and 4 years, and <5 between 5 and 9 years. Because of the low death numbers within our birth cohort from 10 to 19 years, age group-related analysis for SD and SD variants was limited to children 9 years and under (This is assessed further in 5.3.2).

By heart septal defect variants, children with Aortopulmonary septal defect (54.9; 95% CI 13.7-219.6), Atrioventricular septal defect (7.2; 95% CI, 3.0-17.3), and Tetralogy of Fallot (8.1; 95% 4.6-14.3) had the highest mortality rates compared to other defects, although small numbers of children resulted in large confidence limits for some of these estimations.

Table 5.1: Mortality rate for children with and without a congenital anomaly diagnosis

	Number of cases	Deaths	Death to case ratio (%)	Person time (years)	Mortality rate (per 1,000 person- years)	95% CI
No CA	545,454	811	0.15	2,966,486	0.27	(0.26-0.29)
CHD	5,129	166	3.24	29,534	5.6	(4.8-6.5)
SD	2,899	74	2.55	17,173	4.3	(3.4-5.4)
VSD	2,116	52	2.45	12,692	4.1	(3.1-5.4)
ASD	1,032	30	2.91	5,845	5.1	(3.6-7.3)
ToF	233	5	5.15	696	7.2	(3.0-17.3)
AVSD	115	12	4.35	1,478	8.1	(4.6-14.3)
AoSD	10	<5		36	54.9	(13.7-219.6)
Unspecified SD	76	<5		505	4.0	(0.99-15.8)
Other major CA	10,819	195	1.80	69,812	2.8	(2.4-3.2)
Death to case ratio (%) is used to report natural frequencies and is obtained by dividing the number of deaths for each subgroup anomaly by the total number of cases present in the study cohort.						

When reported as natural frequencies, children with no congenital anomaly had the lowest death to case ratio (0.15), whilst children with AVSD had the highest death to case ratio (5.15%), followed by ToF at 4.35%. The death to case ratio for all SD subvariants considered was higher than that of children with other major congenital anomalies. The death to case ratio was not calculated for AoSD and Unspecified SD as in each case, the number of deaths were less than 5 (Table 5.1).

The hazard of death in children with any CHD was 21 times higher than in children without any CA (adjusted HR (aHR) 21.1, 95% CI, 17.9-25.0, $p < 0.001$). Furthermore, the hazard of

death for children with any septal defect was over 16-fold higher than for children without a CA (aHR 16.4, 95% CI, 13.0-20.9, $p<0.001$).

By Septal heart defect subgroups, children with Aortopulmonary septal defect had the highest hazard of death with about 159-fold increase compared to children without a CA (aHR, 159.3, 95% CI, (39.7-641.4), $p<0.001$). This was followed by Tetralogy of Fallot with a 32-fold increase compared to children without a CA and atrioventricular septal defect where the hazard of death was 25.5-fold higher than no CA. The hazard of death was lowest for children with VSD (HR, 15.5, 95% CI, (11.7-20.5); aHR 15.9, 95% CI, 12.0-21.0, $p<0.001$) (Table 5.2).

Table 5.2: Hazard of death in children with congenital heart anomalies compared to children with no congenital anomaly.

	Unadjusted hazard ratios			Adjusted Hazard ratios*		
	HR	95% CI	P value	HR	95% CI	P value
Any Congenital heart defect	21.0	(17.8-24.8)	<0.001	21.1	(17.9-25.0)	<0.001
Septal defect	16.2	(12.8-20.6)	<0.001	16.4	(13.0-20.9)	<0.001
Ventricular Septal defect	15.5	(11.7-20.5)	<0.001	15.9	(12.0-21.0)	<0.001
Atrial Septal defect	19.1	(13.2-27.4)	<0.001	19.2	(13.4-27.7)	<0.001
Atrioventricular septal defect	27.5	(11.4-66.2)	<0.001	25.5	(10.6-61.4)	<0.001
Tetralogy of Fallot	31.4	(17.7-55.5)	<0.001	32.3	(18.2-57.1)	<0.001
Aortopulmonary septal defect	164.6	(41.1-659.5)	<0.001	159.3	(39.7-641.4)	<0.001
Unspecified septal defect	15.6	(3.9-62.3)	<0.001	16.3	(4.1-65.2)	<0.001

*Adjusted for sex, ethnicity, and socioeconomic status.

5.3.1 Mortality by socio-demographic factors

I present the mortality rates and hazard ratios for children in the study population with any septal defects or its subgroups by selected demographic factors, specifically sex, socioeconomic status, and ethnicity. Geographical region did not show significant association with mortality and so it was excluded from final adjusted models.

For overall septal defects, there was no difference in the hazard of death or mortality rate for females compared to males in the unadjusted model, however, adjusting for deprivation and ethnicity substantially alerted the statistical significance where there were more SD deaths in females than males (Table 5.3). There was no significant difference in the mortality rate by ethnicity. In brief, there was no recorded mortality in the Chinese ethnic group, the next lowest mortality rate was in the ethnic group classed as “other” with a mortality rate of 2.5 (95% CI, 0.6-10.1) per 1,000 person-years (HR 0.6, 95% CI, 0.1-2.6; adjusted HR (aHR) 0.6, 95% CI, 0.1-2.6). The highest mortality rate was in the Black or Black British ethnic group with a mortality rate of 9.4 (95% CI, 2.4-37.7) per 1,000 person-years (HR 2.0, 95% CI, 0.4-8.7; adjusted HR (aHR) 1.6, 95% CI, 0.4-6.9). Of note, the 95% confidence intervals for all hazard ratios within the ethnicity sub-group analysis included the null value (Table 5.3). Furthermore, 60% of the subpopulation of children with any septal defect had missing ethnicity data.

By SES, there was a progressive increase in mortality rate from the third quantile to the fifth quantile which is the most deprived sub-group. The third quantile had a mortality rate of 4.4 (95% CI, 2.5-7.6) per 1,000 person-years (HR 1.6, 95% CI, 0.7-3.7; adjusted HR (aHR) 1.7, 95% CI, 0.7-3.9). The fourth quantile had a mortality rate twice as high as the least deprived quantile at 5.6 (95% CI, 3.5-8.9) per 1,000 person-years (HR 2.1, 95% CI, 1.0-4.5; adjusted

HR (aHR) 2.1, 95% CI, 1.0-4.6). The most deprived quantile had a mortality rate approximately 3 times higher than the least deprived quantile, with a mortality rate of 7.4 (95% CI, 5.0-10.8) per 1,000 person-years (HR 2.8, 95% CI, 1.3-5.8; adjusted HR (aHR) 2.9, 95% CI, 1.4-5.9) (Table 5.3).

Table 5.3: Mortality rate and hazard ratios by socio-demographic factors in a subpopulation of children with any septal defects (N=74)

	Mortality rate				Unadjusted HR			Adjusted HR*		
	Deaths	Person time	Mortality rate per 1,000 person-years	95% CI	HR	95% CI	P value	HR	95% CI	P value
Sex							0.30			0.003
Male	31	8,270	3.7	(2.6-5.3)		ref			ref	
Female	43	8,903	4.8	(3.6-6.5)	1.3	(0.8-2.0)		1.3	(0.8-2.0)	
Socio-economic status (IMD quintiles)							0.0003			0.0015
Q1 (least deprived)	10	4,034	2.5	(1.3-4.6)		ref			ref	
Q2	7	3,398	2.1	(1.0-4.3)	0.8	(0.3-2.1)		0.8	(0.3-2.1)	
Q3	13	2,961	4.4	(2.5-7.6)	1.6	(0.7-3.7)		1.7	(0.7-3.9)	
Q4	18	3,225	5.6	(3.5-8.9)	2.1	(1.0-4.5)		2.1	(1.0-4.6)	
Q5 (most deprived)	26	3,533	7.4	(5.0-10.8)	2.8	(1.3-5.8)		2.9	(1.4-5.9)	
Ethnicity							0.45			0.27
1=White	14	3,713	3.8	(2.2-6.4)		ref			ref	
2=Mixed	9	3,146	2.9	(1.5-5.5)	0.7	(0.3-1.7)		0.7	(0.3-1.7)	
3=Asian or Asian British	<5	567	3.5	(0.9-14.1)	0.9	(0.2-3.9)		0.7	(0.2-3.3)	
4=Black or Black British	<5	212	9.4	(2.4-37.7)	2.0	(0.4-8.7)		1.6	(0.4-6.9)	
5=Chinese	0	33	-	-	-	-		-	-	
6=Other	<5	792	2.5	(0.6-10.1)	0.6	(0.1-2.6)		0.6	(0.1-2.6)	
Missing data	45	8,708	5.2	(3.9-6.9)	1.4	(0.7-2.5)		1.4	(0.8-2.6)	

For Ventricular Septal defect, no statistically significant differences were found across all socio-demographic factors (Table 5.4). For SES, there was a modestly progressive increase in mortality rate from the second quantile to the most deprived sub-group compared to the least deprived quantile. The second quantile had a mortality rate of 3.7 (95% CI, 1.9-7.1) per 1,000 person-years (HR 1.4, 95% CI, 0.5-3.6; adjusted HR (aHR) 1.3, 95% CI, 0.5-3.5). The third quantile had a mortality rate of 4.3 (95% CI, 2.3-7.9) per 1,000 person-years. The fourth quantile had a mortality rate at 5.3 (95% CI, 3.0-9.3) per 1,000 person-years, while the most deprived quantile had a mortality rate 2-fold higher than the least deprived quantile, with a mortality rate of 5.4 (95% CI 3.1-9.3) per 1,000 person-years (HR 2.0, 95% CI, 0.8-4.7; adjusted HR (aHR) 1.9, 95% CI, 0.8-4.5). However, this difference was not significant both in the adjusted and unadjusted analysis (Table 5.4).

Table 5.4: Mortality rate and hazard ratios by socio-demographic factors in a subpopulation of children with Ventricular septal defects (N=52)

	Mortality rate				Unadjusted HR			Adjusted HR*		
	Deaths	Person time	Mortality rate per 1,000 person-years	95% CI	HR	95% CI	P value	HR	95% CI	P value
Sex							0.47			0.80
Male	22	6,012	3.7	(2.4-5.6)		ref			ref	
Female	30	6,658	4.5	(3.2-6.4)	1.2	(0.7-2.1)		1.2	(0.7-2.1)	
Socio-economic status (IMD quintiles)							0.10			0.65
Q1 (least deprived)	8	3214	2.5	(1.2-5.0)		ref			ref	
Q2	9	2430	3.7	(1.9-7.1)	1.4	(0.5-3.6)		1.3	(0.5-3.5)	
Q3	10	2343	4.3	(2.3-7.9)	1.6	(0.6-4.0)		1.6	(0.6-4.0)	
Q4	12	2282	5.3	(3.0-9.3)	1.9	(0.8-4.6)		1.8	(0.7-4.4)	
Q5 (most deprived)	13	2401	5.4	(3.1-9.3)	2.0	(0.8-4.7)		1.9	(0.8-4.5)	
Ethnicity							0.25			0.41
1=White	12	2608	4.6	(2.6-8.1)		ref			ref	
2=Mixed	7	2282	3.1	(1.5-6.4)	0.6	(0.3-1.6)		0.7	(0.3-1.7)	
3=Asian or Asian British	<5	411	2.4	(0.3-17.3)	0.5	(0.06-3.8)		0.5	(0.06-3.6)	
4=Black or Black British	<5	100	30.1	(9.7-93.3)	4.3	(1.2-15.3)		3.9	(1.1-14.0)	
5=Chinese	0	23	-	-	-	-		-	-	
6=Other	<5	623	3.2	(0.8-12.8)	0.6	(0.1-2.8)		0.6	(0.1-2.8)	
Missing data	27	6623	4.1	(2.8-5.9)	0.9	(0.5-1.8)		1.0	(0.5-1.9)	

For Atrial Septal defects, there was no difference in the hazard of death between male and female children or between children from different ethnicities. For SES, there was a significant incremental increase in mortality rate from the third quantile to the most deprived sub-group compared to the least deprived quantile. The third quantile had a mortality rate of 5.7 (95% CI, 2.5-12.6) per 1,000 person-years corresponding to a 3-fold increase in the hazard of death compared to the least deprived. The fourth quantile had a mortality rate and hazard ratio also 3-fold as high as the least deprived quantile at 6.1 (95% CI, 2.9-12.8) per 1,000 person-years. Lastly, the most deprived quantile had a hazard ratio approximately 6-fold higher than the least deprived quantile, with a mortality rate of 10.6 (95% CI, 6.3-18.0) per 1,000 person-years (HR 5.9, 95% CI, 1.3-26.1; adjusted HR (aHR) 6.5, 95% CI, 1.5-29.0) (Table 5.5).

Table 5.5: Mortality rate and hazard ratios by socio-demographic factors in the subpopulation of children with Atrial septal defects (N=30)

	Deaths	Person time	Mortality rate per 1,000 person-years	95% CI	Unadjusted HR			Adjusted HR*		
					HR	95% CI	P value	HR	95% CI	P value
Sex							0.31			0.29
Male	11	2,650	4.2	(2.3-7.5)		ref			ref	
Female	19	3,179	6.0	(3.8-9.4)	1.5	(0.7-3.1)		1.5	(0.7-3.1)	
Socio-economic status (IMD quintiles)							0.0003			0.0006
Q1 (least deprived)	<5	1137	1.8	(0.4-7.0)		ref			ref	
Q2	<5	1167	0.9	(0.1-6.1)	0.5	(0.04-5.4)		0.5	(0.04-5.1)	
Q3	6	1060	5.7	(2.5-12.6)	3.1	(0.6-15.4)		3.3	(0.7-16.5)	
Q4	7	1148	6.1	(2.9-12.8)	3.4	(0.7-16.4)		3.5	(0.7-17.1)	
Q5 (most deprived)	14	1317	10.6	(6.3-18.0)	5.9	(1.3-26.1)		6.5	(1.5-29.0)	
Ethnicity							0.12			0.08
1=White	<5	1332	2.3	(0.7-7.0)		ref			ref	
2=Mixed	<5	1166	1.7	(0.4-6.9)	0.8	(0.1-4.5)		0.8	(0.1-5.0)	
3=Asian or Asian British	<5	221	4.5	(0.6-32.1)	1.9	(0.2-18.3)		1.6	(0.2-15.5)	
4=Black or Black British	<5	115	8.7	(1.2-61.8)	3.8	(0.4-36.3)		2.9	(0.3-28.1)	
5=Chinese	0	5.6	-	-	-	-		-	-	
6=Other	<5	237	8.4	(2.1-33.8)	3.3	(0.6-19.9)		4.2	(0.7-25.8)	
Missing data	21	2752	7.6	(5.0-11.7)	3.1	(0.9-10.4)		3.5	(1.1-11.8)	

Due to very small numbers, AVSD, TOF, AOSD, and unspecified septal defects were combined. There was no apparent difference in the hazard of death in children with any of these defects, by sex, deprivation, or by ethnicity. Adjusting for all sociodemographic factors did not substantially change the magnitude or direction of the hazard ratios for this group (Table 5.6).

Table 5.6: Mortality rate and hazard ratios (HR) by socio-demographic factors in a subpopulation of children with AVSD, ToF, AoSD, and Unspecified septal defects combined (N= 21)

	Deaths	Person time	Mortality rate per 1,000 person-years	95% CI	Unadjusted HR			Adjusted HR*		
					HR	95% CI	P value	HR	95% CI	P value
Total	21	2,627	8.0	(5.2-12.3)						
Sex							0.80			0.99
Male	11	1,467	7.5	(4.2-13.6)		ref			ref	
Female	10	1,160	8.6	(4.6-16.0)	1.1	(0.5-2.7)		1.1	(0.4-2.5)	
Socio-economic status (IMD quintiles)							0.23			0.25
Q1 (least deprived)	5	639	7.7	(3.2-18.6)		ref			ref	
Q2	0	490	-	-	-	-		-	-	
Q3	5	415	11.9	(4.9-28.5)	1.4	(0.4-4.7)		1.2	(0.3-4.2)	
Q4	<5	459	8.6	(3.2-22.9)	1.0	(0.3-3.8)		0.9	(0.2-3.5)	
Q5 (most deprived)	7	613	11.3	(5.4-23.6)	1.4	(0.4-4.4)		1.3	(0.4-4.2)	
Ethnicity							0.79			0.88
1=White	6	671	8.9	(4.0-19.9)		ref			ref	
2=Mixed	<5	518	5.8	(1.9-18.0)	0.7	(0.2-2.6)		0.7	(0.2-2.9)	
3=Asian or Asian British	<5	85	11.7	(1.7-83.3)	1.2	(0.1-10.4)		1.0	(0.1-8.8)	
4=Black or Black British	0	28	-	-	-	-		-	-	
5=Chinese	0	11	-	-	-	-		-	-	
6=Other	0	87	-	-	-	-		-	-	
Missing data	11	1,227	9.0	(5.0-16.1)	1.0	(0.4-2.6)		1.0	(0.4-2.8)	

5.3.2 Age group mortality analysis for septal defects and its sub defects.

Here, the mortality rates and hazard ratios are calculated by age group within the study population for children with Septal defects and variants compared to children with major congenital anomalies, and children with no CA (Table 5.7-5.10).

The age groups were divided into post neonatal (after 30 days up to 1year), 1-4 years, and 5-9 years. Survival curves comparing SD and its sub-groups to Major CA and No CA are shown in Figure 5.1.

5.3.2.1 Post neonatal mortality.

For children with VSD, there was higher mortality within the post neonatal period compared to children with major CA and 13-fold higher mortality when compared to children without CA. Mortality rate ratios are 1.4 (95% CI, 0.80-2.5) and 13.03 (95% CI, 8.18-23.80) for VSD mortality compared to major CA and no CA respectively (Table 5.8).

For children with ASD, there was higher mortality compared to children with major CA and over 15-fold higher mortality when compared to no CA. Mortality rate ratios are 1.53 (95% CI, 0.7-3.3) and 15.79 (95% CI, 8.16-33.20) for ASD mortality compared to major CA and no CA respectively (Table 5.9).

For children with either AVSD, TOF, AOSD, or unspecified SD there was 3-fold higher mortality than in children with major CA, and over 33-fold higher mortality when compared to no CA. Mortality rate ratios of 3.03 (95% CI, 1.3-6.70) and 32.76 (95% CI, 14.69-73.87) for SD combined mortality compared to major CA and no CA respectively (Table 5.10). The post neonatal mortality rate was highest for other combined SD than for children with either VSD or ASD.

5.3.2.2 1-4years

For children with VSD, there was no significant difference in mortality compared to children with major CA of the same age but an 8-fold higher mortality when compared to no CA controls. Mortality rate ratios of 0.7 (95% CI, 0.4-1.6) and 8.79 (95% CI, 4.35-17.77) for VSD mortality compared to major CA and no CA respectively (Table 5.8).

For children with ASD, there was no significant difference in mortality compared to children with major CA of the same age and about 8-fold higher mortality when compared to no CA controls. Mortality rate ratios of 0.63 (95% CI, 0.20-2.02) and 7.77 (95% CI, 2.49-24.26) for ASD mortality compared to major CA and no CA respectively (Table 5.9).

For children with either AVSD, TOF, AOSD, or unspecified SD there was no significant difference in mortality compared to children with major CA of the same age and 13-fold higher mortality when compared to no CA controls. Mortality rate ratios of 1.11 (95% CI, 0.27-4.54) and 13.11 (95% CI, 3.26-52.69) for other SD combined mortality compared to major CA and no CA respectively (Table 5.10).

The mortality rates for all the SD subgroups were largely similar, with the mortality rates of other combined SD slightly higher than either VSD or ASD.

5.3.2.3 5-9 years

For children with VSD, there was no significant difference in mortality compared to children with major CA of the same age and 10-fold higher mortality when compared to no CA controls. Mortality rate ratios of 1.16 (95% CI, 0.4-3.4) and 10.31 (95% CI, 3.80-27.97) for VSD mortality compared to major CA and no CA respectively (Table 5.8).

For children with ASD, there was no significant difference in mortality compared to children with major CA or no CA of the same age (Table 5.9).

For children with either AVSD, TOF, AOSD, or unspecified SD there was no significant difference in mortality compared to children with major CA of the same age and 28-fold higher mortality when compared to no CA controls. Mortality rate ratios of 3.14 (95% CI, 0.74-13.29) and 28.68 (95% CI, 7.08-116.21) for other SD combined mortality compared to major CA and no CA respectively (Table 5.10). The mortality rate in this age group was lowest in ASD and highest in children with other combined SD.

Table 5.7: Mortality rate per 1000 person-days in children with SD compared to children with other major CA and no CA

	SD			Major CA					No CA				
	Deaths	Time at risk (person-years)	Rate (95% CI) Per 1000 person years	Deaths	Time at risk (person-years)	Rate (95% CI) Per 1000 person years	Rate ratio (95% C.I.)	P value	Deaths	Time at risk (person-years)	Rate (95% C.I.) Per 1000 person years	Rate ratio (95% CI)	P value
Overall	38	14,191	2.7(1.9-3.7)	159	66,830	2.4 (2.0-2.8)	1.1 (0.8-1.6)	0.65	811	2,966,486	0.27 (0.26-0.29)	10.02(7.24-13.87)	<0.0001
Post neonatal	22	2,288	9.6 (6.1-14.9)	63	9,884	6.4 (4.6 - 8.1)	1.5 (0.9-2.6)		388	507,245	0.76 (0.62-0.80)	12.7 (8.59-21.2)	
1-4yrs	10	6,369	1.6 (0.8-2.9)	63	28,882	2.2 (1.7 - 2.8)	0.7(0.4-1.4)		254	1,332,884	0.19(0.17-0.22)	8.24 (4.38-15.50)	
5-9yrs	<5	3,947	1.0 (0.4-2.7)	22	19,632	1.1 (0.7 - 1.7)	0.9(0.3-2.6)		105	810,436	0.13 (0.11-0.16)	7.82 (2.88-21.23)	

Table 5.8: Mortality rate per 1000 person-days in children with VSD compared to children with other major CA and no CA

	VSD			Major CA					No CA				
	Deaths	Time at risk	Rate	Deaths	Time at risk	Rate	Rate ratio	P value	Deaths	Time at risk	Rate	Rate ratio	P value
		(person-years)	(95% CI) Per 1000 person-years		(person-years)	(95% C.I) Per 1000 person-years	(95% CI)			(person-years)	(95% C.I) Per 1000 person-years	(95% CI)	
Overall	30	10,752	2.8(2.0-4.0)	173	67,872	2.5 (2.2-3.0)	1.1(0.69-1.52)	0.77	811	2,966,486	0.27 (0.26-0.29)	10.47 (7.28-15.08)	<0.0001
Post neonatal	17	1,714	9.9 (6.1-16.9)	73	10,050	7.3(5.4-9.1)	1.4 (0.80-2.5)		388	507,245	0.76 (0.62-0.80)	13.03 (8.18-23.80)	
1-4yrs	8	4,775	1.7 (0.8-3.4)	66	29,342	2.2(1.8-2.9)	0.7(0.4-1.6)		254	1,332,884	0.19(0.17-0.22)	8.79(4.35-17.77)	
5-9yrs	<5	2996	1.3(0.5-3.6)	23	19,952	1.2(0.8-1.7)	1.16(0.4-3.4)		105	810,436	0.13 (0.11-0.16)	10.31(3.80-27.97)	

Table 5.9: Mortality rate per 1000 person-days in children with ASD compared to children with other major CA and no CA

	ASD			Major CA					No CA				
	Deaths	Time at risk (person- years)	Rate (95% CI) Per 1000 person- years	Deaths	Time at risk (person-years)	Rate (95% CI) Per 1000 person- years	Rate ratio (95% C.I.)	P value	Deaths	Time at risk (person- years)	Rate (95% CI) Per 1000 person- years	Rate ratio (95% CI)	P value
Overall	15	4,404	3.4 (2.0-5.6)	180	68,372	2.6 (2.3-3.0)	1.2 (0.7-2.1)	0.5	811	2,966,486	0.27 (0.26-0.29)	12.51(7.51-20.85)	<0.0001
Post neonatal	9	750	12.0(5.7-23.4)	78	10,125	7.8 (6.0-9.8)	1.53(0.7-3.3)		388	507,245	0.76 (0.62-0.80)	15.79(8.16-33.20)	
1-4yrs	<5	2,025	1.5 (0.5-4.6)	69	29,555	2.3 (1.8-3.0)	0.63(0.20-2.02)		254	1,332,884	0.19(0.17-0.22)	7.77(2.49-24.26)	
5-9yrs	<5	1,203	0.8 (0.1-5.9)	22	20,088	1.1(0.7-1.7)	0.76(0.10-5.6)		105	810,436	0.13 (0.11-0.16)	6.42(0.90-45.97)	

Table 5.10: Mortality rate per 1000 person-days in children with AVSD, TOF, AOSD, and unspecified SD compared to children with other major CA and no CA

	AVSD+TOF+AOSD+Unspecified			Major CA					No CA				
	Deaths	Time at risk (person-years)	Rate (95% CI) Per 1000 person-years	Deaths	Time at risk (person-years)	Rate (95% CI) Per 1000 person-years	Rate ratio (95% C.I)	P value	Deaths	Time at risk (person-years)	Rate (95% CI) Per 1000 person-years	Rate ratio (95% CI)	P value
Overall	12	1,827	6.57(3.73-11.57)	186	69,012	2.70(2.33-3.11)	2.40(1.33-4.30)	0.0024	811	2,966,486	0.27 (0.26-0.29)	25.12 (14.21-44.41)	<0.0001
Post neonatal	7	281	24.9 (10.40-51.99)	84	10,226	8.21(6.2-10.06)	3.03(1.3-6.70)		388	507,245	0.76 (0.62-0.80)	32.76(14.6-73.87)	
1-4yrs	<5	801	2.50 (0.62-9.99)	67	29,831	2.23(1.77-2.85)	1.11(0.27-4.54)		254	1,332,884	0.19(0.17-0.22)	13.11 (3.26-52.69)	
5-9yrs	<5	538	3.72 (0.93-14.86)	24	20,280	1.18(0.79-1.77)	3.14(0.74-13.29)		105	810,436	0.13 (0.11-0.16)	28.68 (7.08-116.21)	

The survival plots shown in Figure 5.1 re-enforces that children with any SD have lower survival than children with major CA and substantially less than children with no CA. Similar results are observed for VSD, ASD or where AVSD, AoSD, ToF and unspecified are combined (other SD) (Figure 5.1).

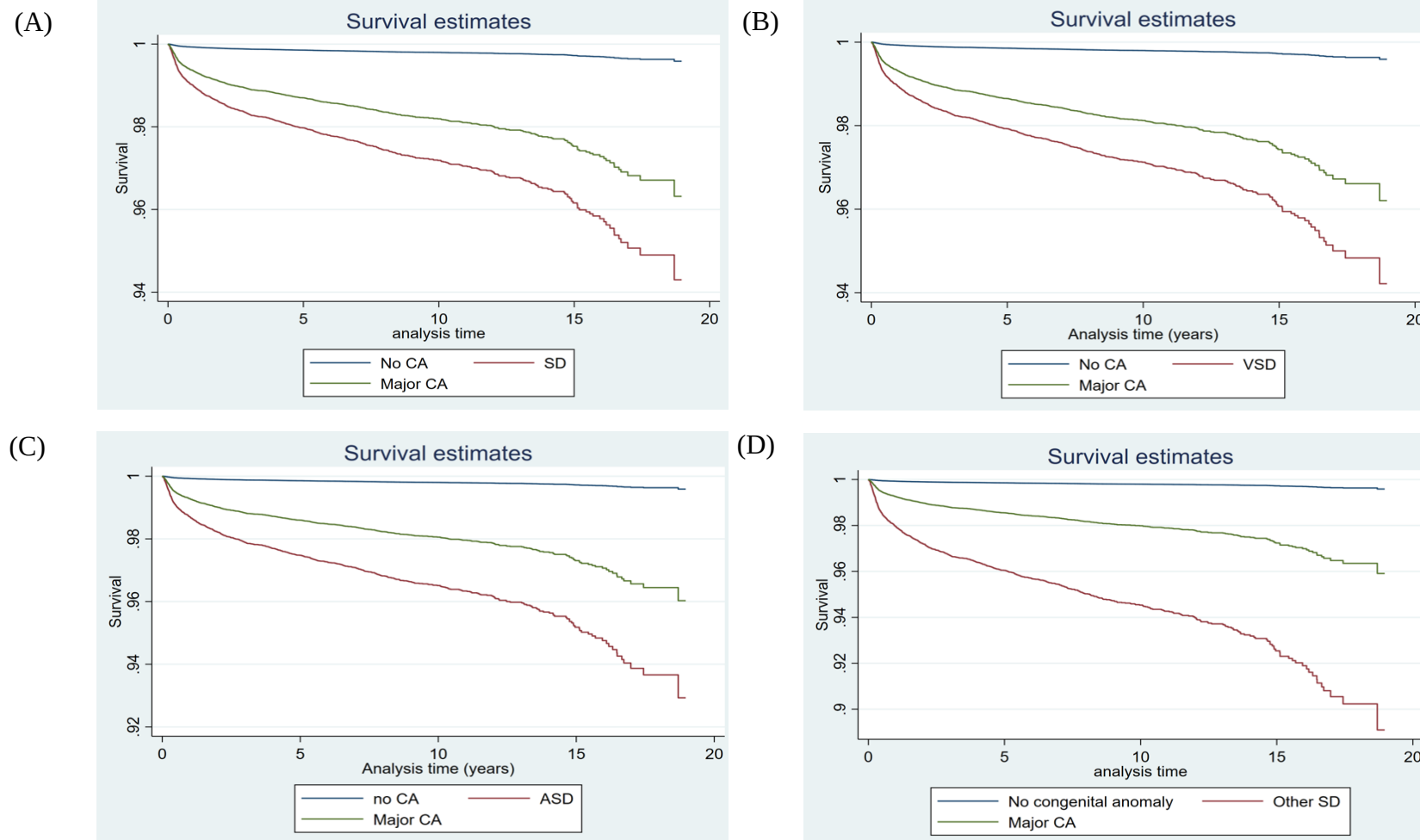


Figure 5.1: Survival estimates for children with any SD (A) VSD (B) ASD (C) or combined analysis for children with AOSD, TOF, AVSD and Unspecified SD (D) compared to those with other major congenital anomaly or no congenital anomaly.

5.3.3 Assessment of mortality amongst cases with a recording of at least one CHD-related intervention as a measure of disease severity

Three hundred and eighty-one (381) patients with CHD were identified to have undergone at least one intervention/procedure related to their CHD in the current data. Of these, 198 (51.97%) were males and 183 (48.03%) were females (Table 5.11). Of the total SD cases in this dataset, 5% (158) had at least one intervention/procedure of which 55.70% were males and 44.30% were females. Of the SD sub variants, VSD and ASD had a lower number of interventions recorded in proportion to the total number of cases of each variant. Whilst 4% of interventions were recorded in the patient population with ASD or VSD, with 48.15% of these in males and 51.85% in females for VSD and 48.72% males and 51.28 females were recorded for cases with ASD, the proportion with at least one intervention/procedure was higher for the other SD sub variants: ToF, AVSD and AoSD were 29%, 36% and 40% respectively. Thirty-two (32) patients who had SD with other CHD had an intervention (18% of this group); of these, 53.13% were males and 46.88% were females. Sixty (600) patients who had SD with other non-CHD congenital anomalies had an intervention (9% of the total number of cases); of these, 68.33% were males and 31.67% were females (Table 5.11).

Table 5.11: Number and percentage of total CHD patients, SD and SD variants with a recording of at least one related intervention/procedure

	Total number of Cases	Number of patients with a recording of at least one intervention (n)	Overall % (of patients with at least one intervention amongst total cases)	Male (% of n)	Female (% of n)
Total CHD	5129	381	7.43	198 (51.97)	183 (48.03)
Total SD	2899	158	5.45	88 (55.70)	70 (44.30)
VSD	2116	81	3.83	39 (48.15)	42 (51.85)
ASD	1032	39	3.78	19 (48.72)	20 (51.28)
ToF	233	68	29.18	44 (64.71)	24 (35.29)
AVSD	115	41	35.65	23 (56.10)	18 (43.90)
AoSD	10	<5	-	-	-
Unspecified SD	76	24	31.58	10 (41.67)	14 (58.33)
SD with other CHD	182	32	17.58	17 (53.13)	15 (46.88)
SD with OCA	638	60	9.40	41 (68.33)	19 (31.67)

Of the 381 CHD patients who had a recording of at least one intervention, 8 patients died.

The subsequent analysis of the SD variants was therefore precluded as for all variants the number of deaths recorded was fewer than 5 (Table 5.14).

Table 5.12 CHD type and SD variants of children with interventions who died

	Number of patients
Total CHD	8*
Total SD	5
VSD	<5
ASD	<5
ToF	<5
AVSD	<5
AoSD	<5
Other CHD	6

*Numbers not adding up because of overlap

5.3.4 Cause of death analysis

The cause of death for the entire birth cohort, together with the frequency of occurrence is presented in (Table 5.13). Congenital malformations, deformations, and chromosomal abnormalities (Q) were the most common cause of death in the entire birth cohort accounting for 17.7% of all the deaths. The most common cause of death for all children with septal defects regardless of the subgroup was also “Q- Congenital malformations, deformations, and chromosomal abnormalities” occurring in 67.13% (49/74) of the cases (Table 5.14). This was followed by “J- Disease of the respiratory system” occurring in 8.22% (6/74) of the cases (Table 5.14).

Table 5.13: Cause of death for entire birth cohort

ICD-10 Chapter	Diagnostic grouping	N	%
Q	Congenital malformations, deformations, and chromosomal abnormalities	205	17.7
R	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	146	12.6
C	Malignant Neoplasms	124	10.7
P	Certain conditions originating in the perinatal period	123	10.6
G	Disease of the Nervous system	105	9.1
J	Disease of the respiratory system	84	7.3
A	Infectious and Parasitic Infections	60	5.2
E	Endocrine, nutritional, and metabolic diseases	56	4.8
W	Other external causes of accidental injury (Falls)	50	4.3
I	Diseases of the circulatory system	48	4.1
Y	External causes of morbidity and mortality (assault by blunt object, pushing, crashing of motor vehicle, sexual, neglect and abandonment, and other maltreatment)	29	2.5
V	External causes of morbidity and mortality (Accidents)	27	2.3
D	In situ, Benign, and Neoplasms of uncertain or unknown behaviour; diseases of blood and blood-forming organ and certain disorders involving immune mechanism	22	1.9
B	Viral, Bacterial, and Parasitic Infections	17	1.5
K	Diseases of the digestive system	17	1.5
U	Codes for special purposes	16	1.4
X	External causes of morbidity and mortality (Assault by chemical, corrosive, gaseous noxious substances)	15	1.3
N	Disease of the genitourinary system	8	0.7
M	Diseases of the musculoskeletal system and connective tissue	<5	0.3
F	Mental and behavioural disorders	<5	0.2
H	Diseases of the eye adnexa, ear, and mastoid process	<5	0.1
T	Injury, poisoning and certain other consequences of external causes	<5	0.1

Congenital malformations, deformations, and chromosomal abnormalities were the leading cause of death for cases with VSD at 71.04% (37/52) cases, ASD at 53.6% (17/29), ToF at 83.34% (10/12), AVSD at 75% (3/4), and 100% (2/2) of unspecified SD cases (Table 5.15). Congenital malformations, deformations, and chromosomal abnormalities were not noted as a cause of death for AoSD. This by far exceeded the next cause of death in all VSD cases which was the disease of the respiratory system at 7.68% (4/52 cases). Other causes of death such as infections, malignancies, metabolic diseases, and external causes, each contributed less than 5% of total morbidity in children with VSD (Table 5.15). Similarly, for ASD, 10.35% (3/29) of all ASD deaths were due to respiratory diseases. For AoSD, the cause of death was split equally between the disease of the respiratory system and the disease of the circulatory system (Table 5.15). Graphical representations for the causes of death of VSD, ASD, ToF, and AVSD are shown in (Figure 5.2).

Table 5.14: Causes of death in children with Septal heart defects.

ICD-10 Chapter	Diagnostic grouping	Frequency (N=74)	%
Q	Congenital malformations, deformations, and chromosomal abnormalities	49	67.13
J	Disease of the respiratory system	6	8.22
I	Diseases of the circulatory system	<5	5.48
G	Disease of the Nervous system	<5	2.74
K	Diseases of the digestive system	<5	2.74
R	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	<5	2.74
Y	External causes of morbidity and mortality (assault by blunt object, pushing, crashing of motor vehicle, sexual, neglect, and abandonment, and other maltreatment	<5	2.74
A	Infectious and Parasitic Infections	<5	1.37
B	Viral, Bacterial, and Parasitic Infections	<5	1.37
C	Malignant Neoplasms	<5	1.37
D	In situ, Benign, and Neoplasms of uncertain or unknown behaviour; diseases of blood and blood-forming organ and certain disorders involving the immune mechanism	<5	1.37
P	Certain conditions originating in the perinatal period	<5	1.37
V	External causes of morbidity and mortality (Accidents)	<5	1.37

Table 5.15: Causes of death in children with SD subgroups.

ICD-10 code	Diagnostic grouping	VSD		ASD		ToF		AVSD		AOSD		Unspecified SD	
		Frequency (N=52)	%	Frequency (N=29)	%	Frequency (N=12)	%	Frequency (N=4)	%	Frequency (N=2)	%	Frequency (N=2)	%
A	Infectious and Parasitic Infections	<5	1.92										
B	Viral, Bacterial, and Parasitic Infections	<5	1.92										
C	Malignant Neoplasms	<5	1.92	<5	3.45								
D	In situ, Benign, and Neoplasms of uncertain or unknown behaviour; diseases of blood and blood-forming organ and certain disorders involving the immune mechanism	<5	1.92										
E	Endocrine, nutritional, and metabolic diseases	<5	1.92										
G	Disease of the Nervous system	<5	3.84	<5	3.45	<5	8.33						
I	Diseases of the circulatory system	<5	3.84	<5	6.90					<5	50		
J	Disease of the respiratory system	<5	7.68	<5	10.35			<5	25.	<5	50		
K	Diseases of the digestive system			<5	3.45	<5	8.33						
P	Certain conditions originating in the perinatal period			<5	3.45								
Q	Congenital malformations, deformations, and chromosomal abnormalities	37	71.04	17	53.6	10	83.34	<5	75			<5	100
R	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified			<5	6.90								
V	External causes of morbidity and mortality (Accidents)	<5	1.92										
Y	External causes of morbidity and mortality (assault by blunt object, pushing, crashing of motor vehicle, sexual, neglect and abandonment, and other maltreatment	<5	1.92	<5	3.45								

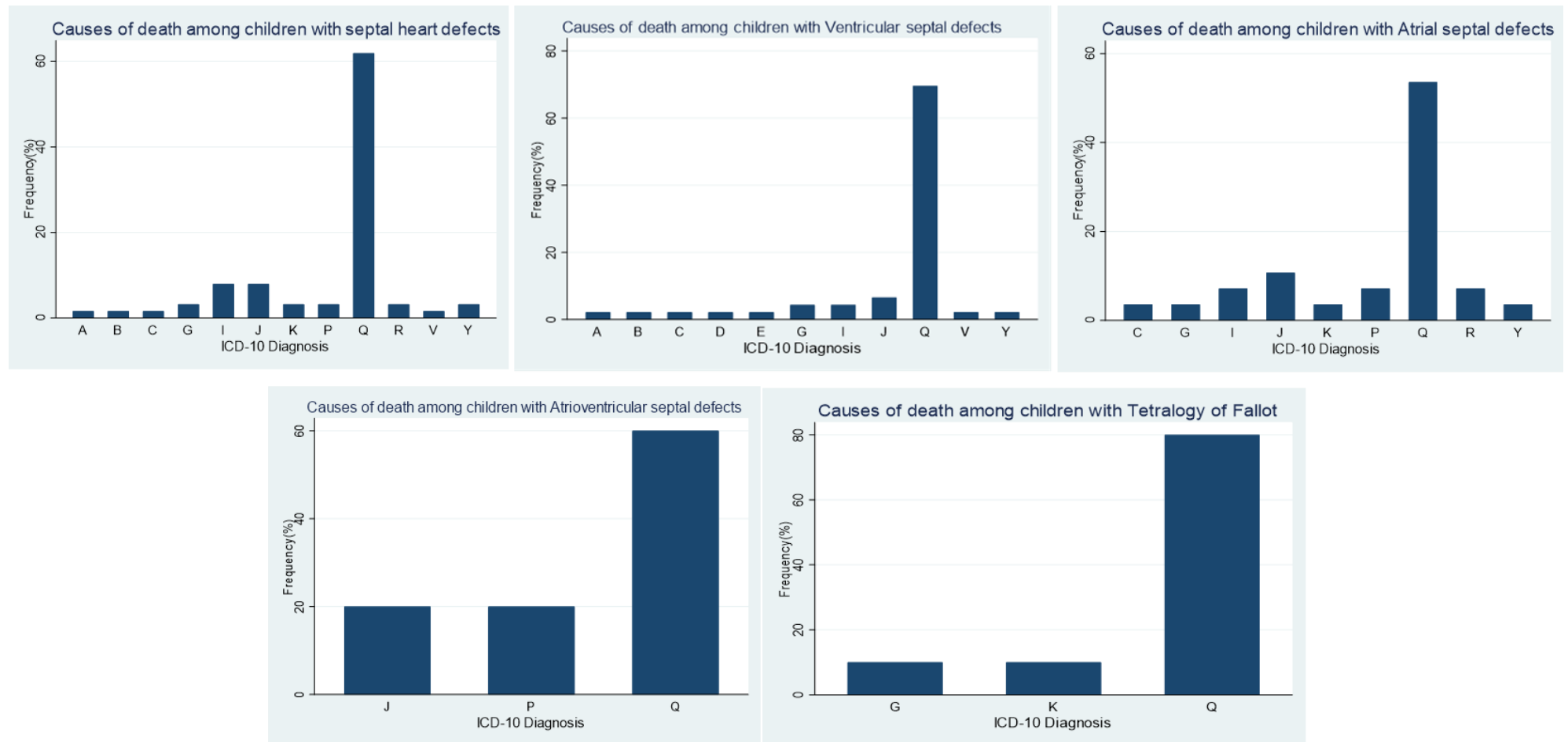


Figure 5.2 Cause of death for SD and SD variant

5.4 Discussion

The aim of this chapter was to assess the post neonatal mortality rates of septal defects and its variants; VSD, ASD, ToF, AVSD, AoSD, and unspecified SD. Here, I calculated mortality rates and hazard of death for SD and its variant defects. Furthermore, the influence of socio-demographic factors such as gender, ethnicity, and socioeconomic status on these rates in children aged 0 to 9 years was assessed. Furthermore, I assessed the causes of death recorded for children diagnosed with the different defects.

5.4.1 Principal findings

Between January 1998 and June 2017, the total number of deaths with CHD for children between the ages 0 - 19 years recorded within this dataset was 166 and the mortality rate was 5.6 per 1000 person-years. For SD, there were 74 deaths in this time period, with a mortality rate of 4.3 per 1000 person-years. Of the variant defects, children with AoSD had the highest mortality rate at 54.9 per 1000 person-years whilst children with VSD had the lowest mortality rate at 4.1 per 1000 person.

For overall septal defects, whilst there was no difference in the hazard of death or mortality rate by gender or ethnicity., there was a significant association with socioeconomic status largely driven by ASD. Due to very small numbers, AVSD, TOF, AOSD, and unspecified septal defects were combined to assess the effects of ethnicity and socioeconomic status, as well as for assessment for mortality within age groups.

For evaluation of mortality according to age groups, only deaths occurring below the age of 9 were assessed due to the low number of deaths between the age groups of 10 and 19 years. For deaths occurring 9 years and under, the analysis was divided into post neonatal (after 30

days up to 1year), 1-4 years, and 5-9 years. Whilst there was substantial variation within the various defects, there was an overall 10-fold increased risk of death for all SD compared to children with no CA in all age groups, with the highest increase in the risk of death of any SD in post neonatal age group with a 12-fold increase.

The most common cause of death for all children with SD and its sub-defects was the congenital malformation itself, assigned as Congenital malformations, deformations, and chromosomal abnormalities. This was followed by the disease of the respiratory system, although for AoSD, the causes of deaths documented were the disease of the respiratory disease and disease of the circulatory system.

5.4.2 Strengths and limitations

This is the first study evaluating the mortality of all the SD sub defects within the same birth cohort at a national level in England over a 10-year period outside an intervention setting. Furthermore, the availability of socio-demographic factors such as ethnicity and deprivation in this dataset allows the assessment of these important factors in the mortality rates of these defects across England.

The major limitation of this current study was the sample size. The total birth cohort was nearly 50% less than the sample size required to detect statistically significant associations following power calculations, so the other analyses had even less power. Nonetheless, some associations were still detected. The limited sample size meant assessing the mortality rates for all SD variants individually could not be done. For example, ToF, AVSD, AoSD, and specified SD were combined for analysis of mortality rates and the effect of socio-demographic factors. Furthermore, attempts were made to separate SD variants into sub-groups consisting of isolated variants, variants with other CHD, variants with OCA, and

variants with both other CHD and OCA for the mortality rate calculations. However, this sub-grouping meant sample sizes were too small for meaningful analysis and interpretation. Also, whilst there is a need to assess the survival of children who had interventions early in life compared to children who did not in England, the death records for these sub-groups were too small to allow these comparisons. More so, the limited sample size resulted in high-confidence intervals across most of the results.

Another limitation is that the birth cohort in this study was from CPRD, so children who died before GP registration were not captured in this mortality analysis. This could explain the low number of total deaths detected within this study compared to other studies in the literature. Linkage to HES would have captured cases and fatalities in hospitals but this was not possible for this current study. This risks an under-estimation of the already high mortality rates of the sickest children. Nonetheless, this study provides information on the long-term survival of children with SD who do not die neonatally.

5.4.3 Interpretation in context of other studies

There are vast differences in the methodology of studies assessing mortality of children with CHD, therefore hampering direct comparisons with this current study. Some studies report mortality relative to live births, some to person-years, and others as survival rates.

In Wren et al., between 1987 and 2006, 458 (10.3%) deaths before the age of one were recorded in 4,437 children diagnosed with cardiac malformations (190) amounting to 7% mortality in the total cohort. Of this total mortality, the cause of death in about 40% of children was cardiac-related, 44% were surgery-related and 16% were non-cardiac-related deaths (190). The authors considered the effect of termination of pregnancy and found a 67% increase in antenatal diagnosis and termination of all pregnancies between the first 5 years

and last 5 years of 1987-2006, where 31% of these had isolated cardiac anomalies (190). An overall decline in mortality rate in CHD patients over the 20 years was reported (190). This study was based on the Northern Congenital Abnormality Survey (NorCAS) in England but did not consider the mortality rates of individual septal defects to allow comparison to this current study. In this current study, we report the post neonatal mortality rate for any CHD as 5.8 per 1,000 person-years (95% CI, 5.0-6.7). The mortality rate in person-years was not reported in the Wren et al. study for direct comparison.

Knowles et al., reported mortality in CHD diagnosed infants undergoing a surgical procedure in England and Wales using linked data from the National Congenital Heart Disease Audit (NCHDA) and Paediatric Intensive Care Audit Network (PICANet) between January 2006 and December 2009 (207). In that study, survival was only considered within the first year of life. Nonetheless, the study is relevant to the current one as they considered the influence of ethnicity and socioeconomic status on the 1-year mortality from CHD. The overall mortality before the age of one reported in that study was 83.9 (95% CI 76.3 to 92.1) per 1000 infants (207). Where children of white ethnicity were the reference, children of British Asian ethnic group had a higher mortality risk (RR 1.6 [95% CI 1.2 to 2.1]). So did children of other ethnic groups which included the Chinese ethnicity and mixed ethnicity (RR, 1.7 [95% CI 1.2 to 2.4]) (207). No significant increase in mortality risk was detected in children of Black British ethnicity. Furthermore, there was no significant association between mortality and deprivation in the study (207). The study also did not delineate the sub defects that contribute to the total CHD burden to allow direct comparison to this study.

In this current study, VSDs which are the most common CHDs had the lowest mortality rates of all the SD variants assessed. The mortality risk ratio was not different from children with other major CA across all the age groups considered. However, the mortality risk ratio was

about 10 times higher compared to children with no CA, with the highest difference in the post neonatal months at 13.03 (95% CI, 8.18-23.80). There was no association of gender, ethnicity, or socioeconomic status on the mortality rate in children with VSD. The cause of death for this age group was predominantly due to cardiac malformations, deformations, and chromosomal abnormalities. In a Norwegian registry study of live births between 1994-2009, 3,495 children with VSD were identified out of the total population of 943,871 within the birth cohort. No difference in the mortality rate was observed in children with and without VSD within the study population (216).

In this current study, ASD followed on VSD having a slightly higher mortality rate than VSD. Nonetheless, the presence of ASD had up to a 15-fold higher risk of death than children with no CA. Between post neonatal months to 9 years, there were no significant differences in the mortality between children diagnosed with ASD and children with other major CA. There were socioeconomic and ethnic differences detected for ASD in this current study with the most deprived having the highest mortality and Black/Black British ethnic group also having the highest mortality. A Danish cohort study of children born before 1994, who got diagnosed with ASD within 1959-2013 and a median follow up time of 18 years, reported an overall higher risk of mortality in ASD patients compared to the general population (aHR 1.7, 95% CI, 1.5–1.9). They reported this increased risk of mortality is less in ASD patients who had undergone a closure compared to those who had not (217). The mortality rate ratio in the current study is 10 times higher than the Danish study (aHR 18.1, 95% CI, 12.5-26.0). In contrast to the Danish study, this current study does not delineate ASD patients into those that had surgery and those that did not, nonetheless, the risk of mortality is higher in patients with ASD than in the general population without CA. Furthermore, similar to this current study, Nyboe et al., also reported cardiac disease as the predominant cause of death in patients with

ASD diagnosis (217). Caution is required in the mortality rate estimates within this current study due to the sample size limitations.

The next highest mortality rate in this current study was in children diagnosed with AVSD, with a mortality rate of 7.1 per 1000 person-years and a hazard of death ratio of 24.0 (95% CI, 10.0-57.9) adjusted for gender, ethnicity, and socioeconomic status. A study done 30 years ago of infants born in Bohemia, recorded a prevalence of AVSD at 0.19 per 10,000 liver births, constituting 2.9% of all CHD (218). In that study, of 1,008 who died due to any cardiac malformation, 6.35% had AVSD, 91% of all children diagnosed with AVSD were expected to survive the first month and 50% survive the first year (218). Around the same time, similar results were recorded in New York, with the mortality rate after complete correction at 43% after 13 months and 46.8% at 5 years (219). Improvement in surgical and overall management is critical for the survival of children diagnosed with AVSD. In a cohort study between 1974 and 2000, with 198 patients who underwent a complete AVSD repair, the overall survival was 82% at 20 years (220). In that study, pulmonary arterial hypertension, as well as complications from cardiac defects, were implicated in AVSD related deaths (220). This matches this current study where the disease of the respiratory systems as well as congenital malformations, were implicated in AVSD deaths. More recent studies assessing the natural risk and survival of the most serious SDs are required with sufficient data size to fully ascertain the needs of this group.

Following on from AVSD were children diagnosed with ToF, with a mortality rate of 8.0 per 1000 person-years and a hazard of death ratio of 30.4 (95% CI, 17.2-53.8) adjusted for gender, ethnicity, and socioeconomic status was observed. Wang et al. reported the mortality risk ratios of various CA including some CHDs in a cohort of children born between 1983-2006 in New York. The authors reported the post neonatal mortality risk was about 40%

higher for children with Tetralogy of Fallot than children with no CA (41.9, 95% CI 37.1-47.3), increasing to 63% for 1-2-year-olds (63.7, 95% CI, 51.4-78.9) and dropping largely for children over 6 years old to 9.5 (95% CI, 7.1-12.7) (221). The absolute number and person-years were not reported for direct comparisons.

In this current study, children with AoSD had the highest mortality rate at 53.7 per 1000 person-years and a hazard of death ratio of 149.8 (95% CI, 37.2-602.4) adjusted for gender, ethnicity, and socioeconomic status. No matched analysis was found looking at mortality of AoSD in general outside of an intervention setting. Therefore, factors affecting AoSD survival in all settings are discussed. In a cohort study in New York of 62 patients who had surgery for AoSD between September 1993 and December 2013, there was a 7% hospital mortality in the patients with isolated AoSD and a 21% hospital mortality in patients who also had other defects such as ToF or VSD (222). No late deaths were recorded within the follow-up time of 2 to 10 years suggesting the survival of these patients (222). However, the varying follow-up time makes this only an assumption. The long-term prognosis of AoSD depends on how quickly intervention occurs and the concomitant cardiac defects present. For example, interruption of the aortic arch was associated with increased mortality where the hazard ratio was 5.87 (95% CI, 1.56-22.0; $p = 0.009$) (223). In another study of patients diagnosed between 1995 and 2005, of 9 patients, there were 2 deaths and 9 surgeries, one of the deaths was as a result of a respiratory infection (224). Furthermore, antenatal diagnosis is critical for survival, as early detection means a repair can be adequately planned as an early repair is critical to long-term survival (225). In general, early detection and surgical repair are associated with improved survival in children diagnosed with AoSD.

For combined analysis of AoSD, AVSD, ToF, and unspecified SD, the mortality risk ratio was 3-fold higher than children with other major CA in post neonatal and 5-9 years age

groups. Furthermore, the mortality risk ratio was higher compared to children with no CA across all age groups, with the highest in the post neonatal age group where there is a 32-fold increase in the risk of death. There was no association of gender, ethnicity, or socioeconomic status on the mortality rate in children with these combined SDs.

Across the analyses presented in this current study, the highest mortality rates for specific defects were often in the post neonatal age group. This has been reported previously in an age-standardized assessment of CHD-linked deaths in England and Wales between 1959 and 2009 where the highest deaths occurred in the age group less than 1 (213). Knowles et al, reported that between 1959–1963, death in children under 1 accounted for 60% of all CHD-linked deaths falling to 22% of all CHD-linked deaths by 2004–2008, still the bulk of the CHD death burden (213). This fall in postnatal death in recent times is attributed largely to advancement in paediatric care.

In this current study, the number of recorded cases of patients who had clinical information on interventions/procedures related to their CHD were generally lower than would be expected. Whilst this current study only identified 7% of all CHD cases as having undergone an intervention, a Swedish study of birth registries reported as high as 23.2% of CHD patients having undergone an intervention related to their CHD diagnosis between birth and the age of 18 (226). However, in this current study the most prevalent and less severe forms had the lowest numbers of interventions recorded and this increased with the more severe forms varying from approximately 30% to 40% for the other forms of SD (ToF, AVSD and AoSD). As this current study defines severe cases as having at least one intervention in the first year of life whereas Mandalenakis et al. assessed interventions that occur anytime between birth and 18 years of age (226), it is important to note that both studies are not directly comparable.

Of the congenital heart defects studied here, Botto et al., classified Tetralogy of Fallot, and aortopulmonary septal defect in Lesion group 1, atrioventricular septal defect also known as endocardial cushion defects in Lesion group 2, ventricular septal defects in Lesion group 4, Atrial septal defect in Lesion group 5 (227). Using this classification system, Mandalenakis et al. reported using Swedish health registries of births between 1980 and 2017, Lesion group 2 had the highest mortality risk with a hazard ratio (HR) of 97.2 (95% CI, 80.4-117.4) followed by lesion group 1 with an HR of 48.8 (95% CI, 41.3-57.6) (226). Lesion group 5 had the lowest mortality risk in the grouping albeit significantly higher than matched controls with HR of 6.8 (95% CI, 5.8-8.0) (226). In the latter study overall, survival of children born with CHD was shown to improve by decade of birth but peaking at 97% in 2010 (226).

In the current study population, there were only 8 recorded deaths in CHD patients who had at least one CHD-related intervention/procedure recorded in their GP record, and this hampered further sub-analysis of the SD sub-variants. As this birth cohort is from CPRD, it is expected to have fewer numbers documented for interventions due to non-linkage to HES. This means that children within the current CPRD study cohort may have procedures or hospital admissions recorded in HES that are not recorded in their GP record (i.e., missing). Linkage to HES would provide this information during the period they are registered with the GP but would have also provided procedures before their registration that happened early in life. These procedures early in life are likely to better reflect the CHD severity of the child, compared with later procedures. Because procedures overall, and particularly hospital procedures before the child was registered, are less likely to have been captured in their GP record, this further limits the ability to determine CHD severity from only using children's GP records.

Another limitation of not having HES data is that the most severe cases may not be registered in CPRD at all (because they never get registered with a GP) whereas they would be captured in HES. Furthermore, children who die early, who may have received an intervention are likely to be missed in this dataset. The completeness and robustness of hospitalisation information transfer into CPRD has been shown to be poor in studies assessing other health indicators (228–230). For example, when compared with HES, the accurate identification of hospitalisations in chronic obstructive pulmonary disease (COPD) within CPRD was poor, with a positive predictive value (PPV) of 50.2% (95% CI, 48.5%–51.8%) (229). Another study found less than 20% of all bleeds in patient with non-valvular atrial fibrillation found within the HES database was found within CPRD (230). No equivalent comparison of HES and CPRD was found for septal defects and their variants, therefore the extent of this disparity is not known.

The completeness of patient's information within CPRD is dependent on how robust each patient record from other healthcare settings such as hospital care is transferred into their primary care records. Inefficiencies in the transition of patient care between healthcare settings is a documented problem worldwide including England (231). Since 1996 about 96% of all general practice records had become computerised in the UK, with a steady improvement in this estimate since then (232). Research published in 2002, reports that the level of digital recording of patient data within the hospital settings in comparison was much lower, with doctors having no incentives to move away from handwritten records (232). Within this time frame, it was estimated that between 40% and 75% of the usually handwritten discharge summaries were illegible either partially or completely (233,234). Therefore, the quality of data transferred between both healthcare settings within this time frame is likely to have been hampered by legibility problems. A comparison of traditional

dictated letters and digital discharge summaries for 30 patients found that digital summaries performed significantly better than the alternative form in meeting the criteria set by the Scottish Intercollegiate Guidelines Network (234) with up to 83% of participating GPs preferring the digital discharge summaries (234). In recent years, there has been a significant increase in the use of digital recording of patient care in hospital care with guidance from the professional record standards body (PRSB) set to encourage electronic discharge summaries been sent to the primary care provider of the patient within 24 hours of discharge in a standardised format (235). With this improvement, there remains some concerns from GPs about the consistency of discharge summaries' adherence to guidelines. In a qualitative study, GPs still reported a lack of completeness in the content of the discharge summaries and inconsistencies arising from a random circulation of the discharge letters with the patients copied in some cases and not others (236).

Another consideration in the organic transfer of data from secondary care to primary care is protecting patient identification. At the point of data transfer, whilst information cannot be anonymised, it is expected to be pseudonymised to protect the patients' identification (237). In this case, there are set guidelines by the NHS Business Service Authority's pseudonymisation and anonymisation of data policy stipulating the appropriate way for this to be done (237). This is a very important aspect of data sharing and getting it right is imperative to the widescale success of information transfer between healthcare settings; nonetheless this introduces an extra layer and avenue for mistakes and possible inconsistencies in patient records.

This problem with CPRD alone not being sufficient in identifying all cases and the severity of cases is further exacerbated because of the number of GP practices that feeds data into the CPRD database; it is estimated that at the time of my study less than 60% were eligible for

linkage to HES (230). Furthermore, not all eligible England-based CPRD practises have consented to linkage with HES as of 2016, although this is likely to improve in coming years (229). Therefore, the inability to link this CPRD to HES hampered the opportunity to effectively assess severity and interventions carried out in a manner that can be generalised for the entire population in England.

Moreover, it is important to note that as this study assessed post neonatal mortality in a CPRD- based database, the mortality reported here only assessed live births among children who lived long enough to be registered with the GP and did not consider pregnancy loss or termination that could occur following perinatal diagnosis of the defects. Also, most severely ill children who do not make it out of hospital will not be represented within this dataset. The consequence of this is a possible under-reporting of the mortality rates for these defects due to omission of severely ill patients dying either from congenital heart defects or other severe anomalies which leads to neonatal deaths. Future studies can take the TOPFA figures into account via mother-baby link, as well as following linkage of the dataset to HES, to get a better overview of the total mortality burden of these defects. All of this must be considered in terms of the limited direct applicability and utility of these findings in a clinical practice setting, particularly for use in informing decisions about terminating pregnancies where the fetus has been diagnosed with CHD in utero.

5.4.4 Conclusion and implications

This study provides an England-specific natural history of children with SD and its various subgroups that were registered in their first year of birth with a GP between 1998 and 2017, for whose death records could be linked beyond the neonatal period. AoSD, ToF, AVSD, and unspecified SD had the highest mortality rates within this cohort. All SD sub-groups

considered had higher mortality than children without CA and, the combined assessment of SD variants (AVSD, ToF, AoSD, and unspecified SD) had a higher risk of mortality than children with other major CA across all age groups considered.

For all SD the predominant cause of death was congenital malformations, deformations, and chromosomal abnormalities, followed by disease of the respiratory system. There was an association between any SD defect and gender in this study; only the mortality of ASD was found to be associated with ethnicity and socioeconomic status. Whilst survival is reported to have improved in recent times, with improved diagnosis, interventions, and long-term clinical management, the survival rate for children with these defects is still a long way behind the general population and more research is required to further improve the prognosis for these children.

Chapter 6: Conclusion

6.1.1 Summary and findings

This study aimed to assess the prevalence and mortality related to septal heart defects. Firstly, to evaluate the prevalence of CHD, SD, and SD variants within the English population using primary care data from CPRD, evaluating how this varies with gender, ethnicity, deprivation, and geographical location. Secondly, to assess the mortality rates of children with these congenital anomalies within the CPRD database, comparing with survival in children with other major CA, and children without any CA. Furthermore, to assess the cause of death in the SD cohort. To address these aims, the key findings were:

Objective 1.

The prevalence estimates of CHD, SD, and SD defects within CPRD were comparable to the literature. Of all the CHDs, VSD was the most prevalent, followed by ASD and then ToF. Other variants were much less prevalent. For any SD, gender was significantly associated with occurrence, with the prevalence higher in females than males. Socioeconomic status, year of birth, or ethnicity was not found to be significantly associated with the risk of any SD occurring. For any SD, the highest prevalence was in the East Midlands of England.

VSD was more prevalent in females than males. Furthermore, I found that the prevalence of VSD progressively dropped between January 1998 and June 2017. The prevalence of VSD did not change with increasing deprivation. The prevalence of VSD varied by geographical region in England with the highest prevalence observed in Southwest and East Midlands and the lowest prevalence of VSD in South East and London.

As with other studies, ASD was also higher in females than males, with ASD being most prevalent in the East Midlands compared to London and the least prevalent in the Southwest of England.

The prevalence of ToF was higher in males than females. I found that the prevalence of ToF was highest in Asian/Asian British ethnic group and least in Black/Black British ethnic group.

The least occurring SD variants were AVSD, AoSD, and unspecified SD. For comparison of CPRD to EUROCAT, the prevalence of CHD, VSD, ASD, and ToF was less in EUROCAT than this current CPRD-based study, however, the prevalence was higher for AVSD in EUROCAT than in this study.

Objective 2.

There were no directly comparable studies in the literature with this study as most mortality studies were carried out over 30 years ago before the advancements in surgeries and other studies assessed the mortality rates in specific settings or following surgical interventions.

Of the sub-defects assed in this study, children with AoSD had the highest mortality rate whilst children with VSD had the lowest mortality rate. For overall septal defects, there was no difference in the hazard of death or mortality rate by gender or ethnicity. However, there was a significant association with socioeconomic status largely driven by ASD. Using CPRD without linkage to HES means the dataset is limited to children who survive until GP registrations, therefore early infant deaths such as occurs in hospital are not captured.

There was an increased risk of death for all SD compared to children with no CA in all age groups and higher than children with other major CA in the post neonatal age group.

The most common cause of death for all children with SD and its variant defects was congenital malformations, deformations, and chromosomal abnormalities followed by the disease of the respiratory system. Although for AoSD, the causes of death documented were diseases of the respiratory and circulatory systems.

6.1.2 Implications and further research

Presently, there is no nationwide view of the prevalence and mortality of the specific septal defects in the same birth cohort, with an opportunity to compare survival with children with other CA and no CA in England. Work within this study presents the outcomes of SD and its sub defects within the general population in England.

Although severe cases who die neonatally will not be captured in this study, the estimates from this research provide useful information about the post neonatal outcome for children who survive until registration with a GP. This is therefore beneficial for health planning as a high proportion of children born with congenital heart defects now live longer with the improvements in diagnosis and management.

Accurate estimates of CHD in children, and importantly, their subtypes using population data are vital for proper planning for the adult subgroups as it is the population that survive childhood that constitute the adult population. As CHD is present at birth but can be diagnosed any time in life, knowledge of prevalence in children and importantly, the subtypes of CHD they have, that will survive into adulthood will give an indication of overall prevalence and CHD subtypes, and thus, the health outcomes and survival rates to be expected in the adult population.

Furthermore, the estimates of prevalence and survival of CHD and subtypes in children from this current study are of some use in planning- both technologically and professionally for the subsequent adult population that will emerge from this population. Knowledge of what to expect years after a CHD is treated has the potential of informing better diagnosis, pre-, peri-, and post-operative care that can mitigate re-interventions and re-admissions and thus reduce the cost burden of these defects. It also has the potential of equipping the medical and social carers with the knowledge to better help family members of CHD patients. This knowledge, when adequately communicated to the patients themselves, helps with acceptance of self and thus, improves quality of life.

More so, as there are several CHD types and sub variants with differing outcomes based on severity, it is important to delineate prognosis and outcomes per type and variants as lumping of outcomes (often seen in results of studies looking at very severe types or after intervention) are not often representative of prognosis and outcomes for all types and variants especially the mild and moderate types/variants.

Although one limitation for the mortality studies was the low sample size that hampered the ability to present detailed and accurate mortality risk estimates, this is a common challenge with research into the survival of children with various forms of congenital anomalies especially from using only a primary care-based registry (CPRD). The problem with not linking this current dataset to HES as previously discussed is multi-faceted and compounded by the difficulties that exist in the transfer of patient hospital records into their GP records. Whereas more information on procedures done in hospital will be recorded within the HES database, the low records of interventions in the GP-record which hampered the assessment of severity of the different septal defect subtypes is likely a reflection of poorly transferred data into CPRD. Furthermore, the total mortality burden and estimation of the most severe of

cases is likely to be greater than reported here as children who die neonatally will most likely be missed within the CPRD database but captured within HES.

Of note also, this problem is not only limited to children born with congenital defects alone, as children within the entire study population who constitute the control groups that die from other severe chronic or acute diseases in the neonatal stages are likely to be missed within the current dataset. Nonetheless this study aims to assess the post neonatal burden of septal defects and its variants using a birth cohort that is representative of the general post-neonatal population.

Future studies combining GP registration data, Hospital records, and death records are required to fully assess the prevalence and mortality of SD sub defects across England, accounting for geographical location. Even with the missing ethnicity data, considerable ethnic variations in the prevalence and mortality of SD and SD sub defects were observed. Therefore, considerable effort to further improve ethnicity recording within CPRD is required to further increase the utility of this dataset in assessing the prevalence and survival of SD sub-defects per ethnic associations at a national level. Furthermore, an assessment of the factors driving ethnic variations is required, as well as the effect of ethnicity in long-term outcomes of the various SD variants.

The current study exposes some of the ineffectiveness of CPRD alone in capturing all of the information required for complete assessment of the mortality and severity burden on CHD, SD and its sub variants in England. Therefore, future studies should compare the effect of using primary care data alone and in combination with HES, to assess how good the transfer of data around secondary care into GP records is, specifically for CHD and its variants. This

will be important for informing the improvement of discharge summaries for CHD and its imputation into GP records in the future.

6.1.3 Conclusion

This thesis evaluated the prevalence and mortality of a critical subset of all CHDs between January 1998 and June 2017, using a study population derived through data linkage between CPRD, ONS, and IMD in England. The prevalence of the septal defect variants aligns with previously published literature on the burden of all septal defects relative to total CHD. Furthermore, this study highlights certain regions in England have a disproportionately higher prevalence for septal defect variants, and more research should be carried out to elucidate the reasons behind this. Whilst the ethnicity recording within CPRD was only available for approximately half the population, this study also shows some disproportionate burden of septal defect variants in minor ethnicities. The overall number of deaths within the timeframe in this study was low, with the inadvertent exclusion of all deaths that occurred before GP registration. Nonetheless, this study reinforces broadly that AoSD, ToF, AVSD constitute the highest mortality variants of SD whilst VSD and ASD are not as lethal. Regardless, all SD variants considered had higher mortality than children without SD. Therefore, considerable effort is required to further improve the survival rates for children with these defects and ultimately improve the prognosis for children diagnosed with these defects. This study further raises the need for the consideration and development of region-specific and ethnicity-specific strategies to improving diagnosis and disease outcomes in England.

Appendices

Appendix 1: CHD code list

medcode	Readcode	chdpat	sdp	otherchd	description
246	P54..00	1	1	0	Ventricular septal defect
247	P6z..00	1	0	1	Congenital heart anomaly NOS
1778	P511.00	1	0	1	Double outlet right ventricle
2670	P735.00	1	0	1	Stenosis of pulmonary artery
2727	P70..00	1	0	1	Patent ductus arteriosus
2728	7A01z00	1	0	1	Open correction of patent ductus arteriosus NOS
2816	P51..00	1	0	1	Transposition of great vessels
3255	P550.00	1	1	0	Atrial septal defect NOS
3300	P641.00	1	0	1	Bicuspid aortic valve
3301	P71..00	1	0	1	Coarctation of aorta
3774	P6y6000	1	0	1	Dextrocardia
3862	P601.00	1	0	1	Congenital atresia of the pulmonary valve
3863	P6z3.00	1	0	1	Cyanotic congenital heart disease NOS
3864	7908z00	1	1	0	Closure of defect of interventricular septum NOS
4864	P52..00	1	1	0	Tetralogy of Fallot
4964	P50..00	1	0	1	Common aorto-pulmonary trunk
5477	7902.00	1	1	0	Correction of tetralogy of Fallot
5621	P6...00	1	0	1	Other congenital heart anomalies
6843	P64z.00	1	0	1	Congenital aortic valve insufficiency NOS
6886	P63..00	1	0	1	Congenital aortic valve stenosis
6945	7903.00	1	0	1	Atrial inversion ops for transposition of great vessels
7262	P6z3.11	1	0	1	Blue baby
7342	7A01.11	1	0	1	Open correction of patent ductus arteriosus (PDA)
7474	P55..00	1	1	0	Ostium secundum atrial septal defect
8636	P64..00	1	0	1	Congenital aortic valve insufficiency
9232	P6yy.12	1	0	1	Hypoplasia of heart NOS
9361	P59..00	1	0	1	Isomerism of atrial appendages
9401	P6y2.00	1	0	1	Pulmonary infundibular stenosis
9573	7A01100	1	0	1	Ligation of patent ductus arteriosus
10047	P736.12	1	0	1	Pulmonary arterio-venous malformation
10916	790B012	1	1	0	Hanlon creation of defect in atrial septum
11127	P73..00	1	0	1	Pulmonary artery anomalies
11293	P72z111	1	0	1	Congenital dilatation of aorta
11945	P72zz00	1	0	1	Other anomaly of aorta NOS
11982	P6zz.00	1	0	1	Congenital heart anomaly NOS
12752	P61..00	1	0	1	Congenital tricuspid atresia and stenosis
12844	7902.11	1	1	0	Repair of tetralogy of Fallot
12889	7A02000	1	0	1	Percut. transluminal prosth. occlusion patent ductus arterios.
16191	7907z00	1	1	0	Closure of defect of interatrial septum NOS

16538	7902000	1	1	0	Correct Fallot tetralogy- valved right ventr. outflow conduit
16539	P6y0.00	1	0	1	Subaortic stenosis
16731	P713.11	1	0	1	Stenosis of aortic arch
17175	14H1.11	1	0	1	H/O: heart anomaly
18395	P55y.11	1	1	0	Other specified atrial septal defect
18785	P5...13	1	1	0	Heart septal defects
18820	14H1.00	1	0	1	H/O: cardiac anomaly
18982	P733.00	1	0	1	Coarctation of the pulmonary artery
19188	7A02011	1	0	1	Percut. translum prosth occlus patent ductus arteriosus (PDA)
19956	7902z00	1	1	0	Correction of tetralogy of Fallot NOS
19969	P53..00	1	0	1	Common ventricle
20153	P545.00	1	1	0	Roger's disease
20466	P6y6.11	1	0	1	Ectopic heart
20772	P67..00	1	0	1	Hypoplastic left heart syndrome
21090	7A01.00	1	0	1	Open correction of patent ductus arteriosus
21272	P610.00	1	0	1	Congenital tricuspid atresia
21851	P603.00	1	0	1	Right hypoplastic heart syndrome
21943	P5...11	1	1	0	Cardiac septal defects
22778	P602.00	1	0	1	Congenital pulmonary stenosis
23692	P520.11	1	1	0	Ventricular septal defect in Fallot's tetralogy
23709	P62..00	1	0	1	Ebstein's anomaly
23752	P6yy900	1	0	1	Congenital epicardial cyst
23754	P5...12	1	1	0	Congenital heart disease, septal and bulbar anomalies
23988	P511100	1	0	1	Dextratransposition of aorta
24533	P6y5.00	1	0	1	Congenital heart block
24714	P6yyz00	1	0	1	Other specified heart anomalies NOS
24789	P6y..00	1	0	1	Other specified heart anomalies
24854	P6yy.00	1	0	1	Other specified heart anomalies
25089	PKyz100	1	0	1	Acardia
25481	P6y4.00	1	0	1	Coronary artery anomaly
26626	P6z0.00	1	0	1	Unspecified anomaly of heart valve
28006	7909300	1	1	0	Primary closure of defect of septum of heart NEC
28174	P550.12	1	1	0	Interatrial septal defect NEC
28355	7904.00	1	0	1	Other correction of transposition of great vessels
28367	7907300	1	1	0	Primary closure of defect of interatrial septum NEC
28705	P6y4411	1	0	1	Congenital coronary arterio-venous fistula
28943	7905.00	1	0	1	Correction of total anomalous pulmonary venous connection
30340	7909.00	1	1	0	Closure of defect of unspecified septum of heart
30403	7A61000	1	0	1	Excision of congenital arteriovenous malformation
30725	P721.00	1	0	1	Aortic arch anomalies
30949	P721100	1	0	1	Dextraposition of aorta
31085	7903.11	1	0	1	Mustard interatrial tr venous return

31101	7907000	1	1	0	Closure defect of interatrial septum using prosthetic patch
31112	P732.00	1	0	1	Pulmonary artery atresia
31373	P6y4400	1	0	1	Anomalous coronary artery communication
31518	P5...00	1	1	0	Bulbus cordis and cardiac septal closure anomalies
32163	7906.00	1	1	0	Closure of defect of atrioventricular septum
32508	P738.00	1	0	1	Atresia of pulmonary artery with septal defect
32748	P6y3000	1	0	1	Uhl's disease
33909	7904000	1	0	1	Repositioning of transposed great vessels
33919	P602z00	1	0	1	Congenital pulmonary stenosis NOS
34007	P6yy200	1	0	1	Congenital cardiomegaly
34067	P54z.00	1	1	0	Ventricular septal defect NOS
34176	P721z00	1	0	1	Aortic arch anomalies NOS
34668	P6y1.00	1	0	1	Cor triatriatum
34902	7907.00	1	1	0	Closure of defect of interatrial septum
36307	P737.11	1	0	1	Dilatation of pulmonary artery
36575	7908.00	1	1	0	Closure of defect of interventricular septum
36606	P74z600	1	0	1	Scimitar syndrome
36668	7A01200	1	0	1	Closure of patent ductus arteriosus NEC
37323	P713.00	1	0	1	Interruption of aortic arch
37405	P50..11	1	1	0	Aortic septal defect
37451	P6yy700	1	0	1	Atresia of heart valve NEC
37515	P722200	1	0	1	Hypoplasia of aorta
37816	P552.00	1	1	0	Persistent ostium secundum
37987	7903.12	1	0	1	Stenning correction for transposition of great vessels
38411	7904z00	1	0	1	Other correction of transposition of great vessels NOS
38436	7906z00	1	1	0	Closure of defect of atrioventricular septum NOS
38731	P721211	1	0	1	Vascular ring
38828	7909y00	1	1	0	Other specified closure of defect unspecified heart septum
38967	P520.00	1	1	0	Tetralogy of Fallot, unspecified
38968	P6z2.00	1	0	1	Acyanotic congenital heart disease NOS
39803	7908000	1	1	0	Close defect interventricular septum using prosthetic patch
39884	7906100	1	1	0	Close defect atrioventric septum using prosthetic patch NEC
39885	7906500	1	1	0	Revision of closure of defect of atrioventricular septum
39992	P60..00	1	0	1	Pulmonary valve anomalies
40025	P511300	1	0	1	Taussig-Bing syndrome
40030	P72..11	1	0	1	Anomalies of the aorta excluding coarction
40673	P550.11	1	1	0	Auricular septal defect NOS
41197	P74z300	1	0	1	Stenosis of superior vena cava
41371	P502.11	1	0	1	Truncus arteriosus
42090	7909000	1	1	0	Closure of defect of heart septum using prosthetic patch NEC

42127	P73z.00	1	0	1	Pulmonary artery anomaly NOS
42132	P540.00	1	1	0	Ventricular septal defect, unspecified
42181	7906300	1	1	0	Closure of persistent ostium primum
42684	P74..00	1	0	1	Anomalies of great veins
43049	P56z100	1	1	0	Common atrioventricular canal
43926	7907100	1	1	0	Closure defect of interatrial septum using pericardial patch
44478	P60z.00	1	0	1	Other pulmonary valve anomalies
44665	790B011	1	1	0	Blalock creation of defect in atrial septum
44767	P6yy.11	1	0	1	Hypoplastic aortic orifice or valve
44781	P72z.00	1	0	1	Other anomalies of aorta NOS
44896	P56z200	1	1	0	Common atrioventricular-type ventricular septal defect
45187	P500.12	1	0	1	Truncus arteriosus
45291	P740.00	1	0	1	Anomaly of great veins, unspecified
45358	7908300	1	1	0	Primary closure of defect of interventricular septum NEC
45452	P602100	1	0	1	Congenital fusion of pulmonary valve segment
45505	P501.00	1	1	0	Aortic septal defect
45910	P7X..00	1	0	1	Congenital malformation of great arteries, unspecified
46117	P58..00	1	0	1	Double outlet left ventricle
46176	P742.00	1	0	1	Partial anomalous pulmonary venous return
46530	P721200	1	0	1	Double aortic arch
46825	P6W..00	1	0	1	Congenital malformation of aortic and mitral valves unsp
47853	P736.11	1	0	1	Pulmonary arterio-venous fistula
48205	P5X..00	1	0	1	Congenital malforms of cardiac chambers+connections unsp
48331	7906400	1	1	0	Primary closure of defect of atrioventricular septum NEC
49133	P6yy300	1	0	1	Congenital left ventricular diverticulum
49279	P712.13	1	0	1	Postductal aortic stenosis
49474	P72z000	1	0	1	Aneurysm of sinus of Valsalva
49702	P56z.00	1	1	0	Endocardial cushion defects NOS
49731	P721300	1	0	1	Kommerell's diverticulum
49901	P6y4500	1	0	1	Congenital coronary aneurysm
50019	7A01000	1	0	1	Division of patent ductus arteriosus
50220	P72..00	1	0	1	Other anomalies of aorta
50284	P6y6300	1	0	1	Ectopia cordis
50310	7909z00	1	1	0	Closure of defect of unspecified septum of heart NOS
50362	P6yy400	1	0	1	Congenital pericardial defect
50529	P6X..00	1	0	1	Congenital malformation of tricuspid valve, unspecified
50626	7908100	1	1	0	Close defect interventricular septum using pericardial patch

50886	P740100	1	0	1	Anomaly of the vena cava, unspecified
51053	P561.00	1	1	0	Ostium primum defect
51418	P501.11	1	1	0	Aortopulmonary window
51649	P521.00	1	1	0	Pentalogy of Fallot
51675	P74z200	1	0	1	Stenosis of inferior vena cava
51897	P544.00	1	1	0	Gerbode's defect
51911	P74z800	1	0	1	Atresia of pulmonary vein
51941	P741.00	1	0	1	Total anomalous pulmonary venous return - TAPVR
52287	7907200	1	1	0	Closure defect of interatrial septum using tissue graft NEC
52310	P6y5100	1	1	0	Congenital complete atrio-ventricular heart block
52411	P73y.00	1	0	1	Other specified anomaly of pulmonary artery
52607	P60z100	1	1	0	Fallot's trilogy
52615	P6y7.00	1	0	1	Myocardial bridge of coronary artery
53088	P55y.00	1	1	0	Other specified ostium secundum atrial septal defect
53546	P6y4z00	1	0	1	Coronary artery anomaly NOS
53964	P722400	1	0	1	Supra-valvular aortic stenosis
54196	P5z..00	1	1	0	Heart bulb or septal closure defects NOS
54243	P55z.00	1	1	0	Ostium secundum atrial septal defect NOS
54487	P734.00	1	0	1	Hypoplasia of the pulmonary artery
54488	P601000	1	0	1	Hypoplasia of pulmonary valve
54772	P54y.00	1	1	0	Other specified ventricular septal defect
55535	P56z000	1	1	0	Common atrium
56081	7A00000	1	0	1	Correction of persistent truncus arteriosus
56200	P72z100	1	0	1	Congenital aneurysm of aorta
56575	P541.00	1	1	0	Interventricular septal defect
56741	7905100	1	0	1	Correct total anomal pulm venous connect to coronary sinus
57091	P65..00	1	0	1	Congenital mitral stenosis
57102	7906000	1	1	0	Close defect atrioventric septum using dual prosthetic patch
57270	7906y00	1	1	0	Other specified closure of defect of atrioventricular septum
57271	7908y00	1	1	0	Other specified closure of defect of interventricular septum
57932	P710.00	1	0	1	Hypoplasia of aortic arch, unspecified
58076	P722z00	1	0	1	Atresia or stenosis of aorta NOS
58189	P722411	1	0	1	Congenital stenosis of ascending aorta
58734	P640.00	1	0	1	Congenital aortic valve insufficiency, unspecified
58886	7903z00	1	0	1	Atrial inversion op for transposition of great vessels NOS
59012	7909100	1	1	0	Closure defect of heart septum using pericardial patch NEC
59144	P553.00	1	1	0	Lutembacher's syndrome
59298	P722100	1	0	1	Aplasia of aorta
59907	P71z.00	1	0	1	Coarctation of aorta NOS
61100	P51y.11	1	0	1	Transposition of aorta

61651	P66..00	1	0	1	Congenital mitral insufficiency
61715	P56z011	1	1	0	Cor triloculare biventriculare
61794	7A00300	1	1	0	Closure of aortopulmonary window
61914	P500.11	1	0	1	Persistent truncus arteriosus
61915	7A00200	1	0	1	Repair of hemitruncus arteriosus
62163	P6y4100	1	0	1	Single coronary artery
62169	P51y.00	1	0	1	Other specified transposition of great vessels
62230	P720.00	1	0	1	Anomaly of aorta, unspecified
62356	7A02.00	1	0	1	Transluminal operations on abnormality of great vessel
62376	P722500	1	0	1	Atresia of aorta
62470	7903000	1	0	1	Atrium reconstruction atrial patch for transpos great vessel
62845	7A00y00	1	0	1	Open operation for combined abnormality of great vessels OS
63046	P52z.00	1	1	0	Tetralogy of Fallot NOS
63069	P652.00	1	0	1	Parachute deformity of the mitral valve
63163	7A01300	1	0	1	Revision of correction of patent ductus arteriosus
63187	P730.00	1	0	1	Pulmonary artery anomaly, unspecified
63297	9RD0.00	1	0	1	Transfer of care from paediatric congenital heart service
63340	P56..00	1	1	0	Endocardial cushion defects
63390	P512.00	1	0	1	Corrected great vessel transposition
63677	P742.11	1	0	1	Anomalous termination of right pulmonary vein
63768	P722300	1	0	1	Stricture of aorta
64470	7904y00	1	0	1	Other correction of transposition of great vessels OS
64778	P6z1100	1	0	1	Anomalous ventricular bands
64859	7A61300	1	0	1	Ligation of congenital arteriovenous malformation
64953	P712.12	1	0	1	Postductal interruption of aorta
65029	P737.00	1	0	1	Pulmonary artery aneurysm
65097	7A02y00	1	0	1	Transluminal operation on abnormality of great vessel OS
65234	7908600	1	1	0	Closure interventricular septal defect us intraop trans pros
65318	P511z00	1	0	1	Double outlet right ventricle NOS
65330	P501.12	1	1	0	Aorticopulmonary septal defect
65401	7902y00	1	1	0	Other specified correction of tetralogy of Fallot
66245	P502.00	1	0	1	Persistent truncus arteriosus
66401	P5y..00	1	1	0	Other heart bulb and septal closure defect
67286	P721000	1	0	1	Anomalous origin of the aortic arch
67299	7907y00	1	1	0	Other specified closure of defect of interatrial septum
67483	7908200	1	1	0	Close defect interventricular septum using tissue graft NEC
67657	P542.00	1	1	0	Left ventricle to right atrial communication
67928	P731.00	1	0	1	Pulmonary artery agenesis
68063	P6yy100	1	0	1	Hypoplasia of cardiac vein

68097	P6y5000	1	0	1	Congenital heart block, unspecified
68198	P722.00	1	0	1	Atresia and stenosis of aorta
68784	P741z00	1	0	1	Total anomalous pulmonary venous return NOS
68888	P65..11	1	0	1	Duroziez's disease
68894	P6yy500	1	0	1	Congenital anomaly of myocardium
68982	P603.11	1	0	1	Pseudotruncus arteriosus
69021	7903100	1	0	1	Atrium reconstruction atrial wall for transpos great vessels
69169	P611.00	1	0	1	Congenital tricuspid stenosis
69200	7903y00	1	0	1	Atrial inversion op for transposition of great vessels OS
69556	P6y6111	1	0	1	Laevocardia
69589	P721111	1	0	1	Overriding aorta
69858	P510.00	1	0	1	Total great vessel transposition
69940	P600.00	1	0	1	Pulmonary valve anomaly, unspecified
70424	7907400	1	1	0	Revision of closure of defect of interatrial septum
70691	P721700	1	0	1	Overriding aorta
70853	P712.00	1	0	1	Postductal coarctation of aorta
70857	7902300	1	1	0	Revision of correction of tetralogy of Fallot
70880	P60zz00	1	0	1	Other pulmonary valve anomaly NOS
70992	P6y5z00	1	0	1	Congenital heart block NOS
71252	P520.12	1	1	0	Dextraposition of aorta in Fallot's tetralogy
71678	P6y6.00	1	0	1	Heart and cardiac apex malposition
71874	P74z700	1	0	1	Transposition of pulmonary veins
71956	P6y4000	1	0	1	Congenital absence of coronary artery
72259	P6y6100	1	0	1	Levocardia
72295	P711.00	1	0	1	Preductal coarctation of aorta
72405	P6y6200	1	0	1	Mesocardia
72576	66g..00	1	0	1	Congenital heart condition monitoring
72577	P550.13	1	1	0	Interauricular septal defect
72604	P500.00	1	1	0	Absent septum between aorta and pulmonary artery
72655	P74z100	1	0	1	Absence of superior vena cava
72825	790C400	1	1	0	Percutaneous transluminal closure patent oval foramen pros
73029	7902100	1	1	0	Correct Fallot tetralogy- right ventric outflow conduit NEC
73476	7906.11	1	1	0	Repair of defect of the atrioventricular septum
73539	P51z.00	1	0	1	Great vessel transposition NOS
73554	P74zz00	1	0	1	Other great vein anomaly NOS
73592	P651.00	1	0	1	Fused commissure of the mitral valve
73663	P74z.00	1	0	1	Other great vein anomalies
73816	P56zz00	1	1	0	Endocardial cushion defects NOS
73817	7906200	1	1	0	Closure defect atrioventricular septum using tissue graft
73820	7905z00	1	0	1	Correction total anomalous pulmonary venous connection NOS
74890	P740000	1	0	1	Anomaly of the pulmonary veins, unspecified

86763	7909.11	1	1	0	Repair of defect of unspecified septum of heart
88479	7902500	1	1	0	Repair of tetralogy of Fallot with absent pulmonary valve
88772	7907.11	1	1	0	Repair of defect of interatrial septum
88842	7902400	1	1	0	Repair of tetralogy of Fallot using transannular patch
89231	790K.00	1	0	1	Repair of double outlet ventricle
89256	P68..00	1	0	1	Congenital heart disease
89697	790L000	1	1	0	Percutan transluminal closure defect intervent sept us pros
89968	7903.13	1	0	1	Atrial inversion operations for transposition of great art
90486	P721600	1	0	1	Vascular ring, aorta
90551	P650.00	1	0	1	Congenital mitral stenosis, unspecified
90605	790J.00	1	0	1	Other repair of transposition of great arteries
91720	7934700	1	0	1	Percutaneous transluminal ablation congenit heart malformat
91759	7A00.00	1	0	1	Open operations for combined abnormality of great vessels
91892	7908.11	1	1	0	Repair of defect of interventricular septum
92020	7908611	1	1	0	Repair interventricular septal defect us intraop trans pros
92426	P6y6z00	1	0	1	Heart or cardiac apex malposition NOS
93089	P6yy000	1	0	1	Atresia of cardiac vein
93161	P561.11	1	1	0	Persistent ostium primum
93561	P601z00	1	0	1	Congenital atresia of pulmonary valve NOS
93719	7902600	1	1	0	Repair Fallot-type pulmonary atresia aortopulmonary collater
93807	790L300	1	1	0	Percutan transluminal closure defect interatrial septum NEC
94023	7908500	1	1	0	Closure of multiple interventricular septal defects
94191	7907011	1	1	0	Repair defect of interatrial septum using prosthetic patch
94257	P70..11	1	0	1	Botalli's patent ductus
94344	P50z.00	1	0	1	Common aorto-pulmonary trunk NOS
94475	7905000	1	0	1	Correct total anomal pulm venous connect to supracard vessel
94503	7A00400	1	0	1	Repair anomalous pulmonary artery origin ascending aorta
95106	790J000	1	0	1	Repositioning of transposed great arteries
95578	7908311	1	1	0	Primary repair of defect of interventricular septum NEC
95755	7906111	1	1	0	Repair defect atrioventricular septum prosthetic patch NEC
95785	P6yyA00	1	0	1	Hemicardia
96130	7908111	1	1	0	Repair defect interventricular septum us pericardial patch

96225	P736.00	1	0	1	Pulmonary arterio-venous aneurysm
97659	7A00z00	1	0	1	Open operation for combined abnormality of great vessels NOS
97818	P6y3z00	1	0	1	Obstructive heart anomaly NEC NOS
98061	P6y8.00	1	0	1	Congenital dextroposition of heart
98273	7908511	1	1	0	Repair of multiple interventricular septal defects
98317	P6yyC00	1	0	1	Fusion of mitral valve cusps
98443	790K200	1	0	1	Repair of double outlet right ventricle
98893	P50..12	1	0	1	Common truncus
98952	7A02z00	1	0	1	Transluminal operation on abnormality of great vessel NOS
99128	P6y3.00	1	0	1	Obstructive heart anomaly NEC
99198	7902200	1	1	0	Correct Fallot tetralogy- right ventricular outflow patch
99346	7906311	1	1	0	Repair of persistent ostium primum
99649	P744.00	1	0	1	Portal vein - hepatic artery fistula
99781	7908011	1	1	0	Repair defect interventricular septum us prosthetic patch
99829	790F200	1	0	1	Repair of cor triatriatum
100065	P61z.00	1	0	1	Congenital tricuspid atresia or stenosis NOS
100291	P65z.00	1	0	1	Congenital mitral stenosis NOS
100622	P51z.11	1	0	1	Transposition of arterial trunk NEC
100772	P74z.11	1	0	1	Persistent left posterior cardinal vein
101307	P743.00	1	0	1	Anomalous portal vein termination
101322	Pyu2100	1	1	0	[X]Other congenital malformations of cardiac septa
101393	P56y.00	1	1	0	Other specified endocardial cushion defects
101520	P74z000	1	0	1	Absence of inferior vena cava
101896	P6yy411	1	0	1	Congenital absence of pericardium
102167	P6y5200	1	1	0	Congenital incomplete atrio-ventricular heart block
102473	790L200	1	1	0	Percutan translum closure defect interatr septum us prosth
102523	790L111	1	1	0	Percutaneous translum repair defect intervent septum NEC
102977	7907311	1	1	0	Primary repair of defect of interatrial septum NEC
102980	P511200	1	0	1	Incomplete great vessel transposition
103039	P741100	1	0	1	Supradiaphragmatic total anomalous pulmonary venous return
103412	P6y4600	1	0	1	Congenital stricture of coronary artery
103432	P6z1000	1	0	1	Anomalous atrial bands
103584	P6y6400	1	0	1	Abdominal heart
103672	P731.11	1	0	1	Congenital absence of pulmonary artery
103894	P6y4300	1	0	1	Coronary artery from pulmonary trunk
103939	7909z11	1	1	0	Repair of defect of unspecified septum of heart NOS
104266	P6y3100	1	0	1	Right ventricular outflow tract obstruction
104708	7906211	1	1	0	Repair defect of atrioventricular septum using tissue graft

105037	P741000	1	0	1	Subdiaphragmatic total anomalous pulmonary venous return
105154	7905y00	1	0	1	Correction of total anomalous pulmonary venous connection OS
105465	7906011	1	1	0	Rep defect atrioventricular septum dual prosthetic patches
105759	7908400	1	1	0	Revision of closure of defect of interventricular septum
106081	7A01y00	1	0	1	Other specified open correction of patent ductus arteriosus
106644	Pyu2600	1	0	1	[X]Other congenital malformations of aorta
106726	790L311	1	1	0	Percutan transluminal repair defect interatrial septum NEC
106756	P711.13	1	0	1	Preductal aortic stenosis
107122	790K100	1	0	1	Repair of Fallot-type double outlet right ventricle
107150	P60z000	1	0	1	Congenital insufficiency of the pulmonary valve
107496	Pyu2G00	1	0	1	[X]Congenital malformation of tricuspid valve, unspecified
107639	Pyu2700	1	0	1	[X]Other congenital malformations of pulmonary artery
107710	Pyu2H00	1	0	1	[X]Congenital malformation of aortic and mitral valves unsp
108021	790Jz00	1	0	1	Other repair of transposition of great arteries NOS
108193	P6yy600	1	0	1	Congenital aneurysm of heart
108307	7907111	1	1	0	Repair defect of interatrial septum using pericardial patch
108402	7902z11	1	1	0	Repair of tetralogy of Fallot NOS
108457	P69..00	1	0	1	Left ventricular outflow tract obstruction
109008	Pyu2200	1	0	1	[X]Other congenital malformations of pulmonary valve
109236	P6z1.00	1	0	1	Anomalous bands of heart
109853	P552.11	1	1	0	Patent ostium secundum
110047	Pyu2500	1	0	1	[X]Other specified congenital malformations of the heart
110418	Pyu2F00	1	0	1	[X]Congenital malforms of cardiac chambers+connections unsp
111039	7906411	1	1	0	Primary repair of defect of atrioventricular septum NEC
111266	7906y11	1	1	0	Other specified repair of defect of atrioventricular septum
111360	P6yyB00	1	0	1	Supernumerary heart valve cusps NEC
111389	P735.11	1	0	1	Congenital stricture of pulmonary artery
111871	790L100	1	1	0	Percutaneous translum closure defect intervent septum NEC
112436	7902y11	1	1	0	Other specified repair of tetralogy of Fallot
112504	7908z11	1	1	0	Repair of defect of interventricular septum NOS

Appendix 2: The code list used for OCA patient extraction.

Readcode	Medterm/description	major	minor	medcode
7010111	Insertion of Halber valve for spina bifida	1	0	98265
7031000	Repair of meningoencephalocele	1	0	29739
7043.00	Repair of spina bifida	1	0	9298
7043200	Closure of spinal meningocele	1	0	29633
7043y00	Other specified repair of spina bifida	1	0	50672
7043z00	Repair of spina bifida NOS	1	0	62742
7502A00	Repair bilateral cleft lip - rotation advancement flap tech	1	0	103535
7502B00	Repair of bilateral cleft lip with quadrilateral flap	1	0	98506
7502C11	Manchester bilateral cleft lip repair	1	0	42525
7502C12	Veau type III bilateral cleft lip repair	1	0	54973
7502D00	Repair of bilateral cleft lip unspecified	1	0	14974
7502E00	Synchronous bilateral cleft lip repair	1	0	48870
7502F00	Asynchronous bilateral cleft lip repair	1	0	58977
7B41000	Other hypospadias repair	1	0	3441
7B41011	Byars hypospadias repair	1	0	71899
7B41013	Denis - Browne hypospadias repair	1	0	11142
7B41014	Ombredanne hypospadias repair	1	0	37920
7B41015	Van der Meulen hypospadias repair	1	0	65156
7B41016	Young hypospadias repair	1	0	55579
7B41017	First stage hypospadias repair	1	0	24238
7B41018	Second stage hypospadias repair	1	0	29709
7B41100	Epispadias repair	1	0	15823
7B41112	Denis-Browne epispadias repair	1	0	94300
7B41113	Young-Dees epispadias repair	1	0	72699
7B41700	MAGPI hypospadias repair	1	0	11036
7B41800	Duckett hypospadias repair	1	0	36187
7F1A300	Drainage of hydrocephalus of fetus to facilitate delivery	1	0	37509
7H01011	Correction of pectus carinatum	0	1	28517
7H01012	Correction of pectus excavatum	0	1	18597
7H0D300	Repair of congenital diaphragmatic hernia	1	0	40984
7L0E.00	Correction of congenital deformity of forearm	1	0	26851
7L0F.00	Correction of congenital deformity of hand	1	0	28034
7L0FF00	Correction of radial polydactyly	1	0	34765
7L0FG00	Excision of radial digit & skeletal repair for polydactyly	1	0	46139
7L0FH00	Excision of ulnar digit and skeletal repair for polydactyly	1	0	22316
7L0Fy00	Other specified correction of congenital deformity of hand	1	0	57917
7L0Fz00	Correction of congenital deformity of hand NOS	1	0	45324
7L0H000	Open reduction of congenital dislocation of knee	1	0	31032
7L0H800	Open reduction congenital dislocation of patella	1	0	43175
7L0J700	Correction of congenital vertical talus	1	0	69268
7L0K300	Separation of tarsal coalition	1	0	48248

7L0N000	Cranio-orbital remodelling for plagiocephaly	0	1	28372
P0...00	Anencephalus and similar anomalies	1	0	72707
P00..00	Anencephalus	1	0	11531
P00..11	Congenital absence of brain	1	0	54714
P000.00	Acrania	1	0	50729
P001.00	Amyelencephalus	1	0	64623
P002.00	Hemicephaly	1	0	110165
P002.11	Hemianencephaly	1	0	68181
P00y.00	Other specified anencephalus	1	0	109394
P00z.00	Anencephalus NOS	1	0	66499
P01..00	Craniorachischisis	1	0	103882
P02..00	Iniencephaly	1	0	63821
P0z..00	Anencephalus and similar anomalies NOS	1	0	94467
P1...00	Spina bifida	1	0	3947
P10..00	Spina bifida with hydrocephalus	1	0	46790
P10..11	Arnold - Chiari syndrome	1	0	72390
P100.00	Unspecified spina bifida with hydrocephalus	1	0	42497
P100000	Spina bifida with hydrocephalus, unspecified	1	0	5306
P100100	Cervical spina bifida with hydrocephalus	1	0	109243
P100200	Thoracic spina bifida with hydrocephalus	1	0	50565
P100300	Lumbar spina bifida with hydrocephalus	1	0	57113
P100z00	Spina bifida with hydrocephalus NOS	1	0	98298
P101.00	Arnold - Chiari syndrome	1	0	9848
P101.11	Closed spina bifida with Arnold-Chiari malformation	1	0	63513
P101000	Chiari malformation type I	1	0	62968
P101100	Chiari malformation type II	1	0	89572
P102.00	Spina bifida with hydrocephalus - open	1	0	98811
P102.11	Fissured spine with hydrocephalus	1	0	104943
P102.13	Myelocele with hydrocephalus	1	0	52683
P102.14	Rachischisis with hydrocephalus	1	0	53471
P102200	Thoracic spina bifida with hydrocephalus - open	1	0	57243
P102300	Lumbar spina bifida with hydrocephalus - open	1	0	103284
P102400	Sacral spina bifida with hydrocephalus - open	1	0	60623
P102z00	Spina bifida with hydrocephalus - open NOS	1	0	47288
P103.00	Spina bifida with hydrocephalus - closed	1	0	93902
P103300	Lumbar spina bifida with hydrocephalus - closed	1	0	105767
P103400	Sacral spina bifida with hydrocephalus - closed	1	0	72928
P103z00	Spina bifida with hydrocephalus - closed NOS	1	0	112518
P103z11	Thoracolumbar spina bifida with hydrocephalus - closed	1	0	90482
P104.00	Spina bifida with hydrocephalus of late onset	1	0	102628
P105.00	Spina bifida with stenosis of aqueduct of Sylvius	1	0	56362
P10y.00	Other specified spina bifida with hydrocephalus	1	0	73085
P10y000	Dandy - Walker syndrome with spina bifida	1	0	59218
P10z.00	Spina bifida with hydrocephalus NOS	1	0	64717
P11..00	Spina bifida without mention of hydrocephalus	1	0	5431
P110.11	Split notochord syndrome	1	0	95743
P110000	Spina bifida without hydrocephalus, site unspecified	1	0	101013

P110100	Cervical spina bifida without mention of hydrocephalus	1	0	68221
P110200	Thoracic spina bifida without mention of hydrocephalus	1	0	96709
P110300	Lumbar spina bifida without mention of hydrocephalus	1	0	96407
P110z00	Unspecified spina bifida without hydrocephalus NOS	1	0	95018
P111.00	Spinal hydromeningocele	1	0	53578
P112.00	Hydromyelocele	1	0	67878
P113.00	Spinal meningocele	1	0	6866
P113000	Spinal meningocele of unspecified site	1	0	53929
P113100	Cervical spinal meningocele	1	0	67351
P113200	Thoracic spinal meningocele	1	0	91600
P113300	Lumbar spinal meningocele	1	0	61862
P113z00	Spinal meningocele NOS	1	0	50365
P114.00	Meningomyelocele	1	0	9722
P114000	Meningomyelocele of unspecified site	1	0	99332
P114100	Cervical meningomyelocele	1	0	107144
P114200	Thoracic meningomyelocele	1	0	99299
P114300	Lumbar meningomyelocele	1	0	47827
P114z00	Meningomyelocele NOS	1	0	57611
P115.00	Myelocele	1	0	31775
P115000	Myelocele of unspecified site	1	0	112803
P115100	Cervical myelocele	1	0	94598
P115200	Thoracic myelocele	1	0	112680
P115300	Lumbar myelocele	1	0	66516
P115z00	Myelocele NOS	1	0	73712
P116.00	Myelocystocele	1	0	59380
P116100	Cervical myelocystocele	1	0	107377
P116300	Lumbar myelocystocele	1	0	101493
P116z00	Myelocystocele NOS	1	0	109893
P117.00	Spina bifida without hydrocephalus - open	1	0	99281
P117.11	Fissured spine	1	0	56386
P117.12	Rachischisis	1	0	67708
P117200	Thoracic spina bifida without hydrocephalus - open	1	0	95478
P117300	Lumbar spina bifida without hydrocephalus - open	1	0	69397
P117400	Sacral spina bifida without hydrocephalus - open	1	0	71525
P117z00	Spina bifida without hydrocephalus - open NOS	1	0	73608
P118.00	Spina bifida without hydrocephalus - closed	1	0	48609
P118000	Unspecified spina bifida without hydrocephalus - closed	1	0	69370
P118100	Cervical spina bifida without hydrocephalus - closed	1	0	72018
P118300	Lumbar spina bifida without hydrocephalus - closed	1	0	65936
P118400	Sacral spina bifida without hydrocephalus - closed	1	0	70923
P118z00	Spina bifida without hydrocephalus - closed NOS	1	0	65246
P11y.00	Other specified spina bifida without hydrocephalus	1	0	99894
P11y.11	Syringomyelocele	1	0	43593
P11z.00	Spina bifida without mention of hydrocephalus NOS	1	0	98280
P11z.13	Billroth's disease	1	0	101793

P11z.14	Congenital hernia of dura mater	1	0	101703
P1z..00	Spina bifida NOS	1	0	21802
P2...00	Other nervous system congenital anomalies	1	0	65088
P20..00	Encephalocele	1	0	4673
P20..11	Hydroencephalocele	1	0	101312
P20..12	Cephalocele	1	0	67556
P20..13	Congenital cerebral hernia	1	0	53474
P20..14	Congenital endaural hernia	1	0	72048
P20..15	Sinus pericranii	1	0	31717
P200.00	Encephalocystocele	1	0	30168
P201.00	Encephalomyelocele	1	0	36116
P202.00	Hydromeningocele - cranial	1	0	103527
P203.00	Meningocele - cerebral	1	0	27686
P203.11	Meningocele - cranial	1	0	25282
P204.00	Meningoencephalocele	1	0	52130
P205.00	Frontal encephalocele	1	0	67264
P206.00	Nasofrontal encephalocele	1	0	65099
P20z.00	Encephalocele NOS	1	0	73055
P20z000	Occipital encephalocele	1	0	48027
P20z100	Encephalocele of other specified site	1	0	100582
P21..00	Microcephalus	1	0	5712
P210.00	Hydromicrocephaly	1	0	85988
P211.00	Micrencephaly	1	0	6515
P21z.00	Microcephalus NOS	1	0	33939
P22..00	Reduction deformities of brain	1	0	54717
P220.00	Agenesis of brain, part unspecified	1	0	23457
P221.00	Aplasia of brain, part unspecified	1	0	100305
P222.00	Hypoplasia of brain, part unspecified	1	0	63668
P223.00	Agyria	1	0	53723
P223.11	Lissencephaly	1	0	34950
P224.00	Arhinencephaly	1	0	93441
P225.00	Holoprosencephaly	1	0	34161
P226.00	Microgyria	1	0	42784
P226000	Congenital bilateral perisylvian syndrome	1	0	95892
P227.00	Anomalies of cerebrum	1	0	39724
P227000	Agenesis of cerebrum	1	0	40777
P227100	Congenital hypoplasia of cerebrum	1	0	103611
P227z00	Anomaly of cerebrum NOS	1	0	111258
P228.00	Anomalies of corpus callosum	1	0	32468
P228000	Congenital absence of corpus callosum	1	0	41775
P228011	Agenesis of corpus callosum	1	0	39486
P228100	Hypoplasia of corpus callosum	1	0	37600
P228200	Aplasia of corpus callosum	1	0	103057
P228300	Aicardi syndrome	1	0	98753
P228z00	Anomaly of corpus callosum NOS	1	0	60648
P229.00	Anomalies of hypothalamus	1	0	46471
P22A.00	Anomalies of cerebellum	1	0	28318
P22A000	Congenital absence of cerebellum	1	0	25316

P22A011	Agenesis of cerebellum	1	0	54877
P22A100	Hypoplasia of cerebellum	1	0	44717
P22A200	Aplasia of cerebellum	1	0	91846
P22Az00	Anomaly of cerebellum NOS	1	0	44253
P22y.00	Other specified reduction deformities of brain	1	0	107378
P22y100	Familial aplasia of the vermis	1	0	67803
P22y111	Joubert syndrome	1	0	34921
P22y200	Gillespie syndrome	1	0	64822
P22y300	Partial absence of septum pellucidum	1	0	58163
P22yz00	Other reduction deformity of brain NOS	1	0	106704
P22z.00	Reduction deformities of brain NOS	1	0	64541
P22z.11	Cerebellar hypoplasia	1	0	37785
P22z.12	Agenesis of part of brain NEC	1	0	58710
P22z.13	Hypoplasia of part of brain NEC	1	0	60216
P23..00	Congenital hydrocephalus	1	0	9611
P230.00	Aqueduct of Sylvius anomaly	1	0	54912
P230.11	Hydrocephalus with anomaly of aqueduct of Sylvius	1	0	40588
P230.12	Stenosis of aqueduct of Sylvius	1	0	46120
P230100	Aqueduct of Sylvius stenosis	1	0	55960
P231.00	Foramen of Magendie atresia	1	0	92350
P232.00	Foramen of Luschka atresia	1	0	59040
P233.00	Atresia of foramina of Magendie and Luschka	1	0	51345
P233.11	Dandy - Walker syndrome	1	0	18537
P233.12	Hydrocephalus with atresia of foramina of Magendie+Luschka	1	0	97663
P234.00	Hydranencephaly	1	0	46583
P23y.00	Other specified congenital hydrocephalus	1	0	111641
P23z.00	Congenital hydrocephalus NOS	1	0	28353
P24..00	Other specified brain anomalies	1	0	47514
P240.00	Congenital cerebral cyst	1	0	39391
P240.11	Congenital intracerebral cyst	1	0	95632
P240000	Single congenital cerebral cyst	1	0	107846
P240100	Multiple congenital cerebral cysts	1	0	109441
P240200	Schizencephaly	1	0	28824
P240z00	Congenital cerebral cyst NOS	1	0	71733
P241.00	Macrocephaly	1	0	37474
P241.11	Megalencephaly	1	0	33442
P241.12	Enlarged brain	1	0	71451
P241.13	Macrocephaly	1	0	27537
P242.00	Macrogyria	1	0	72094
P243.00	Porencephaly	1	0	62992
P244.00	Ulegyria	1	0	110763
P245.00	Congenital adhesions of cerebral meninges	1	0	60195
P246.00	Septo-optic dysplasia	1	0	12284
P247.00	Dysplasia of cerebral cortex	1	0	51745
P248.00	Congenital dilated lateral ventricles of brain	1	0	64134
P249.00	Megalencephaly	1	0	50169
P24A.00	Hemimegalencephaly	1	0	95697

P24z.00	Other specified brain anomalies NOS	1	0	62242
P25..00	Other specified spinal cord anomalies	1	0	70266
P250.00	Diastematomyelia	1	0	15988
P251.00	Hydromyelia	1	0	44939
P252.00	Congenital tethering of spinal cord	1	0	48940
P25y.00	Other specified anomalies of spinal cord	1	0	95591
P25y.11	Neuroenteric cyst	1	0	65162
P25y000	Amyelia	1	0	93903
P25y100	Atelomyelia	1	0	67498
P25y111	Myelatelasia	1	0	69221
P25y112	Myelodysplasia of spinal cord	1	0	45142
P25y200	Congenital anomaly of spinal meninges	1	0	45918
P25y300	Defective development of the cauda equina	1	0	61647
P25y400	Spinal cord hypoplasia	1	0	73166
P25yz00	Other specified spinal cord anomalies NOS	1	0	104035
P25z.00	Spinal cord anomalies NOS	1	0	16164
P2x..00	Other specified nervous system anomalies	1	0	73819
P2x0.00	Agenesis of nerve, unspecified	1	0	67476
P2x1.00	Brachial plexus displacement	1	0	22738
P2x2.00	Familial dysautonomia	1	0	45647
P2x3.00	Jaw-winking syndrome	1	0	61043
P2x4.00	Marcus - Gunn syndrome	1	0	3884
P2x5.00	Riley - Day syndrome	1	0	31616
P2x6.00	Chiari malformation type I	1	0	43808
P2x7.00	Congenital facial nerve palsy	1	0	81446
P2xz.00	Other specified nervous system anomalies NOS	1	0	50663
P2xz000	Agenesis of nerve NEC	1	0	93911
P2xz100	Congenital optic atrophy	1	0	39392
P2y..00	Unspec nervous system anomaly of brain/cord/nervous system	1	0	73574
P2y0.00	Congenital brain anomaly	1	0	8893
P2y1.00	Congenital spinal cord anomaly	1	0	36974
P2yz.00	Unspecified nervous system anomaly NOS	1	0	67870
P2z..00	Nervous system anomalies NOS	1	0	15345
P3...00	Congenital eye anomalies	0	1	4086
P30..00	Anophthalmos	1	0	23605
P300.00	Clinical anophthalmos, unspecified	1	0	31592
P300100	Agenesis of eye	1	0	56285
P300200	Congenital absence of eye	1	0	68208
P300z00	Anophthalmos NOS	1	0	70742
P301.00	Congenital cystic eyeball	1	0	51185
P302.00	Cryptophthalmos syndrome	1	0	65346
P303.00	Congenital absence of eyes	1	0	67756
P30z.00	Anophthalmos NOS	1	0	37557
P31..00	Microphthalmos	1	0	26462
P310.00	Microphthalmos, unspecified	1	0	72284
P310000	Dysplasia of eye	1	0	37781
P310100	Hypoplasia of eye	1	0	23889

P310200	Rudimentary eye	1	0	65888
P310z00	Unspecified microphthalmos NOS	1	0	64325
P311.00	Simple microphthalmos	1	0	31651
P312.00	Microphthalmos with other eye anomaly	1	0	48507
P313.00	Lenz microphthalmia syndrome	1	0	103430
P31z.00	Microphthalmos NOS	1	0	63439
P32..00	Buphthalmos	1	0	31328
P320000	Congenital glaucoma	1	0	23407
P320011	Newborn glaucoma	1	0	98721
P320z00	Unspecified buphthalmos NOS	1	0	111582
P321.00	Simple buphthalmos	1	0	96390
P321.11	Enlarged eye NOS	1	0	92890
P322000	Congenital keratoglobus	1	0	49829
P322100	Congenital megalocornea	1	0	38026
P322111	Enlarged cornea	1	0	104966
P322112	Congenital macrocornea	1	0	94176
P32z.00	Buphthalmos NOS	1	0	70469
P33..00	Congenital cataract and lens anomalies	1	0	4148
P33..11	Congenital lens anomaly	1	0	35351
P330.00	Congenital cataract, unspecified	1	0	299
P331.00	Capsular and subcapsular cataract	1	0	59914
P331000	Capsular cataract	1	0	18089
P331100	Subcapsular cataract	1	0	11255
P331z00	Capsular or subcapsular cataract NOS	1	0	88738
P332.00	Cortical and zonular cataract	1	0	96385
P332000	Cortical cataract - congenital	1	0	60425
P332100	Zonular cataract	1	0	63429
P332z00	Cortical or zonular cataract NOS	1	0	98962
P333.00	Nuclear cataract - congenital	1	0	63212
P334000	Total congenital cataract	1	0	39081
P334z00	Total or subtotal congenital cataract NOS	1	0	71623
P335.00	Congenital aphakia	1	0	69823
P335.11	Congenital absence of lens	1	0	62531
P335.12	Agenesis of lens	1	0	107635
P336.00	Anomalies of lens shape	1	0	66637
P336000	Microphakia	1	0	52652
P336100	Spherophakia	1	0	64018
P336111	Spherical lens	1	0	11691
P336200	Coloboma of lens	1	0	26127
P336z00	Anomalies of lens shape NOS	1	0	61381
P337.00	Congenital ectopic lens	1	0	29474
P337.11	Congenital displaced lens	1	0	95791
P337.12	Congenital dislocation of lens	1	0	55135
P33y.00	Other specified congenital cataract or lens anomaly	1	0	70700
P33y000	Blue dot cataract	1	0	27898
P33y100	Congenital membranous cataract	1	0	99424
P33yz00	Other congenital cataract or lens anomaly NOS	1	0	90279
P33z.00	Congenital cataract or lens anomaly NOS	1	0	45926

P34..00	Anterior chamber anomalies	1	0	21632
P340.00	Corneal size and shape anomalies	1	0	36003
P340000	Microcornea	1	0	57790
P340100	Congenital keratoconus	1	0	23783
P340200	Cornea plana	1	0	47661
P340z00	Corneal size or shape anomalies NOS	1	0	58005
P341.00	Congenital corneal opacities	1	0	11583
P341.11	Arcus juvenilis	0	1	32615
P341000	Congenital corneal opacity with visual deficit	1	0	71732
P341100	Congenital corneal opacity without visual deficit	1	0	86412
P341z00	Congenital corneal opacities NOS	1	0	66259
P342.00	Specified anterior chamber anomalies	1	0	60073
P342000	Axenfield's anomaly	1	0	41777
P342100	Peter's anomaly	1	0	39676
P342200	Rieger's anomaly	1	0	51768
P342z00	Specified anterior chamber anomalies NOS	1	0	62483
P343.00	Aniridia	1	0	24169
P343.11	Congenital absence of iris	1	0	95616
P344.00	Other iris and ciliary body anomalies	1	0	44788
P344.11	Goniodysgenesis	1	0	99401
P344000	Congenital anisocoria	1	0	44851
P344100	Atresia of pupil	1	0	73673
P344200	Coloboma of iris	1	0	15902
P344300	Corectopia	1	0	40571
P344311	Ectopic pupil	1	0	66295
P344400	Polycoria	1	0	92173
P344500	Hypoplasia of iris	1	0	71298
P344600	Aplasia of iris	1	0	59944
P344z00	Other iris or ciliary body anomalies NOS	1	0	63097
P345.00	Specified anomalies of sclera	0	1	17422
P345000	Blue sclera	0	1	30038
P345z00	Specified anomaly of sclera NOS	0	1	48943
P34y.00	Other specified anterior segment anomalies	1	0	112695
P34z.00	Anterior segment anomalies NOS	1	0	69009
P35..00	Posterior chamber congenital anomalies	1	0	62479
P350.00	Vitreous anomalies	1	0	10756
P350000	Congenital vitreous opacity	1	0	21063
P350z00	Vitreous anomalies NOS	1	0	42271
P351.00	Fundus coloboma	1	0	15501
P352.00	Congenital chorioretinal degeneration	1	0	34924
P353000	Congenital folds of the posterior segment	0	1	71724
P353100	Congenital cysts of the posterior segment	1	0	60812
P354.00	Congenital macular changes	1	0	11187
P355.00	Other congenital retinal changes	1	0	62976
P355000	Coloboma of retina	1	0	22114
P355100	Congenital retinal fold	1	0	50584
P355200	Congenital hypertrophy of retinal pigment epithelium	1	0	101194
P355z00	Other congenital retinal changes NOS	0	1	25692

P356.00	Specified optic disc anomalies	1	0	29719
P356.11	Optic disc congenital anomalies	1	0	19244
P356000	Congenital optic disc coloboma	1	0	26024
P356z00	Specified optic disc anomaly NOS	1	0	44929
P357.00	Posterior chamber vascular anomalies	1	0	55127
P357000	Congenital retinal aneurysm	1	0	49791
P357100	Congenital arteriovenous malformation of retina	1	0	62587
P357z00	Posterior chamber vascular anomalies NOS	1	0	65200
P358.00	Specified anomalies of choroid	1	0	30000
P358000	Coloboma of choroid	1	0	21767
P358z00	Specified anomaly of choroid NOS	1	0	41903
P35y.00	Other specified congenital anomalies of posterior chamber	1	0	89873
P35z.00	Congenital anomalies of posterior chamber NOS	1	0	94285
P36..00	Congenital anomalies of eyelid, lacrimal system and orbit	0	1	94280
P360.00	Congenital ptosis	1	0	8319
P360.11	Blepharoptosis	1	0	16690
P361.00	Congenital eyelid deformity	0	1	15587
P361000	Ablepharon -absent eyelids	1	0	60185
P361100	Accessory eyelid	1	0	49494
P361200	Congenital entropion	0	1	7458
P361300	Congenital ectropion	0	1	31998
P361400	Congenital blepharophimosis	0	1	37513
P361500	Coloboma of eyelids	1	0	39789
P361z00	Congenital eyelid deformity NOS	0	1	67169
P362.00	Other specified congenital eyelid anomalies	0	1	48233
P362000	Agenesis of cilia	1	0	67919
P362100	Agenesis of eyelid	1	0	71382
P362200	Fused eyelids	1	0	60907
P362300	Hypoplasia of eyelid	1	0	91657
P362z00	Other specified congenital eyelid anomalies NOS	0	1	61084
P363.00	Congenital lacrimal gland anomalies	0	1	12753
P364.00	Congenital lacrimal passage anomalies	0	1	30468
P364.11	Congenital blocked tear duct	0	1	29686
P364000	Agenesis of lacrimal apparatus	0	1	39152
P364011	Congenital absence of lacrimal apparatus	1	0	93282
P364100	Agenesis of punctum lacrimale	1	0	65781
P364111	Congenital absence of punctum lacrimale	1	0	97779
P364200	Accessory lacrimal canal	0	1	65131
P364300	Stenosis or stricture of lacrimal duct	0	1	41479
P364400	Congenital blocked tear duct	0	1	11463
P364y00	Other specified congenital anomaly of lacrimal passages	1	0	70085
P364z00	Congenital anomaly of lacrimal passages NOS	0	1	16355
P365.00	Congenital orbit anomalies	1	0	50282
P36z.00	Other/unspecified anomalies of eyelid/lacrimal system/orbit	0	1	68836

P36z000	Accessory eye muscles	0	1	54829
P36z100	Hypoplasia of eye muscle	1	0	64255
P36zz00	Eyelid, lacrimal system and orbit congenital anomalies NOS	0	1	20325
P37..00	Macrophthalmos	1	0	58909
P3y..00	Other specified eye anomalies	0	1	45352
P3y0.00	Ocular albinism	0	1	21746
P3yz.00	Other eye anomalies NOS	1	0	49394
P3z..00	Congenital eye anomalies NOS	0	1	43783
P4...00	Ear, face and neck congenital anomalies	1	0	57556
P40..00	Ear anomalies with hearing impairment	1	0	5016
P400.00	Ear anomalies with hearing impaired, unspecified	1	0	50016
P401.00	Congenital absence of external ear	1	0	46122
P401000	Congenital absence of external ear, unspecified	1	0	43777
P401011	Absence of ear NOS	1	0	29900
P401100	Absence of external auditory canal	1	0	67353
P401200	Ear auricle and external auditory canal absent	1	0	60570
P401211	Congenital absence ear auricle	1	0	72932
P401300	Congenital absence of auricle	1	0	70139
P401z00	Absence of external ear NOS	1	0	73496
P402.00	Other external ear anomaly with hearing impairment	1	0	52802
P402000	Atresia of external auditory canal	1	0	25819
P402100	Stenosis of external auditory canal	1	0	35987
P402111	Congenital stricture of external auditory canal	1	0	102497
P402112	Congenital stricture of osseous meatus	1	0	95103
P402z00	Other external ear anomaly with hearing impairment NOS	1	0	72933
P403.00	Middle ear anomaly, excluding ossicles	1	0	15968
P403000	Ear osseous meatus atresia	1	0	73596
P403z00	Middle ear anomaly NEC NOS	1	0	40461
P404.00	Anomaly of ossicles	1	0	41037
P404000	Congenital fusion of ear ossicles	1	0	93483
P404z00	Anomaly of ossicles NOS	1	0	48460
P405.00	Inner ear anomalies	1	0	41206
P405z00	Inner ear anomalies NOS	1	0	63603
P40z.00	Other and unspecified ear anomaly with hearing impaired	1	0	27313
P40z.11	Deafness due to congenital anomaly NEC	1	0	31374
P40z000	Congenital absence of ear NOS	1	0	35677
P40zz00	Ear anomaly with hearing impaired NOS	1	0	57053
P41..00	Accessory ear auricle	0	1	8747
P41..11	Polyotia	1	0	93879
P410.00	Supernumerary ear	1	0	3013
P411.00	Accessory tragus	0	1	36681
P412.00	Supernumerary ear lobule	0	1	44205
P413.00	Preauricular appendage, tag or lobule	0	1	45556
P413.11	Preauricular appendage	0	1	17143
P413.12	Preauricular tag	0	1	8746

P413.13	Preauricular lobule	0	1	43131
P414.00	Other ear appendage or tag	0	1	56864
P414.11	Other ear appendage	0	1	61057
P414.12	Other ear tag	0	1	26004
P41z.00	Accessory ear auricle NOS	0	1	56861
P42..00	Other specified ear anomalies	1	0	39033
P420.00	Congenital ear lobe absence	1	0	14846
P421.00	Macrotia - abnormally big ears	0	1	15391
P421.11	Congenital big ears	0	1	42721
P422.00	Microtia - abnormally small ears	0	1	5624
P422.11	Congenital small ears	0	1	65828
P423.00	Eustachian tube anomalies	1	0	29327
P423100	Congenital stenosis of eustachian tube	1	0	101739
P423z00	Eustachian tube anomalies NOS	1	0	71280
P42z.00	Other specified ear anomalies NOS	0	1	35784
P42z000	Congenital Bat ear	0	1	1162
P42z100	Darwin's tubercle	0	1	38959
P42z200	Congenital pointed ear	0	1	53579
P42z300	Congenital prominent auricle	0	1	48936
P42z400	Congenital ridge ear	0	1	93302
P42z500	Other mis-shapen ear	0	1	48258
P42z511	Aztec ear	0	1	34701
P42z512	Cat ear	0	1	93223
P42z513	Vulcan ear	0	1	98996
P42z600	Misplaced ears	0	1	64038
P42z611	Low-set ears	0	1	54583
P42zz00	Other ear anomalies NOS	0	1	36169
P43..00	Congenital ear anomaly NOS	0	1	1379
P44..00	Branchial cleft, cyst or fistula; preauricular sinus	0	1	41869
P440.00	Branchial cleft sinus and fistula	0	1	26340
P440.11	Branchial cleft	0	1	35369
P440.12	Branchial cleft sinus	0	1	26217
P440000	Branchial cleft vestige, unspecified	0	1	70435
P440100	Branchial cleft external sinus	0	1	37476
P440200	Branchial cleft internal sinus	0	1	70474
P440300	Branchial cleft fistula	0	1	16154
P440z00	Branchial cleft vestige NOS	0	1	71872
P441.00	Branchial cleft cyst	0	1	1324
P442.00	Cervical auricle	0	1	51335
P443.00	Preauricular sinus and fistula	0	1	27852
P443000	Preauricular sinus	0	1	12522
P443100	Preauricular fistula	0	1	43702
P443z00	Preauricular sinus or fistula NOS	0	1	52335
P444.00	Preauricular cyst	0	1	29843
P44y.00	Other branchial cleft anomalies	0	1	73953
P44z.00	Branchial cleft,cyst,or fistula preauricular anomaly OS/NOS	0	1	43843
P44z000	Fistula of congenital auricle	0	1	67579

P44z100	Cervicoaural fistula	0	1	96615
P44zz00	Branchial cleft, cyst or fistula preauricular anomaly NOS	0	1	49632
P45..00	Congenital webbing of neck	1	0	35616
P451.00	Pterygium colli	1	0	58011
P45z.00	Congenital webbing of neck NOS	1	0	99458
P4y..00	Other specified face and neck anomalies	0	1	59565
P4y0.00	Macrocheilia	0	1	63318
P4y0.11	Lip hypertrophy	0	1	26847
P4y1.00	Microcheilia	0	1	55541
P4y2.00	Macrostomia	0	1	34837
P4y3.00	Microstomia	0	1	36831
P4y4.00	Congenital absence of chin	0	1	35942
P4y5.00	Mid-facial hypoplasia	0	1	35256
P4yz.00	Other specified face and neck anomalies NOS	0	1	16271
P4z..00	Congenital face or neck anomaly NOS	0	1	70982
P4z0.00	Congenital anomaly of neck NOS	0	1	93198
P4z1.00	Congenital anomaly of face NOS	0	1	37784
P8...00	Respiratory system congenital anomalies	1	0	46398
P80..00	Choanal atresia	1	0	31027
P800.00	Choanal atresia, unspecified	1	0	66643
P802.00	Atresia of the posterior nares	1	0	68606
P803.00	Congenital stenosis of the anterior nares	1	0	107172
P804.00	Congenital stenosis of the posterior nares	1	0	96389
P80z.00	Choanal atresia NOS	1	0	60514
P81..00	Other anomalies of nose	1	0	45438
P810.00	Congenital nose deformity, unspecified	1	0	15715
P811.00	Absent nose	1	0	52579
P811000	Agenesis of nose	1	0	102794
P812.00	Accessory nose	1	0	60987
P813.00	Congenital cleft nose	1	0	66698
P814.00	Deformity of nasal sinus wall	1	0	37110
P815.00	Congenital notching of tip of nose	0	1	58422
P816.00	Congenital perforation of the nasal sinus wall	1	0	73595
P817.00	Perforated nasal septum	1	0	10793
P818.00	Congenital fissure of nose	1	0	65192
P819.00	Congenital hypoplastic nose	1	0	28199
P81z.00	Other anomalies of nose NOS	1	0	45376
P81z.11	Single nostril	1	0	16933
P82..00	Congenital web of larynx	1	0	31771
P820.00	Congenital web of larynx, unspecified	1	0	111186
P821.00	Congenital glottic web of larynx	1	0	42855
P822.00	Congenital subglottic web of larynx	1	0	97956
P82z.00	Congenital web of larynx NOS	1	0	70985
P83..00	Other anomalies of larynx, trachea and bronchus	1	0	29373
P830200	Agenesis of trachea	1	0	101497
P831.00	Anomaly of laryngeal and tracheal cartilage	1	0	63530
P831000	Anomaly of cricoid cartilage	1	0	44151

P831100	Anomaly of epiglottis	1	0	43205
P831200	Anomaly of thyroid cartilage	1	0	47467
P831300	Anomaly of tracheal cartilage	1	0	31020
P831400	Tracheomalacia	0	1	2910
P831500	Laryngeal hypoplasia	1	0	51933
P831600	Laryngomalacia	0	1	7592
P831z00	Anomaly of laryngeal or tracheal cartilage NOS	1	0	55062
P832.00	Atresia of larynx and trachea	1	0	72001
P832000	Atresia of epiglottis	1	0	61727
P832100	Atresia of glottis	1	0	92834
P832300	Atresia of trachea	1	0	63288
P833.00	Congenital stenosis of larynx, trachea and bronchus	1	0	59273
P833000	Congenital stenosis of larynx	1	0	61450
P833100	Congenital stenosis of trachea	1	0	48818
P833200	Congenital stenosis of bronchus	1	0	71893
P833300	Congenital subglottic stenosis	1	0	49142
P833400	Congenital supraglottic stenosis	1	0	55144
P83y.00	Other anomaly of larynx, trachea and bronchus	1	0	63637
P83y100	Congenital dilatation of trachea	1	0	37835
P83y300	Congenital laryngocele	1	0	45351
P83y400	Congenital diverticulum of bronchus	1	0	112703
P83y500	Congenital diverticulum of trachea	1	0	99683
P83y600	Congenital fissure of epiglottis	1	0	58868
P83y700	Congenital cleft of posterior cricoid cartilage	1	0	105605
P83y800	Rudimentary tracheal bronchus	1	0	55656
P83y900	Congenital laryngeal stridor	1	0	5405
P83yB00	Congenital bronchomalacia	1	0	11845
P83yX00	Congenital malformation of larynx, unspecified	1	0	36474
P83yw00	Other anomaly of larynx	1	0	63507
P83yx00	Other anomaly of trachea	1	0	70193
P83yy00	Other anomaly of bronchus	1	0	104976
P83yz00	Other anomaly of larynx, trachea or bronchus NOS	1	0	103042
P83z.00	Other anomalies of larynx, trachea or bronchus NOS	1	0	36779
P84..00	Congenital cystic lung	1	0	10699
P840.00	Congenital cystic lung disease, unspecified	1	0	66223
P841.00	Congenital polycystic lung	1	0	31820
P841.11	Multiple lung cysts	1	0	57330
P841.12	Multiple congenital bronchogenic cysts	1	0	50980
P842.00	Congenital honeycomb lung	1	0	66951
P843.00	Single lung cyst	1	0	38769
P843.11	Lung cyst	1	0	15639
P843.12	Congenital bronchogenic cyst	1	0	32600
P844.00	Congenital cystic adenomatoid malformation of the lung	1	0	96586
P84y.00	Other specified congenital cystic lung	1	0	64802
P84z.00	Congenital cystic lung NOS	1	0	33804
P85..00	Lung agenesis, hypoplasia and dysplasia	1	0	26838
P850.00	Aplasia of lung	1	0	52664

P851.00	Hypoplasia of lung	1	0	23874
P852.00	Sequestration of lung	1	0	35661
P853.00	Agenesis of lung	1	0	59444
P853.11	Congenital absence of lung	1	0	54384
P853000	Congenital absence of lung fissures	1	0	68268
P853100	Congenital absence of lobe of lung	1	0	97185
P853z00	Agenesis of lung NOS	1	0	89691
P85y.00	Other specified lung agenesis, hypoplasia or dysplasia	1	0	99799
P85y000	Fusion of lobes of lung	1	0	50991
P85yz00	Other lung agenesis, hypoplasia or dysplasia NOS	1	0	100037
P85z.00	Lung agenesis, hypoplasia or dysplasia NOS	1	0	93008
P86..00	Other lung anomalies	1	0	18487
P860.00	Anomaly of lung, unspecified	1	0	63453
P861.00	Congenital bronchiectasis	1	0	56427
P86y.00	Other lung anomaly	1	0	60290
P86y100	Azygos lobe of lung	0	1	48229
P86y200	Accessory lobe of lung	0	1	83570
P86yz00	Other lung anomaly NOS	1	0	64758
P86z.00	Lung anomaly NOS	1	0	8311
P8y..00	Other specified respiratory system anomalies	1	0	89730
P8y0.00	Abnormal pericardio-pleural communication	1	0	70956
P8y1.00	Anomaly, pleural folds	1	0	39900
P8y2.00	Atresia of nasopharynx	1	0	52894
P8y3.00	Congenital cyst of mediastinum	1	0	32883
P8y4.00	Congenital pulmonary lymphangiectasis	1	0	44347
P8yz.00	Other specified respiratory system anomaly NOS	1	0	32416
P8z..00	Respiratory system anomaly NOS	1	0	46397
P9...00	Cleft palate and lip	1	0	5374
P90..00	Cleft palate	1	0	2170
P900.00	Cleft palate, unspecified	1	0	58885
P900.11	Palatoschisis	1	0	57453
P901.00	Unilateral complete cleft palate	1	0	73531
P901.11	Cleft hard palate, unilateral	1	0	38873
P902.00	Unilateral incomplete cleft palate	1	0	73558
P902.11	Cleft uvula	1	0	97631
P902.12	Cleft soft palate, unilateral	1	0	57490
P903.00	Bilateral complete cleft palate	1	0	48948
P904.00	Bilateral incomplete cleft palate	1	0	106078
P904.11	Cleft soft palate, bilateral	1	0	97477
P905.00	Central complete cleft palate	1	0	100787
P905.11	Cleft hard palate, central	1	0	112480
P906.00	Central incomplete cleft palate	1	0	45313
P906.11	Cleft soft palate, central	1	0	68166
P907.00	Complete cleft palate NOS	1	0	93030
P907.11	Cleft hard palate NOS	1	0	65623
P908.00	Incomplete cleft palate NOS	1	0	51377
P908.11	Cleft soft palate NOS	1	0	25740
P909.00	Cleft uvula	1	0	24846

P90A.00	Cleft soft palate, bilateral	1	0	42208
P90B.00	Cleft hard palate, bilateral	1	0	64549
P90C.00	Cleft hard palate, unilateral	1	0	101223
P90z.00	Cleft palate NOS	1	0	15364
P91..00	Cleft lip (harelip)	1	0	2027
P91..11	Cheiloschisis	1	0	16938
P91..12	Congenital fissure of lip	1	0	60474
P910.00	Cleft lip, unspecified	1	0	16457
P911.00	Unilateral complete cleft lip	1	0	63930
P912.00	Unilateral incomplete cleft lip	1	0	54012
P913.00	Bilateral complete cleft lip	1	0	54721
P914.00	Bilateral incomplete cleft lip	1	0	30957
P915.00	Central cleft lip	1	0	52827
P91z.00	Cleft lip NOS	1	0	35374
P92..00	Cleft palate with cleft lip	1	0	5386
P92..11	Cheilopalatoschisis	1	0	105114
P920.00	Cleft palate with cleft lip, unspecified	1	0	51301
P921.00	Unilateral complete cleft palate with cleft lip	1	0	62987
P922.00	Unilateral incomplete cleft palate with cleft lip	1	0	54144
P923.00	Bilateral complete cleft palate with cleft lip	1	0	44977
P924.00	Bilateral incomplete cleft palate with cleft lip	1	0	62690
P927.00	Cleft hard palate with cleft soft palate, bilateral	1	0	112758
P928.00	Cleft hard palate with cleft soft palate, unilateral	1	0	93972
P92A.00	Cleft hard palate with cleft lip, bilateral	1	0	33902
P92B.00	Cleft hard palate with cleft lip, unilateral	1	0	62321
P92z.00	Cleft palate with cleft lip NOS	1	0	68398
P9z..00	Cleft palate or cleft lip NOS	1	0	50430
PA...00	Other congenital upper alimentary tract anomalies	1	0	72991
PA0..00	Tongue tie - ankyloglossia	0	1	8394
PA0..11	Ankyloglossia	1	0	30299
PA0..12	Tongue tie	0	1	2227
PA1..00	Other tongue anomalies	0	1	35634
PA10.00	Anomaly of tongue, unspecified	0	1	37358
PA11.00	Aglossia	1	0	39308
PA12.00	Congenital adhesions of tongue	0	1	24266
PA13.00	Fissure of tongue	1	0	23769
PA13.11	Bifid tongue	0	1	32747
PA13.12	Double tongue	1	0	101593
PA14.00	Macroglossia	0	1	30176
PA14.11	Congenital tongue hypertrophy	0	1	17103
PA15.00	Microglossia	1	0	103145
PA15.11	Hypoplasia of tongue	1	0	67559
PA15.12	Short tongue	0	1	66477
PA16.00	Dislocation of tongue	1	0	72209
PA17.00	Cleft tongue	0	1	102580
PA17.11	Whiteman's syndrome	1	0	83511
PA18.00	Congenital plicated tongue	1	0	65298
PA1z.00	Other tongue anomalies NOS	0	1	33573

PA2..00	Other specified mouth and pharynx anomalies	1	0	96239
PA20.00	Congenital absence of salivary gland	1	0	68884
PA21.00	Accessory salivary gland	0	1	43442
PA22.00	Atresia, salivary duct	0	1	34305
PA23.00	Congenital salivary gland fistula	1	0	49382
PA24.00	Congenital fistula of lip	1	0	96432
PA24.11	Congenital pits of lip	0	1	51454
PA25.00	Other mouth anomalies	0	1	40055
PA25.11	Fordyce's disease of mouth	0	1	38317
PA25000	Congenital absence of uvula	1	0	54524
PA25100	High arched palate	0	1	21406
PA25y00	Other congenital anomaly of palate	0	1	37517
PA25z00	Other mouth anomalies NOS	1	0	24781
PA26.00	Diverticulum of pharynx	1	0	39976
PA26.11	Pharyngeal pouch	1	0	3753
PA27.00	Other pharynx anomalies	1	0	44945
PA27000	Imperforate pharynx	1	0	56901
PA27100	Congenital pharyngeal polyp	1	0	49742
PA27z00	Other pharynx anomalies NOS	1	0	57264
PA28.00	Ranula, congenital	0	1	45210
PA29.00	Other anomalies of salivary glands or ducts	0	1	16343
PA29.11	Displacement of Wharton's duct	1	0	61320
PA2A.00	Other anomalies of lip	0	1	17875
PA2A000	Congenital ectropion of lip	0	1	109860
PA2Az00	Other anomaly of lip NOS	1	0	21244
PA2z.00	Other mouth and pharynx anomalies NOS	0	1	39628
PA3..00	Oesophageal atresia, stenosis and fistula	1	0	37408
PA3..11	Congenital oesophageal ring	1	0	46814
PA30.00	Atresia of oesophagus	1	0	4122
PA31.00	Congenital oesophageal stricture	1	0	16744
PA31.11	Congenital oesophageal stenosis	1	0	49707
PA32.00	Congenital oesophageal fistula	1	0	31730
PA32000	Oesophagobronchial fistula	1	0	48087
PA32100	Oesophagotracheal fistula	1	0	37868
PA32111	Congenital tracheo-oesophageal fistula	1	0	35042
PA32z00	Congenital oesophageal fistula NOS	1	0	95311
PA33.00	Imperforate oesophagus	1	0	98741
PA34.00	Webbed oesophagus	1	0	4620
PA35.00	Congenital absence of oesophagus	1	0	98859
PA36.00	Cong.absence of oesophagus with tracheo-oesophageal fistula	1	0	98860
PA37.00	Atresia of oesophagus with tracheo-oesophageal fistula	1	0	33655
PA3y.00	Other specified oesophageal atresia, stenosis or fistula	1	0	29767
PA3z.00	Oesophageal atresia, stenosis or fistula NOS	1	0	5801
PA4..00	Other specified oesophageal anomalies	0	1	38320
PA40.00	Congenital dilatation of oesophagus	1	0	22560
PA42.00	Congenital diverticulum of oesophagus	1	0	45197

PA43.00	Congenital duplication of oesophagus	1	0	55900
PA44.00	Giant oesophagus	1	0	94472
PA45.00	Congenital oesophageal pouch	1	0	43558
PA4z.00	Other specified oesophageal anomaly NOS	1	0	27895
PA5..00	Congenital hypertrophic pyloric stenosis	0	1	2469
PA50.00	Congenital pyloric hypertrophy	1	0	63866
PA51.00	Congenital pyloric spasm	1	0	69167
PA51.11	Congenital pylorospasm	1	0	64485
PA52.00	Congenital pyloric stenosis	0	1	3263
PA52.11	Congenital pyloric stricture	1	0	69528
PA5y.00	Other specified congenital pyloric obstruction	1	0	22586
PA5z.00	Congenital pyloric obstruction NOS	1	0	60432
PA6..00	Congenital hiatus hernia	0	1	43215
PA7..00	Other specified stomach anomalies	0	1	44972
PA70.00	Congenital cardiospasm	1	0	72271
PA70.11	Congenital achalasia of cardia	1	0	23416
PA71.00	Congenital hourglass stomach	1	0	47776
PA73.00	Congenital stomach diverticulum	1	0	65337
PA74.00	Duplication of stomach	1	0	66130
PA75.00	Megalogastria	1	0	71255
PA76.00	Microgastria	1	0	35278
PA77.00	Transposition of stomach	1	0	66199
PA78.00	Ectopic gastric mucosa	1	0	33453
PA7z.00	Other specified stomach anomaly NOS	1	0	51486
PAy..00	Other specified upper alimentary tract anomaly	0	1	2981
PAz..00	Upper alimentary tract anomalies NOS	1	0	40528
PAz0.00	Unspecified anomalies of mouth and pharynx	0	1	16845
PAz1.00	Unspecified anomalies of oesophagus	1	0	7107
PAz2.00	Unspecified anomalies of stomach	0	1	25280
PAzz.00	Anomalies of upper alimentary tract NOS	1	0	55080
PAzz.11	Malformation of throat	1	0	29785
PB...00	Other congenital digestive system anomaly	0	1	42998
PB0..00	Meckel's diverticulum	0	1	5069
PB0..12	Persistent vitelline duct	1	0	109846
PB00.00	Meckel's diverticulum, unspecified	0	1	29302
PB01.00	Displaced Meckel's diverticulum	0	1	94449
PB03.00	Persistent omphalomesenteric duct	1	0	47428
PB03.11	Persistent vitelline duct	1	0	51731
PB0z.00	Meckel's diverticulum NOS	0	1	33781
PB1..00	Small intestine atresia and stenosis	1	0	60083
PB10.00	Atresia of small intestine	1	0	33584
PB10000	Atresia of small intestine, unspecified	1	0	40252
PB10100	Atresia of duodenum	1	0	19039
PB10200	Atresia of ileum	1	0	53565
PB10300	Atresia of jejunum	1	0	52687
PB10z00	Small intestine atresia NOS	1	0	70579
PB11200	Congenital absence of ileum	1	0	18406
PB12.00	Congenital obstruction of small intestine	1	0	66309

PB13.00	Congenital stenosis of small intestine	1	0	59399
PB13000	Congenital stenosis of duodenum	1	0	20686
PB13100	Congenital stenosis of jejunum	1	0	67021
PB13200	Congenital stenosis of ileum	1	0	69712
PB13z00	Congenital stenosis of small intestine NOS	1	0	99366
PB13z11	Congenital stricture of small intestine	1	0	47939
PB14.00	Imperforate jejunum	1	0	68484
PB1z.00	Small intestine atresia or stenosis NOS	1	0	25042
PB2..00	Atresia and stenosis of large intestine/rectum/anal canal	1	0	51672
PB2..11	Atresia large intestine	1	0	27598
PB2..12	Stenosis large intestine	1	0	50109
PB20.00	Congenital absence of large intestine	1	0	58855
PB20000	Congenital absence of anus	1	0	59430
PB20100	Congenital absence of appendix	1	0	44471
PB20200	Congenital absence of rectum	1	0	50443
PB20211	Agenesis of rectum	1	0	34909
PB20300	Congenital absence of anus with fistula	1	0	93826
PB20400	Congenital absence of rectum with fistula	1	0	58095
PB20411	Agenesis of rectum with fistula	1	0	56383
PB21.00	Atresia of large intestine	1	0	31468
PB21000	Atresia of anus	1	0	31731
PB21100	Atresia of colon	1	0	23593
PB21200	Atresia of rectum	1	0	46123
PB21300	Atresia of appendix	1	0	99653
PB21400	Atresia of anus with fistula	1	0	12610
PB21500	Atresia of rectum with fistula	1	0	71153
PB22.00	Congenital obstruction of large intestine	1	0	65762
PB22.11	Congenital stenosis of large intestine	1	0	108445
PB23.00	Congenital occlusion of anus	1	0	90483
PB23.11	Anal septum	1	0	97750
PB23000	Congenital occlusion of anus with fistula	1	0	101348
PB23z00	Congenital occlusion of anus NOS	1	0	62671
PB24.00	Congenital stricture of anus	1	0	48020
PB24.11	Congenital anal stricture	1	0	35019
PB24000	Congenital stricture of anus with fistula	1	0	41359
PB24011	Congenital stenosis of anus with fistula	1	0	100539
PB24100	Congenital stricture of anus without mention of fistula	1	0	107117
PB24111	Congenital stenosis of anus without mention of fistula	1	0	49089
PB24z00	Congenital stricture of anus NOS	1	0	73497
PB25.00	Congenital stricture of rectum	1	0	49501
PB25.11	Congenital rectal stricture	1	0	38655
PB25000	Congenital stricture of rectum with fistula	1	0	69054
PB25011	Congenital stenosis of rectum with fistula	1	0	88890
PB25111	Congenital stenosis of rectum without mention of fistula	1	0	101122
PB25z00	Congenital stricture of rectum NOS	1	0	42469
PB26.00	Imperforate anus	1	0	4855

PB26000	Imperforate anus with fistula	1	0	61401
PB26z00	Imperforate anus NOS	1	0	67319
PB27.00	Imperforate rectum	1	0	49242
PB27000	Imperforate rectum with fistula	1	0	44953
PB2z.00	Atresia and stenosis of large intestine/rectum/anus NOS	1	0	35968
PB3..00	Hirschsprung's disease and allied congenital conditions	1	0	56630
PB3..11	Aganglioneosis	1	0	94813
PB30.00	Hirschsprung's disease	1	0	8546
PB30000	Long segment Hirschsprung's disease	1	0	63395
PB30100	Short segment Hirschsprung's disease	1	0	70868
PB30z00	Hirschsprung's disease NOS	1	0	70582
PB31.00	Idiopathic congenital megacolon	1	0	37401
PB33.00	Total intestinal aganglioneosis	1	0	52258
PB33.11	Aganglionic macrocolon	1	0	65511
PB33.12	Congenital aganglionic megacolon	1	0	53517
PB3z.00	Hirschsprung's disease and allied congenital conditions NOS	1	0	59085
PB4..00	Intestinal fixation anomalies	1	0	31401
PB40.00	Congenital intestinal adhesions	1	0	67830
PB40000	Congenital omental adhesions	1	0	69684
PB40100	Jackson's membrane	1	0	35714
PB40200	Congenital peritoneal adhesions	1	0	67420
PB40211	Congenital peritoneal bands	1	0	47616
PB40z00	Congenital intestinal adhesions NOS	1	0	69811
PB41.00	Malrotation of colon and caecum	1	0	5532
PB41000	Malrotation of colon	1	0	56743
PB41100	Malrotation of caecum	1	0	57921
PB41z00	Malrotation of colon or caecum NOS	1	0	66375
PB42.00	Universal mesentery	1	0	62998
PB43.00	Other anomalies of mesentery	0	1	50785
PB4y.00	Other specified intestinal fixation anomaly	1	0	107768
PB4z.00	Intestinal fixation anomaly NOS	1	0	72186
PB4z.11	Malfixation of gut NEC	1	0	64436
PB4z.12	Malrotation of gut	1	0	39735
PB4z.13	Malrotation of intestine	1	0	34304
PB5..00	Other anomalies of intestine	1	0	50278
PB50.00	Congenital diverticulum of colon	0	1	20830
PB51.00	Dolichocolon	1	0	62438
PB52.00	Duplication of intestine	1	0	65831
PB52000	Duplication of intestine, unspecified	1	0	73631
PB52100	Duplication of anus	1	0	71858
PB52300	Duplication of caecum	1	0	68728
PB52z00	Duplication of intestine NOS	1	0	69243
PB52z11	Congenital redundant rectal mucosa	1	0	68819
PB52z12	Congenital redundant colon	1	0	48260
PB53.00	Transposition of intestine	1	0	67877
PB53000	Transposition of intestine, unspecified	1	0	71180

PB53100	Transposition of appendix	1	0	59279
PB53200	Transposition of caecum	1	0	66200
PB53300	Transposition of colon	1	0	45857
PB53z00	Transposition of intestine NOS	1	0	20126
PB54.00	Ectopic anus	1	0	34967
PB56.00	Megaloduodenum	1	0	50050
PB57.00	Microcolon	1	0	44201
PB58.00	Persistent cloaca	1	0	41508
PB58.11	Anal fusion	1	0	58998
PB58.12	Anal and urogenital canal fusion	1	0	96419
PB59.00	Congenital anal fistula	1	0	37080
PB5A.00	Enterogenous cyst	1	0	35191
PB5B.00	Dysplasia of colon	1	0	94919
PB5X.00	Congenital malformation of intestine, unspecified	0	1	47726
PB5z.00	Other intestine anomalies NOS	0	1	67644
PB5z.11	Congenital volvulus	1	0	49448
PB5z.12	Short bowel syndrome	1	0	24437
PB5z000	Congenital faecal fistula	1	0	71051
PB6..00	Liver and biliary system anomalies	1	0	60549
PB6..11	Bile duct anomalies	1	0	40425
PB6..12	Biliary anomalies	1	0	17991
PB6..13	Gallbladder anomalies	1	0	32791
PB6..14	Liver anomalies	1	0	31201
PB60.00	Liver and biliary system anomalies, unspecified	1	0	66895
PB60000	Liver anomaly, unspecified	1	0	29801
PB60100	Gallbladder anomaly, unspecified	1	0	62051
PB60200	Bile duct anomaly, unspecified	1	0	53764
PB60z00	Unspecified liver and biliary system anomaly NOS	1	0	70044
PB61.00	Biliary atresia	1	0	25597
PB61000	Congenital absence of bile duct	1	0	16417
PB61200	Congenital obstruction of bile duct	1	0	49479
PB61300	Congenital stricture of bile duct	1	0	95810
PB61311	Congenital stricture of common bile duct	1	0	32803
PB61400	Atresia of bile duct	1	0	38389
PB61411	Intrahepatic atresia of bile duct	1	0	65889
PB61412	Extrahepatic atresia of bile duct	1	0	50458
PB61500	Congenital absence of hepatic ducts	1	0	48269
PB61600	Atresia of hepatic ducts	1	0	50400
PB61z00	Biliary atresia NOS	1	0	50444
PB62.00	Congenital cystic liver disease	1	0	27565
PB62.11	Congenital hepatic cyst	1	0	34903
PB62000	Congenital polycystic liver disease	1	0	18195
PB62100	Fibrocystic liver disease	1	0	28350
PB62z00	Congenital cystic liver disease NOS	1	0	72000
PB63000	Congenital absence of gallbladder	1	0	42256
PB63011	Agenesis of gallbladder	1	0	47576
PB63100	Congenital absence of liver lobe	1	0	98402
PB63300	Riedel's lobe liver	1	0	20610

PB63500	Alagille syndrome	1	0	40029
PB64000	Duplication of biliary duct	1	0	109392
PB64100	Duplication of cystic duct	1	0	70711
PB64200	Duplication of gallbladder	1	0	44475
PB64311	Accessory liver	1	0	100050
PB6y.00	Other liver and biliary anomalies	1	0	21165
PB6y000	Congenital choledochal cyst	1	0	20979
PB6y100	Congenital hepatomegaly	1	0	48738
PB6y200	Congenital floating gallbladder	1	0	72283
PB6y400	Intrahepatic gallbladder	1	0	59270
PB6y500	Hypoplasia of gallbladder	1	0	99447
PB6y600	Atrophy of left lobe of liver	1	0	46723
PB6y700	Congenital dilation of bile duct	1	0	65590
PB6y800	Congenital diverticulum of bile duct	1	0	104752
PB6y900	Liver hyperplasia	1	0	21784
PB6yw00	Other congenital anomaly of liver	0	1	66182
PB6yw11	Liver hamartoma	1	0	18752
PB6yw12	Abnormal liver lobulation	1	0	22504
PB6yw13	Trilobular liver	1	0	110299
PB6yx00	Other congenital anomaly of gallbladder	1	0	46106
PB6yy00	Other congenital anomaly of hepatic or bile ducts	0	1	94116
PB6yz00	Other liver or biliary system anomalies NOS	0	1	23432
PB6z.00	Liver or biliary system anomalies NOS	1	0	55806
PB7..00	Anomalies of pancreas	0	1	18680
PB72.00	Hypoplasia of pancreas	1	0	61593
PB73.00	Accessory pancreas	1	0	67373
PB74.00	Annular pancreas	1	0	31467
PB75.00	Ectopic pancreas	1	0	63612
PB76.00	Pancreatic heterotopia	1	0	59309
PB77.00	Pancreatic cyst, congenital	1	0	49534
PB7y.00	Other specified anomalies of pancreas	0	1	54778
PB7z.00	Anomalies of pancreas NOS	0	1	30055
PBy..00	Other specified digestive system anomalies	1	0	71358
PBy0.00	Congenital absence of digestive system NOS	1	0	60738
PBy1.00	Duplication of digestive system NOS	1	0	51485
PBy2.00	Congenital malposition of digestive system NOS	1	0	39277
PBy2.11	Ectopic digestive organs NOS	1	0	97491
PByz.00	Other specified digestive system anomalies NOS	0	1	27341
PBz..00	Digestive system anomalies NOS	0	1	73044
PC...00	Congenital genital organ anomalies	1	0	44969
PC0..00	Anomalies of ovaries	1	0	16696
PC00.00	Congenital absence of ovary	1	0	42571
PC00.11	Agenesis of ovary	1	0	49230
PC02.00	Ectopic ovary	1	0	52478
PC03.00	Streak ovary	1	0	51619
PC04.00	Developmental ovarian cyst	0	1	17505
PC05.00	Congenital torsion of ovary	1	0	52508
PC0y.00	Other specified congenital anomalies of ovaries	1	0	108796

PC0y.11	Congenital ovarian dysplasia	1	0	106909
PC0z.00	Congenital anomalies of ovaries NOS	1	0	71842
PC1..00	Fallopian tube and broad ligament anomalies	1	0	35862
PC10.00	Fallopian tube and broad ligament anomalies, unspecified	1	0	45459
PC11.00	Embryonic cyst of fallopian tube and broad ligament	1	0	5745
PC11.11	Cyst of mesenteric remnant	1	0	27708
PC11000	Epoophoron cyst	1	0	64055
PC11100	Fimbrial cyst	1	0	10524
PC11200	Gartner's duct cyst	1	0	16519
PC11211	Persistent Gartner's duct	1	0	109824
PC11300	Parovarian cyst	1	0	37765
PC11z00	Embryonic cyst of fallopian tube or broad ligament NOS	1	0	72662
PC1y.00	Other fallopian tube and broad ligament anomalies	1	0	94779
PC1y000	Congenital absence of fallopian tube	1	0	31835
PC1y100	Accessory fallopian tube	1	0	60751
PC1y200	Atresia of fallopian tube	1	0	61770
PC1y300	Absent broad ligament	1	0	99587
PC1y400	Accessory broad ligament	1	0	31924
PC1yz00	Other fallopian tube or broad ligament anomalies NOS	1	0	103718
PC1z.00	Fallopian tube or broad ligament anomalies NOS	1	0	50263
PC2..00	Doubling of uterus	1	0	1210
PC20.00	Doubling of uterus, unspecified	1	0	27316
PC21.00	Didelphic uterus	1	0	34376
PC22.00	Doubling of uterus, including cervix and vagina	1	0	56096
PC2z.00	Doubling of uterus NOS	1	0	73444
PC3..00	Other anomalies of uterus	1	0	29548
PC30.00	Congenital absence of uterus	1	0	5420
PC31.00	Agenesis of uterus	1	0	46449
PC32.00	Aplasia of uterus	1	0	36724
PC33.00	Bicornuate uterus	1	0	3313
PC34.00	Uterus unicornis	1	0	22190
PC35.00	Displaced uterus	1	0	23551
PC35.11	Congenital prolapse of uterus	1	0	10682
PC36.00	Fistulae involving uterus with digestive or urinary tract	1	0	28990
PC36100	Uterovesical fistula, congenital	1	0	73606
PC36z00	Fistula involving uterus with digestive or urinary tract NOS	1	0	34020
PC3y.00	Other specified anomalies of uterus	1	0	49349
PC3z.00	Anomalies of uterus NOS	1	0	20175
PC4..00	Cervical, vaginal and external female genital anomalies	1	0	37166
PC40.00	Cervical/vaginal/external female genital anomalies, unspec	1	0	46001
PC41.00	Embryonic cyst of cervix/vagina/external female genitalia	1	0	98842
PC41000	Congenital cyst of canal of Nuck	1	0	52813
PC41011	Patent canal of Nuck	1	0	94803

PC41100	Embryonal cyst of vagina	1	0	72382
PC41200	Congenital cyst of vulva	0	1	59290
PC41300	Embryonic cyst of cervix	1	0	97489
PC41z00	Embryonic cyst cervix/vagina/external female genitalia NOS	1	0	103074
PC42.00	Imperforate hymen	0	1	9697
PC43.00	Rectovaginal fistula, congenital	1	0	39115
PC4y.00	Other cervical, vaginal and external female genital anomaly	1	0	34242
PC4y000	Congenital absence of cervix	1	0	57934
PC4y100	Agenesis of cervix	1	0	64895
PC4y200	Congenital absence of clitoris	1	0	57747
PC4y400	Congenital absence of vagina	1	0	33252
PC4y411	Rudimentary vagina	1	0	66507
PC4y500	Agenesis of vagina	1	0	31737
PC4y600	Congenital absence of vulva	1	0	102452
PC4y611	Congenital absence of labium major	1	0	66234
PC4y612	Congenital absence of labium minor	1	0	104930
PC4y700	Agenesis of vulva	1	0	57195
PC4y800	Congenital stenosis of cervical canal	1	0	32484
PC4y900	Congenital stenosis of vagina	1	0	37200
PC4y911	Congenital stricture of vagina	1	0	62647
PC4yA00	Atresia of cervix	1	0	65385
PC4yB00	Atresia of vagina	1	0	36548
PC4yB11	Imperforate vagina	1	0	24743
PC4yC00	Congenital vaginal cyst NEC	1	0	30143
PC4yD00	Fusion of vulva	1	0	38892
PC4yD11	Fusion of labia	0	1	18504
PC4yE00	Congenital labial adhesions	0	1	30673
PC4yv00	Other congenital anomaly of cervix	1	0	31869
PC4yw00	Other congenital anomaly of vagina	1	0	34927
PC4yw11	Vaginal septum	1	0	12877
PC4yx00	Other congenital anomaly of vulva	1	0	27838
PC4yy00	Other congenital anomaly of clitoris	1	0	37434
PC4yy11	Hooded clitoris	1	0	94713
PC4yy12	Hypertrophy of clitoris	0	1	44127
PC4yz00	Other cervical/vaginal/external female genital anomaly NOS	1	0	15833
PC4z.00	Cervical, vaginal and external female genital anomaly NOS	1	0	67727
PC5..00	Undescended testicle	0	1	634
PC50.00	Cryptorchidism	0	1	10965
PC50000	Cryptorchidism, unilateral	0	1	44918
PC50100	Cryptorchidism, bilateral	0	1	47565
PC50z00	Cryptorchidism NOS	0	1	33424
PC51.00	Ectopic testis	0	1	5241
PC5z.00	Undescended testicle NOS	0	1	28215
PC5z.11	Retractile testis	0	1	1235

PC5z.12	Maldescent of testicle	0	1	12695
PC5z000	Undescended testis, unilateral	0	1	6794
PC5z011	Maldescent of testis, unilateral	0	1	46552
PC5z100	Undescended testis, bilateral	0	1	6451
PC5z111	Maldescent of testis, bilateral	0	1	19026
PC6..00	Hypospadias and epispadias	1	0	47515
PC60.00	Hypospadias	1	0	2912
PC60000	Hypospadias, penile	1	0	8653
PC60100	Hypospadias, penoscrotal	1	0	44116
PC60200	Hypospadias, perineal	1	0	59186
PC60300	Hypospadias, balanic	1	0	40156
PC60311	Hypospadias, glanular	1	0	22511
PC60312	Hypospadias, glandular	1	0	18716
PC61.00	Epispadias	1	0	29629
PC62.00	Congenital chordee	1	0	6633
PC6z.00	Hypospadias or epispadias NOS	1	0	66442
PC7..00	Indeterminate sex and pseudohermaphroditism	1	0	27395
PC70.00	True hermaphroditism	1	0	46264
PC70.11	Ovotestis	1	0	101448
PC71.00	Male pseudohermaphroditism	1	0	54216
PC72.00	Female pseudohermaphroditism	1	0	64539
PC73.00	Pure gonadal dysgenesis	1	0	36078
PC7z.00	Indeterminate sex or pseudohermaphroditism NOS	1	0	50066
PC7z000	Indeterminate sex NOS	1	0	29508
PC7z011	Intersex NEC	1	0	41272
PC7z100	Pseudohermaphrodite NOS	1	0	48532
PC7z111	False hermaphrodite	1	0	97883
PC8..00	Congenital anomaly of male genital system	1	0	95165
PC80.00	Other specified congenital anomaly of male genital system	1	0	94685
PCy..00	Other specified genital organ anomaly	1	0	27785
PCy0.00	Absence of genital organ NEC	1	0	44106
PCy0000	Congenital absence of penis	1	0	49245
PCy0200	Congenital absence of spermatic cord	1	0	71042
PCy0300	Congenital absence of vas deferens	1	0	35358
PCy0z00	Genital organ absence NEC NOS	1	0	61189
PCy1.00	Congenital aplasia of genital organ NEC	1	0	94282
PCy1000	Congenital aplasia of prostate	1	0	91739
PCy1200	Congenital aplasia of testicle	1	0	4339
PCy1300	Congenital aplasia of scrotum	1	0	38020
PCy1400	Aplasia of penis	1	0	92836
PCy2.00	Hypoplasia of genital organ NEC	1	0	57530
PCy2000	Hypoplasia of penis	0	1	23948
PCy2100	Hypoplasia of testis	1	0	9690
PCy2200	Hypoplasia of scrotum	1	0	51726
PCy2z00	Hypoplasia of genital organ NEC NOS	1	0	67754
PCy3.00	Atresia of genital organ NEC	1	0	95015
PCy3000	Atresia of ejaculatory duct	1	0	56100

PCy3z00	Atresia of genital organ NEC NOS	1	0	62335
PCy4.00	Anorchism	1	0	8983
PCy4.11	Congenital absence of both testes	1	0	53312
PCy4.12	Testicular agenesis, bilateral	1	0	48765
PCy5.00	Monorchism	1	0	27323
PCy5.11	Congenital absence of testis, unilateral	1	0	28912
PCy5.12	Testicular agenesis, unilateral	1	0	38998
PCy6.00	Polyorchism	1	0	66290
PCy7.00	Congenital lateral curvature of penis	0	1	17121
PCy8.00	Fusion of testes	1	0	31019
PCyA.00	Cysts of embryonic remnants NEC	1	0	43603
PCyA000	Hydatid cyst of Morgagni	1	0	29146
PCyA100	Wolffian duct cyst	1	0	59487
PCyA200	Hydatid cyst of Morgagni - male	1	0	28043
PCyA300	Hydatid cyst of Morgagni - female	1	0	57663
PCyA400	Wolffian duct cyst - male	1	0	69548
PCyA500	Wolffian duct cyst - female	1	0	38911
PCyA600	Cyst of embryonic remnant - male	1	0	43727
PCyA700	Cyst of embryonic remnant - female	1	0	43654
PCyB.00	Doubling of vagina	1	0	31397
PCyw.00	Other congenital anomaly of testis or scrotum	1	0	22437
PCyx.00	Other congenital anomaly of vas deferens or prostate	1	0	39361
PCyy.00	Other congenital anomaly of penis	1	0	25455
PCyy000	Hooded penis	0	1	30595
PCyy100	Webbed penis	1	0	17653
PCyyz00	Other congenital anomaly of penis NOS	1	0	64313
PCyz.00	Other specified genital organ anomaly NOS	1	0	4338
PCz..00	Genital organ anomaly NOS	1	0	31756
PD...00	Urinary system congenital anomalies	1	0	25382
PD0..00	Renal agenesis and dysgenesis	1	0	30097
PD00.00	Renal agenesis, unspecified	1	0	27474
PD00000	Bilateral renal agenesis	1	0	63634
PD00100	Unilateral renal agenesis	1	0	31961
PD00z00	Renal agenesis, unspecified NOS	1	0	55985
PD01.00	Congenital renal atrophy	1	0	27471
PD02.00	Congenital absence of kidney	1	0	3314
PD02000	Bilateral congenital absence of kidneys	1	0	71154
PD02100	Unilateral congenital absence of kidney	1	0	23958
PD02z00	Congenital absence of kidney NOS	1	0	65407
PD03.00	Hypoplasia of kidney	1	0	4764
PD03000	Bilateral renal hypoplasia	1	0	42925
PD03011	Potter's syndrome	1	0	23960
PD03100	Unilateral renal hypoplasia	1	0	30650
PD04.00	Dysplasia of kidney	1	0	10063
PD04000	Bilateral renal dysplasia	1	0	9500
PD04011	Bilateral renal dysgenesis	1	0	20878
PD04100	Unilateral renal dysplasia	1	0	24120
PD04111	Unilateral renal dysgenesis	1	0	54656

PD04z00	Dysplasia of kidney NOS	1	0	54798
PD0z.00	Renal agenesis or dysgenesis NOS	1	0	29659
PD1..00	Congenital cystic kidney disease	1	0	15917
PD1..11	Congenital cystic renal disease	1	0	20629
PD1..12	Fibrocystic kidney	1	0	59064
PD1..13	Polycystic kidney	1	0	4504
PD1..14	Sponge kidney	1	0	27436
PD10.00	Congenital renal cyst, single	0	1	17523
PD11.00	Polycystic kidney disease	1	0	4503
PD11000	Polycystic kidneys, infantile type	1	0	21381
PD11100	Polycystic kidneys, adult type	1	0	4505
PD11z00	Polycystic kidney disease NOS	1	0	56852
PD11z11	Cystic kidney disease NEC	1	0	9240
PD12.00	Medullary cystic disease	1	0	42632
PD12000	Medullary cystic disease, juvenile type	1	0	66998
PD12011	Nephronophthisis	1	0	42042
PD12100	Medullary cystic disease, adult type	1	0	47135
PD12111	Medullary sponge kidney	1	0	7718
PD12y00	Medullary cystic disease OS	1	0	64694
PD12z00	Medullary cystic disease NOS	1	0	41522
PD13.00	Multicystic renal dysplasia	1	0	18331
PD13.11	Multicystic kidney	1	0	11946
PD1y.00	Other specified congenital cystic kidney disease	1	0	59018
PD1y000	Fibrocystic kidney disease	1	0	67486
PD1y011	Fibrocystic renal degeneration	1	0	37751
PD1yz00	Other congenital cystic kidney disease NOS	1	0	59031
PD1z.00	Congenital cystic kidney disease NOS	1	0	50331
PD2..00	Renal pelvis and ureter obstructive defects	1	0	30445
PD20.00	Atresia of ureter	1	0	49700
PD21.00	Occlusion of ureter	1	0	29096
PD21.11	Congenital ureteric valves	1	0	59736
PD22.00	Congenital stricture of ureter	1	0	33355
PD22.11	Congenital stenosis of ureter	1	0	50820
PD22000	Congenital stricture of ureter, unspecified	1	0	97464
PD22100	Congenital stricture of ureteropelvic junction	1	0	27646
PD22200	Congenital stricture of ureterovesical orifice	1	0	96829
PD22z00	Congenital stricture of ureter NOS	1	0	69191
PD23.00	Congenital hydronephrosis	1	0	5379
PD23.11	Congenital dilated renal pelvis	1	0	22571
PD24.00	Congenital dilatation of ureter	1	0	26403
PD25.00	Hydroureter - congenital	1	0	46116
PD26.00	Megaloureter - congenital	1	0	5099
PD27.00	Ureterocele - congenital	1	0	37491
PD2y.00	Other specified obstructive defect of renal pelvis or ureter	1	0	43336
PD2z.00	Obstructive defect of renal pelvis or ureter NOS	1	0	46177
PD3..00	Other specified renal anomaly	1	0	4430
PD30.00	Accessory kidney	1	0	52700

PD30.11	Duplication of kidney	1	0	59280
PD30.12	Renal duplication NEC	1	0	32963
PD30.13	Supernumerary kidney	1	0	60051
PD31.00	Congenital calculus of kidney	1	0	56531
PD32.00	Congenital displaced kidney	1	0	38927
PD33.00	Discoid kidney	1	0	67478
PD34.00	Double kidney with double pelvis	1	0	28362
PD34.11	Duplex kidneys	1	0	4431
PD34.12	Pyelon duplex	1	0	24709
PD35.00	Ectopic kidney	1	0	15142
PD35.11	Pelvic kidney	1	0	32543
PD36.00	Fusion of kidneys	1	0	54820
PD37.00	Giant kidney	0	1	56958
PD38.00	Horseshoe kidney	1	0	2810
PD39.00	Hyperplasia of kidney	0	1	16523
PD3A.00	Lobulation of kidney	1	0	45794
PD3A.11	Ren arcuatus	1	0	112306
PD3B.00	Malrotation of kidney	1	0	53965
PD3C.00	Triple kidney with triple pelvis	1	0	92988
PD3C.12	Pyelon triplex	1	0	69272
PD3D.00	Enlarged kidney	1	0	29780
PD3z.00	Other specified renal anomaly NOS	1	0	15420
PD4..00	Other specified ureter anomalies	1	0	42500
PD40.00	Absent ureter	1	0	63227
PD41.00	Accessory ureter	1	0	69810
PD42.00	Deviation of ureter	1	0	64616
PD43.00	Displaced ureteric orifice	1	0	63963
PD44.00	Double ureter	1	0	3725
PD44.11	Duplication of ureter	1	0	38107
PD45.00	Ectopic ureter	1	0	23545
PD45.12	Ectopic insertion of ureter	1	0	105821
PD46.00	Anomalous ureter implantation	1	0	15901
PD47.00	Congenital vesico-uretero-renal reflux	0	1	24918
PD4z.00	Other specified ureter anomaly NOS	1	0	31469
PD5..00	Exstrophy of urinary bladder	1	0	36549
PD5..11	Ectopia vesicae	1	0	108545
PD5..12	Ectopic bladder	1	0	99053
PD50.00	Ectopic bladder	1	0	35770
PD50.11	Ectopia vesicae	1	0	10744
PD5z.00	Exstrophy of urinary bladder NOS	1	0	64965
PD6..00	Urethra and bladder neck atresia and stenosis	1	0	47679
PD60.00	Congenital bladder neck obstruction	1	0	19654
PD60000	Atresia of bladder neck	1	0	97475
PD60100	Stenosis of bladder neck	1	0	31125
PD60z00	Congenital bladder neck obstruction NOS	1	0	47854
PD61.00	Congenital obstruction of urethra	1	0	34741
PD61000	Atresia of anterior urethra	1	0	95045
PD61100	Stenosis of anterior urethra	1	0	16708

PD61z00	Congenital obstruction of urethra NOS	1	0	100419
PD62.00	Congenital urethral valvular stricture	1	0	41342
PD62.11	Congenital posterior urethral valves	1	0	69107
PD63.00	Congenital urinary meatus stricture	1	0	31985
PD63.11	Congenital urinary meatus obstruction	1	0	67371
PD63.12	Congenital pinhole urinary meatus	1	0	32124
PD63100	Stenosis of urinary meatus	1	0	18806
PD63z00	Congenital urinary meatus stricture NOS	1	0	71832
PD64.00	Congenital vesicourethral orifice stricture	1	0	104830
PD65.00	Imperforate urinary meatus	1	0	51541
PD66.00	Impervious urethra	1	0	98164
PD67.00	Congenital posterior urethral valves	1	0	11710
PD6y.00	Other specified urethra or bladder neck atresia or stenosis	1	0	52312
PD6z.00	Urethra or bladder neck atresia or stenosis NOS	1	0	25806
PD7..00	Anomalies of urachus	1	0	30315
PD70.00	Cyst of urachus	1	0	34084
PD71.00	Fistula of urachus	1	0	67153
PD72.00	Patent urachus	1	0	35888
PD72.11	Persistent urachus	1	0	65185
PD73.00	Persistent umbilical sinus	1	0	9751
PD7y.00	Other specified anomalies of urachus	1	0	101112
PD7z.00	Anomalies of urachus NOS	1	0	56889
PDy..00	Other specified bladder and urethral anomalies	1	0	50320
PDy0.00	Congenital absence of bladder	1	0	39970
PDy2.00	Accessory bladder	1	0	58667
PDy3.00	Accessory urethra	1	0	51524
PDy4.00	Congenital bladder diverticulum	1	0	20314
PDy5.00	Congenital bladder hernia	1	0	57166
PDy6.00	Congenital urethrorectal fistula	1	0	29419
PDy7.00	Congenital prolapse of bladder mucosa	1	0	41025
PDy8.00	Congenital prolapse of urethra	1	0	47479
PDy9.00	Double urethra	1	0	27283
PDyA.00	Double urinary meatus	1	0	61128
PDyz.00	Other bladder or urethral anomaly NOS	1	0	34636
PDyz000	Epispadias, female	1	0	65057
PDyz100	Hypospadias, female	1	0	57744
PDz..00	Urinary system anomalies NOS	1	0	4817
PDz0.00	Unspecified anomaly of kidney	1	0	17356
PDz1.00	Unspecified anomaly of ureter	1	0	16257
PDz2.00	Unspecified anomaly of bladder	1	0	44752
PDz3.00	Unspecified anomaly of urethra	1	0	46880
PE...00	Certain congenital musculoskeletal deformities	0	1	44150
PE...11	Congenital musculoskeletal deformities	0	1	3298
PE0..00	Skull, face and jaw congenital deformities	0	1	17914
PE0..11	Face congenital deformities	0	1	36168
PE0..12	Jaw congenital deformities	0	1	30123
PE0..13	Skull congenital deformities	0	1	18808

PE00.00	Asymmetry of face	0	1	8325
PE00000	Hemifacial microsomia	0	1	9371
PE00100	Asymmetrical crying face syndrome	0	1	40969
PE01.00	Compression facies	0	1	26732
PE02.00	Potter's facies	0	1	73612
PE03.00	Depressions in skull	0	1	59811
PE04.00	Dolichocephaly	0	1	38937
PE05.00	Plagiocephaly	0	1	1519
PE05.11	Asymmetric head	0	1	20556
PE06.00	Congenital nasal septum deviation	0	1	16924
PE07.00	Congenital bent or squashed nose	0	1	53454
PE0z.00	Skull, face or jaw congenital deformities NOS	0	1	54258
PE1..00	Congenital sternomastoid torticollis	0	1	8721
PE1..11	Congenital wry neck	0	1	65125
PE1..12	Sternomastoid tumour	0	1	4156
PE2..00	Congenital spine deformity	0	1	22012
PE20.00	Congenital spine deformity, unspecified	0	1	49933
PE21.00	Congenital postural lordosis	0	1	8358
PE22.00	Congenital postural scoliosis	0	1	4330
PE23.00	Congenital scoliosis due to congenital bony malformation	0	1	9567
PE2z.00	Congenital spine deformity NOS	0	1	29412
PE2z.11	Congenital postural curvature of spine NOS	0	1	38363
PE3..00	Congenital dislocation and subluxation of the hip	1	0	9239
PE30.00	Congenital dislocation of hip	1	0	933
PE30000	Unilateral congenital dislocation of hip	1	0	45970
PE30100	Bilateral congenital dislocation of hip	1	0	38373
PE30z00	Congenital dislocation of hip NOS	1	0	33576
PE31.00	Congenital subluxation of hip	0	1	14938
PE31000	Unilateral congenital subluxation of hip	0	1	34019
PE31011	Unstable hip	0	1	63645
PE31012	Preluxation of hip	0	1	93328
PE31013	Predislocation status of hip at birth	0	1	93994
PE31014	Congenital instability of hip joint	0	1	97269
PE31100	Bilateral congenital subluxation of hip	0	1	61870
PE31z00	Congenital subluxation of hip NOS	0	1	62586
PE32.00	Congenital dislocation one hip with subluxation other hip	0	1	99310
PE33.00	Congenital clicking hip	0	1	8356
PE33.11	Clicky hips - congenital	0	1	6454
PE34.00	Dysplastic hip	0	1	3691
PE34000	Unilateral dysplastic hip	0	1	38772
PE34100	Bilateral dysplastic hip	0	1	34285
PE35.00	Unstable hip	0	1	24917
PE35000	Unilateral unstable hip	0	1	34246
PE35100	Bilateral unstable hip	0	1	50468
PE3z.00	Congenital dislocation of hip NOS	1	0	27301
PE4..00	Genu recurvatum and long leg bone bowing	0	1	21522

PE4..11	Congenital leg bone bowing	0	1	41198
PE40.00	Congenital genu recurvatum	0	1	50367
PE41.00	Congenital dislocation of knee	0	1	20745
PE41100	Congenital dislocation of knee grade II	1	0	103268
PE41300	Congenital dislocation of patella	1	0	65011
PE42.00	Congenital bowing of femur	0	1	29298
PE43.00	Congenital bowing of tibia and fibula	0	1	4805
PE43000	Congenital bowing of tibia	0	1	48290
PE43100	Congenital bowing of fibula	0	1	101875
PE44.00	Congenital bowing of long leg bone, unspecified	0	1	38801
PE44.11	Bow legs NOS	0	1	1971
PE4z.00	Genu recurvatum and long leg bone bowing NOS	0	1	61183
PE5..00	Varus deformities of feet	0	1	5955
PE50.00	Congenital talipes varus	0	1	22846
PE50.11	Pes varus	1	0	26456
PE50.12	Congenital clubfoot - varus	1	0	7039
PE51.00	Congenital talipes equinovarus	1	0	156
PE52.00	Metatarsus primus varus	0	1	11093
PE53.00	Congenital metatarsus varus	0	1	1463
PE54.00	Congenital metatarsus adductus	0	1	11198
PE5x.00	Complex varus foot deformities	1	0	63009
PE5y.00	Other specified varus feet deformity	1	0	43154
PE5y000	Congenital talipes calcaneovarus	0	1	7815
PE5yz00	Other specified varus foot deformity NOS	1	0	42135
PE5z.00	Varus foot deformity NOS	0	1	6974
PE6..00	Valgus deformities of feet	0	1	891
PE60.00	Congenital talipes valgus	0	1	29808
PE60.11	Congenital clubfoot - valgus	0	1	23980
PE61.00	Congenital pes planus	0	1	7384
PE61.11	Congenital flat foot	0	1	20004
PE61.13	Rigid flat foot	1	0	90878
PE61.14	Spastic flat foot	1	0	50982
PE61000	Congenital vertical talus	0	1	50065
PE62.00	Congenital talipes calcaneovalgus	0	1	6961
PE6y.00	Other valgus foot deformities	0	1	28010
PE6y000	Congenital talipes equinovalgus	0	1	31013
PE6y100	Congenital planovalgus	0	1	20312
PE6yz00	Other valgus foot deformity NOS	0	1	27621
PE6z.00	Valgus foot deformity NOS	0	1	23411
PE6z.11	Congenital metatarsus valgus	0	1	41807
PE7..00	Other deformities of feet	0	1	24526
PE70.00	Talipes, unspecified	0	1	4335
PE70.11	Clubfoot NOS	0	1	4331
PE71.00	Talipes cavus	0	1	15785
PE71.11	Congenital claw toe	0	1	19703
PE71.12	Pes cavus	0	1	1124
PE72.00	Congenital pes cavus	0	1	7115
PE73.00	Congenital claw foot	0	1	2023

PE74.00	Short Achilles tendon, congenital	0	1	28212
PE7y.00	Other specified foot deformity	0	1	44293
PE7y000	Asymmetric talipes	0	1	29722
PE7y100	Congenital talipes calcaneus	0	1	38386
PE7y200	Congenital talipes equinus	0	1	4334
PE7y300	Congenital positional talipes	0	1	22854
PE7yz00	Other specified foot deformity NOS	0	1	44379
PE7z.00	Feet deformities NOS	0	1	40277
PE8..00	Other specified nonteratogenic anomalies	1	0	60362
PE80.00	Pectus excavatum, congenital	0	1	4014
PE80.11	Congenital funnel chest	0	1	27309
PE81.00	Pectus carinatum, congenital	0	1	22025
PE81.11	Congenital pigeon chest	0	1	25746
PE8y.00	Other nonteratogenic anomalies OS	1	0	67318
PE8y000	Congenital club hand	1	0	45651
PE8y011	Congenital club fingers	1	0	41019
PE8y100	Congenital chest wall deformity NEC	0	1	17068
PE8y111	Congenital thoracic wall deformity NEC	0	1	35125
PE8y200	Congenital dislocation of elbow	1	0	22301
PE8y300	Congenital flexion contractures of leg	1	0	56631
PE8y400	Congenital spade-like hand	1	0	61879
PE8y500	Guerin - Stern syndrome	1	0	47224
PE8y600	Congenital flexion contracture of hip	1	0	50307
PE8y700	Congenital abduction contracture of hip	1	0	20559
PE8y800	Congenital flexion contracture of knee	1	0	29124
PE8y900	Congenital short quadriceps	1	0	61605
PE8yA00	Congenital dislocation of radial head	1	0	37327
PE8yB00	Discoid meniscus - congenital	0	1	31710
PE8yz00	Other nonteratogenic anomaly NOS	1	0	30946
PE8yz11	Specified intrauterine postural deformity NEC	0	1	42648
PE8z.00	Nonteratogenic anomalies NOS	1	0	98081
PE9..00	Other musc skeletal deformity	0	1	26139
PE9..11	Other congenital musculoskeletal deformity	0	1	37167
PEz..00	Congenital musculoskeletal deformity NOS	0	1	33946
PF...00	Other congenital limb anomalies	0	1	14649
PF0..00	Polydactyly - supernumerary digits	1	0	3241
PF00.00	Supernumerary digits, unspecified	1	0	15526
PF01.00	Accessory fingers	1	0	16335
PF01000	Radial polydactyly Wassel 1	1	0	101754
PF01100	Radial polydactyly Wassel 2	1	0	100780
PF01200	Radial polydactyly Wassel 3	1	0	111768
PF01300	Radial polydactyly Wassel 4	1	0	94719
PF01400	Radial polydactyly Wassel 5	1	0	112725
PF01700	Central polydactyly	1	0	99672
PF01800	Ulnar polydactyly	1	0	69795
PF02.00	Accessory toes	1	0	17995
PF02000	Accessory hallux	1	0	59949
PF02100	Accessory little toe	1	0	49767

PF02200	Other accessory toe	1	0	48888
PF03.00	Accessory thumbs	1	0	28246
PF0z.00	Polydactyly NOS	1	0	40691
PF1..00	Syndactyly - webbing of digits	1	0	2483
PF10.00	Syndactyly of multiple digits, unspecified	1	0	63079
PF11.00	Syndactyly of fingers without bone fusion	1	0	41117
PF11.11	Webbed fingers	1	0	33365
PF11000	Simple syndactyly - 1st web	1	0	62902
PF11100	Simple syndactyly - 2nd to 4th web	0	1	70749
PF12.00	Syndactyly of fingers with bone fusion	1	0	4457
PF12.11	Fused fingers	1	0	40398
PF12.12	Osseous syndactyly of fingers	1	0	65604
PF12100	Osseous syndactyly - 2nd to 4th web	1	0	112765
PF13.00	Syndactyly of toes without bone fusion	1	0	56836
PF13.11	Webbed toes	0	1	3642
PF13000	Simple syndactyly of toes 1st web space	1	0	97353
PF13100	Simple syndactyly lesser toes	0	1	24936
PF14.00	Syndactyly of toes with bone fusion	1	0	67014
PF14.11	Fused toes	1	0	33927
PF14.12	Conjoined toes	1	0	36494
PF14.13	Syndactyly of toes with bone fusion	1	0	108734
PF14100	Osseous syndactyly lesser toes	1	0	104916
PF15.00	Polysyndactyly	1	0	38836
PF1z.00	Syndactyly NOS	1	0	43838
PF1z.11	Polysyndactyly	1	0	68991
PF1z.12	Symphalangism	1	0	66229
PF2..00	Reduction deformity of upper limb	1	0	43578
PF2..11	Arm reduction deformity	1	0	54315
PF20.00	Congenital shortening of arm, unspecified	1	0	19667
PF20.11	Brachymelia of arm	1	0	51709
PF20100	Ectromelia of upper limb NOS	1	0	70730
PF20200	Hemimelia of upper limb NOS	1	0	50784
PF20z00	Unspecified congenital shortening of arm NOS	1	0	73622
PF21.00	Transverse deficiency of arm	1	0	32039
PF21.11	Congenital absence part of arm	1	0	37973
PF21000	Transverse deficiency of arm, unspecified	1	0	96910
PF21100	Transverse deficiency of arm, phalangeal level, all fingers	1	0	104822
PF21200	Transverse deficiency of arm, forearm level	1	0	67807
PF21300	Transverse deficiency of arm, shoulder level(amelia)	1	0	61285
PF21400	Congenital amputation of upper limb	1	0	59307
PF21500	Transverse deficiency of arm, elbow level(hemimelia)	1	0	98901
PF21600	Transverse deficiency of arm, wrist level(hemimelia)	1	0	65248
PF21611	Acheiria	1	0	35834
PF21612	Rudimentary hand	1	0	28097
PF21613	Congenital absence of hand	1	0	46835
PF21z00	Transverse deficiency of arm NOS	1	0	103878
PF21z11	Agenesis of hand	1	0	56350

PF22.00	Longitudinal deficiency of arm NEC	1	0	105807
PF22000	Phocomelia of upper limb NOS	1	0	30613
PF22100	Rudimentary arm	1	0	59410
PF22z00	Longitudinal deficiency of arm NEC NOS	1	0	94122
PF23.00	Congenital absence upper arm and forearm with hand present	1	0	37277
PF23.11	Complete phocomelia of upper limb	1	0	97450
PF24.00	Congenital absence of upper arm only	1	0	72180
PF24.11	Proximal phocomelia of upper limb	1	0	61225
PF25.00	Congenital absence of forearm only	1	0	27624
PF25.11	Distal phocomelia of upper limb	1	0	50234
PF26.00	Agenesis of radial ray	1	0	95060
PF26.11	Congenital absence of radius	1	0	90910
PF26000	Hypoplasia of radius	1	0	62500
PF26100	Partial radial absence	1	0	106171
PF26200	Total radial absence	1	0	66061
PF26300	Absent thumb	1	0	44821
PF26400	Hypoplastic thumb-Blauth 1	1	0	93775
PF26500	Hypoplastic thumb-Blauth 2	1	0	36739
PF26600	Hypoplastic thumb-Blauth 3	1	0	103983
PF26700	Hypoplastic thumb-Blauth 4	1	0	101105
PF26800	Hypoplastic thumb-Blauth 5	1	0	104836
PF27.00	Agenesis of ulna	1	0	107677
PF27000	Partial defect of ulna	1	0	104751
PF27100	Total absence of ulna	1	0	68975
PF27200	Ulnar and humeroulnar synostosis	1	0	65514
PF28.00	Agenesis of carpals and metacarpals	1	0	49228
PF28.11	Transverse arrest of carpals and metacarpals	1	0	57346
PF28000	Transverse arrest carpal level	1	0	72940
PF28100	Transverse arrest metacarpal 1st ray	1	0	66066
PF28200	Transverse arrest metacarpal other	1	0	62884
PF29.00	Congenital absence of finger	1	0	33394
PF29.11	Ectrodactyly of finger	1	0	2021
PF29.12	Transverse arrest of phalanges	1	0	106011
PF29000	Transverse arrest phalangeal level 1st ray	1	0	107002
PF29100	Transverse arrest phalangeal level 2nd ray	1	0	105799
PF29300	Transverse arrest phalangeal level 4th ray	1	0	99016
PF29400	Transverse arrest phalangeal level 5th ray	1	0	99017
PF29z00	Congenital absence finger NOS	1	0	57051
PF2y.00	Other specified reduction deformities of upper limb	1	0	62804
PF2z.00	Reduction deformity of upper limb NOS	1	0	68535
PF2z.11	Hypoplasia of upper limb	1	0	22457
PF3..00	Reduction deformity of lower limb	1	0	34660
PF3..11	Leg reduction deformity	1	0	43649
PF30.00	Congenital shortening of leg, unspecified	1	0	4616
PF30.11	Brachymelia of leg	1	0	96366
PF30000	Ectromelia of lower limb NOS	1	0	73653
PF30100	Hemimelia of lower limb NOS	1	0	32907

PF30z00	Unspecified congenital leg shortening NOS	1	0	45385
PF31.00	Transverse deficiency of leg	1	0	65592
PF31100	Transverse deficiency lower limb - ankle level	1	0	106477
PF31112	Hemimelia - ankle level	1	0	67119
PF31200	Congenital absence of leg and foot	1	0	60525
PF31311	Amelia - lower limb	1	0	96409
PF31500	Transverse deficiency lower limb - knee level	1	0	70964
PF31511	Hemimelia - knee level	1	0	108988
PF32.00	Longitudinal reduction deformity of lower limb NEC	1	0	45605
PF32.11	Phocomelia of lower limb NOS	1	0	40975
PF33.00	Congenital absence of thigh and lower leg with foot present	1	0	50564
PF33.11	Complete phocomelia of lower limb	1	0	93219
PF34.00	Congenital absence of thigh only	1	0	95735
PF34.11	Proximal phocomelia of lower limb	1	0	104207
PF34000	Proximal femoral focal deficiency	1	0	99666
PF34100	Congenital short femur	1	0	94734
PF35.00	Congenital absence of lower leg only	1	0	72561
PF35.11	Distal phocomelia of lower limb	1	0	41398
PF36.00	Agenesis of tibia	1	0	66868
PF36000	Congenital tibial deficiency type I	1	0	112449
PF36200	Congenital tibial deficiency type III	1	0	104835
PF37.00	Agenesis of fibula	1	0	60930
PF37100	Congenital fibular deficiency type II	1	0	97903
PF38.00	Agenesis of tarsals and metatarsals	1	0	28646
PF38000	Agenesis of talus	1	0	92289
PF38200	Agenesis of other tarsal bone	1	0	89722
PF38500	Agenesis of 5th metatarsal	1	0	99156
PF38600	Agenesis of other metatarsal	1	0	103879
PF38700	Agenesis of 4th and 5th metatarsals	1	0	70263
PF39.00	Congenital absence of toe	1	0	35699
PF39000	Congenital absence of great toe	1	0	64730
PF39100	Congenital absence of 5th toe	1	0	69248
PF39200	Congenital absence of other lesser toe	1	0	96737
PF39400	Congenital absence of other multiple toes	1	0	64339
PF3A.00	Split foot	1	0	27774
PF3y.00	Other specified reduction deformities of lower limb	1	0	65217
PF3z.00	Reduction deformity of lower limb NOS	1	0	36487
PF3z.11	Hypoplasia of lower limb	1	0	24646
PF4..00	Reduction deformity of unspecified limb	1	0	27365
PF40.00	Congenital absence of limb NOS	1	0	28661
PF41.00	Amelia of unspecified limb	1	0	66912
PF43.00	Hemimelia of unspecified limb	1	0	73649
PF44.00	Phocomelia of unspecified limb	1	0	41471
PF45.00	Congenital amputation of unspecified limb	1	0	53564
PF46.00	Longitudinal reduction deformity of unspecified limb	1	0	60133
PF47.00	Congenital absence of digits NOS	1	0	34321
PF47.11	Adactyly	1	0	59166

PF4y.00	Other specified reduction deformities of unspecified limb	1	0	110673
PF4y000	Brachymelia NOS	1	0	99157
PF4z.00	Reduction deformity of unspecified limb NOS	1	0	62732
PF4z.11	Brachydactyly NOS	1	0	49171
PF4z.12	Withered limb	1	0	65349
PF4z.13	Hypoplasia of limb NOS	1	0	51993
PF5..00	Other upper limb and shoulder anomaly	1	0	44219
PF50.00	Upper limb anomaly, unspecified	0	1	14964
PF51.00	Congenital deformity of clavicle	1	0	28542
PF51.11	Clavicle agenesis	1	0	107012
PF52.00	Congenital elevation of scapula	1	0	15859
PF52.11	Sprengel's deformity	1	0	36940
PF53.00	Radio-ulnar synostosis	1	0	32512
PF53000	Proximal radioulnar synostosis	1	0	64307
PF53100	Radioulnar synostosis and dislocation of radial head	1	0	54805
PF53200	Distal radioulnar synostosis	1	0	109481
PF54.00	Madelung's deformity	1	0	28025
PF55.00	Acrocephalosyndactyly	1	0	63274
PF55.11	Apert's syndrome	1	0	37402
PF55000	Acrocephalosyndactyly (Apert)	1	0	41840
PF55100	Acrocephalosyndactyly (Pfeiffer)	1	0	50251
PF55300	Saethre-Chotzen syndrome	1	0	57986
PF56.00	Accessory carpal bones	0	1	15749
PF57.00	Macroactylia (fingers)	1	0	41345
PF57000	Macroactylly - simple	1	0	56166
PF57100	Macroactylly - fatty nerve tumor	1	0	104353
PF58.00	Congenital cleft hand	1	0	30141
PF58.11	Lobster-claw hand	1	0	33984
PF58200	Cleft hand with syndactylly	1	0	56313
PF58300	Cleft hand with polydactylly	1	0	101514
PF59000	Windblown hand	1	0	71088
PF59300	Aberrant intrinsic muscles	1	0	97774
PF59400	Poland's syndrome	1	0	70743
PF59500	Thumb in palm deformity	0	1	20442
PF59600	Congenital trigger thumb	0	1	17433
PF5A.00	Other failure of differentiation, skeletal tissues of arm	1	0	95375
PF5A100	Capitate-hamate synostosis	1	0	46124
PF5A200	Scaphoid-lunate synostosis	1	0	65714
PF5A300	Other carpal synostosis	1	0	89442
PF5A400	PIP joint symphalangism	1	0	93506
PF5A500	DIP joint symphalangism	1	0	104729
PF5B.00	Other duplication of limb	1	0	37804
PF5B200	Duplication of radius	1	0	112797
PF5Bz00	Duplication of limb NOS	1	0	66174
PF5C.00	Other overgrowth of upper limb	1	0	61661
PF5C100	Overgrowth of partial upper limb	1	0	106182
PF5Cz00	Other overgrowth of limb NOS	1	0	99226

PF5D100	Undergrowth of whole hand	1	0	56203
PF5D200	Brachymetacarpia	1	0	47441
PF5Dz00	Other undergrowth of limb NOS	1	0	105008
PF5E.00	Constriction ring syndrome of upper limb	1	0	24053
PF5E000	Constriction ring	1	0	38896
PF5E100	Constriction ring with lymphoedema	1	0	93038
PF5E200	Acrosyndactyly	1	0	62353
PF5E300	Intra-uterine amputation	1	0	99600
PF5E400	Constriction ring with acrosyndactyly and amputation	1	0	104024
PF5F.00	Congenital absence of both forearm and hand	1	0	48901
PF5G.00	Congenital complete absence of upper limb(s)	1	0	48508
PF5r.00	Other congenital anomalies of fingers	0	1	26291
PF5r000	Triphalangeal thumb	1	0	42203
PF5r100	Brachydactyly of fingers, unspecified	1	0	46129
PF5r200	Camptodactyly	0	1	7998
PF5r300	Clinodactyly	0	1	6342
PF5r400	Flexion deformity of fingers	0	1	10556
PF5r500	Brachydactyly-all 3 phalanges	1	0	67022
PF5r600	Brachydactyly-missing phalanx	1	0	64701
PF5r700	Symbrachydactyly	1	0	45447
PF5r800	Camptodactyly-little finger	0	1	37895
PF5r900	Camptodactyly-other or multiple	1	0	55981
PF5rA00	Clinodactyly with delta phalanx	0	1	53574
PF5rB00	Clinodactyly, no delta phalanx	1	0	102900
PF5rC00	Brachymesophalangia	1	0	68342
PF5rD00	Congenital malformation of thumb	1	0	37965
PF5rz00	Other anomaly of fingers NOS	1	0	48177
PF5s.00	Other congenital anomalies of hand	0	1	5594
PF5t.00	Other congenital anomalies of wrist	1	0	54598
PF5u.00	Other congenital anomalies of forearm	1	0	66010
PF5u000	Radio-ulnar dysostosis	1	0	34717
PF5uz00	Other congenital anomaly forearm NOS	1	0	61558
PF5v.00	Congenital anomalies of elbow and upper arm	1	0	24218
PF5v.11	Cubitus NOS	1	0	31908
PF5w.00	Other congenital anomalies of shoulder	1	0	63972
PF5w.11	Congenital deformity of scapula NEC	1	0	49743
PF5x.00	Other congenital anomalies of whole arm	1	0	48510
PF5y.00	Other upper limb and shoulder anomaly OS	1	0	102633
PF5y000	Cleidocranial dysostosis	1	0	30227
PF5y011	Cleidocranial dysplasia	1	0	56876
PF5y100	Congenital cubitus valgus	1	0	65963
PF5y200	Congenital cubitus varus	1	0	68582
PF5y300	Congenital humeral varus	1	0	62024
PF5y400	Humeroradial synostosis	1	0	102227
PF5y500	Humeroulnar synostosis	1	0	103201
PF5y600	Total elbow synostosis	1	0	70267
PF5yz00	Other upper limb and shoulder anomaly NOS	1	0	97110
PF5z.00	Upper limb or shoulder anomaly NOS	0	1	16058

PF6..00	Other lower limb and pelvic girdle anomalies	1	0	72487
PF60.00	Lower limb anomaly, unspecified	0	1	15502
PF61.00	Congenital coxa valga	1	0	38305
PF62.00	Congenital coxa vara	1	0	40980
PF63.00	Other congenital hip joint deformity	0	1	15949
PF63000	Congenital anteversion of femoral neck	0	1	9549
PF63100	Congenital hip dysplasia	0	1	2889
PF63111	Developmental dysplasia of the hip	0	1	19123
PF63200	Congenital acetabular dysplasia	0	1	32418
PF63X00	Congenital deformity of hip, unspecified	0	1	40517
PF63z00	Other congenital hip joint deformity NOS	1	0	63834
PF64.00	Congenital knee joint deformity	1	0	15124
PF64000	Congenital absence of patella	1	0	61638
PF64100	Congenital genu valgum - knock-knee	0	1	11338
PF64200	Congenital genu varum - bowleg	0	1	17935
PF64300	Rudimentary patella	1	0	95032
PF64400	Congenital dislocation of patella	1	0	21813
PF64500	Bipartite patella	1	0	47736
PF64z00	Congenital knee joint deformity NOS	1	0	50077
PF65.00	Macroductyia of toes	1	0	24643
PF65000	Macroductyly of toes - simple	1	0	72268
PF66.00	Other congenital anomalies of toe	0	1	944
PF66000	Congenital hallux valgus	0	1	7965
PF66100	Congenital hallux varus	0	1	7405
PF66200	Congenital hammer toe	0	1	8626
PF66300	Brachydactyly of toes	0	1	68317
PF66400	Congenital crossed toes	0	1	18517
PF66411	Congenital overlapping toes	0	1	22585
PF66500	Congenital curly toes	0	1	4333
PF66600	Brachyphalangia of little toe	0	1	108865
PF66800	Perodactyilia of great toe	0	1	42733
PF66900	Perodactyilia of lesser toe	0	1	103258
PF66B00	Triphalangeal great toe	0	1	94794
PF66z00	Other toe anomalies NOS	0	1	33960
PF67.00	Congenital anomalies of foot NEC	0	1	2070
PF67000	Astragaloscaphoid synostosis	0	1	60339
PF67100	Calcaneonavicular bar	0	1	12263
PF67200	Coalition of calcaneous	0	1	37141
PF67300	Talonavicular synostosis	0	1	48474
PF67400	Tarsal coalitions	0	1	5376
PF67500	Lobster claw foot	0	1	53079
PF67600	Rocker bottom foot	0	1	46253
PF67700	Accessory tarsal bones	0	1	35097
PF67800	Talocalcaneal bar	0	1	54298
PF67900	Naviculocuneiform bar	0	1	57873
PF67A00	Complex tarsal coalition	0	1	23669
PF67z00	Anomalies of foot NEC NOS	0	1	37404

PF69.00	Failure of differentiation of skeletal tissues of lower limb	1	0	101628
PF69000	Congenital synostosis of lower limb bones	1	0	99687
PF6A.00	Duplication of lower limb bone	1	0	40983
PF6B.00	Congenital overgrowth of lower limb	1	0	46652
PF6B200	Congenital overgrowth of foot	1	0	53673
PF6B300	Congen overgrowth of whole lower limb	1	0	62705
PF6C.00	Congenital undergrowth of lower limb	1	0	62450
PF6C000	Congenital undergrowth of proximal part of limb	1	0	54180
PF6C100	Congenital undergrowth of distal part of limb	1	0	64939
PF6C300	Brachymetapodia of 1st metatarsal	1	0	110670
PF6C400	Brachymetapodia of 4th metatarsal	1	0	69843
PF6C500	Brachymetapodia of other metatarsal	1	0	101472
PF6D.00	Constriction ring syndrome of lower limb	1	0	67293
PF6D000	Constriction ring of lower limb	1	0	93784
PF6D200	Intrauterine amputation of lower limb	1	0	48471
PF6D300	Constriction ring syndrome of lower limb with amputation	1	0	28775
PF6E.00	Congenital absence of thigh and lower leg with foot present	1	0	64988
PF6v.00	Other congenital anomalies of lower leg	1	0	59150
PF6w.00	Other congenital anomalies of upper leg	1	0	92299
PF6x.00	Other congenital anomalies of pelvis	1	0	25190
PF6xz00	Other congenital anomalies of pelvis NOS	1	0	55114
PF6y.00	Other lower limb anomalies	0	1	44728
PF6y000	Congenital angulation of tibia	0	1	54295
PF6y100	Congenital deformity of ankle joint	1	0	27426
PF6y200	Congenital deformity of sacroiliac joint	1	0	64527
PF6y300	Congenital fusion of sacroiliac joint	1	0	67220
PF6y400	Congenital varus ankle	1	0	36277
PF6y500	Congenital valgus ankle	0	1	36791
PF6y600	Congenital pseudarthrosis of tibia	1	0	48469
PF6yz00	Other lower limb and pelvic girdle anomaly NOS	1	0	46734
PFy..00	Other specified anomalies of unspecified limb	1	0	52738
PFy0.00	Arthrogryposis multiplex congenita	1	0	38479
PFy1.00	Larsen's syndrome	1	0	36839
PFy2.00	Arthrogryposis, unspecified	1	0	112462
PFy3.00	Distal arthrogryposis syndrome	1	0	39538
PFy4.00	Other arthrogryposis syndromes	1	0	60165
PFyz.00	Other anomaly of unspecified limb NOS	1	0	66220
PFz..00	Congenital anomaly of unspecified limb NOS	0	1	9723
PG...00	Other congenital musculoskeletal anomalies	0	1	2948
PG0..00	Skull and face bone anomalies	1	0	29367
PG0..11	Face bone anomalies	0	1	46833
PG0..12	Skull and face bone anomalies	0	1	31160
PG00.00	Congenital absence of skull bones	1	0	38119
PG01.00	Acrocephaly	1	0	48272
PG02.00	Congenital forehead deformity	0	1	17050

PG03.00	Craniosynostosis	1	0	16897
PG03.11	Scaphocephaly	1	0	39894
PG03000	Muenke syndrome	1	0	96333
PG04.00	Craniofacial dysostosis	1	0	21281
PG04.11	Crouzon's disease	1	0	25783
PG04.12	Triglorhinophalangeal dysplasia	1	0	107520
PG05.00	Hypertelorism	0	1	14985
PG06.00	Imperfect fusion of skull	1	0	5246
PG07.00	Oxycephaly	1	0	40350
PG08.00	Platybasia	1	0	25250
PG09.00	Premature cranial suture closure	0	1	27292
PG0B.00	Trigonocephaly	1	0	38476
PG0C.00	Pierre - Robin syndrome	1	0	4046
PG0D.00	Mandibulofacial dysostosis	1	0	44666
PG0D.12	Treacher - Collins syndrome	1	0	33385
PG0E.00	Oculomandibular dysostosis	0	1	44064
PG0E.11	Hallerman - Streif syndrome	1	0	69377
PG0F.00	Goldenhar's syndrome	1	0	18098
PG0G.00	Localised skull defects	1	0	51771
PG0G.11	Craniofacial dysplasia	1	0	53631
PG0G.12	Lacunar skull	1	0	32597
PG0G.13	Parietal foramina	0	1	74914
PG0H.00	Macrocephaly	0	1	6435
PG0J.00	Pierre Robin association	1	0	96210
PG0y.00	Other specified skull or face bone anomaly	0	1	60540
PG0y.11	Defect of skull ossification	1	0	42608
PG0y.12	Cranial dysostosis NEC	0	1	40979
PG0y000	Brachycephaly	0	1	33762
PG0yz00	Other anomaly of skull or face bone NOS	0	1	69913
PG0z.00	Skull or face bone anomaly NOS	0	1	15275
PG0z.11	Dysmorphic features	1	0	7462
PG1..00	Anomalies of spine	0	1	20810
PG10.00	Anomaly of spine, unspecified	1	0	60066
PG11.00	Congenital lumbosacral spondylolysis	1	0	35729
PG12.00	Congenital spondylolisthesis	1	0	1871
PG13.00	Congenital absence of vertebra	1	0	62641
PG13000	Congenital absence of cervical vertebra	1	0	68093
PG13200	Congenital absence of lumbar vertebra	1	0	90498
PG13300	Congenital absence of sacrum	0	1	43351
PG13311	Sacral agenesis	1	0	27473
PG14.00	Hemivertebra	0	1	25281
PG14000	Cervical hemivertebra	1	0	55966
PG14100	Thoracic hemivertebra	1	0	44822
PG14200	Lumbar hemivertebra	1	0	61054
PG14800	Lumbar hemivertebra - unbalanced	1	0	97893
PG14z00	Hemivertebra NOS	1	0	63497
PG15.00	Congenital fusion of spine	1	0	15499
PG15.11	Congenital lumbosacral fusion	0	1	29414

PG15000	Congenital complete fusion of spine	1	0	52822
PG15100	Congenital partial fusion of spine - balanced	1	0	91259
PG15200	Congenital partial fusion of spine - unbalanced	1	0	53028
PG15400	Congenit partial fusion spine with hemivertebra, unbalanced	1	0	112764
PG16.00	Klippel-Feil syndrome	1	0	4674
PG16000	Wilderwanck's syndrome	1	0	56152
PG16z00	Klippel - Feil syndrome NOS	1	0	73985
PG17.00	Spina bifida occulta	0	1	3336
PG18.00	Congenital kyphosis	0	1	19669
PG18.11	Congenital kyphoscoliosis	1	0	28717
PG1u.00	Congenital anomalies of cervical vertebrae NEC	1	0	5574
PG1u000	Supernumerary cervical vertebra	1	0	104945
PG1uz00	Congenital anomaly of cervical vertebrae NEC NOS	1	0	41763
PG1v.00	Congenital anomalies of thoracic vertebrae NEC	1	0	40690
PG1vz00	Congenital anomaly of thoracic vertebrae NEC NOS	0	1	71152
PG1w.00	Congenital anomalies of lumbar vertebrae NEC	1	0	48726
PG1w000	Supernumerary lumbar vertebra	1	0	69532
PG1wz00	Congenital anomaly of lumbar vertebra NEC NOS	1	0	66463
PG1x.00	Congenital sacrococcygeal anomalies NEC	1	0	48088
PG1x000	Congenital absence of coccyx	1	0	93830
PG1x100	Congenital absence of sacrum	1	0	68081
PG1xz00	Congenital sacrococcygeal anomaly NOS	0	1	70583
PG1y.00	Other anomaly of spine	1	0	56878
PG1y.11	Congenital deformity of lumbosacral joint	1	0	53416
PG1y.12	Congenital deformity of lumbosacral region	1	0	51156
PG1y000	Platyspondylia	0	1	48194
PG1y100	Supernumerary vertebra	1	0	59334
PG1y300	Defect of vertebral segmentation	0	1	41216
PG1y400	Hypoplasia of spine	1	0	68493
PG1yz00	Other anomaly of spine NOS	0	1	22768
PG1z.00	Anomalies of spine NOS	1	0	45429
PG2..00	Cervical rib	0	1	872
PG3..00	Other rib and sternum anomalies	0	1	15048
PG30.00	Congenital absence of rib	0	1	42378
PG31.00	Congenital absence of sternum	1	0	63291
PG32.00	Congenital fissure of sternum	1	0	57566
PG33.00	Congenital fusion of ribs	1	0	35806
PG34.00	Sternum bifidum	0	1	63241
PG35.00	Mis-shapen ribs	0	1	30675
PG36.00	Extra ribs	0	1	42613
PG36.11	Supernumerary ribs	0	1	103870
PG37.00	Mis-shapen sternum	0	1	36610
PG3x.00	Other congenital anomalies of ribs	0	1	31378
PG3y.00	Other congenital anomalies of sternum	0	1	51424
PG3z.00	Other rib or sternum anomaly NOS	0	1	35735
PG3z.11	Anomalies of thoracic cage unspecified	1	0	66465
PG4..00	Chondrodysplasia	1	0	22756

PG40.00	Chondrodysplasia, unspecified	1	0	73905
PG41.00	Achondroplasia	1	0	12198
PG41.11	Dwarfism	1	0	5006
PG41.13	Achondroplastic dwarf	1	0	57804
PG41000	Hypochondroplasia	1	0	94173
PG42.00	Multiple enchondromata	1	0	35820
PG42.11	Enchondromatosis	1	0	52135
PG42.12	Ollier's disease	1	0	21987
PG42.14	Chondrodystrophy NEC	1	0	85337
PG42.15	Hypochondroplasia	1	0	29840
PG42.16	Osteopathia striata	1	0	59172
PG42.17	Pseudoachondroplasia	1	0	36351
PG42.18	Dyschondroplasia	1	0	36252
PG42000	Multiple enchondromata with haemangioma	1	0	59737
PG42011	Kast's syndrome	1	0	101861
PG42012	Maffucci's syndrome	1	0	61992
PG42100	Myotonic chondrodysplasia	1	0	105696
PG42z00	Dyschondroplasia NOS	1	0	73909
PG43.00	Asphyxiating thoracic dysplasia	1	0	65935
PG43.11	Jeune's syndrome	1	0	50228
PG44.00	Other specified dwarfing syndromes	1	0	65104
PG44000	Diastrophic dwarfism	1	0	68937
PG44011	Diastrophic dysplasia	1	0	71000
PG44100	Metatropic dwarfism	1	0	37743
PG44200	Thanatophoric dwarfism	1	0	56900
PG44211	Thanatophoric dysplasia	1	0	67262
PG44300	Mesomelic dysplasia	1	0	58771
PG44400	Acromesomelic dysplasia	1	0	89328
PG44500	Kniest dysplasia	1	0	45412
PG44600	Pseudoachondroplasia	1	0	43115
PG44z00	Other dwarfing syndromes NOS	1	0	95921
PG45.00	Metaphyseal dysostosis	1	0	26069
PG45.11	Jansen's metaphyseal dysostosis	1	0	67697
PG45.12	Schmid's metaphyseal dysostosis	1	0	56692
PG45.13	Craniometaphyseal dysostosis	1	0	65350
PG45.15	Metaphyseal dysplasia	1	0	45162
PG46.00	Spondyloepiphyseal dysplasia	1	0	27802
PG46000	Spondyloepiphyseal dysplasia congenita	1	0	100727
PG46100	Spondyloepiphyseal dysplasia tarda	1	0	93058
PG47.00	Congenital exostosis	1	0	10164
PG47.11	Multiple congenital exostosis	1	0	21984
PG48.00	Diaphyseal aclasis	1	0	26314
PG49.00	Dysplasia epiphysealis hemimelica	1	0	50583
PG4A.00	Metachondromatosis	1	0	70627
PG4B.00	Lethal retarded ossification syndromes	1	0	92892
PG4B000	Achondrogenesis	1	0	43119
PG4B100	Hypochondrogenesis	1	0	95041
PG4B200	Fibrochondrogenesis	1	0	94825

PG4B300	Short-rib/polydactyly syndrome	1	0	18160
PG4B400	Camptomelia dysplasia	1	0	68768
PG4C.00	Chondrodysplasia punctata	1	0	18193
PG4D.00	Metaphyseal chondrodysplasia	1	0	33811
PG4E.00	Spondylometaphyseal dysplasia	1	0	48184
PG4F.00	Lei-Weill dyschondrosteosis	1	0	40661
PG4z.00	Chondrodysplasia NOS	1	0	14917
PG5..00	Osteodysplasia	1	0	36753
PG5..11	Osteodystrophy	1	0	38450
PG50.00	Osteodysplasia, unspecified	1	0	96403
PG51.00	Osteogenesis imperfecta	1	0	4158
PG51.11	Vrolik's disease	1	0	69122
PG51.12	Eddowes's syndrome	1	0	39440
PG51.13	Adair-Dighton syndrome	1	0	5524
PG51.14	Lobstein's syndrome	1	0	60814
PG51.15	Van der Hoeve's syndrome	1	0	66679
PG51.16	Brittle bone disease	1	0	11588
PG51000	Fragilitas ossium	1	0	5486
PG51100	Osteopsathyrosis	1	0	46402
PG51200	Osteogenesis imperfecta - unclassifiable	1	0	103017
PG51300	Osteogenesis imperfecta type I	1	0	58635
PG51400	Osteogenesis imperfecta type II	1	0	98662
PG51500	Osteogenesis imperfecta type III	1	0	69436
PG51600	Osteogenesis imperfecta type IV	1	0	97751
PG51z00	Osteogenesis imperfecta NOS	1	0	53933
PG52.00	Osteopetrosis	1	0	15343
PG52.11	Albers - Schonberg syndrome	1	0	50325
PG52.12	Marble bones	1	0	92755
PG52000	Osteopetrosis - unclassified	1	0	44759
PG52100	Osteopetrosis - congenita type	1	0	93177
PG52200	Osteopetrosis - tarda type	1	0	103646
PG53.00	Osteopoikilosis	1	0	39943
PG53.11	Buschke-Ollendorff syndrome	1	0	48745
PG54.00	Polyostotic fibrous dysplasia	1	0	30600
PG55.00	Chondroectodermal dysplasia	1	0	23559
PG55.11	Ellis - Van Creveld syndrome	1	0	68007
PG56.00	Multiple epiphyseal dysplasia	1	0	34387
PG56000	Chondrodysplasia calcificans congenita	1	0	58035
PG56011	Chondrodysplasia calcificans congenita	1	0	63146
PG56012	Conradi - Hunermann syndrome	1	0	18321
PG56z00	Multiple epiphyseal dysplasia NOS	1	0	101702
PG57.00	Infantile cortical hyperostosis	1	0	60070
PG57.11	Caffey's syndrome	1	0	54401
PG58.00	Progressive diaphyseal dysplasia	1	0	92546
PG58.11	Engelmann's syndrome	1	0	60016
PG58.12	Camurati-Engelmann disease	1	0	51221
PG5A.00	Diaphyseal dysplasia	1	0	49153
PG5B.00	Multiple synostosis syndrome	1	0	72927

PG5C.00	Craniometaphyseal dysplasia	1	0	65348
PG5D.00	Craniodiaphyseal dysplasia	1	0	50405
PG5y.00	Other specified osteodysplasia	1	0	63819
PG5y.11	Dyschondrosteosis	1	0	40662
PG5y.12	Furst-Ostrum syndrome	1	0	109617
PG5y000	Albright-Sternberg syndrome	1	0	15046
PG5y011	Albright-McCune-Sternberg syndrome	1	0	30601
PG5y012	Albright's polyostotic dysplasia	1	0	57407
PG5yz00	Other osteodysplasia NOS	1	0	37406
PG5z.00	Osteodysplasia NOS	1	0	55331
PG5z.11	Osteochondrodysplasia	1	0	68427
PG6..00	Anomalies of diaphragm	0	1	31416
PG61.00	Congenital diaphragmatic hernia	1	0	49768
PG61.11	Congenital defect of diaphragmatic NEC	1	0	59281
PG62.00	Congenital foramen Morgagni hernia	1	0	24561
PG63.00	Eventration of diaphragm	0	1	14941
PG6y.00	Other specified anomalies of diaphragm	1	0	52883
PG6z.00	Diaphragm anomalies NOS	0	1	40848
PG7..00	Abdominal wall anomalies	1	0	18063
PG70.00	Exomphalos	1	0	22883
PG71.00	Gastroschisis	1	0	15593
PG72.00	Prune belly syndrome	1	0	22853
PG7y.00	Other specified anomaly of abdominal wall	1	0	44634
PG7z.00	Abdominal wall anomaly NOS	1	0	47060
PG8..00	Congenital inguinal hernia	0	1	93540
PGW..00	Osteochondrodyspl with defct growth tub bone spine unspec	1	0	63565
PGX..00	Congenital malformation of bony thorax, unspecified	1	0	52658
PGy..00	Other specified muscle, tendon and fascia anomaly	1	0	44093
PGy0.00	Congenital absence of muscle and tendon	1	0	19949
PGy0000	Absent tendon	1	0	67259
PGy0100	Poland's syndrome	1	0	21049
PGy0200	Other absent muscle	1	0	34141
PGy0211	Muscle agenesis	1	0	69430
PGy0212	Orbinsky syndrome	1	0	56160
PGy0z00	Absent muscle or tendon NOS	1	0	48122
PGy1.00	Accessory muscle	0	1	56707
PGy2.00	Ehlers-Danlos syndrome	1	0	4451
PGy2000	Ehlers-Danlos syndrome type I	1	0	63549
PGy2100	Ehlers-Danlos syndrome type II	1	0	72787
PGy2200	Ehlers-Danlos syndrome type III	1	0	28335
PGy2300	Ehlers-Danlos syndrome type IV	1	0	70415
PGy2500	Ehlers-Danlos syndrome type VI	1	0	53984
PGy2600	Ehlers-Danlos syndrome type VII	1	0	95643
PGy2700	Ehlers-Danlos syndrome type VIII	1	0	98263
PGy3.00	Nail-patella syndrome	1	0	45644
PGy3.11	Osteo-onychodysostosis	1	0	16735
PGy3.12	Onycho-osteodysplasia	1	0	43876

PGy4.00	Fibrodysplasia ossificans congenita	1	0	55372
PGyy.00	Other specified other anomalies of muscle, tendon and fascia	1	0	97640
PGyy.11	Ayala's disease	1	0	71447
PGyy000	Amyotrophica congenita	1	0	57769
PGyy100	Congenital shortening of tendon	1	0	42848
PGyy200	Hypoplasia of muscle	1	0	47471
PGyy300	Popliteal web syndrome	1	0	66604
PGyy400	Aplasia of muscle	0	1	45473
PGyyz00	Other anomaly of tendon, fascia or muscle NOS	1	0	98260
PGyz.00	Other muscle, tendon or fascia anomalies NOS	0	1	66657
PGz..00	Congenital musculoskeletal anomalies NOS	0	1	2709
PGz..11	Congenital deformity of musculoskeletal system NEC	0	1	35801
PGz0.00	Unspecified anomaly of muscle	0	1	16755
PGz1.00	Unspecified anomaly of tendon	0	1	19468
PGz2.00	Unspecified anomaly of bones	0	1	22492
PGz3.00	Unspecified anomaly of cartilage	0	1	16630
PGz4.00	Unspecified anomaly of connective tissue	0	1	28247
PH...00	Congenital integument anomalies	0	1	5681
PH...11	Congenital skin anomalies	0	1	31007
PH0..00	Hereditary oedema of legs	1	0	36990
PH00.00	Congenital lymphoedema	1	0	27326
PH01.00	Hereditary trophoedema	1	0	45279
PH02.00	Milroy's disease	1	0	21453
PH02.11	Meige's disease	1	0	40816
PH03.00	Congenital elephantiasis	1	0	51067
PH0z.00	Hereditary oedema of legs NOS	1	0	67774
PH1..00	Ichthyosis congenita	1	0	370
PH10.00	Congenital ichthyosis, unspecified	1	0	36468
PH11.00	Harlequin fetus	1	0	40376
PH12.00	Ichthyosiform erythroderma	1	0	6693
PH12.11	Sjogren - Larsson syndrome	1	0	11632
PH13.00	Collodion baby	1	0	46239
PH14.00	Ichthyosis vulgaris	1	0	5555
PH15.00	X-linked ichthyosis	1	0	35335
PH1y.00	Other specified ichthyosis congenita	1	0	71520
PH1y000	Netherton's syndrome	1	0	41261
PH1z.00	Ichthyosis congenita NOS	1	0	64322
PH1z.11	Congenital ichthyosiform erythroderma	1	0	57526
PH1z.12	Alligator skin	1	0	99643
PH2..00	Dermatoglyphic anomalies	0	1	58789
PH20.00	Abnormal palmar creases	0	1	32573
PH2z.00	Dermatoglyphic anomalies NOS	0	1	100293
PH3..00	Other specified skin anomalies	0	1	12755
PH30.00	Congenital ectodermal dysplasia	1	0	11513
PH31.00	Vascular hamartomas	0	1	22717
PH31.11	Vascular naevus	0	1	8131
PH31.12	Naevus flammeus	0	1	5436

PH31000	Birth mark, unspecified	0	1	5506
PH31100	Port wine stain	0	1	3384
PH31200	Strawberry naevus	0	1	531
PH31300	Angiomatosis	0	1	15713
PH31z00	Vascular hamartoma NOS	0	1	33776
PH32.00	Congenital pigmentary skin anomalies	0	1	23918
PH32000	Congenital poikiloderma	0	1	48046
PH32100	Urticaria pigmentosa	0	1	1876
PH32111	Mast cell disease	0	1	51029
PH32112	Mastocytosis	0	1	17521
PH32113	Nettleship's syndrome	0	1	60466
PH32200	Xeroderma pigmentosum	0	1	20421
PH32300	Incontinentia pigmenti	1	0	34922
PH32311	Bloch - Sulzberger syndrome	0	1	67501
PH32z00	Congenital pigmentary skin anomaly NOS	0	1	31929
PH33.00	Specified syndromes NEC involving skin anomalies	1	0	60064
PH33000	Brugsch's syndrome	1	0	100671
PH33011	Acropachyderma	1	0	23386
PH33100	Hailey-Hailey disease	1	0	35024
PH33111	Benign familial chronic pemphigus	1	0	49284
PH33200	Mibelli's disease	1	0	63547
PH33300	Rothmund-Thomson syndrome	1	0	40502
PH33311	Atrophic heredofamilial dermatosis	1	0	52648
PH33312	Thomson's disease	1	0	57510
PH33400	Focal dermal hypoplasia	1	0	30177
PH33500	Pseudoxanthoma elasticum	1	0	16440
PH33511	Darier's disease - pseudoxanthoma elasticum	1	0	34877
PH33600	Siemen's syndrome	1	0	66132
PH33z00	Specified syndromes involving skin anomalies NEC NOS	1	0	62805
PH34.00	Other specified birthmark	0	1	5680
PH34.11	Naevus NEC	0	1	3190
PH34000	Naevus sebaceous	0	1	101092
PH35.00	Mongolian blue spot	0	1	7863
PH3y.00	Other congenital skin anomalies	0	1	54235
PH3y.11	Keratosis palmaris	0	1	67307
PH3y000	Congenital accessory skin tags	0	1	9758
PH3y100	Congenital scar	0	1	60246
PH3y200	Epidermolysis bullosa	0	1	4272
PH3y212	Koebner's disease	0	1	24576
PH3y213	Bullous eruption of hand	0	1	25927
PH3y300	Congenital keratoderma	0	1	36991
PH3y400	Congenital keratosis follicularis	0	1	12854
PH3y411	Darier's disease - keratosis follicularis	0	1	27415
PH3y500	Acanthosis nigricans, congenital	0	1	31463
PH3y600	Keratosis palmaris et plantaris	0	1	20412
PH3y611	Tylosis palmaris et plantaris	0	1	24524
PH3y700	Epidermolysis bullosa simplex	0	1	37798
PH3y800	Epidermolysis bullosa letalis	0	1	46794

PH3y900	Epidermolysis bullosa dystrophica	0	1	35420
PH3yA00	Bloom syndrome	0	1	70236
PH3yz00	Other congenital skin anomaly NOS	0	1	23091
PH3yz11	Lichen spinulosus	0	1	44145
PH3z.00	Integument anomalies NOS	0	1	34662
PH4..00	Specified hair anomalies	1	0	11001
PH40.00	Congenital alopecia	1	0	16618
PH40.11	Congenital atrichosis	1	0	59553
PH40000	Congenital alopecia, unspecified	1	0	104030
PH40100	Congenital localised alopecia	1	0	92345
PH40200	Congenital generalised alopecia	1	0	68179
PH40211	Atrichosis	1	0	94887
PH40z00	Congenital alopecia NOS	1	0	98667
PH41.00	Congenital monilethrix	1	0	46296
PH41.11	Beaded hair	1	0	64511
PH42.00	Congenital hypertrichosis	1	0	30154
PH43.00	Persistent lanugo	1	0	46440
PH43.11	Hypertrichosis lanuginosa	1	0	52674
PH44.00	Twisted hair	1	0	55069
PH44.11	Pili torti	1	0	35991
PH4z.00	Specified hair anomalies NOS	0	1	55641
PH5..00	Specified anomalies of nails	0	1	10427
PH50.00	Anonychia	1	0	39931
PH50.11	Congenital absence of nails	1	0	103530
PH51.00	Congenital clubnail	1	0	15453
PH52.00	Congenital koilonychia	1	0	32621
PH53.00	Congenital leukonychia	1	0	95805
PH54.00	Congenital onychauxis	1	0	66070
PH54.11	Enlarged nails	0	1	89466
PH55.00	Congenital pachyonychia	1	0	35067
PH55.11	Hypertrophic nails	0	1	38522
PH5z.00	Specified nail anomalies NOS	0	1	22547
PH6..00	Specified anomalies of breast	1	0	18605
PH60.00	Absent breast	1	0	42379
PH61.00	Absent nipple	1	0	52665
PH62.00	Accessory breast	1	0	4294
PH63.00	Accessory nipple	0	1	4491
PH64.00	Supernumerary breast	1	0	61522
PH65.00	Supernumerary nipple	0	1	24567
PH66.00	Hypoplasia of breast	1	0	28001
PH67.00	Small nipple	0	1	45801
PH67.11	Hypoplasia of nipple	1	0	103993
PH68.00	Ectopic breast tissue	1	0	16754
PH6X.00	Congenital malformation of breast, unspecified	1	0	65092
PH6z.00	Specified breast anomalies NOS	1	0	36066
PH7..00	Cutis marmorata telangiectasia congenita	1	0	86047
PHy..00	Other specified integument anomaly	1	0	102162
PHz..00	Integument anomalies NOS	0	1	70979

PHz..11	Congenital ectodermal defect	0	1	65121
PHz0.00	Unspecified congenital anomalies of skin	0	1	39354
PHz0.11	Congenital dermal defect	0	1	54223
PHz1.00	Unspecified congenital anomalies of hair	0	1	48072
PHz2.00	Unspecified congenital anomalies of nail	0	1	38982
PHz2.11	Congenital deformity of nail	0	1	27676
PJ...00	Chromosomal anomalies	1	0	671
PJ0..00	Down's syndrome - trisomy 21	1	0	1543
PJ0..11	Mongolism	1	0	23489
PJ0..12	Trisomy 21	1	0	18415
PJ00.00	Trisomy 21, meiotic nondisjunction	1	0	42701
PJ01.00	Trisomy 21, mosaicism	1	0	32010
PJ01.11	Trisomy 21, mitotic nondisjunction	1	0	107919
PJ02.00	Trisomy 21, translocation	1	0	61499
PJ02.11	Partial trisomy 21 in Down's syndrome	1	0	101309
PJ0z.00	Down's syndrome NOS	1	0	10759
PJ0z.11	Trisomy 21 NOS	1	0	61627
PJ1..00	Patau's syndrome - trisomy 13	1	0	35665
PJ10.00	Trisomy 13, meiotic nondisjunction	1	0	72139
PJ11.00	Trisomy 13, mosaicism	1	0	43565
PJ12.00	Trisomy 13, translocation	1	0	46133
PJ12.11	Partial trisomy 13 in Patau's syndrome	1	0	102102
PJ1z.00	Patau's syndrome NOS	1	0	72265
PJ1z.11	Trisomy 13 NOS	1	0	19038
PJ2..00	Edward's syndrome - trisomy 18	1	0	33642
PJ20.00	Trisomy 18, meiotic nondisjunction	1	0	103873
PJ21.00	Trisomy 18, mosaicism	1	0	67234
PJ22.00	Trisomy 18, translocation	1	0	93133
PJ22.11	Partial trisomy 18 in Edward's syndrome	1	0	107162
PJ2z.00	Edward's syndrome NOS	1	0	39017
PJ2z.11	TRISOMY 18 NOS	1	0	46787
PJ3..00	Monosomies and deletions from the autosomes	1	0	37105
PJ30.00	Antimongolism syndrome	1	0	107123
PJ30.11	Deletion of long arm of chromosome 21	1	0	57806
PJ31.00	Cri-du-chat syndrome	1	0	31795
PJ31.11	Deletion of short arm of chromosome 5	1	0	98941
PJ32.00	Deletion of short arm of chromosome 4	1	0	66566
PJ32.11	Wolff - Hirschorn syndrome	1	0	33948
PJ33.00	Other deletions of part of a chromosome	1	0	62997
PJ33000	Deletion of long arm of chromosome 13	1	0	67298
PJ33100	Deletion of long arm of chromosome 18	1	0	95440
PJ33111	18p- syndrome	1	0	49236
PJ33200	Deletion of short arm of chromosome 18	1	0	97927
PJ33211	18q- syndrome	1	0	65091
PJ33300	Smith-Magenis syndrome	1	0	36871
PJ33400	Jacobsen syndrome	1	0	100507
PJ33z00	Other deletion of part of a chromosome NOS	1	0	68157

PJ36.00	Whole chromosome monosomy, meiotic nondisjunction	1	0	68256
PJ37.00	Whole chromosome monosomy, mosaicism	1	0	95598
PJ37.12	Autosomal deletion - mosaicism	1	0	31787
PJ37z00	Whole chromosome monosomy, mosaicism NOS	1	0	67815
PJ38.00	Chromosome replaced with ring or dicentric	1	0	100562
PJ38.11	Chromosome replaced with dicentric	1	0	106938
PJ38.12	Chromosome replaced with ring	1	0	47247
PJ3y.00	Other deletions from the autosomes	1	0	106499
PJ3y000	Shprintzen syndrome	1	0	12841
PJ3y011	Velocardiofacial syndrome	1	0	12840
PJ3z.00	Monosomies and deletions from the autosomes NOS	1	0	98395
PJ4..00	Balanced autosomal translocation	1	0	34140
PJ5..00	Other condition due to autosomal anomaly	1	0	49391
PJ50.00	Whole chromosome trisomy syndromes	1	0	37702
PJ50100	Trisomy 7	1	0	37591
PJ50200	Trisomy 8	1	0	69476
PJ50300	Trisomy 9	1	0	65509
PJ50400	Trisomy 10	1	0	110833
PJ50600	Trisomy 12	1	0	70198
PJ50800	Trisomy 22	1	0	100024
PJ50w00	Whole chromosome trisomy, meiotic nondisjunction	1	0	107670
PJ50x00	Whole chromosome trisomy, mosaicism	1	0	45512
PJ50y00	Other specified whole chromosome trisomy syndrome	1	0	101732
PJ50z00	Whole chromosome trisomy syndrome NOS	1	0	101982
PJ51.00	Partial trisomy syndromes	1	0	19062
PJ51000	Major partial trisomy	1	0	71815
PJ51100	Minor partial trisomy	1	0	99674
PJ51z00	Partial trisomy syndrome NOS	1	0	100174
PJ52.00	Trisomies of autosomes NEC	1	0	54377
PJ52000	Duplications seen only at prometaphase	1	0	69288
PJ52100	Duplications with other complex rearrangements	1	0	71880
PJ52200	Extra marker chromosomes	1	0	67991
PJ52300	Triploidy	1	0	34913
PJ52400	Polyploidy	1	0	18017
PJ52z00	Trisomy of autosomes NEC NOS	1	0	107119
PJ53.00	Balanced rearrangements and structural markers NEC	1	0	51677
PJ53.11	Balanced translocations	1	0	22451
PJ53000	Chromosome inversion in normal individual	0	1	54241
PJ53100	Balanced autosomal rearrangement in abnormal individual	1	0	63906
PJ53300	Individual with marker heterochromatin	1	0	103627
PJ53400	Individual with autosomal fragile site	1	0	56371
PJ53500	Shwachman-Diamond syndrome	1	0	62041
PJ5y.00	Other specified conditions due to autosomal anomalies	1	0	74906
PJ5z.00	Unspecified conditions due to autosomal anomalies	1	0	71029
PJ5z.11	Aneuploidy NEC	1	0	61407

PJ6..00	Gonadal dysgenesis	1	0	24383
PJ60.00	Mixed gonadal dysgenesis	1	0	73492
PJ62.00	Ovarian dysgenesis	1	0	47232
PJ63.00	Turner's syndrome	1	0	4943
PJ63000	Turner's phenotype, karyotype normal	1	0	98244
PJ63100	Turner's phenotype, karyotype 45X	1	0	30721
PJ63200	Turner's phenotype, karyotype 46X iso (Xq)	1	0	92599
PJ63300	Turner's, karyotype 46X + abnorm. sex chromosome, not iso(Xq)	1	0	109385
PJ63400	Turner's phenotype, mosaicism 45X/46XX or 45X/46XY	1	0	51868
PJ63500	Turner's, mosaic, 45X/other cell line with abn. sex chromosome	1	0	40570
PJ63600	Turner's phenotype, other variant karyotypes	1	0	65206
PJ63611	Turner's phenotype, ring chromosome karyotype	1	0	97871
PJ63612	Turner's phenotype, partial X deletion karyotype	1	0	64945
PJ63z00	Turner's syndrome NOS	1	0	53168
PJ63z11	Bonnevie-Ullrich syndrome NOS	1	0	60079
PJ63z12	Ovarian dwarfism NEC	1	0	98711
PJ64.00	Other gonadal dysgenesis phenotype	1	0	93450
PJ64000	XY, female phenotype	1	0	41152
PJ6z.00	Gonadal dysgenesis NOS	1	0	34681
PJ7..00	Klinefelter's syndrome	1	0	15846
PJ70.00	Klinefelter's phenotype, karyotype 47XXY	1	0	54490
PJ71.00	Klinefelter's syndrome, male with more than two X chromosomes	1	0	67854
PJ71.11	Klinefelter's syndrome, XXXY	1	0	56545
PJ71.12	Klinefelter's syndrome, XXXXY	1	0	62414
PJ72.00	Klinefelter's syndrome, male with 46XX karyotype	1	0	96257
PJ73.00	Klinefelter's syndrome, XXYY	1	0	91262
PJ74.00	Klinefelter's syndrome, XY/XXY mosaic	1	0	68109
PJ7z.00	Klinefelter's syndrome NOS	1	0	59439
PJ8..00	Balanced translocation and insertion in normal individual	0	1	41556
PJ9..00	Mowat-Wilson syndrome	1	0	93694
PJX..00	Sex chromosome abnormality, male phenotype, unspecified	1	0	4376
PJy..00	Other sex chromosome anomaly	1	0	1933
PJy0.00	Additional sex chromosome	1	0	70365
PJy1.00	Sex chromosome mosaicism	1	0	55119
PJy1000	Mosaic XO/XY	1	0	33269
PJy1100	Mosaic XO/XX	1	0	32783
PJy1200	Mosaic XY/XXY	1	0	64578
PJy1300	Mosaic including XXXXY	1	0	105345
PJy1z00	Sex chromosome mosaicism NOS	1	0	65983
PJy2.00	XXX syndrome	1	0	32782
PJy2.11	Triple X female	1	0	6377
PJy2.12	Karyotype 47, XXX	1	0	99213
PJy3.00	XXY syndrome	1	0	11948

PJy4.00	Female with more than three X chromosomes	1	0	37559
PJy5.00	Mosaicism, lines with various numbers of X chromosomes	1	0	23643
PJy6.00	Male with structurally abnormal sex chromosome	1	0	37484
PJyy.00	Other specified sex chromosome anomaly	1	0	59957
PJyy.11	Absence of sex chromosome	1	0	102328
PJyy000	Chimera 46XX/46XY	1	0	56763
PJyy100	46XX true hermaphrodite	1	0	49246
PJyy200	Fragile X chromosome	1	0	10628
PJyy300	Karyotype 47,YYY	1	0	9768
PJyy400	Fragile X syndrome	1	0	32603
PJyyz00	Other sex chromosome abnormality NOS	1	0	99129
PJyz.00	Sex chromosome anomaly NOS	1	0	34667
PJz..00	Chromosomal anomalies NOS	1	0	20231
PJz0.00	Mosaicism NOS	1	0	26140
PJz1.00	Additional chromosome NOS	1	0	9665
PJz2.00	Deletion of chromosome NOS	1	0	19099
PJz3.00	Duplication of chromosome	1	0	41326
PJzz.00	Conditions due to anomaly of unspecified chromosome NOS	1	0	66770
PK...00	Other and unspecified congenital anomalies	0	1	36463
PK0..00	Anomalies of spleen	1	0	26338
PK00.00	Aberrant spleen	1	0	62999
PK01.00	Absent spleen	1	0	22319
PK01.11	Asplenia	1	0	10505
PK02.00	Accessory spleen	1	0	42026
PK03.00	Congenital splenomegaly	1	0	59741
PK03.11	Hyperplasia of spleen	1	0	62455
PK04.00	Ectopic spleen	1	0	67425
PK06.00	Hypoplasia of spleen	1	0	71462
PK07.00	Mis-shapen spleen	1	0	65558
PK0y.00	Other specified anomalies of spleen	1	0	65103
PK0z.00	Anomalies of spleen NOS	1	0	59625
PK1..00	Anomalies of adrenal gland	1	0	25292
PK10.00	Aberrant adrenal gland	1	0	62636
PK11.00	Absent adrenal gland	1	0	71109
PK12.00	Accessory adrenal gland	1	0	49244
PK13.00	Hypoplasia of adrenal gland	1	0	29818
PK14.00	Ectopic adrenal gland	1	0	83531
PK15.00	Aplasia of adrenal gland	1	0	95752
PK1y.00	Other specified anomalies of adrenal gland	1	0	63824
PK1y000	Congenital cyst of adrenal gland	1	0	42894
PK1yz00	Other congenital anomaly of adrenal gland NOS	1	0	107541
PK1z.00	Anomalies of adrenal gland NOS	1	0	36064
PK2..00	Other endocrine gland anomalies	1	0	50094
PK20.00	Absent parathyroid gland	1	0	46978
PK21.00	Accessory thyroid gland	1	0	70633
PK22.00	Persistent thyroglossal duct	1	0	36110

PK23.00	Thyroglossal duct cyst	1	0	3797
PK24.00	Anomalies of pituitary gland	1	0	32424
PK24000	Aberrant pituitary gland	1	0	57797
PK24100	Congenital absence of pituitary gland	1	0	111629
PK24200	Accessory pituitary gland	1	0	112638
PK24z00	Anomaly of pituitary gland NOS	1	0	70576
PK25.00	Anomalies of thyroid gland NEC	1	0	10638
PK25000	Aberrant thyroid gland	1	0	39281
PK25011	Retrosternal thyroid gland	1	0	10704
PK25100	Congenital absence of thyroid gland	1	0	3374
PK25z00	Anomaly of thyroid gland NEC NOS	1	0	70581
PK26.00	Anomalies of thyroglossal duct NEC	1	0	57704
PK27.00	Anomalies of parathyroid gland NEC	1	0	39588
PK27000	Aberrant parathyroid gland	1	0	111952
PK27z00	Anomaly of parathyroid gland NEC NOS	1	0	100681
PK28.00	Anomalies of thymus	1	0	39366
PK28000	Aberrant thymus gland	1	0	101663
PK28100	Congenital absence of thymus	1	0	73987
PK28z00	Anomaly of thymus gland NOS	1	0	48842
PK2y.00	Other specified endocrine gland anomaly	1	0	110685
PK2z.00	Endocrine gland anomaly NOS	1	0	16201
PK3..00	Situs inversus	1	0	20062
PK30.00	Situs inversus, unspecified	1	0	72246
PK30.11	Transposition of viscera unspecified	1	0	47596
PK31.00	Situs inversus abdominalis	1	0	43560
PK31.11	Transposition of abdominal viscera	1	0	65785
PK32.00	Situs inversus thoracis	1	0	63861
PK33.00	Complete situs inversus with dextrocardia	1	0	36416
PK34.00	Situs inversus with levocardia	1	0	110797
PK35.00	Kartagener's syndrome	1	0	38298
PK3z.00	Situs inversus NOS	1	0	23513
PK4..00	Conjoined twins	1	0	52601
PK40.00	Craniopagus	1	0	59424
PK40100	Craniopagus occipitalis	1	0	68667
PK40300	Craniopagus parasiticus	1	0	66738
PK42.11	Buttock-joined twins	1	0	103378
PK44.00	Xiphopagus	1	0	71039
PK44.11	Xiphoid- and pelvis-joined twins	1	0	65090
PK45.00	Di axial (double) monster	1	0	56147
PK4z.00	Conjoined twins NOS	1	0	19918
PK5..00	Tuberous sclerosis	1	0	4479
PK5..11	Bourneville's disease	1	0	65996
PK5..12	Epiloia	1	0	46103
PK6..00	Other hamartoses NEC	1	0	24075
PK60.00	Peutz - Jegher's syndrome	1	0	15607
PK61.00	Sturge-Weber syndrome	1	0	4749
PK61.11	Kalischer's disease	1	0	52022
PK61.12	Encephalocutaneous angiomatosis	1	0	73205

PK62.00	Von Hippel-Lindau syndrome	1	0	28443
PK62.11	Lindau's disease	1	0	59034
PK63.00	Gardner's syndrome	1	0	23402
PK64.00	Proteus syndrome	1	0	42643
PK6y.00	Other specified hamartoses NEC	1	0	87863
PK6z.00	Hamartoses NOS	1	0	54573
PK7..00	Multiple congenital anomalies NOS	1	0	16530
PK70.00	Monster NOS	1	0	59400
PK7z.00	Multiple congenital anomalies NOS	1	0	98724
PK8..00	Congenital malformation syndromes due to known exogen causes	1	0	58981
PK80.00	Fetal alcohol syndrome	1	0	23945
PK81.00	Fetal hydantoin syndrome	1	0	100342
PK82.00	Dysmorphism due to warfarin	1	0	68279
PK83.00	Fetus and newborn affected by maternal use of alcohol	1	0	66699
PK84.00	Fetal valproate syndrome	1	0	57081
PKy..00	Other specified anomalies	1	0	64037
PKy0.00	Multiple system congenital anomalies NEC	1	0	54569
PKy0.11	Prader-Willi Syndrome	1	0	41461
PKy0.12	Prader-Willi syndrome	1	0	27280
PKy0.13	Noonan's syndrome	1	0	89727
PKy0000	Bannayan-Riley-Ruvalcaba syndrome	1	0	51750
PKy0100	Currarino triad	1	0	48563
PKy0200	Adams-Oliver syndrome	1	0	53221
PKy0300	Weaver syndrome	1	0	94823
PKy1.00	Laurence-Moon-Biedl syndrome	1	0	31426
PKy1.11	Biedl-Bardet syndrome	1	0	57458
PKy2.00	Marfan's syndrome	1	0	936
PKy3.00	Single monster, specified type	1	0	96023
PKy4.00	William syndrome	1	0	16087
PKy5.00	Congen malformation syndromes affecting facial appearance	1	0	30187
PKy5000	Oral - facial - digital syndrome	1	0	49307
PKy5011	Papillon-Leage-Psaume syndrome	1	0	98998
PKy5100	Mohr's syndrome	1	0	67072
PKy5200	Cyclops	1	0	49851
PKy5300	Whistling face syndrome	1	0	49177
PKy5311	Freeman Sheldon syndrome	1	0	38666
PKy5400	Waardenburg's syndrome	1	0	36679
PKy5500	Gorlin-Chaudhry-Moss syndrome	1	0	5550
PKy5600	Marchesani syndrome	1	0	70356
PKy5611	Weill-Marchesani syndrome	1	0	111773
PKy5612	Spherophakia-brachymorphia syndrome	1	0	94558
PKy5700	Otopalatodigital syndrome	1	0	97969
PKy5800	Usher's syndrome	1	0	32441
PKy5900	Oculo-palato-digital syndrome	1	0	111653
PKy5A00	Trichorhinophalangeal syndrome	1	0	36477

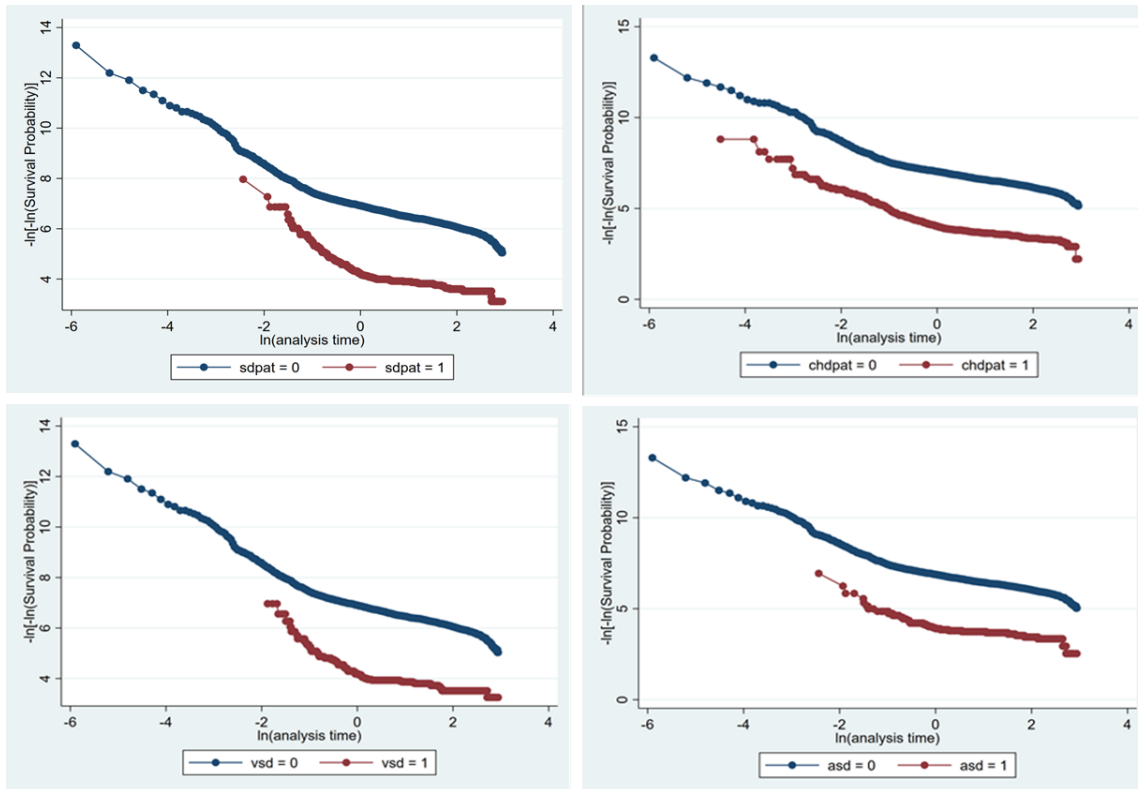
PKy5B00	Costello syndrome	1	0	50508
PKy5C00	Treacher Collins syndrome	1	0	37855
PKy5D00	Kabuki make-up syndrome	1	0	40472
PKy5E00	Branchio-otorenal dysplasia	1	0	44866
PKy5F00	Coffin-Lowry syndrome	1	0	37924
PKy5H00	Simpson-Golabi-Behmel syndrome	1	0	99476
PKy5z00	Congenital malform syndrome affecting facial appearance NOS	1	0	67260
PKy6.00	Congenital malformation syndromes with short stature	1	0	57953
PKy6000	Amsterdam dwarf	1	0	50457
PKy6011	Cornelia de Lange syndrome	1	0	21418
PKy6100	Cockayne syndrome	1	0	36567
PKy6200	Russell - Silver syndrome	1	0	32868
PKy6300	Smith - Lemli - Opitz syndrome	1	0	33522
PKy6400	Seckel syndrome	1	0	34719
PKy6500	Aarskog syndrome	1	0	22048
PKy6600	Dubowitz syndrome	1	0	57043
PKy6700	Robinow syndrome	1	0	57042
PKy6800	Floating-Harbor syndrome	1	0	51148
PKy6z00	Congenital malformation syndrome with short stature NOS	1	0	73575
PKy7.00	Congenital malformation syndromes involving limbs	1	0	45548
PKy7000	Carpenter's syndrome	1	0	44080
PKy7100	Holt - Oram syndrome	1	0	21966
PKy7200	Klippel - Trenaunay - Weber syndrome	1	0	10491
PKy7300	Rubenstein - Tayi syndrome	1	0	43325
PKy7400	Sirenomelia	1	0	66745
PKy7411	Sympus	1	0	90516
PKy7412	Mermaid sirenomelia	1	0	43171
PKy7500	Arachnodactyly	1	0	43396
PKy7600	Aglossia - adactyly syndrome	1	0	94845
PKy7611	Hanhart syndrome	1	0	67552
PKy7700	Caudal dysplasia sequence	1	0	26136
PKy7800	Multiple pterygium syndrome	1	0	50598
PKy7900	Popliteal pterygium syndrome	1	0	66206
PKy7A00	Congenital contractural arachnodactyly	1	0	31211
PKy7A11	Beals syndrome	1	0	57531
PKy7B00	Stickler syndrome	1	0	16711
PKy7z00	Congenital malformation syndrome involving limbs NOS	1	0	95151
PKy8.00	Congenital malformation syndromes with other skeletal change	1	0	97293
PKy8000	Noonan's syndrome	1	0	10068
PKy8z00	Congenital malformation syndrome+other skeletal changes NOS	1	0	100310
PKy9.00	Congenital malformation syndromes with metabolic disturbance	1	0	94910
PKy9000	Alport's syndrome	1	0	24395

PKy9100	Beckwith's syndrome	1	0	12357
PKy9111	Wiedemann - Beckwith syndrome	1	0	32054
PKy9200	Menke's syndrome	1	0	28663
PKy9211	Kinky hair syndrome	1	0	69127
PKy9300	Prader - Willi syndrome	1	0	10956
PKy9400	Zellweger's syndrome	1	0	48084
PKy9600	VATER association	1	0	31942
PKyA.00	Cloacal exstrophy	1	0	93164
PKyB.00	CHARGE association	1	0	36721
PKyC.00	Pena-Shokeir syndrome type I	1	0	61769
PKyD.00	Nicolaides-Baraitser syndrome	1	0	110169
PKyE.00	Barber-Say syndrome	1	0	100175
PKyF.00	Alstrom syndrome	1	0	71526
PKyG.00	Men ret congen heart dis blepharophim blepharop hypopl teeth	1	0	72742
PKyG.11	Ohdo blepharophimosis syndrome	1	0	61322
PKyH.00	Moulded baby syndrome	1	0	64941
PKyJ.00	Lujan-Fryns syndrome	1	0	99652
PKyK.00	Loeys-Dietz syndrome	1	0	102270
PKyz.00	Other specified anomalies NOS	1	0	49498
PKyz.11	Cockayne's syndrome	1	0	108947
PKyz.12	Local gigantism NEC	1	0	29708
PKyz000	Ullrich - Feichtiger syndrome, chimaera	1	0	60673
PKyz100	Acardia	1	0	25089
PKyz500	Happy puppet syndrome	1	0	46766
PKyz511	Angelman syndrome	1	0	25306
PKyz600	Congenital hemihypertrophy	1	0	31853
PKyz700	Angelman's syndrome	1	0	97059
PKyz711	Angelman syndrome	1	0	98617
PKz..00	Other anomalies NOS	0	1	15729
PKz0.00	Anomalies of umbilicus	0	1	18041
PKzz.00	Congenital anomaly NOS	0	1	62537
Pyu0100	[X]Other congenital hydrocephalus	1	0	100673
Pyu0300	[X]Other specified congenital malformations of brain	1	0	105277
Pyu0400	[X]Unspecified spina bifida with hydrocephalus	1	0	106579
Pyu0600	[X]Other specified congenital malformations of spinal cord	1	0	107732
Pyu1.00	[X]Congenital malformations of eye, ear, face and neck	1	0	52137
Pyu1100	[X]Other congenital malformations of lacrimal apparatus	1	0	107079
Pyu1200	[X]Other anophthalmos	1	0	111254
Pyu1300	[X]Other congenital lens malformations	1	0	108933
Pyu1400	[X]Other congenital malformations of iris	1	0	104673
Pyu1600	[X]Other congenital malforms of anterior segment of eye	1	0	104135
Pyu1800	[X]Other specified congenital malformations of eye	1	0	101780
Pyu1900	[X]Other congenital malformations of middle ear	1	0	111422
Pyu1A00	[X]Congenital malformation of inner ear	1	0	97357

Pyu1B00	[X]Malformation of ear with impairment of hearing, unspec	1	0	103542
Pyu1D00	[X]Other specified congenital malformations of ear	1	0	72789
Pyu1E00	[X]Other branchial cleft malformations	1	0	106458
Pyu1F00	[X]Other specified congenital malformations of face & neck	1	0	50639
Pyu3.00	[X]Congenital malformations of the respiratory system	1	0	96542
Pyu3000	[X]Other congenital malformations of nose	1	0	110850
Pyu3200	[X]Other congenital malformations of trachea	1	0	112752
Pyu3300	[X]Other congenital malformations of bronchus	1	0	107040
Pyu3400	[X]Other congenital malformations of lung	1	0	101623
Pyu3500	[X]Other specified congenital malformation respiratory system	1	0	110010
Pyu4.00	[X]Cleft lip and cleft palate	1	0	72027
Pyu4000	[X]Cleft palate, unspecified, bilateral	1	0	93641
Pyu4100	[X]Unspecified cleft palate with cleft lip, bilateral	1	0	48070
Pyu5000	[X]Other congenital malformations of tongue	1	0	98276
Pyu5100	[X]Congenital malformations of palate, NEC	1	0	105089
Pyu5200	[X]Other congenital malformations of mouth	0	1	74903
Pyu5700	[X]Cong absence/atresia/stenosis of small intestine	1	0	111515
Pyu5D00	[X]Other congenital malformations of bile ducts	1	0	101542
Pyu5E00	[X]Other congenital malformations of liver	1	0	105782
Pyu5F00	[X]Other congenital malformation of pancreas & pancreatic duct	1	0	106033
Pyu6.00	[X]Congenital malformations of genital organs	1	0	69013
Pyu6300	[X]Other congenital malformations of uterus and cervix	1	0	91599
Pyu6400	[X]Other congenital malformations of vagina	1	0	64385
Pyu6600	[X]Other specified congenital malformation of female genitalia	1	0	38541
Pyu6700	[X]Other specified hypospadias	1	0	95648
Pyu6800	[X]Other congenital malformations of testis and scrotum	1	0	48850
Pyu6A00	[X]Other congenital malformations of penis	1	0	111591
Pyu6B00	[X]Other specified congenital malformation of male genital organs	1	0	7461
Pyu7.00	[X]Congenital malformations of the urinary system	1	0	74899
Pyu7000	[X]Other cystic kidney diseases	1	0	72877
Pyu7100	[X]Other obstructive defects of renal pelvis and ureter	1	0	53781
Pyu7200	[X]Other congenital malformations of ureter	1	0	111674
Pyu7300	[X]Other specified congenital malformations of kidney	1	0	97874
Pyu7400	[X]Other atresia and stenosis of urethra and bladder neck	1	0	112240
Pyu7500	[X]Other congenital malformations of bladder and urethra	1	0	105804
Pyu8000	[X]Other congenital deformities of hip	1	0	111003
Pyu8100	[X]Other congenital varus deformities of feet	0	1	95320
Pyu8200	[X]Other congenital valgus deformities of feet	0	1	100428

Pyu8300	[X]Other congenital deformities of feet	0	1	67992
Pyu8400	[X]Other congenital deformities of skull, face and jaw	0	1	98773
Pyu8500	[X]Other congenital deformities of chest	0	1	65997
Pyu8700	[X]Other reduction defects of upper limb(s)	1	0	107951
Pyu8A00	[X]Other congenital malformations of upper limb(s), incl shoulder girdle	1	0	52819
Pyu8C00	[X]Other specified congenital malformations of limb(s)	1	0	106160
Pyu8D00	[X]Other specified congenital malformation skull & face bones	0	1	97006
Pyu8F00	[X]Other congenital malformations of ribs	1	0	73157
Pyu8M00	[X]Other congenital malformations of the musculoskeletal system	1	0	101281
Pyu8N00	[X]Congenital deformity of hip, unspecified	1	0	97637
Pyu8P00	[X]Congenital malformation of bony thorax, unspecified	1	0	108841
Pyu9.00	[X]Other congenital malformations	0	1	65095
Pyu9000	[X]Other congenital ichthyosis	1	0	100661
Pyu9100	[X]Other epidermolysis bullosa	1	0	106885
Pyu9200	[X]Other specified congenital malformations of skin	0	1	63103
Pyu9300	[X]Other congenital malformations of breast	1	0	107879
Pyu9700	[X]Other phakomatoses, not elsewhere classified	1	0	112466
Pyu9B00	[X]Other specified congenital malformations	1	0	64425
Pyu9C00	[X]Congenital malformation of breast, unspecified	1	0	109690
Pyu9D00	[X]Primary ciliary dyskinesia	1	0	94925
PyuA.00	[X]Chromosomal abnormalities, not elsewhere classified	1	0	53820
PyuA100	[X]Other deletions of part of a chromosome	1	0	95747
PyuA500	[X]Other variants of Turner's syndrome	1	0	109386
PyuA900	[X]Other specified chromosome abnormalities	1	0	62711
PyuAB00	[X]Pallister-Killian syndrome	1	0	70704
PyuAC00	[X]Townes-Brocks syndrome	1	0	66018
Pz...00	Congenital anomaly NOS	0	1	1299
Q48y500	Megalencephaly	1	0	94733

Appendix 3: Log-log plots for cox proportional hazards assumption.



If plots are parallel, it indicates that the assumption is not violated and so cox regression can be used. There was no indication of violation for all variants as shown in the plots below.

Appendix 4: Code list for procedures/interventions more specifically related to CHD corrective procedures or specifying the name of a CHD (i.e., CHD-specific procedure)

Medcodes	Readcodes	Description/Terms
39810	790..00	Heart wall, septum and chamber operations
16849	790..13	Heart septum operations
60271	790..14	Heart wall operations
5477	7902.00	Correction of tetralogy of Fallot
12844	7902.11	Repair of tetralogy of Fallot
16538	7902000	Correct Fallot tetralogy- valved right ventr outflow conduit
73029	7902100	Correct Fallot tetralogy- right ventric outflow conduit NEC
99198	7902200	Correct Fallot tetralogy- right ventricular outflow patch
70857	7902300	Revision of correction of tetralogy of Fallot
88842	7902400	Repair of tetralogy of Fallot using transannular patch
88479	7902500	Repair of tetralogy of Fallot with absent pulmonary valve
93719	7902600	Repair Fallot-type pulmonary atresia aortopulmonary collater
65401	7902y00	Other specified correction of tetralogy of Fallot
112436	7902y11	Other specified repair of tetralogy of Fallot
19956	7902z00	Correction of tetralogy of Fallot NOS
108402	7902z11	Repair of tetralogy of Fallot NOS
6945	7903.00	Atrial inversion ops for transposition of great vessels
37987	7903.12	Senning correction for transposition of great vessels
89968	7903.13	Atrial inversion operations for transposition of great art
62470	7903000	Atrium reconstruction atrial patch for transpos great vessel
69021	7903100	Atrium reconstruction atrial wall for transpos great vessels
69200	7903y00	Atrial inversion op for transposition of great vessels OS
58886	7903z00	Atrial inversion op for transposition of great vessels NOS
28355	7904.00	Other correction of transposition of great vessels
33909	7904000	Repositioning of transposed great vessels
98383	7904200	Left ventricle aorta tunnel right ventricle pul art val con
91533	7904300	Atrial switch and arterial switch
64470	7904y00	Other correction of transposition of great vessels OS
38411	7904z00	Other correction of transposition of great vessels NOS
28943	7905.00	Correction of total anomalous pulmonary venous connection
94475	7905000	Correct total anomal pulm venous connect to supracard vessel
105154	7905y00	Correction of total anomalous pulmonary venous connection OS
73820	7905z00	Correction total anomalous pulmonary venous connection NOS
32163	7906.00	Closure of defect of atrioventricular septum
73476	7906.11	Repair of defect of the atrioventricular septum
57102	7906000	Close defect atrioventric septum using dual prosthetic patch
105465	7906011	Rep defect atrioventricular septum dual prosthetic patches
39884	7906100	Close defect atrioventric septum using prosthetic patch NEC
95755	7906111	Repair defect atrioventricular septum prosthetic patch NEC
73817	7906200	Closure defect atrioventricular septum using tissue graft
104708	7906211	Repair defect of atrioventricular septum using tissue graft

42181	7906300	Closure of persistent ostium primum
99346	7906311	Repair of persistent ostium primum
48331	7906400	Primary closure of defect of atrioventricular septum NEC
111039	7906411	Primary repair of defect of atrioventricular septum NEC
39885	7906500	Revision of closure of defect of atrioventricular septum
57270	7906y00	Other specified closure of defect of atrioventricular septum
111266	7906y11	Other specified repair of defect of atrioventricular septum
38436	7906z00	Closure of defect of atrioventricular septum NOS
34902	7907.00	Closure of defect of interatrial septum
88772	7907.11	Repair of defect of interatrial septum
31101	7907000	Closure defect of interatrial septum using prosthetic patch
94191	7907011	Repair defect of interatrial septum using prosthetic patch
43926	7907100	Closure defect of interatrial septum using pericardial patch
108307	7907111	Repair defect of interatrial septum using pericardial patch
52287	7907200	Closure defect of interatrial septum using tissue graft NEC
28367	7907300	Primary closure of defect of interatrial septum NEC
102977	7907311	Primary repair of defect of interatrial septum NEC
70424	7907400	Revision of closure of defect of interatrial septum
67299	7907y00	Other specified closure of defect of interatrial septum
16191	7907z00	Closure of defect of interatrial septum NOS
36575	7908.00	Closure of defect of interventricular septum
91892	7908.11	Repair of defect of interventricular septum
39803	7908000	Close defect interventricular septum using prosthetic patch
99781	7908011	Repair defect interventricular septum us prosthetic patch
50626	7908100	Close defect interventricular septum using pericardial patch
96130	7908111	Repair defect interventricular septum us pericardial patch
67483	7908200	Close defect interventricular septum using tissue graft NEC
45358	7908300	Primary closure of defect of interventricular septum NEC
95578	7908311	Primary repair of defect of interventricular septum NEC
105759	7908400	Revision of closure of defect of interventricular septum
94023	7908500	Closure of multiple interventricular septal defects
98273	7908511	Repair of multiple interventricular septal defects
65234	7908600	Closure interventricular septal defect us intraop trans pros
92020	7908611	Repair interventricular septal defect us intraop trans pros
57271	7908y00	Other specified closure of defect of interventricular septum
3864	7908z00	Closure of defect of interventricular septum NOS
112504	7908z11	Repair of defect of interventricular septum NOS
30340	7909.00	Closure of defect of unspecified septum of heart
86763	7909.11	Repair of defect of unspecified septum of heart
42090	7909000	Closure of defect of heart septum using prosthetic patch NEC
59012	7909100	Closure defect of heart septum using pericardial patch NEC
28006	7909300	Primary closure of defect of septum of heart NEC
38828	7909y00	Other specified closure of defect unspecified heart septum
50310	7909z00	Closure of defect of unspecified septum of heart NOS
103939	7909z11	Repair of defect of unspecified septum of heart NOS
36989	790A.00	Other open operations on septum of heart
68073	790A000	Open enlargement of defect of atrial septum
31084	790A100	Open atrial septostomy

36967	790A111	Atrial septostomy NEC
67045	790A300	Atrial septectomy
89333	790A400	Atrial septation procedure
93264	790A600	Surgical atrial septation
41085	790Ay00	Other specified other open operation on septum of heart
66308	790Az00	Other open operation on septum of heart NOS
49625	790B.00	Closed operations on septum of heart
47885	790By00	Other specified closed operation on septum of heart
94040	790Bz00	Closed operation on septum of heart NOS
98240	790C.00	Therapeutic transluminal operations on septum of heart
93381	790C200	Percutaneous transluminal atrial septum fenest closure pros
72825	790C400	Percutaneous transluminal closure patent oval foramen pros
99829	790F200	Repair of cor triatriatum
105637	790Fy00	Other specified refashioning of atrium
42782	790G.00	Other operations on wall of atrium
72279	790Gy00	Other specified operation on wall of atrium
101446	790Gz00	Operation on wall of atrium NOS
103317	790H.00	Other operations on wall of heart
90605	790J.00	Other repair of transposition of great arteries
95106	790J000	Repositioning of transposed great arteries
108021	790Jz00	Other repair of transposition of great arteries NOS
89231	790K.00	Repair of double outlet ventricle
107122	790K100	Repair of Fallot-type double outlet right ventricle
98443	790K200	Repair of double outlet right ventricle
111871	790L100	Percutaneous translum closure defect intervent septum NEC
102473	790L200	Percutan translum closure defect interatr septum us prosth
93807	790L300	Percutan transluminal closure defect interatrial septum NEC
106726	790L311	Percutan transluminal repair defect interatrial septum NEC
94982	790Lz00	Transluminal closure of defect of septum NOS
97058	790M.00	Repair of univentricular heart
96637	790M400	Biventricular repair of hypoplastic left heart syndrome
89257	790My00	Other specified repair of univentricular heart
95951	790Mz00	Repair of univentricular heart NOS
103641	790N100	Repair of double chambered right ventricle
20940	791A200	Repair of subaortic stenosis
62293	791A300	Repair of supraaortic stenosis
111685	791B300	Closure of aorto-left ventricular tunnel
109622	791Dy00	Other specified excision of valve of heart
29167	7930000	Open ablation of atrioventricular node
45234	7932000	Ligation of sinus of Valsalva
28933	7934000	Percutaneous transluminal ablation of atrioventricular node
100570	7A0..11	Great vessel operations
61794	7A00300	Closure of aortopulmonary window
21090	7A01.00	Open correction of patent ductus arteriosus
7342	7A01.11	Open correction of patent ductus arteriosus (PDA)
50019	7A01000	Division of patent ductus arteriosus
9573	7A01100	Ligation of patent ductus arteriosus
36668	7A01200	Closure of patent ductus arteriosus NEC

63163	7A01300	Revision of correction of patent ductus arteriosus
106081	7A01y00	Other specified open correction of patent ductus arteriosus
2728	7A01z00	Open correction of patent ductus arteriosus NOS
12889	7A02000	Percut transluminal prosth occlusion patent ductus arterios
19188	7A02011	Percut translum prosth occlus patent ductus arteriosus (PDA)
70561	7A04000	Creation of aortopulmonary window
42524	7A08200	Repair of anomalous pulmonary artery NEC
66801	7A0y.00	Great vessel or pulmonary artery operations OS
92330	7A18111	Hamilton repair coarctation of aorta using subclavian flap
17111	7A18300	Release of vascular ring of aorta
67046	7A18600	Repair of interrupted aortic arch

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